



ERS | *monograph*

Lung Diseases and Cancer

Edited by
Miguel Ángel Martínez-García,
Mina Gaga and
Kwun M. Fong

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Editor in Chief
Peter M.A. Calverley

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Contents

Lung Diseases and Cancer

Number 98
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Preface	vii
Guest Editors	viii
Introduction	xi
List of abbreviations	xiv

Main pathophysiological pathways and biomarkers

1. Cancer immunosurveillance in respiratory diseases <i>Carolina Cubillos-Zapata, Elena Díaz-García and Francisco García-Río</i>	1
2. Respiratory infections and cancer <i>Jennifer Pollock, Chloe Hughes and James D. Chalmers</i>	15
3. Continuous and intermittent hypoxia in cancer <i>Cliona O'Donnell, Ailbhe King and Silke Ryan</i>	31
4. Future challenges and their impact on respiratory health and lung cancer <i>David Chi-Leung Lam, Yoichi Nakanishi and Yoshinosuke Fukuchi</i>	48

Pulmonary-related risk factors for cancer

5. Smoking, vaping, nicotine and the risk of cancer <i>Carlos A. Jiménez-Ruiz, Carlos Rabade-Castedo, Marcos García-Rueda, Eva Cabrera-César and Eva de Higes-Martinez</i>	59
6. Occupational exposure to respirable carcinogens and the risk of cancer <i>Preston Ngo, Peter Sarich, Eleonora Feletto, Timothy Driscoll, Paul Grogan, Marianne Weber and Karen Canfell</i>	71
7. Exposure to thoracic radiation and the risk of cancer <i>Catherine Bettington, Philip Chan and Gary Pratt</i>	82


Airway diseases and cancer

8. COPD: the risk of cancer and the impact on cancer care <i>Ian A. Yang, Janet G. Shaw, Edward K.H. Stephens, Tian Mun Chee, Edwina E. Duhig, Rayleen V. Bowman, Gerard N. Olive, Henry M. Marshall and Kwun M. Fong</i>	91
9. Emphysema: the risk of cancer and the impact on cancer care <i>Jessica Gonzalez-Gutierrez, Pablo Sanchez-Salcedo and Juan P. de Torres</i>	105

10. Allergy: the risk of cancer and the impact on cancer care <i>Thu-Phuong Phan, Giap Vu-Van, Bach Tran-Xuan, Ha Pham-Ngoc, Chau Ngo-Quy and Anh Tuan Dinh-Xuan</i>	118
11. Cystic fibrosis and bronchiectasis: the risk of cancer and the impact on cancer treatment <i>Florie Akdime, Eloise Alababan, Clémence Martin and Pierre-Régis Burgel</i>	123
Parenchymal pulmonary disorders and the risk of cancer	
12. Idiopathic pulmonary fibrosis: the risk of cancer and the impact on cancer care <i>Carlo Vancheri</i>	134
13. Other interstitial lung diseases: the risk of cancer and the impact on cancer care <i>Ivette Buendía-Roldán, Hiram Aguilar-Duran and Fortunato Juarez</i>	145
Infections, other pulmonary diseases and the risk of cancer	
14. Viruses and the risk of lung cancer: prevention and treatment <i>Catia Cillóniz, Juan M. Pericàs and Joseph A. Pinto</i>	152
15. Pulmonary tuberculosis and the risk of cancer <i>Jean-Pierre Zellweger</i>	163
16. Obstructive sleep apnoea and the risk of cancer <i>Miguel Ángel Martínez-García, Grace Oscullo and José Daniel Gómez-Olivas</i>	168
Pulmonary manifestations of cancer	
17. Venous thromboembolism: an indicator of malignancy <i>Emily Sascha Louise Martens, Menno Volkert Huisman, Maarten Klemens Ninaber and Frederikus Albertus Klok</i>	178
18. Pulmonary metastasis: from pathophysiology to management <i>Andriani Charpidou, Emmanouil Panagiotou, Stamatis Karakatsanis, Konstantinos Samitas, Kyriaki Tavernaraki, Iris Vlachantoni, Eleftherios Zervas and Mina Gaga</i>	190
19. Pulmonary metastasis from haematological cancers <i>Stamatis Karakatsanis, Andriani Charpidou, Emmanouil Panagiotou, Konstantinos Samitas, Kyriaki Tavernaraki, Iris Vlachantoni, Eleftherios Zervas and Mina Gaga</i>	201
20. Pulmonary metastasis of solid tumours <i>Eleftherios Zervas, Konstantinos Samitas, Iris Vlachantoni, Stamatis Karakatsanis, Emmanouil Panagiotou, Kyriaki Tavernaraki, Andriani Charpidou and Mina Gaga</i>	212
21. Interstitial abnormalities from solid and haematological cancers <i>John A. Mackintosh, Edwina E. Duhig, Taryn Reddy, Edward K.H. Stephens, Kwun M. Fong and Ian A. Yang</i>	225
22. Pulmonary infections in cancer patients <i>Sita Andarini, Farhan Hilmi Taufikulhakim, Salsabiila Maryam and Jamal Zaini</i>	241

23. Pulmonary effects of cancer treatments 253
Theodoros Karampitsakos, Fotios Sampsonas, Paolo Spagnolo and Argyris Tzouveleakis
- Drugs used in lung disorder treatment and the risk of cancer**
24. Biological and immunosuppressive therapies for lung disease:
a potential reciprocal influence between their use and malignancy 265
Maria Gabriella Matera, Paola Rogliani, Andrea Bianco and Mario Cazzola
25. Inhaled corticosteroids and lung cancer in COPD: evaluating their role
in chemoprevention 281
Hyun Lee and Don D. Sin
25. Antibiotics for lung disease and cancer 299
*Antonella Arcadu, Margherita S. Silani, Francesco Amati, Andrea Gramegna,
Francesco Blasi and Stefano Aliberti*

Preface

Peter M.A. Calverley 

This preface, my first as the Chief Editor of the *ERS Monograph*, gives me an opportunity to do two important things. First, to thank the European Respiratory Society (ERS) for appointing me to this role, which is an exciting challenge. Second, to thank my predecessor Professor John R. Hurst for all his hard work with the *Monograph*. John's enthusiasm and vision allowed the *Monograph* to flourish; my task, together with our newly appointed Deputy Chief Editor Christian B. Laursen, is to ensure the *Monograph* continues to do so. We have plans about how we can make the *Monograph* even better, but our core mission will not change – namely, to provide up-to-date, authoritative overviews of topics relevant to all who work in respiratory medicine.



Although each issue of the *Monograph* is produced on a very rapid timescale for a book of its size, there is inevitably an overlap between work commissioned by one Editor and the next. This is true of this latest issue on Lung Diseases and Cancer, which reflects the hard work of John and his colleagues and especially of the Guest Editors – Miguel Ángel Martínez-García, Mina Gaga and Kwun M. Fong.

This issue provides a complimentary approach to many discussions of cancer and the lung, and explores the common causal pathways of cancer and lung disease, as well as the many ways in which they interact to influence the management of patients. The distinguished international experts who have contributed provide the reader with insights that range from basic disease mechanisms, through epidemiology and lung conditions predisposing to cancer, to the impact of lung disease on cancer outcomes and treatment. This kind of information is hard to come by in more conventional publications and shows how the *Monograph* provides data relevant to clinical practice that cannot be easily found elsewhere. So please enjoy this stimulating and wide-ranging review of a very important topic.

Disclosures: P.M.A. Calverley reports receiving grants, personal fees and non-financial support from pharmaceutical companies that make medicines to treat respiratory disease. This includes reimbursement for educational activities and advisory work, and support to attend meetings.

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Guest Editors

Miguel Ángel Martínez-García



Miguel Ángel Martínez-García is Section Head, Research Coordinator and Sleep Disordered Breathing Unit Head of the Pulmonary Disorder Division of the University and Polytechnic La Fe Hospital in Valencia, Spain. His research mainly focuses on obstructive sleep apnoea and airways diseases, particularly bronchiectasis and COPD. He has a Masters in airway diseases, bronchiectasis and hospital management.

Miguel Ángel is currently a fellow of the European Respiratory Society (ERS) and was a member of the ERS' sleep working group for 3 years. He is a member of the bronchiectasis–airway disease working group of EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration), and was a member of the Scientific Committee of SEPAR (the Spanish Society of Pneumology and Thoracic Surgery), Director of the Bronchiectasis Scientific Program Project (PII) and Chair of the Spanish Bronchiectasis Registry (RIBRON) of SEPAR for 8 years.

Miguel Ángel is the current Editor in Chief of *Archivos de Bronconeumología*, a Q1 journal in respiratory diseases with an impact factor of 6.3. He has been a member of the *European Respiratory Journal (ERJ)* Editorial Board for the last 8 years and served on the *SLEEP* Editorial Board for 2 years. He is the author/co-author of seven national/international guidelines or task forces on sleep apnoea, bronchiectasis and COPD, and has had >320 peer-reviewed scientific papers published. He has edited 12 books on respiratory diseases. His H-index is 43.

Miguel Ángel has received >40 grants and 12 scientific awards from national and international medical societies, such as “Reviewer of the Year” for the *ERJ* in 2014. He has been a speaker at >300 invited lectures at national and international meetings.

Mina Gaga

Mina Gaga is a consultant pulmonologist at Athens Chest Hospital (Athens, Greece), where she also served as Medical Director.

She started her career at Athens Chest Hospital, and then moved to the UK, to the Department of Allergy and Clinical Immunology, Imperial College and the Royal Brompton Hospital (London, UK), where she was Research Fellow and later Visiting Academic.

Mina served as Assistant Professor at Athens University and Director of the 7th Respiratory Medicine Department and Asthma Centre at Athens Chest Hospital, as well as Medical Director of the hospital, which is the biggest centre for respiratory medicine in Greece. Her appointments involved mainly clinical work and educating students and trainees, as well as administration.

Mina's research focuses on asthma, particularly severe asthma and pathophysiological pathways but also quality patient care. She has been involved as principal investigator in multiple clinical trials, has been active internationally in guideline development for severe asthma and lung cancer screening, and has published extensively in these research areas.

She, moreover, has an important international role: she has served as Secretary General and later President of the European Respiratory Society, Secretary of the European Board of Accreditation in Pneumology (EBAP), advisor to the World Health Organization (WHO) and as an Executive Committee Member of the Global Alliance Against Chronic Respiratory Diseases (GARD).

Since August 2021, Mina has been the Alternate Minister of Health in Greece, and since September she has also been a member of the Standing Committee of the European WHO office.



Kwun M. Fong



Kwun M. Fong is a Thoracic and Sleep Physician at The Prince Charles Hospital (Brisbane, QLD, Australia) and a Professor at the University of Queensland School of Medicine (Brisbane). He is Clinical Manager of the Pulmonary Malignancy Unit at The Prince Charles Hospital, and Director of the University of Queensland Thoracic Research Centre and the Australian Cancer Research Foundation's Lung Cancer Early Detection Centre, which undertakes molecular, genomic and translational research in lung diseases.

Kwun's respiratory medicine career began with a PhD in the molecular genetics of lung cancer and a post-doctoral fellowship with the legendary lung cancer researchers Dr John D. Minna and Dr Adi F. Gazdar. As a clinician-scientist, Kwun remains fully focused on lung cancer assessment, diagnosis, early detection and screening to enable improved curative and personalised medicine approaches.

Kwun is privileged to have served as Chair of the Australian Lung Foundation's Lung Cancer Consultative Group, inaugural Chair of the Australasian Lung Cancer Trials Group and Past President of the Asian Pacific Society of Respiriology (APSR). Kwun is Co-Editor of the *Cochrane Lung Cancer* Review Group and Associate Editor-in-Chief of the *Journal of Thoracic Diseases*. He has an increasing trajectory of over >280 articles (H index 73).



Introduction

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Respiratory diseases and cancer are frequently linked as both are highly prevalent. Their bidirectional relationship means that each can be a risk factor or a protective factor for the other, significantly impacting diagnosis, management and outcome. <https://bit.ly/3CBf3H>

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Respiratory diseases and cancer are two of the most frequent causes of morbidity and mortality in the world. As such, the coexistence of both diseases in the same person is a frequent occurrence. There is a consistent body of scientific evidence to suggest that this goes beyond chance; in fact, both disease types are associated and the presence of one of them can be a risk factor or protective factor for the other. Notably, one of the fundamental characteristics is the bidirectionality of this relationship.

There are multiple reasons why respiratory diseases can be related to cancer. 1) Some respiratory diseases share environmental or genetic risk factors with cancer. For example, the relationship between COPD and cancer is mediated by smoking, where tobacco smoke is a powerful carcinogen as well as an inducer of inflammation. 2) Beyond association, a clear causative relationship has been established in some cases, such as the relationship between asbestos exposure and pleural mesothelioma. 3) Respiratory diseases and cancer can share common pathophysiological pathways, such as those relating to pulmonary inflammation, infection and/or hypoxaemia. 4) Cancer can first present with symptoms associated with lung diseases, such as pulmonary thromboembolism. 5) Treatment for some respiratory diseases can pose an elevated risk of adverse events, such as the loss of cancer immunosurveillance from immunosuppressants. Conversely, some treatments for respiratory diseases can reduce the risk of cancer, such as the use of inhaled corticosteroids in certain circumstances. 6) There is speculation that certain respiratory diseases may protect against cancer, as has been proposed in allergic diseases.

There are also a number of reasons why certain individuals diagnosed with cancer may be predisposed to the development of some types of lung diseases. 1) Direct cancer involvement in the lung, *e.g.* lung cancer. 2) The large vascular bed and filtration function of the lung, which

gives rise to a propensity for exposure to cancer cells or their by-products, *e.g.* lung metastases. 3) The higher incidence of pulmonary thromboembolism caused by indirect paraneoplastic activation of the pathophysiological pathways of some cancers in common with lung disease, such as the state of hypercoagulability. 4) The unintended effect of a variety of cancer treatments, such as cytotoxics, radiation, targeted therapy and immunotherapy (*e.g.* a higher incidence of pulmonary infections, interstitial pulmonary diseases or lung infection).

In this *ERS Monograph*, we have brought together renowned clinical and scientific experts to provide an exhaustive review of the bidirectional relationship between respiratory diseases and cancer in general (not just lung cancer). To this end, and given the vast quantity of literature in the area, the *Monograph* is divided into different thematic blocks, covering the most important pathophysiological mechanisms that are prevalent in both diseases [1–4], the assessment of the impact of each disease on the other in terms of risk factors and protective factors [5–7], diagnosis, treatment [8–10] and prognosis. Finally and importantly, this *Monograph* addresses patient-focused outcomes, such as the influence of cancer on the care and outcome of respiratory patients and *vice versa*.

We hope that the valuable knowledge diligently compiled by our authors, to whom we are deeply grateful, will help generate a better understanding of the relationship between these two important diseases, from an epidemiological, clinical and therapeutic point of view. Such knowledge will undoubtedly give rise to a greater awareness of the possible development of lung diseases in people with cancer, and of the different types of cancer that are frequently seen in those with lung diseases. This will help optimise diagnosis and treatment: “*scientia potentia est*”, knowledge is power. The ultimate objective of this *Monograph* is, of course, to improve the health both of our communities and of those affected by these diseases – the patients we have the privilege of helping.

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List of abbreviations

COVID-19	coronavirus disease 2019
CT	computed tomography
D_{LCO}	diffusing capacity of the lung for carbon monoxide
EGFR	epidermal growth factor receptor
EMT	epithelial–mesenchymal transition
FEV ₁	forced expiratory volume in 1 s
FVC	forced vital capacity
HPV	human papillomaviruses
HRCT	high-resolution computed tomography
ICI	immune checkpoint inhibitor
IH	intermittent hypoxia
IL	interleukin
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
LDCT	low-dose CT
NF- κ B	nuclear factor- κ B
NSCLC	nonsmall cell lung cancer
OSA	obstructive sleep apnoea
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
ROS	reactive oxygen species
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCC	squamous cell carcinoma
SCLC	small cell lung cancer
TGF	transforming growth factor
Th	T-helper cell
TKI	tyrosine kinase inhibitor
TNF	tumour necrosis factor
VEGF	vascular endothelial growth factor