Assessing the association of diabetes with lung cancer risk

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Background: Diabetes is a well-established risk factor for many cancers, but its relationship with lung cancer incidence remains unclear. In this study, we aimed to assess if diabetes is independently associated with lung cancer risk and histology subtype among participants in a screening study.

Methods: In a retrospective cohort study using data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) study, we assessed the association of self-reported diabetes with lung cancer incidence using Poisson regression while adjusting for other established risk factors in the PLCOM2012, a validated lung cancer prediction model. The adjusted association of diabetes and lung cancer cell type was evaluated using nominal regression. Stratified analyses were also conducted according to sex, smoking history, and body mass index categories.

Results: Overall, 140,395 participants were included in our analysis. Diabetes was not significantly associated with lung cancer incidence [incidence rate ratio (IRR): 1.03, 95% confidence interval (CI): 0.91–1.17]. Similarly, stratified analyses also did not show significant associations between diabetes and lung cancer risk (all P values >0.05). We found no significant difference in the distribution of lung cancer histology in participants with *vs.* without diabetes (P=0.30).

Conclusions: Diabetes was not an independent risk factor for lung cancer in a large cohort of PLCO participants. We did not observe differences in histology according to diabetes status. These results suggest that patients with diabetes do not need more aggressive lung cancer screening. Future research including more detailed metabolic parameters may further elucidate the relationship between metabolic disease and lung cancer risk.

Keywords: Lung neoplasms; lung cancer incidence; early detection of cancer; lung cancer screening; metabolic disease and cancer

Introduction

Multiple malignancies, including breast, pancreatic and liver cancer have been linked to diabetes (1,2). Type 2 diabetes (which comprises >90% of cases worldwide) is associated with hyperinsulinemia and hyperglycemia, two factors known to promote tumor cell growth (1,3). Cancer cells are known to be more dependent on glucose metabolism for growth than non-cancer cells and hyperinsulinemia is known to promote cancer cell growth directly through the

insulin receptor and indirectly through insulin-like growth factor 1 (IGF-1) and IGF-1 receptor (IGF-1R) (4,5).

Lung cancer is the leading cause of cancer deaths in the United States (US) and worldwide (6). Diabetes is also a growing major public health problem in the US with an estimated prevalence of 13% in 2020 (7). Preclinical studies have demonstrated that hyperglycemia promotes lung cancer growth (8,9). Additionally, high levels of insulin receptor expression are linked to lung cancer progression and the IGF-1/IGF-1R pathway is known to play an important role in lung cancer pathogenesis (10-12). Prior epidemiologic studies evaluating the potential relationship between diabetes and lung cancer risk have shown mixed results (13). Of note, a meta-analysis showed that there was no association between diabetes and lung cancer risk in high-quality studies [relative risk (RR): 1.03; 95% confidence interval (CI): 0.99–1.23] but a significant association in studies labeled as low-quality (RR: 1.18; 95% CI: 1.06–1.31). These prior studies have included heterogenous populations, did not record lung cancer subtype, and many did not control for important lung cancer risk factors, such as smoking duration and body mass index (BMI) (13).

Moreover, how diabetes impacts lung cancer incidence may differ according to sex, BMI, and smoking status has varied in prior studies. A recent meta-analysis showed that diabetes increased lung cancer risk in men and women, but this was only statistically significant for women, increased lung cancer risk in patients with lower (<25 kg/m^2) and higher BMI (≥25 kg/m^2), but only was statistically significant in the higher BMI group, and increased lung cancer risk in current smokers (13). Additionally, prior research has shown that hyperglycemia and insulin resistance may be more strongly associated with squamous cell carcinoma development compared to other histologic subtypes, suggesting that the relationship between diabetes and lung cancer risk may vary according to cell type (12,14-16). However, the impact of diabetes on lung cancer histologic subtypes has not yet been determined.

Given the increasing prevalence of diabetes, establishing how diabetes may impact lung cancer risk is important for optimizing lung cancer prevention programs, enhancing screening efforts, and elucidating the pathogenesis of lung cancer histologic subtypes. In this study, we aimed to assess the association of diabetes with lung cancer incidence and whether this association varies according to lung cancer histologic subtype. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-601).

Methods

We analyzed data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening dataset (17). The PLCO was a randomized control trial of screening tests for prostate, lung, colorectal and ovarian cancer. A total of 154,901 men and women between the ages of 55 and 74 years were enrolled between November 1993 and July 2001 and randomized in equal proportions to a control group versus an active cancer screening arm. In terms of lung cancer, the control group received usual care (i.e., no screening at the time of study), while the intervention group received annual chest radiography for 3 years (as the PLCO study was conducted prior to the publication of the United States Preventive Services Task Force's recommendation for low dose computed-tomography screening in 2013). Further details regarding the PLCO trial cohort have been previously published (17,18). For our study, we limited the PLCO trial cohort to participants with complete data about the presence or absence of diabetes diagnosis. We excluded patients without follow up data or information about smoking status.

Our primary outcome of interest was lung cancer incidence. Cancer diagnosis was ascertained by a mailed annual study update questionnaire, supplemented with data from the National Death Index, and confirmed with medical record abstraction. The secondary outcome of interest was lung cancer histologic subtype which was abstracted from medical records and was categorized as squamous cell carcinoma, adenocarcinoma, small cell lung cancer, or other. Our primary predictor of interest was a diagnosis of diabetes, which was ascertained by self-report of physician diagnosis on a baseline questionnaire completed at randomization.

Co-variates included age, education level (less than high school, high school graduate, college education, or post-college education), BMI (continuous and stratified by World Health Organization categories [underweight: <18.5 kg/m^2, normal weight: $18–24.99$ kg/m^2, overweight $25–29.99$ kg/m^2, and obese ≥30 kg/m^2], family history of lung cancer, history of any cancer (except for PLCO cancers), chronic obstructive pulmonary disease, smoking status with quit time for former smokers (never smoker, current smoker, and quit <10, 10–20, 20–30, or >30 years ago), and cigarette smoking quantity and duration (calculated as pack-years, continuous). These variables were chosen as they are known risk factors for lung cancer in the PLCO dataset and included in the PLCO$_{M2012}$
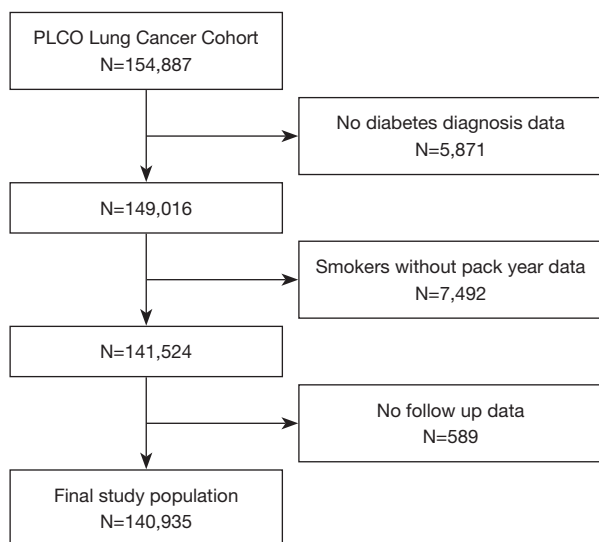
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Figure 1 Flow diagram of study population. PLCO, Prostate, Lung, Colorectal, and Ovarian.

risk score, a validated prediction model for estimating the risk of lung cancer in smokers (19).

Statistical analysis

We assessed the baseline characteristics of the PLCO cohort included in the study according to diabetes status. PLCO participants with and without diabetes were compared using the chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. Unadjusted and adjusted Poisson models were fitted to assess the association of diabetes and lung cancer incidence while incorporating patient follow-up time (to either lung cancer diagnosis or last follow-up). We conducted secondary analyses stratifying the sample by smoking status (never, former, and current smoker), sex, and BMI category (normal, overweight and obese). We excluded the underweight group due to low sample size. All adjusted models included individual terms representing the factors included in the $PLCO_{M2012}$ risk score (the actual score was not used as it cannot be calculated in non-smokers) and did not include patients with missing co-variate data. For stratified analyses focused on smokers, we also fitted models adjusting for $PLCO_{M2012}$ risk scores.

The chi-square test and adjusted (for other lung cancer risk factors as specified above) nominal regression models were used to compare lung cancer histology types in lung cancer cases with and without diabetes. We also conducted an analysis taking into account the screening arm group.

Based on the PLCO trial sample, we estimated that the study had a >80% power to detect if diabetes was associated with a ≥1.10 incidence risk ratio of lung cancer. We used STATA v14 (Statacorp, College Station, TX, USA) to conduct statistical analyses. A P value less than 0.05 was considered statistically significant.

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Icahn School of Medicine at Mount Sinai Institutional Review Board 20-01308 and individual consent for this retrospective analysis was waived.

Results

We included 140,935 PLCO participants in the study (*Figure 1*). Overall, 10,847 (7.7%) reported a physician diagnosis of diabetes. Median study follow-up time was 12 years. Baseline characteristics of participants with and without diabetes are reported in *Table 1*. Participants with diabetes were older {median age 63 [interquartile range (IQR), 59–68] *vs.* 62 years (IQR, 58–67), P<0.01}, more likely to be male (56% *vs.* 46%, P<0.01), less likely to be college graduates (13% *vs.* 18%, P<0.01) and were more likely to have BMI in the obese category (45% *vs.* 23%, P<0.01). Participants with diabetes were also more likely to be former smokers (50% *vs.* 44%, P<0.01) and had higher median smoking pack year history [12 (IQR, 0–41) *vs.* 5 pack-years (IQR, 0–33), P<0.01].

Unadjusted analyses (*Table 2*) showed that diabetes was significantly associated with lung cancer incidence [incidence rate ratio (IRR): 1.19; 95% confidence interval (CI): 1.05–1.35]. Adjusted analyses (*Table 2*) including the entire cohort showed that diabetes was not significantly associated with lung cancer incidence (IRR: 1.03; 95% CI: 0.91–1.17) after controlling for other risk factors (*Table 2*). Stratified analyses also showed that diabetes was not associated with lung cancer incidence in groups stratified by sex, smoking status (never, current, former), and BMI category (normal, overweight, obese). Similar results were obtained among ever smokers (IRR: 1.01; 95% CI: 0.88–1.14) in analyses adjusting for $PLCO_{M2012}$ risk scores.

Analyses assessing the association of diabetes and lung cancer histology are reported in *Tables 3,4*. The distribution of lung cancer histology did not significantly differ between patients with diabetes *vs.* without diabetes (P=0.30).

Table 1 Characteristics of study population according to pre-existing diabetes diagnosis

Variable	Total, N=140,395	No diabetes, N=130,116	Diabetes, N=10,819	P value
Active screening arm	71,189 [51]	65,726 [51]	5,463 [50]	0.97
Age, years (median, interquartile range)	62 [58–67]	62 [58–67]	63 [59–68]	<0.01
Male, N [%]	66,380 [47]	60, 331 [46]	6,049 [56]	<0.01
Race/ethnicity, N [%]				
White	124,593 [88]	116,211 [89]	8,382 [78]	<0.01
Black	7,225 [5]	5,905 [5]	1,320 [12]	
Asian	2,628 [2]	2,263 [2]	365 [4]	
Hispanic	5,278 [4]	4,729 [4]	549 [5]	
Pacific Islander or American Indian	1,146 [1]	964 [1]	182 [2]	
Education, N [%] (missing, n=254)				<0.01
<High school	10,433 [7]	9,153 [7]	1,280 [12]	
High school grad	50,775 [36]	46,581 [36]	4,194 [39]	
College education	54,594 [39]	50,722 [39]	3,872 [36]	
Post-college education	24,879 [18]	23,426 [18]	1,453 [13]	
BMI, kg/m^2, N [%]				<0.01
Underweight	1,087 [1]	1,046 [1]	41 [0]	
Normal	47,066 [33]	45,308 [35]	1,758 [16]	
Overweight	58,170 [41]	54,066 [42]	4,114 [38]	
Obese	34,612 [25]	29,706 [23]	4,906 [45]	
Smoking status, N [%]				<0.01
Never	62,901 [45]	58,541 [45]	4,360 [40]	
Current	15,684 [11]	14,643 [11]	1,041 [10]	
Former	62,350 [44]	56,932 [44]	5,418 [50]	
Pack years (median, interquartile range)	6 [0–33]	5 [0–33]	12 [0–41]	<0.01
Chronic obstructive pulmonary disease	9,391 [7]	8,438 [6]	953 [9]	<0.01
Personal history of cancer[†]				0.79
No	134,373 [95]	124,072 [95]	10,301 [95]	
Yes	6,548 [5]	6,031 [5]	517 [5]	
Unknown	14 [0]	13 [0]	1 [0]	
Family history of lung cancer (missing, n=959)				<0.01
No	121,503 [87]	112,268 [87]	9,235 [86]	
Yes	14,809 [11]	13,666 [11]	1,143 [11]	
Possibly/unclear	3,664 [3]	3,301 [3]	363 [3]	

[†], except for prostate, lung, colorectal, and ovarian cancers.

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Table 2 Association of diabetes with lung cancer incidence: unadjusted analyses

Analysis	Number of PLCO participants	Lung cancer cases	Incidence rate ratio (95% confidence interval) unadjusted	Incidence rate ratio (95% confidence interval) adjusted[†]
Full cohort	149,935	3,449	1.19 (1.05–1.35)	1.03 (0.91–1.17)
Stratification variable				
Smoking status				
Never	62,901	239	1.06 (0.64–1.76)	1.09 (0.65–1.83)
Current	15,684	1,463	0.99 (0.80–1.23)	0.91 (0.73–1.15)
Former	62,350	1,747	1.35 (1.16–1.58)	1.10 (0.94–1.29)
Ever smoker (mPLCO)[‡]	76,240	3,138		1.01 (0.88–1.14)
Sex				
Male	66,380	2,068	1.23 (1.07–1.43)	1.09 (0.94–1.26)
Female	74,555	1,381	0.93 (0.74–1.18)	0.92 (0.72–1.17)
Body mass index				
Normal	47,066	1,292	1.30 (1.00–1.70)	1.05 (0.80–1.37)
Overweight	58,170	1,436	1.28 (1.07–1.57)	0.93 (0.76–1.13)
Obese	34,612	676	1.29 (1.05–1.58)	1.15 (0.93–1.41)

[†], all models adjusted with age (continuous), sex, body mass index (continuous), education, race/ethnicity, smoking status (never, former, current, with years since stopped smoking), pack-years of smoking (continuous), chronic obstructive pulmonary disease, personal history of cancer, family history of lung cancer except for [‡] which indicates adjusted using mPLCO risk score; Included 137,811 participants after excluding patients with missing covariate data. PLCO, Prostate, Lung, Colorectal, and Ovarian.

Table 3 Lung cancer histology according to pre-existing diabetes diagnosis: unadjusted analyses

Lung cancer histology	Total N=3,467 [%]	No diabetes N=3,182 [%]	Diabetes N=285 [%]	P value
Adenocarcinoma	1,243 [36]	1,154 [36]	89 [31]	0.30
Squamous cell carcinoma	713 [21]	649 [20]	64 [22]	
Small cell	477 [14]	431 [14]	46 [16]	
Other	1,033 [30]	947 [30]	86 [30]	

Table 4 Association of diabetes and lung cancer histology: adjusted analyses

Lung cancer histology	Relative risk ratio for diabetes[†]	95% confidence interval
Adenocarcinoma	Reference	
Squamous cell carcinoma	1.20	0.84–1.71
Small cell	1.23	0.83–1.84
Other	1.19	0.86–1.64

[†], adjusted with age, sex, body mass index, education, race/ethnicity, smoking status (never, former, current), pack years, chronic obstructive pulmonary disease, personal history of cancer, family history of lung cancer.

Nominal regression analysis adjusting for other risk factors showed that diabetes did not significantly increased the odds of having a squamous cell carcinoma [odds ratio (OR): 1.2; 95% CI: 0.9–1.8), other non-small cell carcinoma (OR: 1.2; 95% CI: 0.9–1.6) or a small cell carcinoma (OR: 1.3; 95% CI: 0.8–1.9) *vs.* adenocarcinoma. Analyses incorporating randomization arm or stratified by sex, smoking status or BMI showed similar results.

Discussion

In a large cohort of individuals enrolled and prospectively

followed in the PLCO trial, diabetes was not independently associated with lung cancer incidence. We also showed similar results in subgroup analyses based on sex, smoking status or BMI status. Additionally, diabetes was not associated with lung cancer histology. This study shows that diabetes, a known risk for several malignancies, does not increase the risk for developing lung cancer in general or specific lung cancer subtypes. Patients with diabetes should be evaluated for lung cancer screening eligibility using similar criteria to smokers without the disease.

Diabetes is an established risk factor for many malignancies, as hyperglycemia and hyperinsulinemia, hallmarks of diabetes pathogenesis, are known tumor growth factors (3). In lung cancer in particular, preclinical studies have demonstrated that hyperglycemia promotes lung tumor cell proliferation and invasiveness (8,9). Hyperglycemia and diabetes may also differentially impact different lung cancer histologic subtypes. *In vitro* data show that squamous cell carcinoma is more reliant on glucose metabolism for growth compared to other subtypes (14). Patients exposed to high glycemic index diets are at higher risk for squamous cell carcinoma lung cancer, but not adenocarcinoma (15).

While these studies show a potential role of diabetes for promoting lung cancer, previous large cohort studies examining the association of diabetes and lung cancer risk have reported mixed results, including decreased or increased risk and null associations (20-38). These studies have included relatively heterogeneous populations and adjusted for different potential cofounders in their risk models, which may explain in part the conflicting findings. Moreover, most of these studies lacked power to evaluate the association of diabetes specifically with lung cancer risk. Even the studies focused on lung cancer did not comprehensively adjust for established lung cancer risk factors such as smoking duration and/or, in former smokers, time since smoking cessation (23,28,34,39). Our study extends these results by demonstrating a lack of relationship between diabetes and lung cancer risk in a large and well characterized cohort with a comprehensive and standardized protocol to ascertain lung cancer diagnoses. Moreover, our study is also novel by showing that diabetes is not associated with lung cancer histologic subtype.

Two other conditions closely related to diabetes, hyperinsulinemia and abdominal obesity, may influence the risk of developing lung cancer. Hyperinsulinemia has been shown to increase lung cancer risk (39). A Mendelian randomization study showed that genetic predisposition to insulin resistance, but not diabetes, was associated with increased lung cancer risk, particularly squamous cell and small cell carcinoma (16). While insulin resistance and diabetes are correlated, it is possible that only the former may lead to an increased risk of lung cancer, explaining our negative results. Similarly, increased waist circumference, a measure of obesity not well represented by BMI and highly correlated with diabetes, has been linked to increased lung cancer risk (40,41). Unfortunately, these variables were not captured in the PLCO study and should be the focus of further research.

Our study has strengths and weaknesses that should be discussed. Compared to prior studies, the PLCO included a larger sample of participants, collected more detailed information about other risk factors for lung cancer, and had rigorous methods for ascertaining lung cancer diagnoses. The PLCO was a screening trial and thus, participants may have been selected among individuals with more 'healthy' habits that may not be fully representative of the general population (42). Diabetes was measured by self-report, which may lead to reporting bias and miss patients without diagnosed diabetes. However, this method has been applied and found to be relatively accurate in several national studies (43,44), and the prevalence of diabetes of 7.7% is consistent with the rate of diagnosed, self-reported diabetes during the years of data collection (7). Additionally, duration of diabetes, severity of diabetes (hemoglobin A1C and other glycemic measures) and diabetes type (1 *vs.* 2) are unknown. However, the vast majority of diabetes cases (90–95%) are type 2 (7). Some studies suggest that cancer risk may be highest in the years immediately following diabetes diagnosis (25,45). Our study was also not powered for subgroup analyses. The PLCO did not report medication data, such as use of metformin and insulin among study participants. These medications may influence the risk of lung cancer and may have confounded the association of diabetes with lung cancer incidence (23,46,47).

Conclusions

In conclusion, our study showed a lack of association between diabetes and lung cancer incidence. Additionally, we found no relationship between diabetes and lung cancer histology. Future studies that include more information regarding metabolic parameters, such as waist circumference, insulin and glucose levels, and diabetes medications may elucidate further how metabolic disease impacts lung cancer pathogenesis and risk. This study provides evidence that a

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diabetes diagnosis should not be a consideration in existing lung cancer risk stratification protocols.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tlcr-21-601

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tlcr-21-601). EJG is on the advisory board for Novartis and received consulting honorarium from Seattle Genetics and SynDevRx and has received payment for educational events from Infomedica and the American Diabetes Association. FRH reports consulting fees from Bristol-Myers Squibb, Merck, Amgen, AstraZenica/Daiichi, Sanofi, Regeneron, Novartis, OncoCyte, and Genentech, honoraria for lectures from AstraZeneca and Roche, and payment for expert testimony from Gehrson Lehrman Group. JPW received consulting honorarium from Banook, GSK, Sanofi and Atea Pharmaceutical and research grants from Sanofi and Arnold Consultants. The other 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). The study was approved by Icahn School of Medicine at Mount Sinai Institutional Review Board 20-01308 and individual consent for this retrospective analysis was waived.

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References

1. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674-85.

2. Pearson-Stuttard J, Zhou B, Kontis V, et al. Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment. Lancet Diabetes Endocrinol 2018;6:e6-e15.

3. Gallagher EJ, LeRoith D. Obesity and Diabetes: The Increased Risk of Cancer and Cancer-Related Mortality. Physiol Rev 2015;95:727-48.

4. Gallagher EJ, LeRoith D. Hyperinsulinaemia in cancer. Nat Rev Cancer 2020;20:629-44.

5. Warburg O, Wind F, Negelein E. THE METABOLISM OF TUMORS IN THE BODY. J Gen Physiol 1927;8:519-30.

6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.

7. Prevention CDC. National Diabetes Statistics Report, Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services 2020.

8. Liao YF, Yin S, Chen ZQ, et al. High glucose promotes tumor cell proliferation and migration in lung adenocarcinoma via the RAGE NOXs pathway. Mol Med Rep 2018;17:8536-41.

9. Kang X, Kong F, Wu X, et al. High glucose promotes tumor invasion and increases metastasis-associated protein expression in human lung epithelial cells by upregulating heme oxygenase-1 via reactive oxygen species or the TGF-β1/PI3K/Akt signaling pathway. Cell Physiol Biochem 2015;35:1008-22.

10. Dziadziuszko R, Camidge DR, Hirsch FR. The insulin-like growth factor pathway in lung cancer. J Thorac Oncol 2008;3:815-8.

11. Dziadziuszko R, Merrick DT, Witta SE, et al. Insulin-like growth factor receptor 1 (IGF1R) gene copy number is associated with survival in operable non-small-cell lung cancer: a comparison between IGF1R fluorescent in situ

hybridization, protein expression, and mRNA expression. J Clin Oncol 2010;28:2174-80.

12. Kim JS, Kim ES, Liu D, et al. Prognostic impact of insulin receptor expression on survival of patients with nonsmall cell lung cancer. Cancer 2012;118:2454-65.

13. Yi ZH, Luther Y, Xiong GH, et al. Association between diabetes mellitus and lung cancer: Meta-analysis. Eur J Clin Invest 2020;50:e13332.

14. Goodwin J, Neugent ML, Lee SY, et al. The distinct metabolic phenotype of lung squamous cell carcinoma defines selective vulnerability to glycolytic inhibition. Nat Commun 2017;8:15503.

15. Melkonian SC, Daniel CR, Ye Y, et al. Glycemic Index, Glycemic Load, and Lung Cancer Risk in Non-Hispanic Whites. Cancer Epidemiol Biomarkers Prev 2016;25:532-9.

16. Carreras-Torres R, Johansson M, Haycock PC, et al. Obesity, metabolic factors and risk of different histological types of lung cancer: A Mendelian randomization study. PLoS One 2017;12:e0177875.

17. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000;21:273S-309S.

18. Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA 2011;306:1865-73.

19. Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. N Engl J Med 2013;368:728-36.

20. Atchison EA, Gridley G, Carreon JD, et al. Risk of cancer in a large cohort of U.S. veterans with diabetes. Int J Cancer 2011;128:635-43.

21. Lo SF, Chang SN, Muo CH, et al. Modest increase in risk of specific types of cancer types in type 2 diabetes mellitus patients. Int J Cancer 2013;132:182-8.

22. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. Diabetologia 2012;55:948-58.

23. Luo J, Chlebowski R, Wactawski-Wende J, et al. Diabetes and lung cancer among postmenopausal women. Diabetes Care 2012;35:1485-91.

24. Jee SH, Ohrr H, Sull JW, et al. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194-202.

25. Dankner R, Boffetta P, Balicer RD, et al. Time-Dependent Risk of Cancer After a Diabetes Diagnosis in a Cohort of 2.3 Million Adults. Am J Epidemiol 2016;183:1098-106.

26. Johnson JA, Bowker SL, Richardson K, et al. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia 2011;54:2263-71.

27. Hu Y, Zhang X, Ma Y, et al. Incident Type 2 Diabetes Duration and Cancer Risk: A Prospective Study in Two US Cohorts. J Natl Cancer Inst 2021;113:381-9.

28. Yang WS, Yang Y, Yang G, et al. Pre-existing type 2 diabetes and risk of lung cancer: a report from two prospective cohort studies of 133 024 Chinese adults in urban Shanghai. BMJ Open 2014;4:e004875.

29. Inoue M, Iwasaki M, Otani T, et al. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006;166:1871-7.

30. Stocks T, Rapp K, Bjørge T, et al. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. PLoS Med 2009;6:e1000201.

31. Khan M, Mori M, Fujino Y, et al. Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study. Asian Pac J Cancer Prev 2006;7:253-9.

32. Rapp K, Schroeder J, Klenk J, et al. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. Diabetologia 2006;49:945-52.

33. Wotton CJ, Yeates DG, Goldacre MJ. Cancer in patients admitted to hospital with diabetes mellitus aged 30 years and over: record linkage studies. Diabetologia 2011;54:527-34.

34. Hall GC, Roberts CM, Boulis M, et al. Diabetes and the risk of lung cancer. Diabetes Care 2005;28:590-4.

35. Stattin P, Björ O, Ferrari P, et al. Prospective study of hyperglycemia and cancer risk. Diabetes Care 2007;30:561-7.

36. Yeh HC, Platz EA, Wang NY, et al. A prospective study of the associations between treated diabetes and cancer outcomes. Diabetes Care 2012;35:113-8.

37. Ehrlich SF, Quesenberry CP Jr, Van Den Eeden SK, et al. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Diabetes Care 2010;33:55-60.

38. Park HJ, Joh HK, Choi S, et al. Type 2 diabetes mellitus does not increase the risk of lung cancer among never-smokers: a nationwide cohort study. Transl Lung Cancer Res 2019;8:1073-7.

39. Argirion I, Weinstein SJ, Männistö S, et al. Serum

Insulin, Glucose, Indices of Insulin Resistance, and Risk of Lung Cancer. Cancer Epidemiol Biomarkers Prev 2017;26:1519-24.

40. Yu D, Zheng W, Johansson M, et al. Overall and Central Obesity and Risk of Lung Cancer: A Pooled Analysis. J Natl Cancer Inst 2018;110:831-42.

41. Ardesch FH, Ruiter R, Mulder M, et al. The Obesity Paradox in Lung Cancer: Associations With Body Size Versus Body Shape. Front Oncol 2020;10:591110.

42. Pinsky PF, Miller A, Kramer BS, et al. Evidence of a healthy volunteer effect in the prostate, lung, colorectal, and ovarian cancer screening trial. Am J Epidemiol 2007;165:874-81.

43. Jackson JM, DeFor TA, Crain AL, et al. Validity of diabetes self-reports in the Women's Health Initiative. Menopause 2014;21:861-8.

44. Schneider AL, Pankow JS, Heiss G, et al. Validity and reliability of self-reported diabetes in the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2012;176:738-43.

45. Hense HW, Kajüter H, Wellmann J, et al. Cancer incidence in type 2 diabetes patients - first results from a feasibility study of the D2C cohort. Diabetol Metab Syndr 2011;3:15.

46. Xiao K, Liu F, Liu J, et al. The effect of metformin on lung cancer risk and survival in patients with type 2 diabetes mellitus: A meta-analysis. J Clin Pharm Ther 2020;45:783-92.

47. Tseng CH. Human Insulin Therapy Is Associated With an Increased Risk of Lung Cancer: A Population-Based Retrospective Cohort Study. Front Endocrinol (Lausanne) 2019;10:443.