Long-term incidence of cancer after index treatment for symptomatic peripheral arterial disease – a health insurance claims data analysis

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Summary: *Background:* Cancer as a concomitant condition in symptomatic peripheral arterial disease (PAD) patients could have an impact on further therapy and the long-term prognosis of these patients. Aim of this study was to investigate whether there is an increased incidence of cancer in PAD patients and to quantify the corresponding effect size. *Materials and methods:* Between January 1st, 2008 and December 31st, 2017, we analysed health insurance claims data from Germany's second-largest insurance fund, BARMER. Symptomatic PAD patients suffering from intermittent claudication (IC) or chronic limb-threatening ischaemia (CLTI) were stratified by gender at index treatment. PAD patients were then followed until an incident cancer diagnosis was recorded. To adjust for age and gender, standardized incidence ratios (SIR) were computed using the 2012 German standard population as reference. *Results:* 96,528 PAD patients (47% female, 44% IC, mean age 72 years) were included in the current study. When compared to the overall population, female and male PAD patients have a significantly increased risk of incident cancer of the lung (SIR 3.5 vs. 2.6), bladder (SIR 3.2 vs. 4.0), pancreas (SIR 1.4 vs. 1.6), and colon (SIR 1.3 vs. 1.3). During ten years of follow-up, some 7% of males and 4% of females developed lung cancer. For bladder, colon and pancreas cancer, the cumulative hazards were 1% vs. 3.2%, 2.2% vs. 2.8%, and 0.7% vs. 0.9%, respectively. *Conclusions:* Patients suffering from symptomatic PAD face a markedly higher risk for incident cancer in the long-term follow-up. The cancer risk increased continuously for certain types and PAD was strongly associated with cancer of the lung, bladder, pancreas, and colon. Taking these results into account, PAD patients could benefit from secondary and tertiary screening. These results also emphasize the impact of common risk factors such as tobacco smoke as target for health prevention.

Keywords: peripheral arterial disease, cancer, health services research, gender differences

Introduction

More than 200 million patients worldwide and approximately 20% of German inhabitants aged over 70 years are affected by a peripheral arterial disease (PAD) leading to rapidly rising healthcare costs [1–3].

PAD patients have a substantially higher risk for major adverse cardiovascular and limb events when compared to the general population associated with an impaired life expectancy [4]. While cardiovascular outcomes have been extensively studied, concomitant malignant diseases have been neglected so far, despite they are known to be in general the second most frequent cause of death [5–7].

In Germany, more than 226,000 people died of cancer in 2015, which corresponds to around 25% of all deaths and is thus the second most frequent cause of death after diseases of the cardiovascular system [8].

The medical and economic relevance of both PAD and cancer is important and continues to increase [3, 9]. Whether PAD patients have an enhanced risk of malignant tumours compared to the general population has only been investigated in a comparatively small scale to date [10–15].

The diagnosis of PAD usually represents a considerable life restriction for affected patients [16]. The prognosis and further therapy depend decisively on other relevant concomitant diseases of the patient [17]. Hence, the early

detection of malignant tumours in these patients may be of clinical relevance. This study aimed to determine to what extent PAD patients have a different incidence of cancer when compared to the overall population in Germany. Furthermore, the corresponding effect size should be estimated. We hypothesize that there is an association between PAD and certain cancer entities known to be strongly caused by the same risk factors, notably tobacco smoke.

Materials and methods

Data source and study population

Health insurance claims data of Germany's second-largest insurance fund, BARMER, were used. This cohort includes the outpatient and inpatient medical care provided to approximately 9 million German citizens (10.8% of Germany's population) and is similar compared to the entire German population [18]. The study population consisted of fully inpatient patients aged 40 years and older treated for symptomatic PAD diagnosis (primary diagnosis, coding of the International Classification of Diseases in its German Modification [ICD-10-GM]) in accordance to Kreutzburg et al. [3] and Behrendt et al. [4] during the period January 1st, 2008 to December 31st, 2017.

To identify symptomatic PAD patients, the Fontaine classification [19] was used including disease stage II (intermittent claudication), stage III (ischaemic rest pain), and stage IV (ischaemic ulcer or gangrene).

Longitudinal data of PAD patients was subsequently analysed for cancer incidence. Cancer patients were grouped in accordance to following cancer types as primary or secondary inpatient diagnosis (ICD-10-GM coding): Breast (C50), colon (C18-C20), bladder (C67), lung (C33-C34), stomach (C16), melanoma (C43), ovaries (C56), pancreas (C25), prostate (C61), uterine (C54-C55) and other (C00-C97 without C77-79). PAD and cancer types with corresponding ICD-10-GM codes are listed in Table I in electronic supplementary material 1.

The index hospital stay was defined as the first diagnosis for PAD, respectively cancer. As a reference, age- and gender-specific cancer incidence rates and population counts from the overall population in Germany from 2012 (GSP, mean observation period of our study time frame) from the Robert Koch-Institute, Berlin, Germany (RKI) were used [20].

Statistical analysis

Patients were described with numbers (n) and percentages (%) of the total numbers (for each subgroup) for age and gender. The age was grouped into 5-years intervals.

To estimate the time until cancer, cumulative hazard functions of the different cancer types with a 95% confidence interval (CI) were plotted.

Starting with the index PAD diagnosis, all patients were observed until cancer event, end of insurance (e.g., death) or censoring (December 31st, 2017). Patients with a history of cancer before index stay were excluded from the study.

Furthermore, standardized incidence ratios (SIRs) were calculated to compare the incidence of cancer in PAD patients with the German standard population of 2012. The term standard population was defined as the estimated cancer incidence of the Center for Registry Data of the RKI (<https://www.krebsdaten.de>) for the year 2012. SIRs, adjusted for age (5-year age groups), were calculated for all observed cancer types.

All analyses were stratified by gender as the prevalence of specific cancer types differs by gender (e.g. breast cancer, prostate cancer).

All analyses were performed with software SAS (SAS Institute Inc., North Carolina, United States of America) Version 9.04 for data processing and R version 3.1 for incidence estimation and visualization. Visualization was performed with software Adobe Illustrator version 24.1.2 (Adobe, California, United States).

Results

Patient characteristics

In the current study, we included 96,528 patients aged 40 years and older who were treated for symptomatic PAD (47% female) during the period January 1st, 2008 to December 31st, 2017. The most represented age group was between 70–74 years, including 15,524 patients (16.1%). The mean age of all patients in the PAD cohort was 72 years. 42,536 patients (44%) were admitted for intermittent claudication, 41,037 patients (42.5%) were admitted for ischaemic wound healing disorders, and 12,955 patients (13.4%) suffered from ischaemic rest pain.

Incidence of cancer in the PAD cohort and the German overall population

Cancer incidence of the lung, bladder, pancreas, and colon were mostly increased with PAD, while the risk for cancer of melanoma, breast, uterine and prostate did not differ from the general population. Standardized incidences of the most common cancer entities for male and female patients by different age groups are presented in Figure 1. For lung cancer, there is an increased incidence in the PAD cohort in all age groups, except in the 85+ age group. The greatest difference among female is found in the age group 60–65 years (764 per 100,000 in PAD vs. 103 per 100,000 in GSP). For men, the most pronounced difference was found in the age group 65–70 years (902 per 100,000 in PAD vs. 279 per 100,000 in GSP) (Figure 1A).

For bladder cancer, both genders show an increased incidence in the PAD cohort in all age groups. The most pronounced difference for females was also found in the age

Figure 1. Gender-specific incidences of the three most common tumours by different age groups: A) Lung, B) Bladder, C) Colon, D) Pancreas. PAD: Peripheral arterial disease.

group 60–65 (108 per 100,000 in PAD vs. 12 per 100,000 in GSP). For males, the greatest difference was found in the age group of 80–85 years (675 per 100,000 in PAD vs. 207 per 100,000 in GSP) (Figure 1B).

For colon cancer, the greatest difference among females was found in the 65–70 age group (266 per 100,000 in PAD vs. 120 per 100,000 in GSP). Among males, the most pronounced difference was found in the age group of 75–80 years (552 per 100,000 in PAD vs. 373 per 100,000 in GSP) (Figure 1C).

For pancreas cancer, the greatest difference among females was found in the 65–70 age group (119 per

100,000 in PAD vs. 44 per 100,000 in GSP). Among males, the major difference was found in the age group of 70–75 years (160 per 100,000 in PAD vs. 79 per 100,000 in GSP) (Figure 1D).

Sensitivity analyses stratified by disease severity

All calculations have been performed using subgroups stratified by different Fontaine stages. Sensitivity analyses confirmed the findings of the current study.

Figure 2. Standardized incidence ratio (SIR) of peripheral arterial disease (PAD) patients compared to the 2012 German standard population.

Standardized incidence ratio (SIR) of peripheral arterial disease patients compared to German overall population

Figure 2 illustrates the SIRs for common cancer entities in PAD patients when compared to GSP stratified by gender. A strong association between symptomatic PAD and cancer in female and male patients, respectively, was found for cancer of the lung (SIR 3.5 vs. 2.6), bladder (SIR 3.2 vs. 4.0), pancreas (SIR 1.4 vs. 1.6), and colon (SIR 1.3 vs. 1.3). Whereas for ovaries cancer (SIR 1.2) and male melanoma (0.9) no strong association and female melanoma (SIR 0.9), breast (SIR 0.9), uterine (SIR 0.9) and prostate cancer (SIR 0.9) an opposite association was found.

Incident cancer after treatment of symptomatic PAD

Figure 3 illustrates the cumulative hazards for incident cancer after index treatment for symptomatic PAD stratified by gender. In the entire study sample, some 8% of the patients were diagnosed for any common cancer (e.g., lung, breast, colon, bladder, prostate) during five years after the index treatment for symptomatic PAD. After a follow-up of five years, 4% of male patients and 2% of female patients were diagnosed for incident lung cancer (6.5% vs. 4% after ten years). For men, the cumulative hazards for prostate, bladder, colon, and pancreas were 2.2%, 1.8%, 1.7%, and 0.5% (3.7%, 3.1%, 2.5%, and 0.9% after ten years). For female, the cumulative hazards for breast, colon, bladder, and pancreas were 1.8%, 1.2%, 0.6%, and 0.5% (3%, 2.3%, 0.9%, and 0.7% after ten years) respectively.

Discussion

To our knowledge, this is the first large-scale health insurance claims study determining incidences of cancer in the

long-term after index treatment for symptomatic PAD. A large cohort insured by a nationwide insurance fund was used and compared to the German overall population. The analyses were stratified by age and gender and extensive sensitivity analyses have been conducted to address differences between disease severity groups. We observed a strong association between four common cancer entities and symptomatic PAD in both genders. Cancer incidence of the lung, bladder, pancreas, and colon were mostly increased with PAD, while the risk for cancer of melanoma, breast, uterine and prostate did not differ from the general population. Importantly, some 8% of the patients were diagnosed for any common cancer during five years after the index treatment for symptomatic PAD.

To date, only a few other studies have investigated this important research topic. A study from Pehrsson et al. [12] evaluated 63,921 patients below 80 years during 1972 and 1991 in Stockholm County regarding cancer incidence. While the current study found the highest SIRs for cancer of the lung, bladder, and pancreas, they reported in men larynx followed by pharynx and lung cancer. Andersson et al. [21] lists colon, lung and bladder cancer as the three most common tobacco smoke associated tumours in the Nordic countries. Therefore, we assume that the described differences from Pehrsson et al. are the result of a regional phenomenon, as the study population was limited to the Stockholm area. However, we do not have any valid data to support this assumption.

Onega et al. examined in a population-based cohort study in Denmark 53,762 patients with intermittent claudication. The three most frequently observed cancer entities in this patient cohort were lung followed by tongue and larynx cancer. Unfortunately, this study did not distinguish between genders, limiting their comparability.

Similar to the study by Pehrsson et al., oropharyngeal carcinomas are among the three most common cancers. However, this does not correspond to the observations for the most common tobacco smoke associated tumours for

Figure 3. Cumulative hazards for incident cancer after index treatment of symptomatic peripheral arterial disease.

Nordic countries. We, therefore, assume that in Nordic countries other risk factors, especially in PAD patients, probably lead to an increased incidence of oropharyngeal tumours.

Further studies investigated a common occurrence of PAD and cancer. A recent prospective study from Rantner et al. [10] analysed results from the CAVASIC-study (CArdioVAScular disease in patients with Intermittent Claudication). In this study, 255 male patients with intermittent claudication were included and followed for 7 years. As one main result, the authors described that most of the patients died from cancer and not from vascular complications. Fiotti et al. [22] confirmed these results in their study.

In a related prospective study with a follow-up of 10 years, Taute et al. [11] investigated the possible risk of cancer in 109 patients with intermittent claudication. The main result of this study also was the observed high incidence of cancer (2.11 per 100 patient-years) and cancer mortality (1.05 per 100 patient-years) in patients with intermittent claudication. The mortality from cancer was almost as high as that from vascular events (36% cancer vs. 39% vascular events). The results of these studies were confirmed by the results of the current study. PAD patients exhibited a higher incidence of cancer when compared to the standard population.

In contrast to this Naschitz et al. [14] e.g. described in 1987 that the cancer incidence of patients with intermittent claudication is not significantly increased compared to the American urban, white population. Concerning this, a previous study by Jernes et al. [23] from 1986 interestingly describes only mortality from the malignancy of 27% in patients with intermittent claudication.

When comparing the results of Rantner et al. [10], Taute et al. [11], Fiotti et al. [22] and the current study with these older studies, it is noticeable that cancer mortality in PAD appears to have increased over the last decades.

An explanation of the described differences in the mortality could be that modern vascular medicine has led to a higher survival rate of PAD, thus increasing the chance of developing cancer. However, to date, there is no study to prove this hypothesis.

Apart from the studies of Naschitz et al. [14] and Jernes et al. [23], all other cited studies show an increased incidence of cancer in PAD patients compared to the normal population.

The most obvious explanation for this observation is certainly the presence of common risk factors, especially tobacco smoke. A significant association with tobacco smoke has been described both for PAD [24] as well as for the highest cancer incidences described in our study and other studies [25].

Another result of our study is the earlier development of certain cancers in PAD patients compared to the standard population. For example, male PAD patients show approximately 15 years earlier incidence-peak of lung cancer in comparison to the standard population. Although this effect is less pronounced in women, it is still noticeable (Figure 1A).

This phenomenon can also be explained by common risk factors such as tobacco smoke, as PAD patients are thought to have increased tobacco consumption compared to the standard population and, in conjunction with this, to be more likely to develop lung cancer.

Furthermore, we could show that the cumulative hazards for the development of cancer in PAD patients increase continuously linear within the first 10 years after index treatment. It can be assumed that common risk factors, primarily continued tobacco smoke, triggers the development. In this context, it remains to be seen whether specific smoking cessation programs, in addition to the prognosis of PAD, can also positively influence the incidence of cancer development.

In summary, the results of our study show that PAD patients are likely to benefit from timely cancer screening. However, the current guidelines for the treatment of PAD do not yet take this into account.

Limitations

Firstly, health insurance claims data are not collected for scientific evaluation but rather for reimbursement purposes [26]. However, such claims are subject to increase awareness from scientific audience [27]. There is corroboration that there might be a progression toward upcoding of comorbidities and complications in claims [27]; while registry data are known to be affected by some degree of underreporting [28, 29]. Furthermore, a regular external cross-sample validation is performed by an independent service and peer-reviewed evidence is available showing excellent results for mortality and major outcomes in administrative data. We performed analyses separately for each cancer site and did not consider that cancer incidence and death are competing for events influencing each other. The insurance fund included in the current study only covered a proportion of the entire population in Germany. Besides statutorily insured, there is a small proportion (10%) of privately insured patients, and it remains unknown if there is a relevant selection bias. Hence, the current study used commonly accepted standardisation methods (age, gender) to address this issue, and the comparative study design makes it less affected by methodological challenges related to differences between insured cohorts.

In this study, only in-patients were included. However, it can be assumed that the proportion of symptomatic PAD patients treated outpatient in Germany is very low.

Conclusions

Patients suffering from symptomatic PAD face a markedly higher risk for incident cancer in the long-term follow-up. The cancer risk increased continuously for certain types and PAD was strongly associated with cancer of the lung, bladder, pancreas, and colon. Taking these results into account, PAD patients could benefit from secondary and tertiary screening. These results also emphasize the impact of common risk factors such as tobacco smoke as a target for health prevention.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at <https://doi.org/10.1024/0301-1526/a000901>

ESM 1. ICD codes for cancer types (Table).

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Conflicts of interests

No conflicts of interest exist.

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