

E. Haydn Walters, M.A., D.M., D.Sc., F.R.C.P.

University of Melbourne
Melbourne, Victoria, Australia

and

University of Tasmania
Hobart, Tasmania, Australia

ORCID IDs: 0000-0002-6954-9611 (C.W.); 0000-0002-5721-5710 (M.J.M.).

*Corresponding author (e-mail: chris.ward@ncl.ac.uk).

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Reply: Epithelial–Mesenchymal Plasticity as a Potential Common Link between Lung Disease and Increased Risk of Lung Cancer

From the Authors:

We would like to thank Professor Ward and colleagues for reading and providing valuable comments on our study investigating the association between noncystic fibrosis bronchiectasis and lung cancer risk (1). Our findings indicated that participants with bronchiectasis have a higher risk of incident lung cancer compared with those without bronchiectasis, regardless of smoking status. We explained that chronic inflammation in bronchiectasis, as in chronic obstructive pulmonary disease (COPD), which is now recognized as a risk of lung cancer, may be a potential mechanism for lung cancer development (2).

Professor Ward and colleagues suggested epithelial–mesenchymal transition (EMT) as a culprit in lung cancer development in bronchiectasis. EMT is the gradual transformation of basal epithelial cells into mesenchymal-like cells (3). During the process, subepithelial reticular basement membrane fragmentation and hypervascularity develop, and the epithelial cells lose their characteristics and functionality. EMT is known to be involved in the tissue remodeling in COPD and lung cancer progression (3, 4). In this context, we

agree with their suggestion that EMT can be a key mediator between chronic inflammation and lung cancer development in airway conditions with high cancer risk, including COPD and bronchiectasis.

As mentioned by Professor Ward and colleagues, chronic airflow limitation and gastroesophageal reflux disease (GERD) are significant comorbid conditions that influence the severity of chronic airway inflammation in bronchiectasis (5). Consequently, these factors may interact with bronchiectasis. Unfortunately, because of the absence of pulmonary function measurement data in our dataset, we could not analyze the impact of chronic airflow limitation (defined as forced expiratory volume in 1 second/forced vital capacity less than 0.7). However, we evaluated the impact of GERD on the association between bronchiectasis and lung cancer development using our prevalent cohorts. GERD was defined as at least one claim under the ICD (International Statistical Classification of Diseases and Related Health Problems), 10th Revision, code K21, within the preceding year before health screening. Stratified analysis revealed no significant interaction between the presence of GERD and bronchiectasis and the risk of developing lung cancer (P for interaction in Model 3 = 0.29). In addition, compared with that of participants without bronchiectasis or GERD, the risk of lung cancer was significantly increased in participants with GERD alone (adjusted hazard ratio [HR] in Model 3, 1.08; 95% confidence interval [CI], 1.04–1.11), those with bronchiectasis alone (adjusted HR, 1.24; 95% CI, 1.15–1.34), and those with both bronchiectasis and GERD (adjusted HR, 1.24; 95% CI, 1.12–1.38) (Table 1).

Although GERD is associated with the severity and progression of bronchiectasis, our results showed no significant synergistic effect of GERD and bronchiectasis on the risk of incident lung cancer. Considering that GERD can aggravate airway inflammation in bronchiectasis, which may induce an

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Table 1. Incidence and hazard ratio of incident lung cancer in participants with bronchiectasis versus those without bronchiectasis stratified by gastroesophageal reflux disease

	Participants, <i>n</i>	Lung Cancer, <i>n</i>	IR (/1,000 PY)	IRR* (95% CI)	HR (95% CI)			
					Unadjusted	Model 1	Model 2	Model 3
Stratified analysis 1								
Without GERD								
No BE	3,169,602	18,084	0.694	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
BE	46,582	758	2.041	1.25 (1.16–1.35)	2.94 (2.74–3.16)	1.37 (1.28–1.48)	1.26 (1.17–1.36)	1.23 (1.14–1.33)
With GERD								
No BE	623,515	5,031	0.983	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
BE	18,723	334	2.242	1.20 (1.07–1.35)	2.28 (2.05–2.55)	1.34 (1.20–1.50)	1.21 (1.08–1.35)	1.18 (1.05–1.32)
<i>P</i> for interaction	—	—	—	0.33	<0.001	0.51	0.29	0.29
Stratified analysis 2								
No BE/no GERD	3,169,602	18,084	0.694	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
GERD alone	623,515	5,031	0.983	1.06 (1.03–1.09)	1.41 (1.37–1.46)	1.06 (1.03–1.10)	1.06 (1.02–1.09)	1.08 (1.04–1.11)
BE alone	46,582	758	2.041	1.26 (1.17–1.36)	2.94 (2.74–3.16)	1.38 (1.28–1.48)	1.27 (1.18–1.37)	1.24 (1.15–1.34)
BE and GERD	18,723	334	2.242	1.25 (1.12–1.39)	3.23 (2.90–3.60)	1.40 (1.26–1.56)	1.25 (1.12–1.39)	1.24 (1.12–1.38)

Definition of abbreviations: BE = bronchiectasis; CI = confidence interval; GERD = gastroesophageal reflux disease; HR = hazard ratio; IR = incidence rate; IRR = incidence rate ratio; PY = person-years.

Model 1 was adjusted for age, sex, body mass index, smoking history (never, ever-smoker with less than 10 pack-years, ever-smoker with 10–19 pack-years, and ever-smoker with 20 or more pack-years), alcohol consumption (none, mild, or heavy), income amount (low or high), physical activity (regular or nonregular), and Charlson Comorbidity Index (0, 1, or ≥2); Model 2 was further adjusted for the number of chest computed tomography performed; and in addition, Model 3 considered mortality as a competing risk.

*Variables in Model 3 were adjusted.

airway microenvironment favorable to the development of lung cancer (6), future research is needed to elucidate this issue. ■

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Hayoung Choi, M.D., Ph.D.
Hallym University College of Medicine
Seoul, Republic of Korea

Juhwan Yoo, M.S.
Catholic University of Korea
Seoul, Republic of Korea

Kyungdo Han, Ph.D.
Soongsil University
Seoul, Republic of Korea

Hyun Lee, M.D., Ph.D.*
Hallym University College of Medicine
Seoul, Republic of Korea

ORCID ID: 0000-0003-4812-0653 (H.C.).

*Corresponding author (e-mail: namuhanayeyo@hanyang.ac.kr).

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