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Pre-existing diabetes and lung cancer prognosis

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Background: The aims of this study are to investigate the impact of pre-existing diabetes and diabetes treatments on lung cancer prognosis.

Methods: A total of 2484 women with confirmed incident lung cancer from the Women's Health Initiative were followed for an average of 2.9 years through the date of death or 29 August 2014.

Results: Compared with women with lung cancer but without diabetes, women with lung cancer and diabetes had significantly increased risk of overall mortality (HR = 1.27, 95% CI: 1.07–1.50). Women with diabetes receiving insulin or metformin or women who had long duration of diabetes also had increased risk of overall mortality.

Conclusions: Our large prospective study provides evidence that pre-existing diabetes is associated with poor overall survival among women with lung cancer, but do not support the hypothesis that metformin use may have a protective effect in women with lung cancer and diabetes.

Diabetes may influence lung cancer progression and outcome by several mechanisms, including hyperinsulinemia, hyperglycaemia, or chronic inflammation, which have been shown to be associated with cell proliferation and cancer progression (Morss and Edelman, 2007; Garcia-Jimenez *et al*, 2014). In addition, pre-existing diabetes may have adverse effects on lung cancer outcome by influencing clinical decisions regarding lung cancer treatment or response to treatment (van de Poll-Franse *et al*, 2007).

Studies of mortality outcomes for lung cancer participants with pre-existing diabetes are conflicting (De Giorgio *et al*, 2000; Park *et al*, 2006; Hatlen *et al*, 2011; Shieh *et al*, 2012). Previous studies were retrospective and often only examined overall mortality. Thus, prospective studies are needed to clarify whether diabetes influences overall and cancer-specific mortality among lung cancer participants.

Data regarding effects of diabetic therapy on lung cancer outcomes are sparse and retrospective. Some studies (Tan *et al*, 2011; Lin *et al*, 2015) found that metformin may improve chemotherapy outcomes for participants who have non-small cell lung carcinoma (NSCLC) compared with other therapies (e.g. insulin, sulfonylureas). Other studies found that metformin use has no impact or worsens survival for lung cancer participants (Mazzone *et al*, 2012; Ahmed *et al*, 2015).

In the current study, we used Women's Health Initiative (WHI) data to compare lung cancer outcomes between participants with and without pre-existing diabetes, and between metformin and non-metformin treatment.

METHODS

Study population. The WHI enrolled 161 808 postmenopausal women aged 50–79 years between 1993 and 1998 from 40 clinical centres throughout the United States into an observational study (OS) and three clinical trials (CT) (Hays *et al*, 2003; Jackson *et al*, 2003; Langer *et al*, 2003; Ritenbaugh *et al*, 2003; Stefanick *et al*, 2003).

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Incident lung cancer cases were identified by self-report questionnaires with all cases confirmed by medical record review. All incident lung cancer cases diagnosed by August 2014 were initially included in the study ($N = 2800$). We excluded 296 women with a history of any cancer at baseline (other than non-melanoma skin cancer), 7 type 1 diabetes cases based on self-report of a diabetes diagnosis at age 21 years or younger, and 13 women with missing values for diabetes at baseline and follow-up. After exclusions, a total of 2484 cases were available for analysis. By August 2014, 1347 died from lung cancer among 1824 deaths. Available tumour characteristics include stage, size, positive lymph nodes, grade, and histology.

Measurements

Outcomes. Overall mortality and lung cancer-specific mortality. Cause of death was classified by trained physician adjudicators based on available documents that included medical records and death certificate (WHI, 2016).

Diabetes status, diabetes therapies, and diabetes duration. Prevalent diabetes at enrollment was defined as a positive answer to the question 'did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant'. Age at first diagnosis was also self-reported. Medically treated diabetes at enrollment was defined as reporting ever having been treated for diabetes with pills or insulin shots. Initiation of diabetes treatment, but not a new diagnosis of diabetes, was assessed at follow-up visits at year 3 for participants in the OS and at years 1, 3, 6, and 9 for those in the CT. As such, in this analysis, incident diabetes was defined as treated diabetes. At baseline and follow-up visits, participants were asked to bring all current prescription medications. Prescription of anti-diabetic medications was categorised into insulin (used alone or with other oral medications), metformin (used alone or with other oral medications), or only used other anti-diabetic medications. We determined diabetes status up to the date of lung cancer diagnosis. Duration of diabetes was estimated from the date or age of the first diabetes diagnosis to the date of lung cancer diagnosis. Self-reported diabetes in the WHI has been found to be reliable (Margolis *et al*, 2008; Jackson *et al*, 2013).

Demographics, lung cancer risk factors, and other covariates. Covariates included age at lung cancer diagnosis, tumour stage, and baseline variables including race/ethnicity, education, body mass index (BMI), smoking, physical activity, alcohol intake, participation in OS or different CT arms. Cumulative number of comorbid conditions such as cardiovascular diseases, depression, osteoporosis and arthritis, and so on, was updated the date of lung cancer diagnosis and categorised as 0, 1, 2, 3, and $\geqslant 4$. Measurement of these variables is described in detail in Table 1.

Statistical analysis. Multivariable Cox proportional hazards regression analysis was employed to estimate hazard ratios for overall mortality according to diabetes status after adjusting for covariates. The proportional subdistribution hazard model proposed by Fine and Gray (Fine and Gray, 1999) was used to estimate hazard ratios for lung cancer-specific mortality associated with diabetes status by accounting for non-lung cancer mortality as competing risk.

In addition, we used a subset (1053) of WHI data linked with claims data among women aged 65 years or older at cancer diagnosis to further adjust for cancer treatment as a sensitivity analysis.

RESULTS

Of the 2484 women with lung cancer, 276 (11.1%) had prevalent or incident diabetes before lung cancer diagnosis. Compared with women without diabetes, women with diabetes were significantly more likely to be members of non-White race/ethnicity groups, have a higher BMI, be physically inactive, have no current alcohol use, be less educated, and have greater number of comorbid conditions. However, there was no substantial difference between the diabetes group and no diabetes group in age at cancer diagnosis and smoking habits (Table 1).

Women with or without diabetes had no statistically significant differences on tumour characteristics (Supplementary Table 1). Compared with women without diabetes, women with diabetes had significantly increased risk of overall mortality (HR = 1.27, 95% CI: 1.07–1.50). The unadjusted Kaplan–Meier survival curves stratified by diabetes status are provided online (Supplementary Figure 1A and B), as is overall mortality in relation to diabetes stratified by stage (Supplementary Table 2). Women who received insulin or metformin or with diabetes duration longer than 7 years prior to lung cancer diagnosis had significantly higher risk of overall mortality (Table 2).

Women who received insulin had significantly increased risk of cancer-specific mortality after adjusting for age and stage (HR = 1.45, 95% CI: 1.00–2.11). Further adjustment for other potential risk factors did not change the magnitude substantially (HR = 1.52, 95% CI: 0.99–2.34), but the effect became nonsignificant. In addition, we did not find significant associations between lung cancer-specific mortality and diabetes, metformin use, or diabetes duration (Table 3).

We conducted two sensitivity analyses: (1) restricting analyses to only non-small cell lung carcinoma (Supplementary Table 3); (2) using WHI linked with CMS data and restricting the analysis to women who were 65 years or older and further adjusting for cancer treatment (including surgery, radiation and chemotherapy). All results were similar.

Table 1. Baseline characteristics of 2484 patients with lung cancer by diabetes status

	No diabetes (2208 patients)	Diabetes (276 patients)	*P*-value
Age at breast cancer diagnosis (mean, s.d.)	72.9 (7.3)	73.2 (6.6)	0.6
White (not of Hispanic origin) (%)	1992 (90.2)	216 (78.3)	<0.0001
BMI at baseline (mean, $kg\,m^{-2}$, s.d.)	26.8 (5.2)	31.2 (6.0)	<0.0001
METs—hours per week[a] (mean, s.d.)	12.3 (14.3)	9.1 (12.3)	0.0002
Current smoking (%)	615 (27.9)	72 (26.1)	0.4
Current alcohol drinker (%)	1702 (77.1)	168 (60.9)	<0.0001
Education: college or higher (%)	785 (35.6)	71 (25.7)	0.001
Co-morbidity (4 or more)	715 (32.4)	157 (56.9)	<0.0001

[a]MET-hours per week–Metabolic equivalent. A total physical activity variable was computed by multiplying the MET level for the activity by the hours exercised per week and then summing values for all of the types of activities.

Table 2. HRs for overall mortality in relation to diabetes among 2484 patients with lung cancer

		HR (95% CI) for total mortality	
	Deaths (total cases)	Age and stage adjusted	Multivariable adjusted[a]
No diabetes	1623 (2208)	1	1
Diabetes	201 (276)	1.27 (1.10, 1.47)	1.27 (1.07, 1.50)
Duration of diabetes at cut-point of median value			
<7 years	97 (143)	1.24 (1.01, 1.52)	1.22 (0.98, 1.53)
⩾7 years	104 (133)	1.30 (1.07, 1.59)	1.31 (1.05, 1.64)
Type of diabetic drugs in medication inventory			
Insulin (alone or with oral medication)	37 (46)	1.51 (1.09–2.10)	1.54 (1.06–2.23)
Metformin	50 (62)	1.54 (1.16–2.04)	1.48 (1.09–2.00)
Other drugs	47 (56)	1.26 (0.94–1.69)	1.29 (0.94–1.77)
Untreated/drugs unknown	67 (112)	1.05 (0.82–1.34)	1.06 (0.82–1.38)

[a]Model adjusted age at diagnosis (<55, 55–59, 60–64, 65–69, 70–74, ⩾75), stage (localised, regional, and distant), race/ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, Hispanic/Latino, non-Hispanic white, and other), education (high school or less, some college/technical training, college or some post-college, and master or higher), BMI (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, >40), physical activity (metabolic equivalent task (MET)—hours per week: <5, 5—<10, 10—<20, 20—<30, ⩾30)), alcohol intake (non-drinker, past drinker, <1 drink per month, and current drinker–including frequency: <1 drink per month, 1 drink per month to <1 drink per week, 1 to <7 drinks per week, >7 drinks per week), smoking (never, former, and current), and comorbidity (0, 1, 2, 3, 4, or more) and different WHI clinical assignments.

Table 3. HRs for lung cancer-specific mortality in relation to diabetes among 2484 patients with lung cancer

		HR (95% CI) for lung cancer-specific mortality	
	Deaths (total cases)	Age and stage adjusted	Multivariable adjusted[a]
No diabetes	1328 (2208)		
Diabetes	149 (276)	1.15 (0.97, 1.36)	1.15 (0.95, 1.39)
Duration of diabetes at cut-point of median value			
<7 years	76 (143)	1.16 (0.92, 1.46)	1.15 (0.90, 1.48)
⩾7 years	73 (133)	1.13 (0.90, 1.44)	1.14 (0.88, 1.49)
Type of diabetic drugs in medication inventory			
Insulin (alone or with oral medication)	28 (46)	1.45 (1.00–2.11)	1.52 (0.99–2.34)
Metformin	36 (62)	1.34 (0.96–1.87)	1.30 (0.91–1.86)
Other drugs	34 (56)	1.10 (0.78–1.55)	1.18 (0.81–1.70)
Untreated/drugs unknown	51 (112)	0.96 (0.72–1.27)	0.96 (0.72–1.29)

[a]Model further adjusted age at diagnosis (<55, 55–59, 60–64, 65–69, 70–74, >75), stage (localised, regional, and distant), for race/ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, Hispanic/Latino, non-Hispanic white, and other), education (high school or less, some college/technical training, college or some post-college, and master or higher), BMI (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, >40), physical activity (metabolic equivalent task (MET)—hours per week: <5, 5—<10, 10—<20, 20—<30, >30), alcohol intake (non-drinker, past drinker, <1 drink per month, and current drinker–including frequency: <1 drink per month, 1 drink per month to <1 drink per week, 1 to <7 drinks per week, >7 drinks per week), smoking (never, former, and current) and comorbidity (0, 1, 2, 3, 4, or more) and different WHI clinical assignments.

DISCUSSION

Women with lung cancer and pre-existing diabetes had significantly poorer overall survival compared with women with lung cancer but without diabetes. Women with diabetes receiving insulin or metformin, or women who had longer duration of diabetes, had lower overall survival. Our study is the first prospective study to examine these relationships.

Experimental data suggest that metformin may improve lung cancer prognosis via radiosensitisation of NSCLC cells (Storozhuk *et al*, 2013) or via suppression of the detrimental effects of hyperinsulinemia on lung tumour growth (Algire *et al*, 2008). However, our data were not supportive of the hypothesised anti-cancer effects of metformin. Previous epidemiological data regarding the effects of types of diabetic therapy on lung cancer outcomes are sparse and provide inconsistent results. Two studies reported that metformin was associated with improved survival for participants with advanced lung cancer (Tan *et al*, 2011; Lin *et al*, 2015), but two other studies reported that metformin was associated with no benefit or even a worse prognosis (Mazzone *et al*, 2012; Ahmed *et al*, 2015). It is possible that the benefit of metformin observed in other studies is due to indication, as metformin is typically prescribed to those with short duration of diabetes as shown in our data, and without contraindicating factors (such as advanced age, liver, or kidney disease). Another possibility is that metformin may only benefit specific participants, such as people with advanced NSCLC.

Our data revealed a borderline significant increased risk for lung cancer-specific mortality for women who received insulin. The biological mechanism by which diabetes with insulin treatment increases lung cancer-specific mortality may involve the growth promoting effect of insulin (IGF-I) directly or indirectly (Richardson and Pollack, 2005; Ho *et al*, 2016). Another explanation is that diabetes may have indirect impacts on cancer outcome. For example, cancer participants with pre-existing diabetes may be diagnosed at advanced stages or be treated less aggressively than those without diabetes (van de Poll-Franse *et al*, 2007), which may contribute to increased cancer mortality. However, this proposed hypothesis was not supported by the current data that show no significant differences in lung cancer characteristics among women with and without diabetes.

The strengths of the study include the prospective design, rich data on demographic variables, potential risk factors and tumour characteristics, and physician-adjudicated causes of death. However, several limitations also deserve mention, including self-report

diabetes, small sample size for specific diabetes medications, postmenopausal women, and lack of information regarding glucose control, diabetes progression, and untreated incident diabetes.

In conclusion, our large prospective study provides evidence that pre-existing diabetes is associated with poor overall survival among women with lung cancer, but do not support the hypothesis that metformin may have a protective effect among women with lung cancer and diabetes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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