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RESEARCH ARTICLE

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Pulmonary hypertension is associated with an increased incidence of cancer diagnoses

Christoph Roderburg[1] | **Sven H. Loosen**[1] | **Hans-Joerg Hippe**[2] | **Tom Luedde**[1] | **Karel Kostev**[3] | **Mark Luedde**[4,5]

[1]Clinic for Gastroenterology, Hepatology and Infectious Diseases, University Hospital Düsseldorf, Medical Faculty of Heinrich Heine University Düsseldorf, Düsseldorf, Germany

[2]Department of Cardiology, Marien-Hospital Witten, Witten, Germany

[3]Department of Epidemiology, IQVIA, Frankfurt, Germany

[4]Christian-Albrechts-University of Kiel, Kiel, Germany

[5]Cardiology Joint Practice Bremerhaven, Bremerhaven, Germany

Correspondence
Christoph Roderburg, Clinic for Gastroenterology, Hepatology and Infectious Diseases, University Hospital Düsseldorf, Medical Faculty of Heinrich Heine University Düsseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany.
Email: Christoph.Roderburg@med.uni-duesseldorf.de

Mark Luedde, KGP Bremerhaven, Postbrookstr. 105, 27574 Bremerhaven, Germany.
Email: mark.luedde@web.de

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Abstract

Pulmonary hypertension (PH) is a complex disease with increasing global incidence that eventually leads to right ventricular failure and is associated with a poor prognosis. The importance of noncardiac comorbidities in disease progression and prognosis has gained increasing recognition in recent years. In the present study, we investigated a potential association between PH and cancer in an outpatient cohort in Germany. Using the IQVIA Disease Analyzer database, we identified a total of 11,109 patients with PH and a propensity score matched cohort of equal size without PH who received medical treatment between 2005 and 2019. Logistic regression models were used to evaluate the potential association between PH and cancer. Within the 10-year observation period, the incidence of cancer was significantly higher in PH patients than non-PH patients (23.2% vs. 8.5%, log-rank $p < 0.001$). Importantly, this association was observed for both male (HR = 1.24, $p = 0.002$) and female (HR = 1.37, $p < 0.001$) patients, and was most pronounced in patients >80 years (HR = 1.50, $p < 0.001$). In terms of a specific tumor site, we found a significant association for respiratory organ cancer (HR = 1.60, $p = 0.007$) and skin cancer (HR = 1.48, $p < 0.001$). Our study provides strong evidence that PH is associated with an increased incidence of cancer. This finding should help raise awareness of this important comorbidity and could trigger specific screening programs in patients with PH.

KEYWORDS
association, comorbidities, epidemiology, pulmonary hypertension

Christoph Roderburg and Sven H. Loosen share first authorship.

Karel Kostev and Mark Luedde share senior authorship.

INTRODUCTION

Pulmonary hypertension (PH) remains a challenging chronic condition, the pathophysiology and course of which is not yet totally understood. The disease is defined as a mean pulmonary arterial pressure >20 mmHg at rest, as determined by the Sixth World Symposium on Pulmonary Hypertension in 2018[1] or greater than 25 mmHg, as determined by the guidelines issued by the European Society of Cardiology (ESC)/European Respiratory Society (ERS) in 2015.[2] The global burden of PH is significant: about 1% of the total global population is affected, including up to 10% of people aged >65 years. According to the different causes of the disease, PH can be divided into five subgroups as defined in the Nice classification: (1) pulmonary arterial hypertension, (2) PH due to left heart disease, (3) PH due to pulmonary disease and/or hypoxia, (4) PH due to chronic thromboembolism, (5) PH due to unclear multifactorial mechanisms.[2] The last classification in particular makes it clear that the pathophysiology of the disease is not yet sufficiently understood. Although innovative and effective therapies have been found in recent years, the life expectancy and quality of life of those affected is still severely limited.[3–5] A deeper understanding of the disease is therefore of eminent importance. One way to gain a better understanding of the disease may be to learn more about its interplay with a spectrum of comorbidities that typically co-occur with PH.[6] These may include conditions such as arterial hypertension, obesity, sleep apnea, clinical depression, obstructive airway disease, thyroid disease, diabetes mellitus, and ischemic cardiovascular events.[7] Comorbidities of PH may be present at the time of PH diagnosis or may develop during the course of PH treatment. The co-occurrence of PH and one or more comorbidities may increase the complexity of disease management. Patients may require multiple pharmacological interventions to treat PH and the respective comorbidities.

The connection between PH and tumors seems to be particularly significant—so much so indeed, that people also speak of tumoral PH.[8] Pulmonary tumor "microvascular disease" includes both pulmonary tumor microembolism (PTME) and pulmonary tumor thrombotic microangiopathy (PTTM).[8] The numerical significance of the association between PH and cancer is still not entirely clear. We therefore investigated a possible association between these two diseases in a cohort of 11,103 PH-patients matched with a cohort of equal size without PH using the Disease Analyzer database (IQVIA). The aim of our study was to find out whether PH promotes the development of cancer in general or cancer of specific organs.

MATERIALS AND METHODS

Database

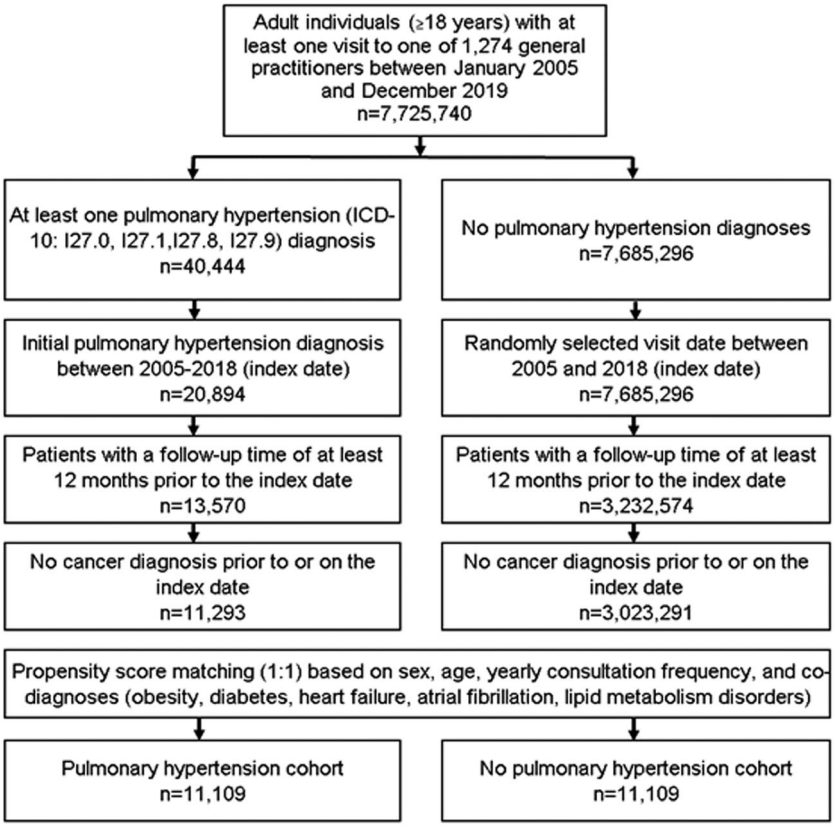
This study was based on data from the Disease Analyzer database (IQVIA), which contains drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists.[9] The database covers approximately 3% of all outpatient practices in Germany. Diagnoses (according to International Classification of Diseases, 10th revision [ICD-10]), prescriptions (according to Anatomical Therapeutic Chemical [ATC] Classification system), and the quality of reported data are monitored by IQVIA on an ongoing basis. In Germany, the sampling methods used to select physicians' practices are appropriate for obtaining a representative database of general and specialized practices. It has previously been shown that the panel of practices included in the Disease Analyzer database is representative of general and specialized practices in Germany.[9] Rathmann et al. demonstrated good agreement between the outpatient DA database with German reference data with respect to the incidence or prevalence of cancer diagnoses.[9] Finally, this database has already been used in previous studies focusing on cardiovascular disorders[10,11] as well as cancer.[12,13]

Study population

This retrospective cohort study included adult patients (≥18 years) with an initial diagnosis of PH (ICD-10: I27 + original diagnosis text) in 1274 general practices in Germany between January 2005 and December 2018 (index date; Figure 1). One further inclusion criterion was an observation time of at least 12 months before the index date. Patients with cancer diagnoses (ICD-10: C00-C99) before the index date were excluded.

After applying inclusion criteria, patients without PH were matched (1:1) to patients with PH based on propensity scores using a greedy algorithm and derived from the logistic regression using sex, age, yearly consultation frequency, and codiagnoses (obesity, diabetes, heart failure, atrial fibrillation, lipid metabolism disorders). Diabetes and obesity were used as they are associated with cancer. Heart failure, atrial fibrillation, lipid metabolism disorders were used due to their strong correlation with PH diagnosis. As PH patients have much higher GP consultation frequency due to their PH treatment, and higher consultation frequency can increase the probability that other diagnoses will be documented, we included consultation frequency per year in the

FIGURE 1 Selection of study patients



matching process. For the non-PH individuals, the index date was that of a randomly selected visit between January 2005 and December 2018 (Figure 1).

Study outcomes and covariates

The main outcome of the study was the incidence of cancer (ICD 10: C00-C99) in general and cancer of different organs including, lip, oral cavity, and pharynx (ICD 10: C00-C14), digestive organs (ICD 10: C15-C26), respiratory organs (ICD 10: C30-C39), skin (ICD 10: C43, C44), breast (ICD 10: C50), female genital organs (ICD 10: C51-C58), male genital organs (ICD 10: C60-C63), urinary tract (ICD 10: C64-C68), and lymphoid and hematopoietic tissue (ICD 10: C81-C96) as a function of PH.

Statistical analyses

Differences in the sample characteristics between those with and those without PH were tested using χ^2 tests for categorical variables and Wilcoxon tests for continuous variables. Hazard regression models were used to study the association between the PH and cancer incidence. These models were applied separately for different cancers. To counteract the problem of multiple comparisons, p-values <0.01 were considered statistically significant. Analyses were carried out using SAS version 9.4 (SAS Institute).

Ethical standards

Only aggregated, anonymized patient data were used in these analyses. This study was performed in accordance with the Declaration of Helsinki, the guidelines for Good Practice of Secondary Data Analysis,[14] and the ICMJE Recommendations for the Conduct, Reporting Editing and Publication of Scholarly Work in Medical Journals. Since only anonymized data were used, which could not be traced back to individual persons, the research protocol did not have to be approved by the local ethics committee, and it was not necessary to obtain informed consent from individual patients to participate in the study.

RESULTS

Basic characteristics of the study sample

The present study included 11,109 patients with PH and 11,109 patients without PH. The basic characteristics of the study patients are displayed in Table 1. The mean age

TABLE 1 Basic characteristics of the study sample (after 1:1 propensity score matching)

Variable	Proportion affected among patients with pulmonary hypertension (%) $N = 11{,}109$	Proportion affected among patients without pulmonary hypertension (%) $N = 11{,}109$	p-value
Age (mean, SD)	70.9 (13.8)	70.8 (13.8)	0.821
Age ≤60	20.1	20.3	0.879
Age 61–70	19.6	20.0	
Age 71–80	37.7	34.2	
Age >80	25.6	25.5	
Women	57.0	57.0	1.000
Men	43.0	43.0	
Yearly consultation frequency	4.6 (4.8)	4.6 (4.8)	1.000
Diabetes	32.5	32.2	0.735
Obesity	14.2	14.4	0.598
Lipid metabolism disorders	41.3	42.2	0.227
Hypertension	68.1	67.2	0.233
Atrial fibrillation	25.3	25.5	0.795
Heart failure	32.6	32.4	0.675

Note: Proportions of patients are given in % unless otherwise indicated.
Abbreviation: SD, standard deviation.

of the PH group was 70.9 years (standard deviation [SD]: 13.8), the mean age of the control group was 70.8 years (SD: 13.8, $p = 0.821$, Table 1). In both groups 57% of patients were women. On average, patients of both groups visited their GPs 4.6 (SD: 4.8, $p = 1.000$) times per year during the follow-up time. There were no significant differences between PH and non-PH patients in terms of specific comorbidities.

Association between PH and incidence of cancer

Within 10 years of the index date, 23.2% of patients with PH and 18.5% of non-PH patients had been diagnosed with cancer (log-rank $p < 0.001$) (Figure 2). There were 2843 cancer cases per 100,000 patient years in PH and 2119 in non-PH patients.

Regression analyses revealed a significant association between PH and the incidence of cancer (HR = 1.30, $p < 0.001$ in total, HR = 1.37, $p < 0.001$ in women, HR = 1.24, $p = 0.002$ in men). In the age-stratified analyses, this association was only significant in patients aged 71–80 (HR = 1.29, $p < 0.001$) and aged >80 (HR = 1.50, $p < 0.001$), but not in patients in the age groups ≤60 and 61–70 years (Table 2).

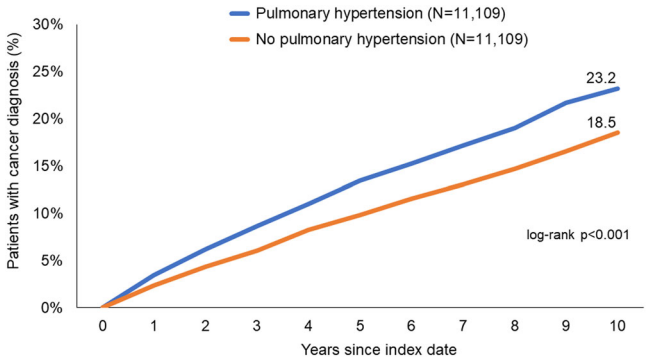


FIGURE 2 Kaplan–Meier curves for time to cancer diagnosis in patients with and without pulmonary hypertension

Association between PH and specific types of cancer

Based on the striking association between PH and cancer in general we hypothesized that this association might be stronger in the case of specific disease etiologies such as smoking-related cancers and therefore performed additional regression analyses to investigate this theory. These analyses detected a significant association between PH and two cancer types (Figure 3). The strongest association was found for cancer of the respiratory organs

TABLE 2 Association between pulmonary hypertension and the incidence of cancer diagnoses in patients followed in general practices in Germany (Cox regression models) by age and sex

Cancer incidence per group	Incidence (cases per 100,000 patient years) among patients with pulmonary hypertension	Incidence (cases per 100,000 patient years) among patients without pulmonary hypertension	Hazard ratio (95% CI)	*p*-value
Cancer total	**2843**	**2119**	**1.30 (1.18–1.43)**	**<0.001**
Age ≤60	1121	826	1.32 (0.98–1.78)	0.070
Age 61–70	2521	2032	1.20 (0.97-1.48)	0.091
Age 71–80	3591	2746	**1.29 (1.11–1.50)**	**<0.001**
Age >80	4637	3122	**1.50 (1.23–1.50)**	**<0.001**
Women	2521	1774	**1.37 (1.19–1.57)**	**<0.001**
Men	3291	2587	**1.24 (1.08–1.429**	**0.002**

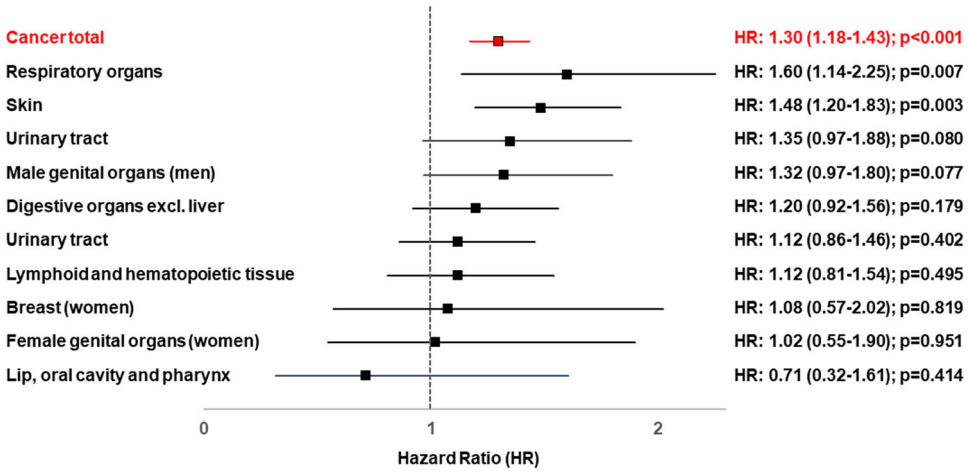


FIGURE 3 Association between pulmonary hypertension and the incidence of cancer diagnoses in patients followed in general practices in Germany (Cox regression models) by cancer type

(HR = 1.60, $p = 0.007$), followed by skin cancer (HR = 1.48, $p < 0.001$). We did not identify any significant associations between PH and other cancer types.

DISCUSSION

We examined the association between PH and the occurrence of cancer in a retrospective, cohort-based design. Using two age- and sex-matched cohorts of 11,109 patients with PH and 11,109 patients without PH, we identified PH as an independent risk factor for cancer development within 10 years after initial diagnosis of PH. This significant difference was driven by two cancer types: respiratory cancers and skin cancers. Common risk factors for PH and cancer such as obesity, diabetes, heart failure, atrial fibrillation, and lipid metabolism disorders were considered in the study design and were equally prevalent in both cohorts after propensity score matching.

PH is a major problem, the incidence of which appears to be increasing,[15] and the mortality rate among those affected is very high. An important paper by Wijeratne et al. showed that the most common form of PH is Group 2 according to the Nice classification, alone or in combination with Group 3. A diagnosis of PH increased the 1-year standardized mortality rate by a factor of 7.2. Interestingly, in this survey PH was present in only 3.6% of subjects with left heart failure, 0.7% of those with lung disease, and 1.4% of those with thromboembolic disease.[15] It is therefore probably not prevalent enough to attribute the particularly strong association between cancer and PH to chronic thromboembolic disease with an undoubtedly increased risk of pulmonary artery embolism in cancer.

It must be emphasized that our study shows a statistical association between PH and cancer and not a specific causality. Nevertheless, we believe that the possible causal links between the two entities deserve closer consideration.

A causal relationship could exist as a result of the phenomenon of pulmonary tumor embolism (PTE). This term describes the occlusion of pulmonary capillaries by contiguous tumor cells without the presence of pulmonary metastases per se.[16,17] The majority of PTE cases to date have been reported in patients with adenocarcinomas, including liver, kidney, stomach, and urinary bladder.[8] This does not explain the particular association between this condition and respiratory and skin tumors identified in our study.

There is also another entity that is distinguished from PTE: PTTM, which is characterized by the presence of pulmonary vascular tumor microembolic "nests" with evidence of the activation of coagulation, obliterative intimal proliferation, and ultimately PH.[18] One common feature is the presence of additional metastatic disease, often with lymphangitic spread.[8] This entity could be one of many reasons why we found a strong association between cancer and PH in our study especially in tumors of the respiratory system. The mechanisms involved are not yet fully understood at the molecular level, although it is possible that tumor cells and endothelial cells interact and initiate clot formation. Tumor-associated cytokines such as vascular endothelial growth factor and platelet-derived growth factor then lead to further activation of macrophages and intimal proliferation ultimately resulting in PH.[8] There is therefore a very unfavorable cooperation between tumorigenic and vascular factors.

Another important aspect in this context could be the possibility that it is not only cancer that leads to PH, but also cancer therapies.[19] Various mechanisms involving both the lung parenchyma (pulmonary fibrosis) and the pulmonary vessels have been discussed in the literature. First and foremost, the cardiotoxic effect of various chemotherapeutic agents must certainly be mentioned. Group 2 PH is one of the most common forms of PH. Traditional chemotherapeutic agents, such as anthracyclines, and newer targeting drugs such as monoclonal antibodies have been connected with cardiotoxicity.[20] Alkylating chemotherapeutic agents, especially cyclophosphamide, cause direct damage to pulmonary endothelial cells. Cyclophosphamide is involved in a wide range of solid tumor treatment regimens, including melanomas.[21,22] Alkylating agents may promote injury of pulmonary endothelial cells through DNA cross-linked inhibition of cell proliferation and repair capacity of endothelial cells,[19] triggering a cascade that ultimately results in PH. Many other mechanisms may be involved, and much mechanistic study remains to be done to elucidate the complex interactions between cancer and PH. Studies like ours could help to generate hypotheses and to ensure that PH, an important and highly prognostic complication, is considered and tested for in cancer patients.

Our study is subject to a number of limitations, which are unavoidable due to the database analysis and the study design. Firstly, we cannot exclude the possibility that diagnoses have been misclassified or that their coding is missing within the ICD-10 coding system. Furthermore, due to data protection guidelines, the German Disease Analyzer Database does not contain laboratory analyses or information on patient lifestyle or socioeconomic status. Our database, based on the input of patient data by general practitioners, does not capture a specification regarding the individual groups of PH, so that the individual groups could not be correlated with the different types of cancer, which would certainly have been very interesting and informative. We cannot provide data on mortality or possible specific therapies for PH and/or cancer. However, the database provides a good overview of GP consultations in Germany and the identification of PH as an independent risk factor for the development of cancer may be important for the initiation of further studies on this issue.

In summary, cancer is a particularly significant comorbidity in PH patients. The care of cancer and PH patients must take this comorbidity into account to a greater extent, especially if we wish to further extend the lifespans of these patient groups.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

Only aggregated, anonymized patient data were used in these analyses. This study was performed in accordance with the Declaration of Helsinki, the guidelines for Good Practice of Secondary Data Analysis, and the ICMJE Recommendations for the Conduct, Reporting Editing and Publication of Scholarly Work in Medical Journals. Since only anonymized data were used, which could not be traced back to individual persons, the research protocol did not have to be approved by the local ethics committee, and it was not necessary to obtain informed consent from individual patients to participate in the study. This was confirmed by the local ethics committee

of the Christian-Albrechts-University (CAU) of Kiel, Kiel, Germany (File reference D413/21).

AUTHOR CONTRIBUTIONS

Christoph Roderburg, Sven H. Loosen, Karel Kostev, and Mark Luedde designed the study, Karel Kostev performed statistical analyses and generated figures and tables, Mark Luedde, Sven H. Loosen, Christoph Roderburg, and Karel Kostev wrote the manuscript, Hans-Joerg Hippe and Tom Luedde provided intellectual input and corrected the manuscript, all authors agreed to the final version of the manuscript.

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