Potentiale von GKV-Routinedaten für die gesundheitsökonomische Analyse onkologischer Erkrankungen

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Master of Science Kristine Kreis
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Referent: Prof. Dr. J.-Matthias Graf von der Schulenburg

Korreferent: Prof. Dr. Christian Krauth

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Zusammenfassung

Aufgrund der demografischen Entwicklung wird die Krebsinzidenz weiter steigen. Gleichzeitig wird die Lebenserwartung durch den medizinisch-technischen Fortschritt verbessert. Damit wird Krebs zunehmend zu einer chronischen Erkrankung mit komplexen Behandlungspfaden und einem wachsenden Versorgungsbedarf. Um die Qualität der Versorgung systematisch zu erhöhen und Ressourcen effizient einzusetzen, bedarf es einer Untersuchung der Versorgungsstrukturen unter Alltagsbedingungen. Aufgrund ihrer originären Zweckbestimmung bieten Routinedaten der gesetzlichen Krankenversicherung (GKV) ein nahezu vollständiges Abbild sektorübergreifender abrechnungsrelevanter Kontakte innerhalb des Gesundheitswesens. Trotz der zunehmenden wissenschaftlichen und politischen Akzeptanz dieser Datenquelle ist unklar, ob sie den Besonderheiten und Herausforderungen der onkologischen Versorgung vollumfänglich gerecht wird.

Das Ziel dieser Dissertation liegt in der Prüfung des methodischen Potentials von Routinedaten zur gesundheitsökonomischen Analyse onkologischer Erkrankungen und der Bewertung ihres inhaltlichen Beitrags zu einer effizienten Gestaltung und Weiterentwicklung der Versorgung. In den ersten beiden Modulen werden der Status und die Perspektiven der Nutzung von Routinedaten für wissenschaftliche Zwecke systematisch aufgearbeitet. Anschließend wird am Beispiel des Kolorektal-, Mamma-, Prostata- und Bronchialkarzinoms die onkologische Versorgungsrealität im Hinblick auf die Nutzung von Früherkennungsmaßnahmen, die Inanspruchnahme und Kosten von Krebstherapien sowie ihre Effektivität und Sicherheit untersucht. Zusätzlich werden Behandlungserfahrungen und Präferenzen aus Patientensicht analysiert.

Im Zeitverlauf zeigt sich eine zunehmende Nutzung von Routinedaten für wissenschaftliche Analysen sowie eine Erhöhung der Qualität der Studien und ihrer gesundheitspolitischen Relevanz. In Bezug auf die Onkologie ist die Aussagekraft von Routinedaten vom Erkenntnisinteresse, zugrunde liegenden Annahmen und der Wahl des methodischen Vorgehens abhängig. Die Datengrundlage eignet sich besonders zur Beschreibung von Leistungsinanspruchnahmen, Behandlungspfaden und Kosten und kann damit eine Grundlage für rationale gesundheitspolitische Allokationsentscheidungen bieten. Um beim Mammakarzinom das gesamte Behandlungskontinuum von der Diagnose bis zum möglichen Versterben differenzierter abbilden zu können, wurden nach amerikanischem Vorbild die Länge der Behandlungsphasen erstmals auf Basis deutscher Routinedaten empirisch bestimmt und die Behandlungskosten je Phase ermittelt. Ebenfalls zum ersten Mal wurden bei Patienten mit einem metastasierten kastrationsresistenten Prostatakarzinom simultan fünf verschiedene Therapieoptionen, darunter zwei Chemotherapien (Docetaxel und Cabazitaxel) und zwei Hormontherapien, im Hinblick auf die Behandlungskosten und den zusätzlichen, therapiebedingten Behandlungsbedarf analysiert. Die höchsten monatlichen Kosten zeigten sich bei Cabazitaxel-Patienten und waren, sogar im direkten Vergleich mit der Docetaxel-Chemotherapie, durch höhere Arzneimittelkosten (u.a. für Begleitmedikation) und einen größeren stationären Behandlungsbedarf gekennzeichnet.

Die Effektivität einer Therapie im Sinne des Gesamtüberlebens ist mittels Routinedaten ebenfalls gut darstellbar. Die Abbildbarkeit weiterer patientenrelevanter Endpunkte, wie der Verträglichkeit, ist abhängig von der Behandlungs- und Abrechnungsrelevanz sowie dem Leistungssektor. In der Versorgungsrealität war innerhalb von 8 Monaten nach Therapiebeginn bei 31% der Patienten in der Docetaxel-Kohorte und bei 61% der Patienten in der Cabazitaxel-Kohorte die Behandlung einer therapiebedingten hämatologischen Toxizität erforderlich. Bei jedem zehnten Cabazitaxel-Patienten wurde die Therapie bis in den letzten Lebensmonat fortgesetzt. In beiden Chemotherapie-Kohorten wurden zytotoxische Behandlungen trotz schwerwiegender Komorbiditäten durchgeführt. Für die Beurteilung der Angemessenheit einer medizinischen Maßnahme ist die Kenntnis des patientenindividuellen Therapieziels erforderlich, welches mittels Routinedaten in der Regel nicht abgebildet werden kann. Eine Bewertung von Versorgungsstrukturen in Hinblick auf medizinische Leitlinien ist möglich, wenn die medizinischen Vorgaben klar definiert und die Leistungen mittels Routinedaten identifizierbar sind. Routinedatenanalysen können einen Beitrag dazu leisten, Hinweise auf Über-, Unter- oder Fehlversorgung unter Alltagsbedingungen zu generieren. Um methodische Limitationen zu überwinden und die Aussagekraft zu erhöhen, ist eine Verknüpfung mit weiteren Datenquellen unerlässlich.

Schlagwörter: GKV-Routinedaten, Sekundärdatenanalyse, Onkologie, Krebs, Gesundheitsökonomie, Versorgungsforschung

Abstract

Due to demographic developments, the incidence of cancer continues to rise. Concurrently, life expectancy has improved owing to advances in medical technology. As a result, cancer is increasingly becoming a chronic disease with complex treatment pathways and a growing need for care. To systematically increase the quality of care and use resources efficiently, it is necessary to examine structures of care under real-life conditions. Due to their original purpose, claims data of statutory health insurance provide a complete picture of cross-sectoral and billing-relevant contacts in the health care system. Despite the increasing scientific and political acceptance of this data source, it is unclear whether the specifics and challenges of oncology care are fully addressed.

The aim of this dissertation is to examine the methodological potential of claims data for health economic analysis of oncological diseases and to evaluate their substantive contribution to an efficient design and the further development of healthcare. In the first two modules, the status and perspectives of the use of claims data for scientific purposes were systematically reviewed. Subsequently, the oncological care reality with regard to the use of early detection measures, the utilisation and costs of cancer therapies, and their effectiveness and safety will be examined using the example of colorectal, breast, prostate, and bronchial cancer. Additionally, treatment experiences and preferences from the patient's perspective were analysed.

Over time, there has been an increasing use of claims data for scientific purposes, as well as an improvement in the quality of studies and their relevance to health policy. Regarding oncology, the informative value of claims data depends on the research interest, underlying assumptions, and the choice of methodological approach. The data basis is particularly suitable for describing service utilisation, treatment paths, and costs; thus, a basis for rational health policy allocation decisions can be provided. To depict the treatment continuum for breast cancer from diagnosis to possible death in a differentiated manner, the length of the treatment phases was empirically determined for the first time based on German claims data, following the American model. Furthermore, the treatment costs per phase were calculated. For the first time, five different treatment options, including two chemotherapies (docetaxel and cabazitaxel) and two hormone therapies, were simultaneously analysed in patients with metastatic castration-resistant prostate cancer regarding the health care costs and additional therapy-related treatment requirements. The highest monthly costs were found for cabazitaxel patients and, even in direct comparison with docetaxel chemotherapy, were characterised by higher drug costs for concomitant medication and a greater need for inpatient treatment.

The effectiveness of a therapy in terms of overall survival can also be easily assessed using claims data. Whether other patient-relevant endpoints, such as tolerability, can be depicted depends on their treatment and billing relevance, as well as service sector. In real-life care, within 8 months of treatment initiation, some kind of treatment for haematological toxicity was documented in 31% of patients given docetaxel and in 61% of patients given cabazitaxel. For one in ten cabazitaxel patients, therapy was

continued into the last month of life. In both chemotherapy cohorts, cytotoxic treatment was administered despite the presence of severe comorbidities. To assess the appropriateness of a medical intervention, it is necessary to know the patient's individual therapy goal; this usually cannot be mapped using claims data. An evaluation of care structures is possible if medical guidelines are clearly defined, and the services can be identified by means of claims data. Claims data analyses can contribute to generating indications of overuse, underuse, or misuse of care under real-life conditions. To overcome methodological limitations and increase the informative value of claims data, a linkage with other data sources is essential.

Keywords: claims data, secondary data analysis, oncology, cancer, health economics, health services research

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1 Motivation und Zielsetzung

In Europa ist mehr als einer von vier Todesfällen auf eine onkologische Erkrankung zurück zu führen. Damit zählen onkologische Erkrankungen zur zweithäufigsten Todesursache nach Herz-Kreislauf-Erkrankungen. Zwischen 1995 und 2018 ist die absolute Krebsinzidenz um 50% angestiegen. Die Gründe hierfür stellen u. a. die demografische Entwicklung, die Zunahme von Risikofaktoren (Lebensstil), die Einführung von Screening-Programmen sowie die günstige epidemiologische Entwicklung konkurrierender Erkrankungen dar. Im gleichen Zeitraum ist ein Anstieg der absoluten Krebstodesfälle um etwa 20% zu verzeichnen. Ein Vergleich altersstandardisierter Raten bestätigt die Zunahme der Inzidenz, wobei die Krebssterblichkeit in den meisten Ländern zurückgegangen ist. Dies spiegelt sich ebenfalls in der kontinuierlichen Zunahme der 5-Jahres-Überlebensraten wider. Als Gründe für diese Entwicklung werden Fortschritte im Krebsmanagement angeführt, wie die primäre und sekundäre Prävention, verbesserte und frühere Diagnostik, kurative Therapien, Rehabilitation und die palliative Versorgung [1, 2].

In den letzten zwei Jahrzehnten haben sich in Europa die Gesundheitsausgaben für onkologische Erkrankungen (direkte Kosten) fast verdoppelt, und sind damit gegenüber der Inzidenz überproportional gestiegen, wobei der Anteil an den Gesamtausgaben für Gesundheit mit 4-7% relativ stabil geblieben ist. Im Vergleich dazu sind die indirekten Kosten im genannten Zeitraum um 9% gesunken, was auf eine Reduzierung von Produktivitätsverlusten aufgrund der Abnahme der Mortalität in der erwerbsfähigen Bevölkerung zurück zu führen ist [1, 3, 4]. Im europäischen Vergleich der altersstandardisierten Raten liegt Deutschland im Mittelfeld bei Inzidenz und Mortalität und – je nach Krebstyp – im oberen Drittel der 5-Jahres-Überlebensraten [1, 2, 5, 6]. In Bezug auf die ökonomische Krankheitslast gehört Deutschland zu den Ländern mit dem höchsten Anteil krebsbedingter medizinischer Kosten an den Gesamtausgaben für Gesundheit (6,8%) sowie den höchsten Gesamtkosten pro Kopf aus gesellschaftlicher Perspektive [4].

Die demografische Entwicklung wird zu einer weiteren Zunahme der Krebsinzidenz führen, wobei aufgrund der wachsenden diagnostischen und therapeutischen Möglichkeiten gleichzeitig die Lebenserwartung verbessert wird. Damit wird Krebs zunehmend zu einer chronischen Erkrankung, die mit einer andauernden oder wiederkehrenden erhöhten Inanspruchnahme von Gesundheitsleistungen einhergeht. Der medizinische Fortschritt führt zu komplexeren Behandlungspfaden sowie zu einer zunehmenden Spezialisierung und Kooperation unterschiedlicher Fachdisziplinen [7].

Besonders bei Therapieentscheidungen in der Onkologie wird die hochgradig asymmetrische Informationsgrundlage zwischen Patient und Arzt deutlich [8, 9]. Aufgrund der Bedrohlichkeit der Erkrankung ist die psychische Belastung der Patienten häufig extrem, und der Wunsch nach einer individuell best-

möglichen und vollumfänglichen Therapie stark ausgeprägt. Während der Arzt über detaillierte medizinische Kenntnisse zu Prognose, Therapieoptionen und erwarteten Nebenwirkungen verfügt, kann der Patient die Wirkungen der Leistungen in der Regel nicht einschätzen. Der Arzt kann somit in einem gewissen Rahmen das Nachfrageverhalten des Patienten im Sinne seiner ökonomischen Interessen steuern (Moral Hazard zweiter Art), verfügt jedoch über ein Informationsdefizit in Bezug auf das behandlungsbegleitende Verhalten des Patienten (Compliance), welches den Behandlungserfolg ebenfalls beeinflussen kann[1] [9, 10].

Darüber hinaus ist die onkologische Versorgung mit weiteren Besonderheiten und Herausforderungen konfrontiert, wie die folgenden Beispiele verdeutlichen [1, 7, 11–14]:

- Onkologische Erkrankungen erfordern in besonderem Maße eine individuell angepasste Versorgung und Therapie (u. a. bedingt durch Stadium, Tumorbiologie, Symptomlast, Präferenzen)
- Steigende Komplexität onkologischer Therapien aufgrund der altersbedingten überproportionalen Zunahme der Komorbiditätslast
- Einführung innovativer Arzneimitteltherapien vor allem in der Onkologie, die oft hohe Kosten und eine Veränderung bzw. Erweiterung des Nebenwirkungsspektrums implizieren
- Risiko der Fehlversorgung am Lebensende: kurative Übertherapie und palliative Untertherapie
- Zunehmender Bedarf an flächendeckenden Versorgungsmodellen, insb. Hospiz- und Palliativeinheiten

Mit dem Ziel, die onkologische Versorgungslandschaft zu verbessern, wurde 2008 der Nationale Krebsplan durch das Bundesministerium für Gesundheit initiiert. Die vier definierten Handlungsfelder mit 13 Zielen umfassen die Weiterentwicklung der Früherkennungsprogramme, die Optimierung der Behandlungsstrukturen und der Qualitätssicherung, die Sicherstellung einer effizienten Versorgung mit Fokus auf die onkologische Arzneimitteltherapie sowie die Stärkung der Patientenorientierung und -kompetenz [15].

Die exemplarisch beschriebenen Herausforderungen in der onkologischen Versorgung und die Ziele des Nationalen Krebsplans verdeutlichen die Notwendigkeit einer Untersuchung der Versorgungsrealität. Das Ziel der Versorgungsforschung ist es, ergänzend zur Grundlagenforschung und der klinischen Forschung, Versorgungsstrukturen und -prozesse unter Alltagsbedingungen zu beschreiben und zu erklären und auf Basis dessen neue Versorgungskonzepte zu entwickeln sowie begleitend zu evaluieren [16]. Während bei randomisierten kontrollierten Studien die klinisch-pharmakologische Wirksamkeit eines neuen Arzneimittels bei einem homogenen, stark selektierten Patientenkollektiv untersucht

[1] Zur Vollständigkeit sei an dieser Stelle erwähnt, dass im Gesundheitswesen grundsätzlich drei Beziehungen existieren: zwischen Arzt und Patient, zwischen Patient und Krankenkasse sowie zwischen Krankenkasse und Arzt, die jeweils durch einen wechselseitigen Informationsvorsprung gekennzeichnet sind.

wird, steht bei der Versorgungsforschung die Wirkung, d. h. der therapeutische Effekt für alle Betroffenen in der täglichen Praxis, im Mittelpunkt, um die Versorgungsqualität zu optimieren. Darüber hinaus kann aus ökonomischer Sicht die Frage der Effizienz, d. h. der Kosten-Nutzen-Bewertung von Therapien und Interventionen, unter Berücksichtigung verschiedener Perspektiven, beantwortet werden. Versorgungsforschung kann damit als Informationsgrundlage für Allokationsentscheidungen dienen [17].

Die Diskrepanz der Einschlusskriterien und Charakteristika der Patientengruppen zwischen klinischen Studien und der Versorgungsrealität wird besonders bei Krebspatienten deutlich. Aufgrund der strikten Zulassungskriterien sind ältere und multimorbide Patienten in klinischen Studien häufig unterrepräsentiert. Bei Zulassungsstudien wird die Wirksamkeit des Arzneimittels zur zweckmäßigen Vergleichstherapie in Beziehung gesetzt; die in der Versorgungsrealität übliche Sequenzierung und Kombination verschiedener Therapie wird selten untersucht. Zudem ist die Anzahl eingeschlossener Patienten häufig zu gering, um seltene unerwünschte Therapieeffekte adäquat untersuchen zu können [18, 19].

Wie im nationalen Krebsplan verankert, sind daher Daten aus der klinischen Praxis erforderlich. Routinedaten der GKV stellen eine wichtige Datenbasis für die Versorgungsforschung und Gesundheitsökonomie dar [20]. Als eine Form von Sekundärdaten werden sie regelhaft für die Abrechnung und Erstattung von Gesundheitsleistungen erhoben und beinhalten damit ein nahezu vollständiges Abbild gegenüber der GKV abrechenbarer Leistungsansprüche. Aufgrund ihrer Generierung im Zuge der Leistungserbringung sind sie schnell und kostengünstig verfügbar. Sie ermöglichen es, die Versorgung einer großen Population leistungs- und sektorübergreifend sowie im Längsschnitt zu untersuchen. Im Gegensatz zu Primärdatenerhebungen sind Routinedaten frei von Verzerrungen durch Non-Response oder Recall-Bias. Jedoch weisen sie aufgrund ihrer originären Zweckbestimmung einen Abrechnungs-Bias auf, d.h. es werden nur abrechnungsfähige Leistungen erfasst und diese unterliegen dem Risiko der Abrechnungsoptimierung. Zu den größten Limitationen zählt des Weiteren, dass detaillierte klinische Informationen, wie z. B. zur Krankheitsaktivität, dem Stadium, der Symptombelastung, Laborparametern, der Lebensqualität und der individuell verordneten Arzneimitteldosis fehlen.

Die gesundheitsökonomische Analyse onkologischer Erkrankungen unter Verwendung von Routinedaten der GKV erfordert spezifische Kenntnisse zu Epidemiologie, Diagnostik und Therapie in diesem Indikationsgebiet, der Vergütung von Leistungsinanspruchnahmen sowie den strukturellen und methodischen Besonderheiten bei der Nutzung von Abrechnungsdaten. Das Ziel der vorliegenden kumulativen Dissertation ist es, den Stand und die Perspektiven der Nutzung von Routinedaten für wissenschaftliche Fragestellungen aufzuzeigen und zu verdeutlichen, inwiefern sich diese Datengrundlage zur Analyse onkologischer Erkrankungen eignet. Auf der Grundlage eigener Routinedatenstudien werden

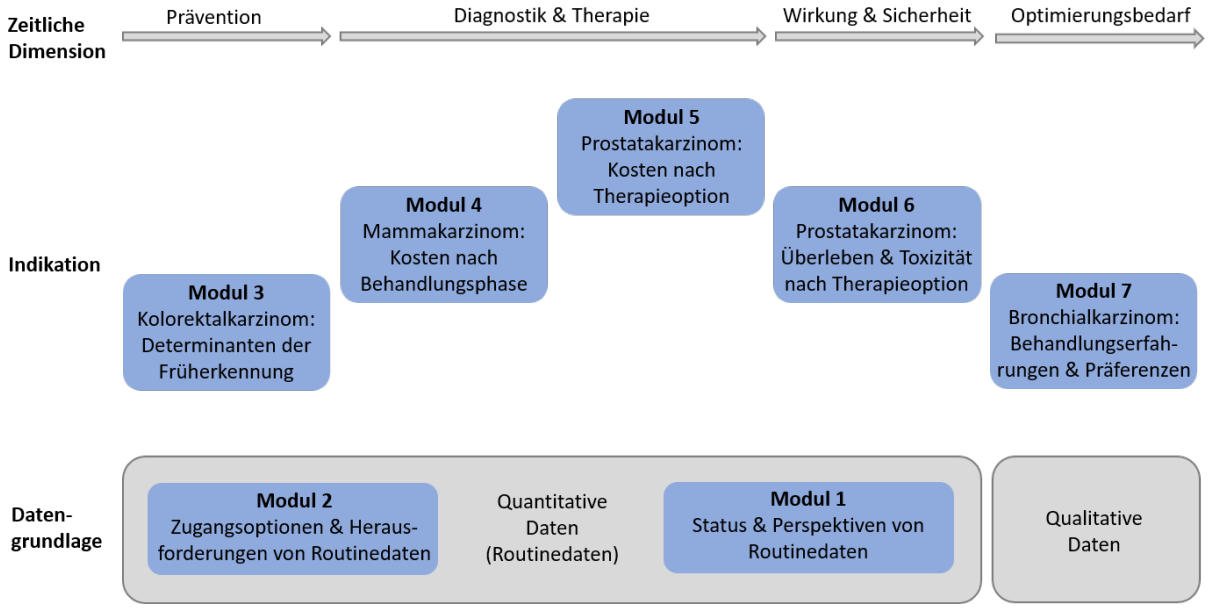
Potentiale und Limitationen im Hinblick auf verschiedene Parameter herausgearbeitet und Lösungsansätze diskutiert.

Die Dissertation verfolgt dabei folgende Fragestellungen:

1. *Wie hat sich die Versorgungsforschung auf Basis von Routinedaten entwickelt und welchen Stellenwert nehmen Fragestellungen mit gesundheitspolitischer Relevanz ein?*
2. *Welche methodischen Aspekte müssen bei der Analyse onkologischer Erkrankungen auf Basis von Routinedaten beachtet werden?*
3. *Welchen Beitrag leisten Routinedatenanalysen zu einer effizienten Gestaltung der onkologischen Versorgung?*

Die vorliegende Dissertation gliedert sich in verschiedene Module (siehe Abbildung 1). Zunächst wird der Entwicklungsprozess von Routinedaten als Grundlage für wissenschaftliche Analysen in Hinblick auf politisch-rechtliche Rahmenbedingungen sowie Qualität und Relevanz systematisch aufgearbeitet (Module 1, 2). Anschließend wird am Beispiel der vier häufigsten onkologischen Erkrankungen [5], dem Kolorektal-, Mamma-, Prostata- und Bronchialkarzinom, die Versorgungssituation onkologischer Patienten in Hinblick auf die folgenden Aspekte analysiert: Determinanten der Früherkennung (Modul 3), Diagnostik, Therapie und Behandlungskosten (Module 4, 5), Therapiesicherheit und Wirkung (Modul 6) sowie den Behandlungserfahrungen aus Sicht des Patienten (Modul 7).

Abbildung 1: Module der kumulativen Dissertation



Quelle: Eigene Darstellung

2 Beitrag der vorliegenden kumulativen Dissertation

2.1 Routinedaten als Grundlage der Versorgungsforschung und Gesundheitsökonomie

Um die Eignung und Relevanz von Routinedaten für wissenschaftliche Analysen im Bereich der Versorgungsforschung und Gesundheitsökonomie einschätzen zu können, ist zunächst ein Überblick über den Entstehungskontext, die Anwendungsmöglichkeiten sowie die Zugangsoptionen für Wissenschaftler erforderlich. Das Ziel der Publikation „Status and perspectives of claims data analyses in Germany – A systematic review" (Modul 1) war es, die historische Entwicklung der Datenbasis nachzuzeichnen, ihre Nutzung zu Forschungszwecken zu analysieren sowie das Potential und die Limitationen im gesundheitspolitischen und internationalen Kontext zu ermitteln. Mittels einer umfangreichen systematischen Literaturreche in einschlägigen Datenbanken und zusätzlichen Handrecherchen wurden in den Jahren 2000 bis 2014 veröffentlichte Publikationen und Buchbeiträge identifiziert, die Routinedaten der deutschen GKV als Datenbasis im Rahmen der Gesundheitsökonomie und Versorgungsforschung nutzten (empirische Publikationen) und / oder methodische bzw. konzeptionelle Aspekte der Nutzung dieser Datenbasis diskutierten (methodische Publikationen). Aus den empirischen Veröffentlichungen wurden ausgewählte Publikations-, Datenbank- und Studiencharakteristika extrahiert; bei den methodischen Publikationen wurde der inhaltliche Fokus erfasst. Zudem wurde die zeitliche Entwicklung im Hinblick auf die grundsätzliche Nutzung der Datengrundlage, die Häufigkeit von Beiträgen mit gesundheitspolitisch relevanten Fragestellungen, den Anteil internationaler Publikationen sowie die Qualität der Veröffentlichungen nachgezeichnet.

Auf der Basis von 435 eingeschlossenen Veröffentlichungen zeigt sich, dass die wissenschaftliche Nutzung von Routinedaten seit der Jahrtausendwende stark zugenommen hat. Fast die Hälfte aller eingeschlossenen Studien wurde in den letzten drei Beobachtungsjahren veröffentlicht. Begünstigt wurde diese Entwicklung u. a. durch Änderungen gesetzlicher Rahmenbedingungen, in deren Folge immer mehr Krankenkassen ihre Daten für wissenschaftliche Zwecke zur Verfügung stellen und sich der Variablenumfang ebenfalls erhöht hat. Im Zeitverlauf erfolgte die Publikation routinedatenbasierter Analysen vermehrt in Zeitschriften mit höherem „Scientific Journal Ranking Indicator", was eine steigende wissenschaftliche Qualität der Beiträge vermuten lässt. Der zunehmende Stellenwert dieser Datengrundlage wird ebenfalls durch die steigende Internationalisierung der Publikationen deutlich.

Die Studie belegt zudem, dass mittels Routinedaten eine Vielzahl unterschiedlichster Fragestellungen aus dem Bereich der Versorgungsforschung adressiert werden kann. In fast der Hälfte der Studien stand eine epidemiologische Fragestellung im Mittelpunkt der Analyse. In den verbleibenden Studien waren Kosten- und Kostenvergleichsstudien, Interventions- und Evaluationsstudien sowie Analysen bestehender Gesundheitsstrukturen zu ähnlichen Anteilen vertreten. Eine Betrachtung der beiden zuletzt genannten Studienformen über die Zeit verdeutlicht die Zunahme von Veröffentlichungen mit

gesundheitspolitischer Relevanz. Der Bedeutungszuwachs von Routinedaten wird ebenso durch ein wachsendes öffentliches Interesse bekräftigt. Mit der Etablierung des Innovationsfonds und der inhärenten Forderung einer Einbindung von Krankenkassen(daten) wurden Routinedaten zu einer zunehmend etablierten Datenbasis.

Der steigenden Nutzung dieser Datengrundlage für Forschungszwecke und ihrem Bedeutungszuwachs als Informationsquelle für politische Entscheidungsträger stehen verschiedene politisch-rechtliche Herausforderungen, wie zum Beispiel der grundsätzliche und standardisierte Zugang zu den Kassendaten für alle Forscher und das Fehlen einer einheitlichen Datenbank mit bundesweiten Daten aller Leistungsträger im Gesundheitssystem, gegenüber. Die Ergebnisse der systematischen Literaturrecherche belegen, dass in 70% der Studien die Grundlage der Analyse die Daten einer Einzelkasse darstellten und Datenbanken nur sehr selten genutzt wurden. Aufgrund der historischen Entwicklung der Krankenkassen unterscheiden sich diese jedoch in ihrer Versichertenstruktur sowie der regionalen Verortung, was die Repräsentativität der Ergebnisse für die gesamte deutsche Versichertenstruktur verringern kann. Eine Möglichkeit, die Validität der Aussagen zu erhöhen, stellt die Standardisierung der Ergebnisse dar, welche jedoch nur in knapp einem Viertel der Studien explizit berichtet wurde.

Die Erörterung dieser rechtlich-politischen Herausforderungen, ihre Einordnung im internationalen Kontext sowie die Formulierung von Lösungsansätzen stehen im Mittelpunkt des Artikels „Access, use, and challenges of claims data analyses in Germany" (Modul 2). Neben der eingeschränkten Repräsentativität der Nutzung von Einzelkassendaten besteht für Wissenschaftler grundsätzlich kein gleichberechtigter Datenzugang, da die Herausgabe der Daten häufig wesentlich von den institutionellen Kooperationsnetzwerken mit der jeweiligen Krankenkasse abhängt. Der Datenpool des Deutschen Instituts für Medizinische Dokumentation und Information (DIMDI), welcher die aggregierten Gesundheitsdaten aller gesetzlich Versicherten auf Basis des morbiditätsorientierten Risikostrukturausgleichs zusammenführt, war ein erster Schritt in Richtung einer großen Forschungsdatenbank mit transparenten Zugangskriterien. Jedoch erwies sich diese Datenbasis aufgrund der niedrigen Informationsdichte durch starke Aggregation der Daten, verringertem Variablenumfang (verglichen mit Einzelkassendaten), hohem Zeitverzug zwischen Leistungsinanspruchnahme und Datenbereitstellung sowie der langen Bearbeitungszeit im Zuge der Antragstellung nur als begrenzt nutzbar für Forschungszwecke. Daher besteht weiterhin die Forderung nach besseren Zugangsmöglichkeiten zu Abrechnungsdaten, der Zusammenführung der Daten aller Leistungsträger und der Erhöhung des Variablenumfangs nach dem Vorbild internationaler Datenbanken. Im Gegensatz zu deutschen Routinedaten beinhalten amerikanische und kanadische Datenbanken eine umfangreichere Studienpopulation (inkl. privat und gesetzlich Versicherter), längere Beobachtungszeiträume, eine größere Anzahl an Variablen sowie die Möglichkeit der Datenverknüpfung zu internen und externen Quellen (z. B. klinischen Daten).

2.2 Gesundheitsökonomische Analyse onkologischer Erkrankungen

Vor dem Hintergrund steigender Ausgaben bei knappen Ressourcen gewinnen Maßnahmen zur Prävention zunehmend an Bedeutung. Durch den Einsatz geeigneter Screeningmaßnahmen können Krebserkrankungen bereits in einem asymptomatischen Frühstadium entdeckt, die Krankheits- und Kostenlast verringert und die langfristigen Überlebensaussichten verbessert werden. Für die Früherkennung des kolorektalen Karzinoms sind in Deutschland der fäkale Okkultbluttest und die präventive Koloskopie Bestandteil des Leistungskatalogs der GKV. Mittels der Koloskopie kann durch die Identifizierung und Entfernung von Vorstufen die Entstehung eines invasiven Karzinoms sogar gänzlich verhindert werden. Trotz positiver Kosten-Nutzen-Bilanz [21] und nachgewiesener Effektivität ist die Akzeptanz in der Bevölkerung nach wie vor gering. Die Inanspruchnahmeraten des fäkalen Okkultbluttests sind seit Jahren rückläufig und die der präventiven Koloskopie konstant auf einem relativ niedrigem Niveau [22].

Das Ziel der Publikation „Determinants of colorectal cancer screening in Germany – a claims data analysis" (Modul 3) war es, Einflussfaktoren auf die Inanspruchnahme des fäkalen Okkultbluttests und der präventiven Koloskopie im Rahmen der gesetzlichen Früherkennung zu ermitteln. Die Basis der Analyse stellen anonymisierte Stamm- und Leistungsdaten aller Versicherten der AOK Niedersachsen dar, die aufgrund ihres Alters grundsätzlich anspruchsberechtigt waren. Da sich Präventionsleistungen nur an asymptomatische Versicherte richten, wurden im Zuge des Aufgriffs Versicherte mit diagnostischen Leistungen des Darms, benignen und malignen Neubildungen des Darms sowie ausgewählten chronischen Darmerkrankungen ausgeschlossen. Mittels komplexer Ein- und Ausschlussalgorithmen wurden, getrennt für die Koloskopie und den Okkultbluttest, Studienkollektive bestehend aus Teilnehmern und Nichtteilnehmern identifiziert und auf Basis multivariater logistischer Regressionen die Chance einer Inanspruchnahme anhand soziodemografischer Variablen geschätzt. Während der Einfluss des Geschlechts und des Alters hinreichend untersucht ist, trägt diese Studie darüber hinaus zu einer Erweiterung der Evidenz in Bezug auf die Bedeutung der Staatsangehörigkeit und des sozialen Status in Hinblick auf den Schul- und Berufsabschluss sowie der Versichertenart bei.

Die Studienergebnisse zeigen, dass in der anspruchsberechtigten Bevölkerungsgruppe für das Koloskopie-Screening (≥ 55 Jahre)[2] die Teilnahmeraten mit steigendem Alter sinken. In Bezug auf die Inanspruchnahme des Okkultbluttests (≥ 50 Jahre) zeigt sich dieser Alterseffekt ebenfalls bei Frauen, wohingegen bei Männern mit zunehmendem Alter die Chancen der Inanspruchnahme überwiegend steigen. Bei beiden Früherkennungsmaßnahmen wird deutlich, dass der Alterseffekt vom Geschlecht ab-

[2] Seit der Überführung in ein einladungsbasiertes Screening-Programm im Jahr 2019 haben gesetzlich krankenversicherte Männer bereits ab einem Alter von 50 Jahren Anspruch auf eine Früherkennungskoloskopie. Die vorliegende Datenanalyse bezieht sich jedoch auf den Leistungszeitraum von 2012 bis 2016.

hängig ist. Im Vergleich zu Männern zeigen Frauen bis zu einem Alter von 69 bzw. 74 Jahren (Okkultbluttest bzw. Koloskopie) eine signifikant höhere Inanspruchnahmerate, wohingegen in höheren Altersgruppen ein inverses Verhältnis sichtbar wird. Die geringere Teilnahmerate bei Männern im frühen Anspruchsalter könnte beim Okkultbluttest auf die im Vergleich zu Gynäkologen geringere Verordnungsrate bei Urologen zurückzuführen sein. Türkische Staatsangehörige haben im Vergleich zu Deutschen eine geringere Inanspruchnahmerate der Koloskopie, allerdings eine höhere für den Okkultbluttest. Höhere Teilnahmeraten zeigen sich im Vergleich zu sozialversicherungspflichtig Beschäftigten bei Pensionären und freiwillig Versicherten, niedrigere Raten hingegen bei Arbeitssuchenden. In Bezug auf den sozialen Status zeigt sich zudem eine niedrige Teilnahmerate bei Versicherten ohne Schulabschluss im Vergleich zu einem hohen Abschluss bzw. ohne Berufsausbildung im Vergleich zu Akademikern. Auf Basis eines großen Versichertenkollektivs (n=973.981) konnten mittels der vorliegenden Routinedatenanalyse Personengruppen mit niedriger Teilnahmerate an Früherkennungsmaßnahmen beim kolorektalen Karzinom identifiziert werden. Bei gezielter Ansprache, z. B. durch die Beratungsgespräche der Haus- und Fachärzte, können die Erkenntnisse dazu beitragen, die Inanspruchnahmeraten zu erhöhen. Dies könnte zu einer Verringerung der Krankheitslast der Bevölkerung sowie der erkrankungs- und behandlungsbedingten Folgekosten führen.

Die Kosten der Diagnostik und Behandlung onkologischer Erkrankungen stehen im Mittelpunkt der folgenden beiden Module. Trotz der immensen ökonomischen Belastung ist die Evidenz zu den krebsbedingten Gesundheitsausgaben in Deutschland als gering einzustufen. Die wenigen verfügbaren Studien basieren auf hoch aggregierten oder veralteten Daten bzw. beziehen nur eine limitierte Anzahl an Leistungssektoren mit ein, was die Identifizierung von Kostentreibern erschwert. In den Modulen 4 und 5 werden daher zwei Kostenanalysen aus der Perspektive der GKV präsentiert. Im Fokus stehen die häufigsten geschlechtsspezifischen Krebserkrankungen, das Mamma- und das Prostatakarzinom.

Die Erfassung von Gesundheitskosten mittels Routinedaten erfordert regelhaft die Definition eines Zeithorizonts, in dem die Kosten erfasst werden. In Ermangelung standardisierter Berichtszeiträume werden Kosten häufig nach Ermessen des Forschers für ein spezifisches Jahr, einen Zeitraum oder ein bestimmtes Ereignis (z. B. Rezidiv) ausgewiesen. Jedoch ist gerade bei onkologischen Erkrankungen eine Veränderung der ökonomischen Krankheitslast im Zeitverlauf zu erwarten, beginnend mit der ersten Krebsdiagnose, der kurativen Therapie, der anschließenden Nachsorge bis zum Langzeitüberleben oder Tod. In Studien aus den USA hat sich daher der Phasenansatz bei der Kostenberechnung etabliert, bei dem die inkrementellen Kosten für die folgenden Behandlungsphasen berechnet werden:

(1) Initial: Erstdiagnose und Therapie (Operation, Radiotherapie, Chemotherapie),
(2) Intermediär: Reguläre Nachsorge, aktive Beobachtung, Behandlung von Komplikationen aus der Initialphase, medikamentöse Prävention von Rezidiven,

(3) Terminal (im Falle des krebsbedingten Versterbens): Behandlung von Rezidiven, Metastasen und krebsbedingten Komorbiditäten, palliative Versorgung.

Das Ziel der Publikation „Healthcare costs associated with breast cancer in Germany: a claims data analysis" (Modul 4) war es daher, den international anerkannten Phasenansatz auf den deutschen Versorgungskontext und die national zur Verfügung stehenden Routinedaten zu übertragen, am Beispiel des Mammakarzinoms die Länge der Behandlungsphasen empirisch zu bestimmen und die Behandlungskosten je Phase zu ermitteln. Auf der Grundlage der Abrechnungsdaten der AOK Bayern wurden inzidente und prävalente Patientinnen mit einem Mammakarzinom identifiziert. Um die krankheitsattributablen Kosten des Mammakarzinoms zu erfassen, wurde mittels eines Kontrollgruppendesigns das Inkrement aus dem Vergleich der Zielpopulation mit einer exakt gematchten Kontrollgruppe (im Verhältnis 1 zu 2) ermittelt, wobei für das Alter, das Geschlecht und die Komorbiditäten im Vorjahr (mittels des Elixhauser Score) adjustiert wurde. Um die Länge klinisch relevanter Behandlungsphasen bestimmen zu können, wurden zunächst die durchschnittlichen inkrementellen Kosten pro Monat ausgehend von der Diagnose bis zum Versterben unter Nutzung von Subgruppenanalysen berechnet. Mittels der Joinpoint-Regression wurden die monatlichen Kosten als Funktion der Zeit modelliert und Trendumkehrpunkte ermittelt, an denen statistisch signifikante Änderungen im Kostenverlauf auftraten. Aus der Anwendung dieses Verfahrens ergab sich eine Dauer von jeweils 11 Monaten in der initialen und terminalen Phase. Alle verbleibenden Monate wurden der intermediären Phase zugeordnet und als Jahreskosten ausgewiesen.

Die Ergebnisse der Studie belegen, dass die Behandlung des Mammakarzinoms mit substanziellen Kosten für die GKV verbunden ist, diese jedoch in Abhängigkeit der Behandlungsphase und -art stark variieren. Analog zu internationalen Studien folgen die inkrementellen Behandlungskosten einer u-förmigen Kurve, wobei die höchsten Kosten im zeitlichen Zusammenhang mit der Diagnose und dem Versterben auftreten. Die höchsten altersstandardisierten inkrementellen Behandlungskosten sind mit durchschnittlichen 33.237€ je inzidentem und 28.211€ je prävalentem Fall in der terminalen Phase (11 Monate) zu verzeichnen. In Abhängigkeit der Behandlungsart variierten die Kosten dabei zwischen 11.608€ bei aktiver Überwachung (weder Operation noch Radio-/Chemotherapie) und 52.651€ bei Radio-Chemotherapie. In der initialen Phase (11 Monate) ergaben sich mittlere inkrementelle Kosten von 21.455€ (bzw. 3.032 bis 60.000€ je nach Behandlungsart). In der intermediären Phase beliefen sich die inkrementellen Jahreskosten auf 2.851€ je inzidentem und 2.387€ je prävalentem Fall. Auch wenn die Kosten in der intermediären Phase deutlich geringer erscheinen, werden sie in Zukunft aufgrund verlängerter Überlebenszeiten an ökonomischer Bedeutung gewinnen. Insgesamt nahmen die Gesundheitskosten in den meisten Phasen mit dem Alter ab. Die Kostentreiber variieren in Abhängigkeit von der Behandlungsphase und -art, wobei Zytostatika und stationäre Behandlungen in den meisten Phasen die höchsten wirtschaftlichen Auswirkungen zeigten.

Die Variation der Kosten verdeutlicht die Notwendigkeit einer theoretischen und empirischen Fundierung des zeitlichen Horizonts der Kostenerfassung, um das gesamte Kontinuum der Behandlung abbilden und aussagekräftige Ergebnisse erzielen zu können. Dies ist die erste Studie, die die Behandlungskosten des Mammakarzinoms für Deutschland nach dem Vorbild des amerikanischen Phasenansatzes ermittelt hat. Unter Hinzunahme weiterer Parameter, z. B. Inzidenz- und Überlebens- bzw. Mortalitätsraten, können die Erkenntnisse einen Beitrag zur Projektion der zukünftigen ökonomischen Krankheitslast und zur Abschätzung des Einflusses der Einführung von Interventionen (z. B. präventiver Maßnahmen) leisten.

Aus Kostensicht leistet die vorliegende Studie zusätzlich einen Beitrag, indem die Kosten von Zytostatika-Rezepturen erfasst und isoliert werden konnten. Diese Infusionslösungen werden individuell für die Patienten in Steril-Apotheken hergestellt und über eine einheitliche Sonder-Pharmazentralnummer (PZN) für Zubereitungen abgerechnet. Bis zum Ende des ersten Quartal 2010 war der ursprüngliche Verordnungstext nicht verfügbar, sodass die Untersuchung der ambulanten Tumortherapie nur sehr eingeschränkt möglich war [23]. Erst seit einer Novelle des Arzneimittelgesetzes liegen den Krankenkassen Informationen zur Zusammensetzung der Zubereitungen vor, da die für die Zytostatika-Zubereitung verwendete PZN des Fertigarzneimittels auf dem Rezept angegeben werden muss[3] [13, 24].

Die Analyse der Behandlungskosten beim Mammakarzinom verdeutlicht die hohe ökomische Last am Lebensende, geprägt durch zytotoxische Behandlungen und stationäre Aufenthalte. Die Vielfalt unterschiedlicher Therapieoptionen in der letzten Lebensphase und der daraus resultierende zusätzliche Behandlungsbedarf in der Versorgungsrealität stehen im Mittelpunkt der Publikation „Treatment-related healthcare costs of metastatic castration-resistant prostate cancer in Germany – a claims data study" (Modul 5). Beim metastasierten kastrationsresistenten Prostatakarzinom (mCRPC) handelt es sich um Patienten, die nach kurativer Intervention durch Operation oder Bestrahlung eines lokal begrenzten Tumors behandelt wurden und danach in eine Tumorprogression gerieten und auch solche, die mit einer bereits bestehenden Metastasierung diagnostiziert wurden. Obwohl es sich um eine palliative Behandlungssituation mit stark begrenzter Lebenserwartung handelt, haben sich die Therapieoptionen in den letzten beiden Jahrzehnten stark ausgeweitet. Dazu zählen u. a.

(1) die Hormontherapien Abirateron und Enzalutamid,
(2) die Chemotherapien Docetaxel und Cabazitaxel,
(3) „Best Supportive Care"[4] (BSC).

[3] Die Herausgabe dieser Daten zu Forschungszwecken erfolgte erst sukzessive durch die Krankenkassen.
[4] BSC stellt eine unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität dar.

Abgesehen davon, dass Cabazitaxel nur für Docetaxel-vorbehandelte Patienten zugelassen ist, gibt die medizinische Leitlinie keinen klaren Therapiealgorithmus vor. Das Ziel der Studie war es, die Leistungsinanspruchnahmen und Behandlungskosten von Patienten zu ermitteln, die mittels einer der fünf genannten Therapieoptionen behandelt wurden. Auf der Basis von GKV-Routinedaten der Techniker Krankenkasse wurde das Grundkollektiv mittels eines Algorithmus aus Diagnosen, Arzneimitteln und Prozedurenschlüsseln identifiziert und der patientenindividuelle Behandlungszeitraum ermittelt. Anschließend wurden die monatlichen Leistungsinanspruchnahmen und Behandlungskosten für jede Therapiekohorte ermittelt. Um einen Vergleich der Kohorten zu ermöglichen, wurden multivariate mehrstufige Regressionsmodelle geschätzt, in denen für Gruppenunterschiede zu Therapiebeginn kontrolliert wurde.

Die vorliegende Studie bietet damit erstmals für Deutschland einen Vergleich der Versorgungssituation und Kosten im Hinblick auf fünf verschiedene Therapieoptionen bei Patienten mit einem metastasierten kastrationsresistenten Prostatakarzinom. In den meisten Sektoren war die Inanspruchnahme von Leistungen bei Patienten mit Cabazitaxel-Therapie am höchsten und in der Gruppe der BSC am niedrigsten. Patienten mit Chemotherapie wiesen im Vergleich zu Patienten, die mittels Hormontherapien oder BSC behandelt wurden, eine erhöhte Rate an Arzneimittelverschreibungen, ambulanten Arztkontakten und stationären Aufnahmen auf. Die Studie verdeutlicht, dass die Behandlung dieser Patientengruppen eine hohe wirtschaftliche Belastung für die Krankenkassen darstellt, in Abhängigkeit der Therapieoption jedoch stark variiert. Die monatlichen indikationsspezifischen Behandlungskosten und Gesamtkosten waren in der Cabazitaxel-Kohorte mit 6.343€ und 7.631€ am höchsten, gefolgt von Abirateron (4.579€ / 5.226€), Enzalutamid (4.416€ / 5.079€), Docetaxel (1.580€ / 2.392€) und BSC (438€ / 959€). Die wesentlich höheren Ausgaben in der Cabazitaxel-Kohorte resultieren aus höheren Arzneimittelkosten und einem größeren stationären Behandlungsbedarf, auch im direkten Vergleich mit der Docetaxel-Chemotherapie. Die Studie gibt Hinweise darauf, dass für die Cabazitaxel-Therapie ein größerer Umfang an (kostspieliger) Begleitmedikation erforderlich ist, um die Sicherheit des Arzneimittels zu gewährleisten bzw. unerwünschte Wirkungen zu behandeln. Die erhöhte Anzahl von Krankenhauseinweisungen könnte auf geplante Krankenhausaufenthalte zur Verabreichung einer Chemotherapie zurückzuführen sein bzw. das Ergebnis von schwerwiegenden unerwünschten Ereignissen (z. B. febrile Neutropenie) im Zusammenhang mit Cabazitaxel darstellen.

Da Unklarheit über den optimalen Zeitpunkt, die Sequenzierung und die Kombination verschiedener Arzneimittel vorherrscht, rückt in der Entscheidungssituation die Abwägung patientenrelevanter Endpunkte, wie z. B. die Verlängerung des Überlebens oder das Risiko schwerwiegender unerwünschter Wirkungen, stärker in den Vordergrund. Im Gegensatz zur Hormonmanipulation, die in der Regel gut verträglich ist, sind Chemotherapien häufig mit einer enormen Belastung für die Patienten verbunden. Mit einem medianen Überlebensvorteil von 2,4 Monaten handelt es sich bei Cabazitaxel um eine der

letzten Möglichkeiten der Tumorbeeinflussung, die in der Zulassungsstudie mit einem großen Risiko unerwünschter schwerwiegender Ereignisse assoziiert war. Das größte Therapierisiko stellen hämatologische Toxizitäten, insbesondere die Neutropenie, dar, welche nicht nur zu Dosismodifikation, Therapieverzögerung und -abbruch, sondern auch zu Blutungen, neutropenischem Fieber und im Falle einer schweren Infektion sogar zum Tod führen können. Aufbauend auf der Routinedatenanalyse aus Modul 5 war es das Ziel der Publikation „Safety and survival of docetaxel and cabazitaxel in metastatic castration-resistant prostate cancer“ (Modul 6), die Überlebenszeit und die Schwere therapiebedingter Toxizitäten in der Cabaztaxel- und Docetaxel-Kohorte in der Versorgungsrealität zu untersuchen.

Die Studie verdeutlicht, dass innerhalb von 8 Monaten nach Therapiebeginn bei 31% der Patienten in der Docetaxel-Kohorte und bei 61% der Patienten in der Cabazitaxel-Kohorte die Behandlung einer therapiebedingten hämatologischen Toxizität erforderlich war. 15% der Patienten mit Docetaxel-haltiger Therapie und 32% der Patienten mit Cabazitaxel-haltiger Therapie erhielten innerhalb von 3 Monaten nach Therapiebeginn Granulozyten-Kolonie-stimulierende Faktoren[5] zur Prävention der Neutropenie. Ein anämischer Zustand, der eine Bluttransfusion erforderte, trat innerhalb von 8 Monaten bei 17% der Patienten in der Docetaxel-Kohorte und bei 33% der Patienten in der Cabazitaxel-Kohorte ein.

Die Gesamtüberlebenszeit war mit 21,9 Monaten in der Docetaxel-Kohorte und 11,3 Monaten in der später therapierten Cabazitaxel-Kohorte kürzer als in vielen klinischen Studien. Dies könnte die unterschiedliche Zusammensetzung und prognostische Ausgangsparameter von Patienten in und außerhalb von kontrollierten klinischen Studien widerspiegeln.

Die Studie gibt zudem Hinweise auf eine mögliche Übertherapie: Aggressive zytotoxische Behandlungen sollen nur bei Patienten mit reversiblen Komorbiditäten (z. B. Mangelernährung) durchgeführt werden. Ein nicht unerheblicher Anteil der Patienten hatte jedoch schwere Grunderkrankungen, wie z. B. kardiovaskuläre Erkrankungen oder Nieren-/Leberversagen im Endstadium. Trotz der Tatsache, dass Patienten nur dann von einer Chemotherapie profitieren, wenn noch eine reelle Möglichkeit zur Lebensverlängerung oder Symptomlinderung besteht, erhielt jeder zehnte Patient in der Cabazitaxel-Kohorte mindestens eine zytotoxische Infusion im letzten Lebensmonat. Diese Studie zeigt den Bedarf an Leitlinien auf, die Kriterien für die Indikation und den Zeitpunkt einer aggressiven Behandlung am Lebensende festlegen.

Die Stärke von Routinedaten liegt darin, dass sie im Vergleich zu klinischen Studien eine Abbildung der Versorgungsprozesse unter Alltagsbedingungen auf der Grundlage eines, vor allem im Hinblick auf die Komorbiditätslast, weniger homogenen Kollektivs ermöglichen. Die Studie zeigt, dass über Behand-

[5] Dabei handelt es sich um einen Wachstumsfaktor, der die Neubildung neutrophiler Granulozyten im Knochenmark anregt. Dieser kann die Dauer und Schwere einer Chemotherapie-assoziierten Neutropenie reduzieren.

lungskosten hinaus mittels Routinedaten auch patientenrelevante Endpunkte zur Effektivität und Sicherheit einer onkologischen Therapie analysiert werden können. Aus methodischer Sicht verdeutlicht die Studie, wie sich klassische Ansätze der klinischen Forschung, wie zum Beispiel der Kaplan-Meier-Schätzer, die Cox-Regression oder auch die Analyse konkurrierender Risiken, auf Routinedaten übertragen lassen.

Das Modul 6 hat verdeutlicht, dass die Wahl der Behandlung ein Arzt-Patienten-Gespräch über die Prognose unter sorgfältiger Berücksichtigung der Optionen zur Lebensverlängerung, der bestehenden Komorbiditäten, der Risiken und der Verträglichkeit von unerwünschten Ereignissen sowie der Präferenzen des Patienten für die verbleibende Lebenszeit erforderlich macht. Um auch die Patientenperspektive mit einzubeziehen, ist eine Erfassung der Erwartungen, Erfahrungen und Präferenzen von Patienten mit onkologischen Erkrankungen unerlässlich. Im Rahmen der Publikation "Treatment-related experiences and preferences of patients with lung cancer: a qualitative analysis" (Modul 7) wurden 18 leitfadengestützte halbstrukturierte Interviews mit Patienten durchgeführt, die sich zum Zeitpunkt des Interviews aufgrund eines Bronchialkarzinoms in einer laufenden palliativen Chemotherapie befanden. Die Interviews wurden aufgenommen, transkribiert und nach dem Verfahren von Mayring inhaltsanalytisch ausgewertet.

Die berichteten Erfahrungen der Patienten betrafen sowohl organisatorische als auch psychosoziale und ökonomische Folgen für die Patienten und ihre Familien. Die inhaltsanalytische Auswertung der Interviews ergab, dass die Grunderkrankung und ihre Therapie bei allen Betroffenen mit starken Ängsten, Unsicherheiten und Hoffnungen verbunden ist, die Bedürfnisse und Wünsche jedoch individuell stark variieren. Zu den organisatorischen Aspekten, die als belastend empfunden wurden, gehörten im Behandlungsalltag lange Wartezeiten, eine geringe Privatsphäre sowie ein häufiger Wechsel des behandelnden Arztes. In sozialrechtlicher Hinsicht wurden Hürden in der Antragstellung und Kommunikation mit der betreffenden Krankenkasse berichtet, vor allem in Bezug auf die Erstattung von Fahrtkosten, die außerhalb der regulären Radio- oder Chemotherapie, beispielsweise zu Zwecken der Therapievorbereitung (z. B. Blutbildkontrolle), anfielen. Aus Sicht der Patienten besteht hier ein organisatorischer Optimierungsbedarf, um unnötige Fahrten zu vermeiden, da diese mit ökonomischen Zusatzbelastungen für die Betroffenen einhergehen. Abgesehen von ökonomischen Existenzängsten, u. a. bedingt durch bestehende Arbeitsunfähigkeit, wurde der Konflikt zwischen dem Wunsch nach lebensverlängernden Maßnahmen und der gleichzeitigen Angst vor therapiebedingten körperlichen Beeinträchtigungen, die mit einem Verlust der Selbstständigkeit und Pflegebedürftigkeit einhergehen können, beschrieben. In diesem Zusammenhang wurde ein Informationsmangel im Hinblick auf die Ansprechpartner und die Behandlungsoptionen von unerwünschten Wirkungen beschrieben und ein auf den Patienten zugeschnittenes, übergreifendes Therapiekonzept gefordert, das in Abhängigkeit der Komorbiditäten alle relevanten Facharztgruppen miteinbezieht.

Die Kenntnis der Patientenperspektive in Bezug auf organisatorische Defizite, ökonomische Belastungen sowie psychosoziale Folgen ist essenziell für eine effizientere Gestaltung der Versorgung. Mittels einer zielgerichteten Therapieplanung können Mehrfachuntersuchungen und -behandlungen sowie damit verbundene Anreisen vermieden werden. Die Studie zeigt auch, dass von den Patienten ein individuell zugeschnittenes Therapiekonzept gewünscht wird, das nicht nur eine Lebensverlängerung beinhaltet, sondern vor allem den individuellen Bedürfnissen in Hinblick auf eine gute Symptomkontrolle und die Erhaltung der Lebensqualität gerecht wird. Das Modul 7 verdeutlicht, dass zur Integration der Patientenperspektive ein Mixed-Methods-Ansatz erforderlich ist, bei dem die Erkenntnisse der quantitativen Routinedatenanalyse mittels eines qualitativen Designs erweitert und vertieft werden.

3 Beantwortung der Forschungsfragen und Ausblick

Aufgrund des wachsenden onkologischen Versorgungsbedarfs kommt der Analyse und Optimierung von Versorgungsstrukturen unter Alltagsbedingungen eine immer größere Bedeutung zu. Die in der vorliegenden kumulativen Dissertation eingebrachten Module leisten einen wesentlichen Beitrag zur Beurteilung des methodischen und inhaltlichen Potentials sowie der Limitationen von GKV-Routinedaten für die gesundheitsökonomische Analyse onkologischer Erkrankungen. Im Folgenden werden die zentralen Forschungsfragen beantwortet.

1. *Wie hat sich die Versorgungsforschung auf Basis von Routinedaten entwickelt und welchen Stellenwert nehmen Fragestellungen mit gesundheitspolitischer Relevanz ein?*

In den letzten beiden Jahrzehnten ist ein kontinuierliches Wachstum der Versorgungsforschung auf Basis von Routinedaten zu verzeichnen. Die Grundlage hierfür bilden gesetzliche Rahmenbedingungen, die zunehmende Bereitschaft von Krankenkassen, die Daten zu Forschungszwecken zur Verfügung zu stellen sowie eine Erhöhung des Inhalts und Umfangs der Datengrundlage. Das Wachstum spiegelt sich nicht nur in der Anzahl empirischer Studien, sondern auch der Veröffentlichung von Artikeln mit methodischem Schwerpunkt, Leitlinien / Leitfäden und Handbüchern wider. Ferner zeigt sich im Zeitverlauf eine Steigerung der durchschnittlichen Publikationsqualität sowie eine zunehmende Internationalisierung der Beiträge, was die Akzeptanz und Bedeutung dieser Datenquelle bekräftigt (Modul 1).

Die Etablierung von Routinedaten als Informationsgrundlage für gesundheitspolitische Entscheidungsprozesse wird auch durch die zunehmende öffentliche Förderung von Forschungsprojekten, wie beispielsweise durch den Gemeinsamen Bundesausschuss im Rahmen des Innovationsfonds, deutlich. Mittels Routinedaten kann eine Vielzahl unterschiedlicher Fragestellungen aus dem Bereich der Versorgungsforschung und Gesundheitsökonomie adressiert werden. Mindestens ein Drittel der in den Jahren 2000 bis 2014 veröffentlichen Routinedatenstudien hatte einen gesundheitsökonomischen

Schwerpunkt. Zudem hat sich die Anzahl an Beiträgen mit gesundheitspolitischer Relevanz, d. h. vor allem Interventions- und Evaluationsstudien sowie die Analyse von Gesundheitsstrukturen, kontinuierlich gesteigert (Module 1, 2).

Um die Nutzungsmöglichkeiten und die Aussagekraft von Routinedaten im Rahmen von gesundheitspolitischen Entscheidungsprozessen weiter zu erhöhen, bedarf es eines gleichberechtigten Zugangs aller Wissenschaftler und Forschungsinstitutionen zu dieser Datenquelle sowie der Etablierung einer hochwertigen umfangreichen Forschungsdatenbank. Nach internationalem Vorbild sollte diese einen erhöhten Variablenumfang aufweisen, neben bundesweiten Kassendaten die Daten weiterer Leistungsträger zusammenführen sowie eine Verlinkung zu internen und externen Quellen (z. B. klinischen Daten), unter Wahrung des Datenschutzes, ermöglichen. Die Einführung des DIMDI-Datenpools stellt einen wichtigen Schritt in Richtung einer einheitlichen Basis für die Abrechnungsdaten gesetzlich Versicherter dar, erwies sich jedoch aus strukturellen und inhaltlichen Gründen als begrenzt nutzbar für Forschungszwecke (Module 1, 2).

2. *Welche methodischen Aspekte müssen bei der Analyse onkologischer Erkrankungen auf Basis von Routinedaten beachtet werden?*

Aufgrund ihrer originären Zweckbestimmung beinhalten Routinedaten der GKV zeitnahe Informationen zu einer Vielzahl an Leistungssektoren und ermöglichen damit ein Abbild abrechnungsrelevanter Versorgungsprozesse unter Alltagsbedingungen (Modul 1).

Neben den Stammdaten zu Geburtsjahr, Geschlecht, Nationalität und Versichertenart, beinhalten Routinedaten mittels des Tätigkeitsschlüssels u. a. Angaben zum ausgeübten Beruf, dem höchsten allgemeinbildenden Schulabschluss sowie dem höchsten beruflichen Ausbildungsabschluss. Dies ermöglicht Analysen zu soziodemografischen Unterschieden in der Inanspruchnahme von Gesundheitsleistungen, wie der Teilnahme an Früherkennungsmaßnahmen beim kolorektalen Karzinom (Modul 3). Im Vergleich zu Primärdatenerhebungen, insbesondere standardisierten Befragungen, liegt das Potential von Routinedaten in der Untersuchung eines großen Versichertenkollektivs bei gleichzeitiger Vermeidung des Recall-Bias. Routinedaten ermöglichen zudem die Ermittlung von Versicherten mit formaler Leistungsberechtigung und erlauben eine Differenzierung von präventiven und kurativen Koloskopien. Eingeschränkt wird die Analyse durch den begrenzt verfügbaren Datenzeitraum von Routinedaten und die Tatsache, dass der Tätigkeitsschlüssel nur für das Kollektiv der sozialversicherungspflichtig Beschäftigen zur Verfügung steht.

Am Anfang jeder Routinedatenanalyse stehen die Definition und der Aufgriff der Studienpopulation. Eine zentrale Limitation von Routinedaten stellt das Fehlen klinischer Informationen, sowohl zur patientenindividuellen Biologie (z. B. Stadium der Erkrankung, Progression, Laborparameter) als auch zur

Therapie (z. B. Dokumentation der Therapielinie) dar. Die Analyse des metastasierten kastrationsresistenten Prostatakarzinoms (Modul 5) hat gezeigt, dass sich trotz dieser Einschränkung mittels eines Algorithmus aus Codes zu Diagnosen, Arzneimitteln und Prozeduren auch komplexe Krankheitsbilder identifizieren und Therapielinien approximativ abbilden lassen. Die Voraussetzung hierfür ist, dass in den medizinischen Leitlinien die Therapielinien eindeutig beschrieben und mittels abrechnungsrelevanter Leistung in den Routinedaten identifizierbar sind [25].

Das große Potential von Routinedaten liegt aufgrund ihres Ursprungs in der Erfassung von Leistungsinanspruchnahmen und Kosten. Die zunehmende Bereitstellung von Daten zu Zytostatika-Zubereitungen seitens der Krankenkassen stellt einen Meilenstein dar, indem sie die Beschreibung der Strukturen und der Kosten in der ambulanten onkologischen Versorgung erst ermöglicht (Module 4-6). Der zunehmend chronische Charakter onkologischer Erkrankungen und variierende Muster der Leistungsinanspruchnahme verdeutlichen die Notwendigkeit eines Phasenansatzes bei der Berechnung der Kosten, um das gesamte Kontinuum der Behandlung abbilden und aussagekräftige Ergebnisse erzielen zu können. Die Übertragung des amerikanischen Phasenansatzes auf deutsche Routinedaten (Modul 4) war mit einigen Herausforderungen verbunden:

(1) Eine Voraussetzung der Joinpoint-Analyse zur Ermittlung der Phasendauer stellt eine hinreichend lange Zeitreihe dar, um die Identifikation signifikanter Änderungen im Zeitverlauf zu ermöglichen. Eine Limitation deutscher Routinedaten stellt hier der begrenzte Zeitraum von meist vier Datenjahren inkl. der Notwendigkeit einer Definition von Vor- bzw. Nachbeobachtungszeiträumen (z. B. zur Unterscheidung inzidenter und prävalenter Fälle) dar. Um dieser Herausforderung entgegenzuwirken, wurden monatliche inkrementelle Kosten berechnet und die Joinpoint-Regression getrennt für die initiale und terminale Phase durchgeführt.

(2) Die Berechnung monatlicher Kosten erfordert die Möglichkeit einer tagesgenauen Zuordnung der Leistungsausgaben, welche im ambulanten Sektor durch pauschale Vergütungsstrukturen und die quartalsweise Abrechnung erschwert wird und eine annahmebasierte Vorgehensweise (z. B. Gleichverteilung der Kosten) erforderlich macht.

(3) Die Tatsache, dass der Grund des Versterbens in deutschen Routinedaten nicht dokumentiert ist, birgt grundsätzlich das Risiko einer fälschlichen Zuordnung der Versicherten zur terminalen Phase des Mammakarzinoms. Der hohe Anteil an Patientinnen mit einer Kombination unterschiedlicher indikationsspezifischer Therapien in der letzten Lebensphase bekräftigt jedoch in dieser Studie die Schwere der Erkrankung und eine korrekte Zuordnung.

Eine weitere analytische Herausforderung besteht in der ausschließlichen Erfassung der Kosten, die auf die onkologische Zielindikation entfallen. Grundsätzlich lassen sich inkrementelle Kosten mit quasi-

experimentellen Studiendesigns gut abbilden (Module 4, 5). Der Vorteil eines direkten Kontrollgruppenvergleichs bei der Ermittlung der inkrementellen Kosten des Mammakarzinoms (Modul 4) liegt in der gleichzeitigen Erfassung der Kosten, die durch Begleitmedikation und -erkrankungen entstehen. Die Kombination des Expertengestützten Ansatzes mit Regressionsanalysen ermöglicht die Erfassung und den Vergleich von indikationsspezifischen Kosten und Gesamtkosten unterschiedlicher Behandlungsoptionen beim Prostatakarzinom (Modul 5). Der Expertengestützte Ansatz setzt voraus, dass auf Grundlage standardisierter Klassifikationsinstrumente nur diejenigen Ressourcenverbräuche angesetzt werden, die auf die Zielerkrankung entfallen. Limitationen von Routinedaten ergeben sich somit bei Leistungen, die nicht ausschließlich für die Zielindikation zugelassen sind und bei Leistungssektoren ohne grundsätzliche Diagnosedokumentation (z. B. Arzneimitteldaten). Bei der Nutzung des Expertengestützten Ansatzes im Rahmen der onkologischen Versorgung lassen sich somit unterstützende Maßnahmen, die der Prophylaxe oder Behandlung therapiebedingter unerwünschter Wirkungen (z. B. Antiemetika, Kortison), dienen, schwer zuordnen. Das Gleiche gilt für assoziierte Begleiterkrankungen und ihre Therapie, wie z. B. die Schmerzbehandlung aufgrund von Metastasen. Die Nutzung des Expertengestützten Ansatzes in Kombination mit Regressionsanalysen im Rahmen von Modul 5 führt somit zu einer Unterschätzung der indikationsspezifischen Kosten. Um dennoch die Spanne der Kosten angeben zu können, wurden zudem die Gesamtkosten berechnet. Der Mehrwert dieser Vorgehensweise im Rahmen der Studie zum Prostatakarzinom liegt darin, dass in Hinblick auf die medikamentöse Versorgung, mittels der rechnerischen Differenz aus den Gesamtkosten und den Kosten der Zielmedikation, Aussagen über den Umfang notwendiger Begleitmedikation zwischen den verschiedenen Formen der Chemo- und Hormontherapien getroffen werden können.

Die Ermittlung indikationsspezifischer Kosten setzt eine ausreichend adjustierte Kontrollgruppe voraus. Dies ist bei Krebspatienten von besonderer Bedeutung, da dieses Kollektiv aufgrund des häufig fortgeschrittenen Alters mit zahlreichen behandlungsbedürftigen Komorbiditäten belastet ist und bei prävalenten Patienten die Ausgangslage bezüglich Vortherapien sehr unterschiedlich sein kann. GKV-Routinedaten bieten das Potential einer umfangreichen Adjustierung auf Basis des Geschlechts, des Alters und der Komorbiditäten, jedoch bleibt eine Adjustierung ausschließlich auf die in den Routinedaten vorhandenen Variablen begrenzt. Die Erfassung der Komorbiditäten mittels Diagnosedaten (z. B. Elixhauser Score, Modul 4) ist sehr etabliert, wohingegen Arzneimitteldaten (z. B. Pharmacy-based metrics, Module 5, 6) bisher wenig zur Komorbiditätsmessung und -adjustierung genutzt wurden. Diese bieten allerdings den Vorteil, dass nur diejenigen Erkrankungen erfasst und für die Adjustierung genutzt werden, für die aus Sicht des Patienten ein tatsächlicher Behandlungsbedarf besteht.

In Abhängigkeit des Erkenntnisinteresses kann sich bei der Nutzung von Einzelkassendaten aufgrund historisch bedingter soziostruktureller Unterschiede von Krankenkassen die Frage der Repräsentativität der Ergebnisse stellen. In Bezug auf die Kostenanalyse des Mammakarzinoms hat sich gezeigt, dass

die Behandlungskosten mit zunehmendem Alter sinken. Eine Gewichtung der Kostenparameter in Hinblick auf die Altersstruktur der gesamten weiblichen GKV-Population (Modul 4) bietet gute Möglichkeiten, auch bei Einzelkassendatennutzung altersstandardisierte Aussagen treffen zu können. Unberücksichtigt bleibt allerdings der Einfluss weiterer sozioökonomischer Faktoren [26], die mittels Routinedaten nur bedingt abbildbar sind.

Neben den Kostenstrukturen können mittels Routinedaten auch Nutzenparameter, wie der Behandlungserfolg oder die Therapiesicherheit, im Rahmen der onkologischen Versorgung ermittelt werden. Im Vergleich zu klinischen Studien liegt ein weiteres Potential administrativer Daten in der Möglichkeit, medizinische Ereignisse kontinuierlich über mehrere Jahre hinweg sektorübergreifend zu erfassen. Die Durchführung von Ereigniszeitanalysen macht ein tagesgenaues Start- und Enddatum erforderlich. Solange der Beginn einer Therapie eindeutig identifizierbar ist, kann das Gesamtüberleben mittels Routinedaten gut abgebildet werden (Modul 6). Aufgrund fehlender klinischer Informationen ist der in klinischen Studien häufig betrachtete Endpunkt des progressionsfreien Überlebens in der Regel nicht darstellbar[6].

Die Sensitivität der Erfassung therapiebedingter unerwünschter Wirkungen ist ebenfalls abhängig von der Behandlungs- und Abrechnungsrelevanz sowie dem Leistungssektor. Mittels Routinedaten lassen sich eher schwere Komplikationen erfassen, die eine (unmittelbare) medizinische Behandlung mittels Arzneimitteln oder einen medizinischen / operativen Eingriff erfordern, wie zum Beispiel schwerwiegende hämatologische Toxizitäten (Modul 6). Eine tagesgenaue Erfassung unerwünschter Ereignisse mittels kodierter Diagnosen ist im ambulanten Sektor aufgrund der quartalsweisen Dokumentation und Abrechnung nicht möglich. Ebenso lässt sich die Behandlung klassischer Nebenwirkungen im Rahmen der Chemotherapie, wie zum Beispiel Nausea oder Diarrhö, trotz tagesgenauem Verordnungs- und Abgabedatum im Arzneimittelsektor nur bedingt abbilden, da diese zum einen häufig prophylaktisch verordnet werden und zum anderen viele Arzneimittel nicht eindeutig der Zielerkrankung zugeordnet werden können.

[6] Eine approximative Darstellung wäre möglich, wenn die Progression eine eindeutig identifizierbare abrechenbare Leistung nach sich zieht.

3. *Welchen Beitrag leisten Routinedatenanalysen zu einer effizienten Gestaltung der onkologischen Versorgung?*

Das große Potential von GKV-Routinedaten in Hinblick auf die Onkologie liegt in der Möglichkeit, die Versorgungsrealität von Patientengruppen untersuchen zu können, die aufgrund der Schwere ihrer Erkrankung, der Komorbiditäten oder des Alters selten Bestandteil klinischer Studien und nur schwer über Primärdatenerhebungen zugänglich sind (z. B. Krebspatienten in der letzten Lebensphase). Gerade dieses Kollektiv spiegelt jedoch die Versorgungsrealität wieder. Routinedaten bieten das Potential, komplexe sektor- und leistungsübergreifende Versorgungsprozesse zu beschreiben und zu erklären und somit ggf. auch Hinweise auf Unter-, Über- und Fehlversorgung zu generieren.

Mittels Routinedaten konnten auf der Basis einer umfangreichen Untersuchungspopulation soziale Gruppen identifiziert werden, welche die Früherkennungskoloskopie und den Okkultbluttest trotz nachgewiesener Effektivität seltener nutzen (Modul 3). Diese Erkenntnisse sind für politische Entscheidungsträger bedeutsam, indem sie, wie im Rahmen des Nationalen Krebsplans gefordert [15], dazu beitragen können, relevante Personengruppen mit niedriger Inanspruchnahme gezielt anzusprechen, Teilnahmeraten zu erhöhen und zu einer Vermeidung von tumorbedingten Erkrankungs- und Therapiekosten beizutragen. Inzwischen werden diese Früherkennungsmaßnahmen im Rahmen eines organisierten Einladungsprogramms durchgeführt. Zukünftige Studien könnten auf Basis von Routinedaten das seit dem 1. Juli 2019 etablierte einladungsbasierte Screening mit dem opportunistischen Screening in Hinblick auf die Teilnahmeraten und ihre Determinanten untersuchen und evaluieren, inwiefern die in dieser Studie identifizierten Personengruppen mit geringer Inanspruchnahme besser adressiert werden und Ungleichheiten in der Inanspruchnahme reduziert werden können.

Krankheitskostenstudien stellen eine wichtige Informationsgrundlage für politische Entscheidungsträger im Rahmen der Budgetplanung dar. Unter der Vielzahl an Erkrankungen kommt onkologischen Erkrankungen vor dem Hintergrund steigender Ausgaben und der demografisch bedingten steigenden Inzidenz eine besondere Bedeutung zu. Um die Versorgung effizienter zu gestalten, ist eine Quantifizierung der Behandlungskosten im Zuge des gesamten Therapieweges erforderlich. Die Diagnostik und Therapie des Mammakarzinoms (Modul 4) ist mit substanziellen Kosten für die GKV verbunden, wobei diese in Abhängigkeit der Behandlungsphase, der Behandlungsart und des Alters stark variieren. In den 11 Monaten vor dem Versterben sind die Kosten, geprägt durch die Chemotherapie und stationäre Behandlungen, am höchsten, gefolgt von der initialen Phase. Auch wenn die Behandlungskosten in der intermediären Phase deutlich geringer erscheinen, wird ihre ökonomische Relevanz aufgrund der steigenden Rate von Langzeitüberleben zunehmen. Die Erkenntnisse dieser Studie können somit dazu beitragen, die potenziellen Auswirkungen von Präventionsleistungen, Behandlungsoptionen und Interventionen im Hinblick auf den Kostenverlauf einzuschätzen, indem diese mit Inzidenzzahlen und Überlebensraten bzw. -zeiten in Relation gesetzt werden können.

Mittels Routinedaten konnten fünf verschiedene Therapieoptionen bei Patienten mit einem metastasierten kastrationsresistenten Prostatakarzinom (Modul 5) simultan untersucht und der über die reinen Kosten der Zielmedikation hinaus gehende zusätzliche Behandlungsbedarf aufgrund von Nebenwirkungen und Therapiefolgen quantifiziert werden. Diese Studie gibt keine Auskunft darüber, welche Behandlungsalternative zu präferieren ist, sondern macht die ökonomischen Relationen deutlich. Patienten, die mit dem Zytostatikum Cabazitaxel behandelt werden, welches zu den letzten Möglichkeiten der Tumorbeeinflussung in der Behandlungskaskade zählt, zeigen sogar im direkten Vergleich mit der Chemotherapie mittels Docetaxel unter laufender Therapie höhere Arzneimittelmittelkosten (u.a. durch Begleitmedikation) und einen größeren Bedarf an stationärer Versorgung. Die Studie gibt damit Hinweise auf eine höhere (antizipierte) therapiebedingte Toxizität in der Versorgungsrealität.

In der nachfolgenden Analyse der Effektivität beider Chemotherapien (Modul 6) wurde deutlich, dass die mediane Überlebenszeit kürzer war als in klinischen Studien und zytotoxische Behandlungen auch bei Patienten mit schwerwiegenden Grunderkrankungen durchgeführt wurden. Patienten mit Cabazitaxel-Therapie wiesen zudem ein erhöhtes Risiko für schwerwiegende behandlungsbedürftige hämatologische Toxizitäten auf und bei einem von zehn Patienten wurde die Chemotherapie noch im letzten Lebensmonat verabreicht. Die medizinische Versorgung effizienter zu gestalten, kann auch den Verzicht auf eine Behandlung bedeuten, wenn der Behandlungserfolg unwahrscheinlich ist. Die Angemessenheit und Wirtschaftlichkeit einer Maßnahme kann jedoch nur in Abhängigkeit des Therapieziels beurteilt werden und macht die Berücksichtigung klinischer Parameter notwendig. Beide Aspekte können mittels Routinedaten in der Regel nicht abgebildet werden. Die Definition des Therapieziels und die Wahl der Behandlung machen ein Arzt-Patienten-Gespräch über die Prognose der Erkrankung erforderlich, bei dem neben der Lebenserwartung, den Nebenwirkungen und den Komorbiditäten auch die Lebensqualität und die Präferenzen des Patienten (Modul 7) berücksichtigt werden sollten. Die Perspektive des Patienten bleibt in den Routinedaten jedoch unberücksichtigt. Trotz dieser Limitationen können Routinedatenanalysen einen Beitrag dazu leisten, Hinweise auf Übertherapie unter Alltagsbedingungen aufzuzeigen, zu beschreiben und damit den Bedarf von Leitlinien zu verdeutlichen. Diese sollten die Indikation und den Zeitpunkt einer aggressiven Behandlung am Lebensende festlegen und damit als Entscheidungsgrundlage für Ärzte und Patienten dienen.

Zusammenfassend lässt sich festhalten, dass die Eignung und Aussagekraft von Routinedaten im Rahmen der onkologischen Versorgungsforschung und Gesundheitsökonomie von der Forschungsfrage, zugrunde liegenden Annahmen und der Wahl des methodischen Vorgehens abhängig ist. Das große Potential der Datengrundlage liegt in der Möglichkeit, Patienten- und Behandlungspfade in der Versorgungsrealität abbilden und beschreiben zu können. Sie eignen sich daher besonders zur Erfassung von Leistungsinanspruchnahmen und Kosten. Eine Beschreibung der Versorgungsstrukturen ist dem-

nach gut realisierbar. Die Abbildbarkeit von Nutzenparametern ist eng verknüpft mit ihrer Abrechnungsrelevanz. Eine Erklärung und Bewertung kann nur in Hinblick auf die Vorgaben medizinischer Leitlinien erfolgen und setzt klare, in den Routinedaten identifizierbare Therapieempfehlungen voraus. Eine Bewertung in Hinblick auf das Therapieziel oder die Patientenpräferenzen ist nicht möglich. Trotzdem können Routinedatenanalysen einen Beitrag dazu leisten, Hinweise auf Fehlversorgung unter Alltagsbedingungen aufzuzeigen.

Aus methodischer Sicht zeigten sich die größten Limitationen im Hinblick auf das Fehlen klinischer Informationen, die begrenzte Verfügbarkeit der Datenjahre, die aggregierte Datenlagerung von Diagnosen und Kosten im ambulanten Sektor sowie die fehlende Dokumentation der rechtfertigenden Diagnose bei Arzneimittelverordnungen. Um das Potential von Routinedaten weiter zu erhöhen und methodische Limitationen zu überwinden, ist eine Erweiterung der Datenbasis durch Erhöhung des Variablen- und Zeitumfangs verfügbarer Daten sowie einer Verknüpfung mit weiteren Datenquellen unerlässlich. Eine Lösung könnte die Verknüpfung mit Registern (z. B. epidemiologische / klinisches Krebsregister), den Routinedaten anderer Leistungsträger (z. B. Rentenversicherung), weiteren Sekundärdatenquellen (z. B. elektronische Patientenakten) oder Primärdaten (z. B. Befragungsdaten zur Lebensqualität) darstellen, wobei dies mit großen personellen, zeitlichen und finanziellen Herausforderungen in Bezug auf Datenschutz und Datensicherheit verbunden ist.

Auf Basis des am 19. Dezember 2019 in Kraft getretenen Digitale-Versorgung-Gesetzes [27] wird die Datenaufbereitungsstelle des DIMDI zu einem Forschungsdatenzentrum ausgebaut. Durch die Neufassung der §§303a-f SGB V sowie der Datentransparenzverordnung [28] ermöglicht das Forschungsdatenzentrum nutzungsberechtigten Institutionen Zugang zu den pseudonymisierten Abrechnungsdaten der GKV. Im Vergleich zum DIMDI-Datenpool sollen langfristig aktuellere, umfangreichere und vielfältigere Daten (z. B. elektronische Patientenakte) zur Verfügung stehen, allerdings ist eine Möglichkeit der Verlinkung mit externen Daten bisher nicht geplant [29].

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Module der kumulativen Dissertation

Modul 1:

Kreis K, Neubauer S, Klora M, Lange A, Zeidler J:

Status and perspectives of claims data analyses in Germany – A systematic review. Health Policy 2016; 120(2): 213-226. DOI: 10.1016/j.healthpol.2016.01.007.

Modul 2:

Neubauer S, **Kreis K,** Klora M, Zeidler J:

Access, use, and challenges of claims data analyses in Germany. The European Journal of Health Economics 2017; 18(5): 533-536. DOI: 10.1007/s10198-016-0849-3.

Modul 3:

Pardey N, **Kreis K**, Schmidt T, Stahmeyer J, Krauth C, Zeidler J:

Determinants of colorectal cancer screening in Germany: a claims data analysis. Zeitschrift für Gastroenterologie 2021; 59(7): 644-656. DOI: 10.1055/a-1480-8861.

Modul 4:

Kreis K, Plöthner M, Schmidt T, Seufert R, Schreeb K, Jahndel V, Maas S, Kuhlmann A, Zeidler J, Schramm A:

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Modul 5:

Kreis K, Horenkamp-Sonntag D, Schneider U, Zeidler J, Glaeske G, Weissbach L:

Treatment-related healthcare costs of metastatic castration-resistant prostate cancer in Germany: a claims data study. PharmacoEconomics – Open 2021; 5(2): 299-310. DOI: 10.1007/s41669-020-00219-6.

Modul 6:

Kreis K, Horenkamp-Sonntag D, Schneider U, Zeidler J, Glaeske G, Weissbach L:

Safety and survival of docetaxel and cabazitaxel in metastatic castration-resistant prostate cancer. British Journal of Urology International 2021, online first, DOI: 10.1111/bju.15542.

Modul 7:

Aumann I, **Kreis K,** Damm K, Golpon H, Welte T, Graf von der Schulenburg JM:

Treatment-related experiences and preferences of patients with lung cancer: a qualitative analysis. Health Expectations 2016; 19(6): 1226-1236. DOI: 10.1111/hex.12417.

Modul 1

Status and perspectives of claims data analyses in Germany – A systematic review

Kreis, Kristine

Neubauer, Sarah

Klora, Mike

Lange Ansgar

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Status and perspectives of claims data analyses in Germany—A systematic review

Kristine Kreis*, Sarah Neubauer, Mike Klora, Ansgar Lange, Jan Zeidler

Leibniz University Hannover, Center for Health Economics Research Hannover (CHERH), Otto-Brenner-Str. 1, 30159 Hannover, Germany

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ABSTRACT

Background: The aim of this article is to evaluate the status, development, and perspectives of German claims data analyses in the international and health political context.
Methods: We conducted a comprehensive literature search in PubMed, Scopus, and DIMDI to identify empirical and methodological articles focusing on health insurance claims data studies published between 2000 and 2014. Inclusion criteria were (1) English/German full text articles or chapters in edited books that (2) focused on the claims data of statutory health insurance funds.
Findings: In total, 435 articles were included. Over time, the number of claims data studies has increased strongly and the frequency of policy-relevant research types increased. Along with the historical improvement path of claims data in Germany, we observed a rising percentage of international publications and an increase in the average quality of publications. In contrast to the US or Canada where comprehensive databases have been established, the most common data source in this search was data from a single SHI fund, while databases were rarely used.
Conclusions: Claims data are an important source of information for healthcare stakeholders, and their use for research purposes has further increased during recent years in Germany. Despite its potential in optimising the health system, we found a lack of German comprehensive all-payer claims databases compared to the US and Canada.

1. Introduction

Claims data research has a long history in Germany and worldwide. For example, in North America, claims data were analysed since the early 1980s. The United States (US) were one of the first countries to initiate claims data analyses, for instance, by utilising drug data, for research purposes and health-related political decisions [1]. In addition, in Canada, administrative healthcare utilisation databases were used to support health policy development and the evaluation of health service delivery and quality [2]. As opposed to North America, claims data in Europe have been involved in health-related political decisions more recently. In Germany, this development started with the implementation of the Social Security Code (§ 299 SGB V) in 1988, the legal basis for statutory health insurance (SHI) funds to collect and process data as well as use them (e.g. for quality assurance) [3]. The law states that healthcare providers are committed to transmit all data on services to the SHI funds.

The development of claims data analyses can directly be linked to the historical evolution of the German healthcare system. With the introduction of the electronic health insurance card in 1995, every claim could be matched to

* Corresponding author. Tel.: +49 511 762 17998; fax: +49 511 762 5081.
E-mail addresses: kjk@cherh.de (K. Kreis), sn@cherh.de (S. Neubauer), mk@cherh.de (M. Klora), al@cherh.de (A. Lange), jz@cherh.de (J. Zeidler).

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0168-8510/

the insured person individually [4]. In 1997, additional data on drug prescriptions from pharmacies were added to the databases of health insurance funds. Since 2003, data on remedies (e.g. physiotherapy) and medical aids (e.g. wheelchairs) [5] as well as on rehabilitation [6] are available in the data warehouse of the SHI funds. Before 2004, mainly information on drugs, hospitalisation, incapacity for work, sick leave payments, and demographic of insurance holders existed in German claims data [5]. However, since 2004, all resident physicians have been obliged to transmit claims data to the responsible fund via the regional Associations of Statutory Health Insurance Physicians (ASHIP), as this information is an important part of the calculation of risk structure compensation (Risikostrukturausgleich—RSA). However, general coding guidelines did not exist then. A significant development that contributed to improving the claims data research in Germany was the introduction of the DRG-system in 2005, after which extended data for inpatient care became available (from 2007) [7]. This, in turn, increased the number of diagnoses, and some researchers observed upcoding in the DRG system [8,9]. Since the introduction of RSA and the subsequent implementation of the morbidity-oriented RSA scheme in 2009, electronic data transmission has been increasingly used and physicians were obligated to code diagnoses [10–12]. Nevertheless, claims data are a valuable source of information and comprise cross-sector contacts between the insured and the healthcare system, as compared to medical records [13].

In Germany, nationwide claims data were not available in the past due to the broad number of individual SHI funds, which claims data only consist of information for their specific insured persons. In the US, developments towards an all-payer claims database (APCD) (i.e. aggregation of claims data from different SHI funds) had already started in 2000 [14]. It was only approximately 15 years later that the German Institute of Medical Documentation and Information (DIMDI) offered access to comprehensive aggregated SHI claims data based on morbidity-oriented RSA [15]. The reason for this is that not all SHI funds operate nationwide, and have the same compositions of insured persons, because it was only since 1996 that they started to have a free choice among the individual 124 SHI funds [16,17]. In contrast, the DIMDI data pool provides comprehensive data access to all SHI funds, including individual data for 86% of the German population who are covered by the SHI [18]. Access to the DIMDI data pool is regulated by the German Social Security Code (§§ 303a to 303e SGB V) and depends on the type of institution and intended use. SHI funds, the Federal Joint Committee (G-BA), representations of patients and service providers at the national/federal level, and institutions for research and healthcare reporting are among the institutions that have legal access to these data. However, it is not open for commercial use [19]. The introduction of the DIMDI data pool is a first step towards greater transparency regarding the real-life healthcare provisions in Germany. Its advantages include providing comprehensive and thus representative evaluations for all publicly insured, analysis options for service providers, a single point of contact, and ways of calculating treatment prevalence.

Prior to the introduction of the DIMDI data pool, scientific institutions had to cooperate with the individual SHI funds to get access to data and to initiate health services-related research projects. Consequently, the SHI funds were mostly, but not always, the main option for accessing scientific analyses of claims data. This development is important because claims data are becoming an increasingly important source of information for healthcare stakeholders, researchers, and policy decision makers. As a form of secondary data, in the following we refer to claims data which belong to the category of administrative data and are primarily collected for billing and reimbursement purposes. As it is acquired directly from healthcare providers, this data source could reflect real-life healthcare provisions. This data source has previously been used, for instance, for health services research [20], epidemiology studies [21], and health economic studies [22,23], and also as an input factor for modelling studies [24]. Moreover, the American National Association of Health Data Organizations emphasised that publically available claims data are an important source of information for all stakeholders making (rational) allocation decisions [14]. As Germany is one of the largest healthcare systems in the world, not only German researchers are using this data source. The RAND study is an example for international usage of German claims data [25]. In addition, international cooperation between German and foreign researchers can be found [26,27].

Therefore, claims data analyses could contribute to increasing transparency, efficiency, and thus high performing health systems [28], and could be a source to evaluate the effects of healthcare reforms and health policy changes, such as the introduction of gate-keeping [29,30], and disease management programmes (DMPs) [31–33]. Despite its historical development, little is known about the number, quality, type, and content of claims data research. In the international context, published articles using claims databases have already been reviewed (i.e. Canadian databases [2]), but in Germany, only Hoffmann [34] evaluated the use of German claims data on statutory and private health insurance, undertaking a systematic search for relevant articles published between 1998 and 2007. The review shows an increasing trend in the number of studies dealing with claims data over time. Based on 70 identified publications, the author showed that more than 50% of all the identified articles had been published within the final two years of the observation period. However, the author focused only on medications-related claims data, and his search was limited to articles published until 2007.

In sum, claims data present a powerful source of information regarding various aspects of the healthcare system. Therefore, the aim of this study is to evaluate the number, quality, type, and content of German SHI claims data for scientific purposes, health policy development, and evaluation of health service delivery and quality by presenting the findings from a comprehensive systematic literature search covering the period from 2000 to 2014. In this study, we focus only on the SHI because statutory schemes are the major source of healthcare financing. In detail, this study reflects the development of claims data analysis over time, analyses the improvement path of claims data research in Germany, discusses the methodological and conceptual

characteristics of the included studies, and reports the standards and limitations compared to international databases, which are important to consider when working with claims data.

2. Materials and methods

2.1. Data sources and search strategy

We conducted a comprehensive systematic literature search of the electronic databases of PubMed, Scopus, and DIMDI following the methods recommended by the PRISMA guidelines [35]. All searches within titles, keywords, and abstracts covered the period from 2000 to 2014. Only articles written in German or English were included.

The following search terms were used: 'claims data?' OR 'administrative data?' OR 'routine data?' OR 'secondary data?' OR 'Abrechnungsdaten?' OR 'Routinedaten?' OR 'GKV-?Daten?' OR 'Sekundärdaten?'. These terms were combined with AND using the keywords 'German?' OR 'Deutsch?' to limit the results to German claims data. '?' was used to represent any number of characters.

The literature search of PubMed and Scopus included only English keywords and this was performed in January 2015. Further, this was limited to articles published between 2000 and 2014. To generate a broad range of publications, we also performed a further systematic search in MEDLINE, BIOSIS Previews, EMBASE (Alert), gms, and SciSearch of DIMDI in February 2015 using both English and German keywords.

2.2. Inclusion and exclusion criteria

To be included in this review, publications had to be presented as full text articles or chapters in edited books. Moreover, studies had to meet at least one of the following criteria. First, we included studies that analysed data on one or more German SHI funds, the ASHIP, and/or claims databases (using SHI data) (empirical publications). Second, we included articles that presented an overview and/or reported on conceptual or methodological approaches in German SHI claims data studies (methodological publications).

Thus, we excluded studies that did not focus on German SHI data (empirical and/or methodological), and/or were presented only as conference proceedings, abstracts, letters, editorials, commentaries, posters, oral presentations, or grey literature (e.g. periodical reports of SHI funds). We did not limit the research strategy to specific outcomes or research questions. In addition, we conducted a manual search to include studies not identified by the automated search.

2.3. Organisation of results

All titles, abstracts, and full text articles were screened independently by two researchers using the inclusion and exclusion criteria. Disagreements were settled through discussion. If the title or abstract did not provide adequate information to meet the inclusion or exclusion criteria, the full text was additionally screened.

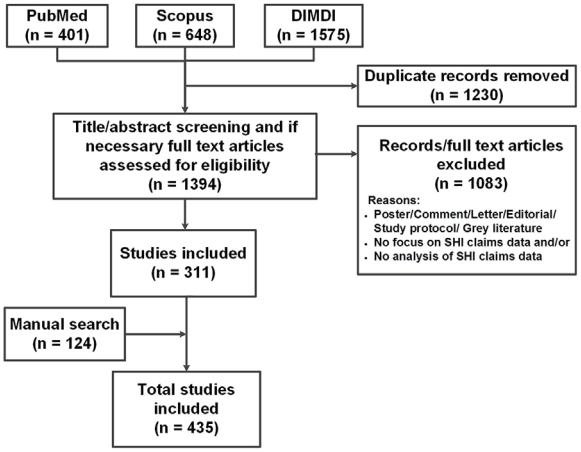

Fig. 1. Selection process of studies.

Studies meeting the inclusion criteria were clustered into three groups depending on the type of paper: empirical, methodological, and empirical–methodological. The same two researchers independently collected relevant information on each included article depending on the type of paper. The first group included papers analysing claims data on SHI funds for research purposes. The second group focused on articles describing, examining, and comparing conceptual approaches in a theoretical context without analysing the data. The third group was a mixture of the preceding groups as it contained publications that primarily addressed methodological issues based on data analysis.

The review focused on three specific areas: publication characteristics (e.g. year and journal), database characteristics (e.g. data sources) and study characteristics (e.g. research type), as well as the topic. Moreover, as German claims data have developed strongly in the past two decades, within the specific areas we also examined the trend of the selected characteristics (e.g. international publications, quality of scientific contributions) over time.

We assessed the quality of the publications based on the rank of the corresponding journal in which the article has been published. For every journal article, we extracted the indicator of the corresponding journal and publication year from the portal of the SCImago Journal & Country Rank (SJR) [36].

Relevant information on the publication characteristics was abstracted for all the included studies. As methodological publications under our definition do not analyse data, information on the study and database characteristics was only collected for empirical and empirical–methodological publications. However, the topic of empirical–methodological and methodological publications was reported.

3. Results

As illustrated in Fig. 1, the initial search returned 2624 records from the PubMed, Scopus, and DIMDI databases, including duplicate articles because of parallel searches. After removing the duplicates, the remaining 1394 records

Table 1
Publication characteristics of all the included articles ($n = 435$).

Language		
German	249	57.2%
English	186	42.8%
Publication format		
Full text publication	390	89.7%
Chapter in an edited book	45	10.3%
Journal		
Gesundheitswesen	46	11.8%
Bundesgesundheitsbl	28	7.2%
Pharmacoepidemiol Drug Saf	19	4.9%
Dtsch Med Wochenschr	14	3.6%
Dtsch Arztebl Int	12	3.1%
Z Evid Fortbild Qual Gesundhwes	11	2.8%
Z Gerontol Geriatr	11	2.8%
Gesundh ökon Qual manag	10	2.6%
Dtsch Arztebl	8	2.1%
Eur J Clin Pharmacol	8	2.1%
BMC Health Serv Res	6	1.5%
Eur J Health Econ	6	1.5%
PLoS ONE	6	1.5%
Schmerz	6	1.5%
GMS Med Inform Biom Epidemiol	5	1.3%
Health Policy	5	1.3%
Z Allg Med	5	1.3%
Z Rheumatol	5	1.3%
Others[a]	179	45.8%
Book		
Swart, Ihle, Gothe, Matusiewicz, editors (2014): Routinedaten im Gesundheitswesen	25	55.6%
Swart, Ihle, editors (2005): Routinedaten im Gesundheitswesen	17	37.8%
Others[b]	3	6.7%

[a] Journals between one and four relevant articles each.
[b] Books with one relevant article each.

were screened for eligibility. In sum, we identified 311 articles meeting the inclusion criteria. We conducted an additional manual search identifying 124 articles, mainly methodological articles derived from edited books. Thus, 435 studies were included in this review.

3.1. Publication characteristics

A total of 282 (64.8%; Supplement A 1–282) articles were categorised as empirical, 94 (21.6%; Supplement A 283–376) as methodological, and 59 (13.6%; Supplement A 377–435) as empirical–methodological. As shown in Fig. 2, during 2000–2014, the number of publications dealing with claims data on SHIs increased significantly. Almost half (47.4%) of the identified articles were published during 2012–2014. No publication was identified for the year 2001.

Table 1 summarises the publication characteristics of all the included articles. Over half of the studies (57.2%) were written in German. Almost 90% were full text publications in journals, while 10% were published in edited books. Over 90% of all the chapters in edited books addressed methodological issues.

The full text publications were published in 144 journals, ranging from 1 to 46 articles per journal. The most common journal was *Gesundheitswesen* (11.8%), followed by *Bundesgesundheitsbl* (7.2%), and *Pharmacoepidemiol Drug Saf* (4.9%). Over 90% of the included chapters were published in two single books. The time lag of publication, measured as the difference between the publication year and last year of data used, ranged from 0 to 12 years with a median of four years.

Regarding the international development of claims data research, Fig. 3 shows that up to and inclusive of 2010, between 30% and 50% of the empirical and empirical–methodological publications were written in English. However, since 2011, the number of international publications increased slightly over the years up to nearly 70%.

Moreover, in general, our analysis showed a continuous upward trend in the average SJR factor from 2000 to 2014 with a peak in 2005, that is, over time, empirical and methodological articles have been published in higher-ranked journals. This might be an indicator of an increased quality of publications based on German SHI claims data over time (Fig. 4).

3.2. Study and database characteristics

Table 2 provides an overview of the study and database characteristics of empirical and empirical–methodological publications. Between 2000 and 2014, almost half of the empirical and empirical–methodological studies analysed the prevalence/incidence of medical indications or therapies/medications. The remaining studies were almost equally distributed between the analysis of healthcare structures, cost analysis/cost comparison, and intervention and evaluation studies.

Regarding the development of research types over time, our analysis showed in general, an increased frequency of publications dealing with interventions/evaluations or healthcare structures from 2000 to 2014, although there was much variation (Fig. 5). The main topic of most intervention/evaluation studies was the assessment of the benefit or efficiency of different healthcare models, which aim at improving the treatment of patients by, for instance, promoting collaboration and coordination between different healthcare providers and sectors. Identified studies, for instance, dealt with the evaluation of DMPs such as diabetes [37–44], and asthma [45] as well as gate-keeping-centred healthcare (HzV) [29,30,46,47], and programmes of integrated care for selected diseases, such as heart diseases [48], osteoporosis [49], and schizophrenia [50]. Further topics included, for instance, adverse drug effects [51–55], drug interactions [56], as well adverse effects of medical procedures [57,58].

Studies that analysed healthcare structures, for instance, focused on regional differences in the provision [59] and utilisation [60] of healthcare services as well as their impact on healthcare quality [61,62]. Further topics included the comparison of outpatient and inpatient care [63,64] as well as health policy-related relevant discussions, for instance, concerning the centralisation of breast cancer management [65], volume–outcome-relationship in total hip replacement [66], significance of reimported pharmaceuticals [67] and the steering effects of the implementation of "aut idem" against the background of rebate contracts [68]. Moreover, the measurement of quality

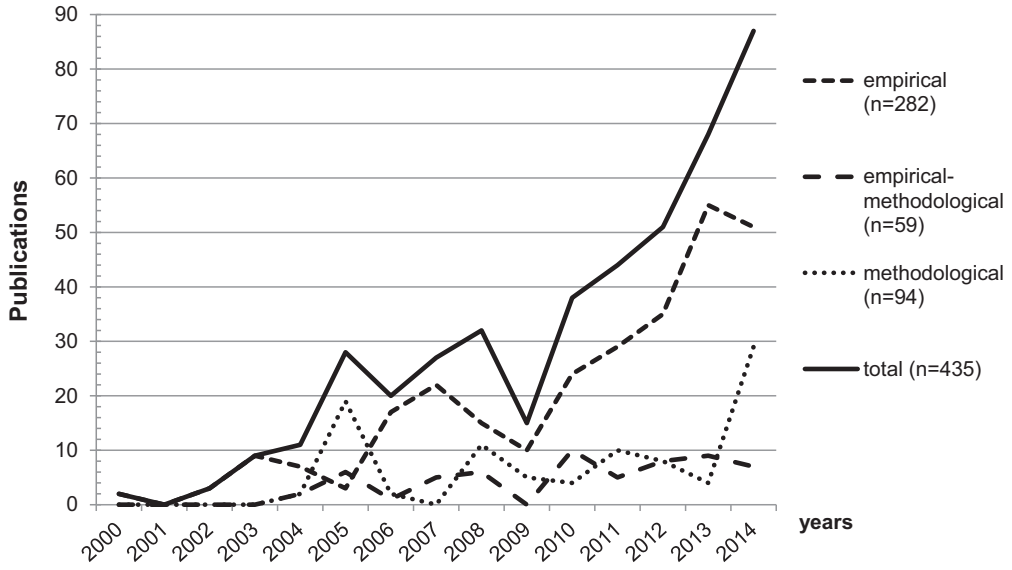

Fig. 2. Frequency of publications dealing with claims data on SHIs over time.

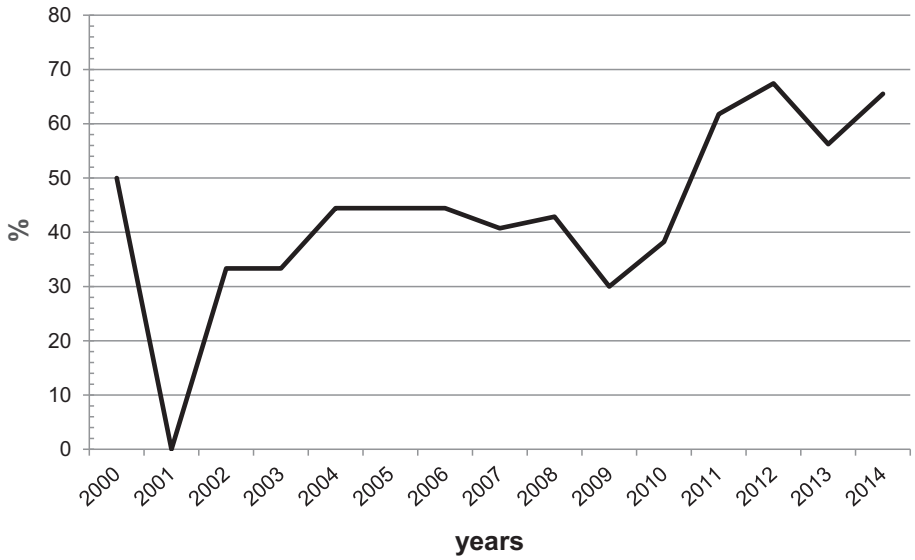

Fig. 3. Percentage of international publications over time (empirical and empirical–methodological publications; $n = 341$).
Note: We identified no publication for the year 2001.

assurance was of importance, as shown by, for instance [69–71].

In observational studies, the eligibility criteria and methods of selecting the study population should be reported to increase the transparency and replicability of the study. Approximately two-thirds of the studies used medical indications (44.0%) or therapies/medications (23.2%) to select the study population, compared with 17.3% using both indication and medication/therapy as inclusion criteria. Moreover, 15.5% used other inclusion criteria (e.g. participation in DMPs) or the whole database was analysed. Of the studies using indication, medication/therapy, or both as inclusion criteria, 75.0% reported the corresponding code (e.g. ICD code for medical indications, Anatomical Therapeutic Chemical Classification (ATC) code for medications). Since 2002, the percentage of publications reporting the corresponding code increased slightly up to nearly 90%, but also varied considerably (Supplement B). Before 2002, either no publication was identified (2001) or other inclusion criteria were used to select the study population (2000).

By far the most frequent data source combination used during 2000–2014 was an individual SHI fund (70.4%), followed by a combination of SHI funds and ASHIPs (11.1%), and several SHI funds (8.5%). According to this, only 10.0% of the studies reported analysing data on (a single or several) ASHIPs or pooled databases (e.g. the German Pharmacoepidemiological Research Database, GePaRD)

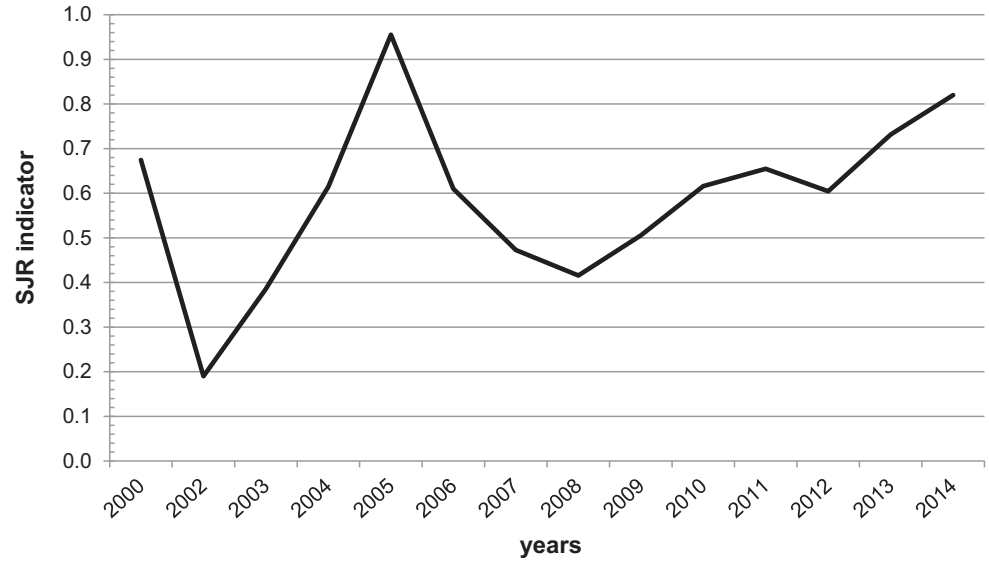

Fig. 4. Average SJR indicator over time (all journal articles with available SJR indicator; $n = 361$).
Note: For 29 out of 390 journal articles (7.4%), no SJR indicator was available.

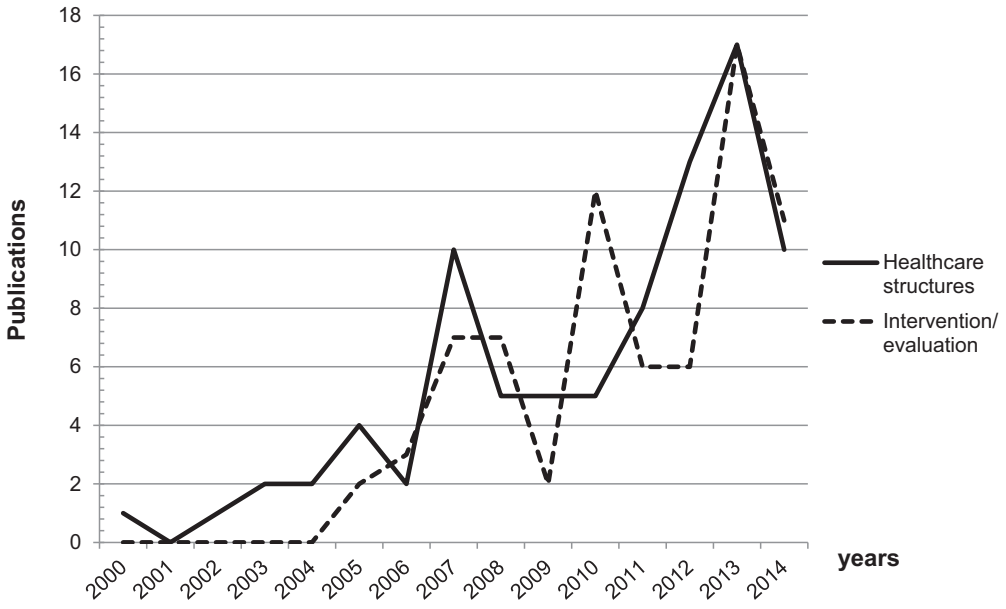

Fig. 5. Frequency of publications dealing with intervention/evaluation and healthcare structures (empirical and empirical–methodological publications; $n = 158$).
Note: Multiple choices possible (maximum of three).

[72]. While ASHIP data are similar to data on SHI funds, the former only comprise outpatient data.

According to this review, claims data from insurance funds were the first and only data source used for scientific purposes from 2000 to 2002 ($n = 5$). In 2003 and 2004, eight studies reported using a combination of claims data from single SHI funds and data on ASHIPs. Since 2005, further claims data sources were used. According to our systematic research, the first study analysing data from a pooled database (i.e. GePaRD) was published in 2008 [73].

Table 2 also presents in detail all the data sources used. As SHI funds differ in the number and composition of insured persons, the choice of data source determines the study population and hence the results. Half of all the studies analysed claims data from only two SHI funds, namely, the 'Allgemeine Ortskrankenkasse (AOK)/WidO' (28.4%) and the 'Barmer (Ersatzkasse), Barmer GEK, Gmünder Ersatzkasse' (21.5%). Additional claims data on SHIs were often derived from 'Techniker Krankenkasse' (11.1%), 'Betriebskrankenkassen' (5.0%), and 'Deutsche

Table 2
Study and database characteristics of the empirical ($n = 282$) and empirical–methodological ($n = 59$) publications.

Research type[a]		
Prevalence/incidence indication	117	23.9%
Prevalence/incidence therapy/medication	117	23.9%
Healthcare structures	85	17.4%
Cost analysis/cost comparison	79	16.1%
Intervention/evaluation	73	14.9%
Other	19	3.9%
Inclusion criteria		
Indication	150	44.0%
Medication/therapy	79	23.2%
Indication and medication/therapy	59	17.3%
Other	53	15.5%
Codes adequately reported		
Yes	216	75.0%
No	72	25.0%
Data source combination		
Single SHI fund	240	70.4%
Several SHI funds	29	8.5%
Single ASHIP	18	5.3%
Several ASHIPs	3	0.9%
Single database	12	3.5%
Several databases	1	0.3%
SHI fund and ASHIP	38	11.1%
Data source[b,c]		
Allgemeine Ortskrankenkasse (AOK)[d] [24.3 mil.]/WidO	120	28.4%
Barmer (Ersatzkasse), Barmer GEK, Gmünder Ersatzkasse[e] [8.5 mil.]	91	21.5%
Association of Statutory Health Insurance Physicians (ASHIP)	61	14.4%
Techniker Krankenkasse (TK) [9.5 mil.]	47	11.1%
Betriebskrankenkassen (BKK) [11.7 mil.]	21	5.0%
Deutsche Angestellten Krankenkasse (DAK) [6.2 mil.]	19	4.5%
German Pharmacoepidemiological Research Database (GePaRD)	11	2.6%
Kaufmännische Krankenkasse (KKH) [1.8 mil.]	7	1.7%
Innungskrankenkasse (IKK) [5.5 mil.]	5	1.2%
Handelskrankenkasse (HKK) [0.4 mil.]	4	1.0%
Other SHIs fund(s)	7	1.7%
Not further specified	30	7.1%
Standardisation		
Yes	83	24.3%
No/not reported	258	75.7%

[a] Multiple choices possible (maximum of three).
[b] Some studies used multiple data sources.
[c] In square brackets: number of members (in million) of biggest SHI funds in 2014.
[d] The Federal Association of Local Health Insurance Funds (AOK) consists of 11 individual SHI funds accounting for 28.4%.
[e] The Barmer GEK evolved from the merger between Barmer Ersatzkasse and Gmünder Ersatzkasse in January 2010.

Angestellten Krankenkasse' (4.5%). As mentioned before, other data sources such as pooled databases were of lesser importance: Only 2.6% of all the studies analysed data from GePaRD. No publication used DIMDI data, because this source has only been available since the beginning of 2014.

Claims data from SHIs were used by all empirical and empirical–methodological studies since this was an inclusion criterion for this review. Only four studies additionally analysed claims data derived from other countries. One study focused on the question if education, income, and occupational class can be used interchangeably as indicators of social inequality in social epidemiological research using German SHI data as well as Swedish census and registry data [74]. Three of the multinational studies examined psychotropic medication prevalence using data from German SHIs and additionally two (The Netherlands, the US) [75], three (Denmark, The Netherlands, the US) [76] or four countries [77]. The latter publication was the most comprehensive international study identified through this systematic search comparing the annual prevalence of antiepileptic drug prescribing across seven European healthcare databases (claims data, medical record databases, and registries) derived from Germany, Spain, Denmark, The Netherlands, and the United Kingdom [77].

Moreover, the analysis period of included claims data studies ranged from 1 to 14 years with a mean of three years. This was measured as the difference between the last year of data analysed and the first year of data plus one.

As mentioned before, the data in the majority of the studies were derived from a single SHI fund; comprehensive databases were rarely used for research purposes. For historical reasons, health insurance funds differ in the socio-economic composition of their members, and the insured sample is not generally comparable to all SHI members or the entire German population. To account for these differences, the results of claims data analysis, in the context of many research questions, need to be standardised according to the respective distributions of overall SHI members and the German population. Close to one-quarter of the publications reported that data were standardised according to the age and gender distribution of the German (SHI) population in the corresponding year (e.g. based on data from the German Federal Statistics Office) [78]. In general, the percentage of studies performing standardisation increased very slightly over the years, although it varied considerably.

Table 3
Topic of methodological ($n = 94$) and empirical–methodological ($n = 59$) publications.

Topic[a]		
Research type	43	18.0%
Data quality/validity	39	16.3%
Resource and cost domains	34	14.2%
Data transparency, protection, access, and linkage	30	12.6%
Method comparison	18	7.5%
Overview of the research field	18	7.5%
Quality of care	17	7.1%
Identification of the target population	16	6.7%
Specific statistical methods	12	5.0%
Database/sample description	6	2.5%
Guidelines	4	1.7%
Other	2	0.8%

[a] Multiple choices possible.

3.3. Topic

Apart from the study and database characteristics of the empirical and empirical–methodological studies,

the topic of articles identified as methodological (or empirical–methodological) was captured (Table 3). The most common topics (addressed in about half of the studies) were research types (18.0%), data quality/validity (16.3%), and resource and cost domains (14.2%). Articles dealing with research types described the methodological and conceptual approaches of using claims data to calculate the prevalence or incidence of medical indications or therapies/medications, perform cost analyses/cost comparisons, carry out intervention/evaluation studies, or examine healthcare structures. The most common research type described was an intervention/evaluation study. Articles broaching the issue of resource and cost domains were mainly derived from chapters in edited books and these provided an overview of the historical availability/background, legal basis, method of data transfer, data owner and access, data structure and coverage, relevant parameters, and limitations of data analysis in selected SHI domains (e.g. inpatient care).

The specific statistical methods of claims data studies were only addressed in 5.0% of all publications. Moreover, only two guidelines in different revised versions (i.e. recommendations for best practice) were found, targeting the setting up of standards for claims data analysis and reporting.

4. Discussion

Based on the 435 examined publications, this comprehensive systematic review showed that claims data were increasingly used for scientific analyses between 2000 and 2014. Moreover, the majority of the included publications were empirical. However, during the observation period, two peaks appeared because of methodological articles derived from an edited handbook on claims data in healthcare published in 2005 and a special issue on the use of secondary data published in 2008. Furthermore, more than half of all the included studies were written in German and 90.0% were published as full text articles in 144 national or international journals, indicating the widespread and interdisciplinary use of this data source.

Concerning the study characteristics of the empirical and empirical–methodological publications, the review showed that all defined research types were found, with the prevalence/incidence of medical indications or therapies/medications analysed in nearly half of all the studies. Thus, claims data analyses can be applied in a variety of research fields. Furthermore, over time the frequency of publications dealing with healthcare structures and interventions/evaluations has increased strongly showing that SHI claims data have become an increasingly important source of information. As identified publications covered, for instance, the evaluation of different healthcare models or the implementation of legal requirements, they are of importance not only for physicians, patients, and researchers, but also for healthcare stakeholders and policy decision makers. Compared to randomised controlled trials (RCTs), which are often viewed as the gold standard for providing information on treatment efficacy and safety in the clinical setting (based on relatively low patient numbers), claims data provide the opportunity to offer insights into real-life treatment based on a large number of patients. Thus, claims data can complement the results from RCTs [79].

A weakness of many of the publications identified through this research was that their reporting of methods and results was neither transparent nor standardised. First, of the studies selecting their study population through medical indications, medication/therapies, or a combination of both, one-quarter did not report the respective code completely. Studies with missing or incomplete codes cannot be replicated. Second, 30 studies (7.1%) did not provide information on the origin of their data. Hoffmann reported a comparable result [80]. Third, a further lack of transparency resulted from those studies not standardising their results with regard to the German (SHI) population. Thus, in the majority of the publications, it is not clear whether the authors consciously decided against applying standardisation or if it was not required in the context of the study design. As standardisation serves as an important method to generalise the results, it should be addressed in publications, and reasons should be mentioned in case it is not applied.

Although claims data are increasingly analysed in health services research, there is no specific standard for the systematic, meaningful, and comparable reporting of claims data in Germany. This reporting standard is, however, essential for the further development of research based on claims data because it could strengthen considerably the policy relevance, effectiveness, generalisability, and impact of these research activities. Based on the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) Statement [81], Swart and Schmitt (2014) modified the existing criteria, added new items and finally proposed the STandardised Reporting Of Secondary data Analyses (STROSA) checklist [82].

This review also suggests that claims data publications lack standardised recommendations and guidelines for the analysis of claims data covering conceptual and methodological issues. Through this systematic literature search, only two methodological articles (in different revised versions) dealing with guidelines were identified: STROSA (already discussed above) and ‘Good Practice Secondary Data Analysis’ (GPS) (for the English version of the first revision, see [83]). The updated third version of GPS [84] provides recommendations for the analysis of secondary data (defined as data from statutory health, pension, and accident insurance funds as well as disease registers). Moreover, in 2014, Neubauer et al. [12] developed guidelines on basic and methodological approaches by providing a stepwise approach to the process of conducting a claims data analysis. In the same year, a revised edited handbook on routine healthcare data [85] was published, largely dedicated to claims data from SHI funds.

As described in Section 1, in the past 20 years, German claims data have developed significantly. Due to legal requirements, data transfer to SHI funds as well as the extent and content of data provided for research purposes have further developed and predominantly improved. Along with this improvement path, we observed a rising percentage of English language publications showing an increase in the importance of healthcare research based on

German SHI claims data for the international community. We further observed an increase in the average quality of publications on SHI claims data. Note that until 2005 only few articles had been published (2000: $n = 2$; 2002: $n = 2$; 2003: $n = 8$; 2004/2005/2006: $n = 8$), attaching a high value to single publications in the computation of the mean. This might explain the peak in the year 2005: Only few articles were published in 2005 ($n = 8$), three of which were in journals with an SJR indicator between 1.5 and 3.1. Moreover, there were also slight improvements in the number of studies reporting the corresponding code of selecting their study population. All the improvements in the past 15 years might be due to strong developments in the extent and utility of German claims data.

Despite these improvements, in Germany, there is still a lack of a comprehensive APCD with a comparable level of information as that from most databases in the US or Canada. The literature search revealed that claims data from single SHI funds were by far the most important data source used. In contrast, few studies analysed claims databases such as GePaRD. Moreover, none of the studies reported using the DIMDI data pool. This result is not surprising because the DIMDI data pool was implemented only a year before the end of the search period. Until today (October 2015) approximately 30 project proposals have been submitted to DIMDI. This might be due to the strong disadvantages of this database and the fact that it is not open for commercial use. Although the DIMDI database provides representative data for all publicly insured (approximately 70 million), in general, it has a smaller extent of variables compared to data from single SHI funds. For example, there are restrictions on the demographic information (no precise entry/leaving date, no information on type of insurance, no exact date of death) and a lack of regional information (e.g. zip code) for most years. Due to strong data aggregation, some variables contain reduced information (e.g. only for a precise month or year). Moreover, information on medical aids, long-term care insurance, rehabilitation, outpatient services as well as medical procedures and operations is missing completely. One of the strongest limitations is that there are no institutional identifiers for hospitals or physicians. Thus, for all institutional researchers this database is not an option. Furthermore, a time disadvantage is that data are only available with a delay of approximately four years. In sum, all the above mentioned content- and time-related limitations of the DIMDI database restrict the possibilities of executing healthcare research substantially [12,86,87]. Nonetheless, the DIMDI data pool is undergoing continuous structural development and enhancement to extend its importance in claims data analyses.

Claims data from single SHI funds maintain a greater extent of variables and are available without long delays (approximately nine months) [12]. However, so far, access is only possible with good relations to one of several SHI funds, which does not provide equal chances to all researchers. In comparison, in the US and Canada, a considerable number of claims databases are available on request for research purposes, for instance, those from American Health Maintenance Organisations (HMOs; e.g. Kaiser Permanente), the US Government (Medicaid, Medicare, Veterans Affairs) or Canadian Provinces (e.g. Saskatchewan) [88].

As all the claims data mentioned above are primarily recorded for accounting purposes and not for research, they face specific limitations, which have to be addressed in every scientific study based on this data source to avoid misinterpretation [89]. Therefore, the typical limitations of German claims data from health insurance funds are discussed in the following section and compared to claims data derived from other countries to demonstrate the basic restrictions of German and foreign claims data studies (Supplement C).

A main difference between German and US/Canadian claims data(bases) lies in their lengths of follow-back and follow-up periods. While German SHI funds are only allowed to store claims data for research purposes, at least with the option to track back until a period of five years, US and Canadian databases generally have longer follow-back periods, because they started electronic data collection in the early 1980s [1]. Despite its long history in electronic data collection, in HMO claims databases, follow-up periods might be very short. As insurance status is often associated with employment status, job changes can cause insurance switches [90].

A further common limitation of retrospective analyses with German claims data is that detailed clinical input data are unavailable (e.g. disease activity, severity grades of a disease, symptom scores, clinical test results, quality of life data) [20,91]. This restriction limits the ability of analyses to focus on clinical outcomes (e.g. in cost-effectiveness analyses). Additionally, the reason for or impact of a withdrawal, discontinuation, or dose increase in medication studies cannot be assessed directly because of missing clinical data. Assumptions and algorithms enabling indirect inferences must thus be defined to solve this problem. In contrast, research database centres maintained by HMOs in the US are able to overcome some of these shortcomings. HMOs include not only claims data, but mainly also electronic medical records (EMRs) and registries, which can be linked to claims data. Information from EMRs can improve healthcare research by adding patient assessments and procedures, like clinical notes, diagnoses, clinician orders, test results as well as information on race, ethnicity, and health behaviours (increasingly available). Moreover, HMOs have direct access to outpatient and inpatient paper medical records prior to the electronic age. Apart from that, depending on the type of registry (e.g. tumour, diabetes, or cardiovascular registries), further information on subjects including complications, therapeutic interventions, laboratory, medications, adherence, and patient-reported outcomes can be obtained. HMO research centres additionally have the ability to contact insured persons, thus encouraging clinical trials, patient interviews, or surveys [92].

An inherent systematic limitation affects the documentation of prescribed doses in German medication data. In contrast to US and Canadian claims data where the 'days of supply' for every prescription are broadly documented to enable individual precise calculations of the medication possession ratio, German claims data contain no information about the dosage scheme intended by the

physician. Moreover, as opposed to most HMOs, German claims data do not provide information on co-payment amounts [92,93]. Nonetheless, claims data do not provide information about the medications administered during an inpatient episode, neither in Germany nor in the US or Canada [94]. In Germany, hospitals receive no additional payments on top of the respective diagnosis-related group to supply medication [95]. Therefore, studies focusing on medication treatment patterns could be limited by this lack of information.

Generally, when working with German claims data the validity of diagnoses and procedures has to be verified to avoid over-, under-, or misclassification because of the character of secondary data. The validity of every variable stored in claims data depends on the quality of the information transferred by care providers. Therefore, in every claims data analysis, a comprehensive validation process that adheres to the official guidelines is recommended to ensure the accuracy of the data source in the context of the particular research question [83,96]. This also applies to US and Canadian claims databases, but as an opportunity to validate diagnosis data HMOs generally offer the advantage of a fairly easy access to complete electronic or paper primary inpatient and outpatient medical records [97,98].

Moreover, the generalisability of the results from analyses based on German claims data from a single or few SHIs is limited because each SHI fund differs in terms of the group of insured individuals for historical reasons (e.g. age and gender distribution or social status) [99]. Therefore, the use of generalisation methods to address this limitation is recommended if the research question requires a standardisation. The challenge that data is unrepresentative of the target population (e.g. the entire population) also applies to private (HMOs) and public (Medicaid, Medicare) US claims databases as they only provide coverage for selected population groups [92,98]. However, as the healthcare programme of Canada covers almost the entire population, regardless of age or socioeconomic status, Canadian databases provide a nearly comprehensive picture of its provinces [93].

In the context of the diversified healthcare system in Germany, a further limitation is that claims data only contain information on treatment financed directly by the SHI [20]. Information about the costs and treatment patterns of the other institutions involved in the treatment process are unavailable. This limitation affects rehabilitation financed by the statutory pension insurance, for example, which is responsible for financing the inpatient or outpatient rehabilitation of the patients in employment [100]. Therefore, the informative value of German claims data is limited in all the cases when treatment is not financed by the SHI. In contrast, in the US, there are developments towards APCDs combining data from all payers in a state, public and private, thus offering opportunities for provider-independent state-wide analysis [14]. According to the Agency for Healthcare Research and Quality (AHRQ), by the end of 2014, 18 US states had enacted APCDs [101]. The Healthcare Cost and Utilization Project (HCUP) sponsored by the AHRQ is a family of healthcare all-payer databases and has the largest collection of all-payer inpatient data in the US. It combines and transforms claims data from HCUP partner states (47 states provide inpatient data, 34 states ambulatory data, and 32 states emergency department data) into uniform research databases, beginning in 1988.

In sum, the strengths of the US and Canadian claims databases compared to German claims data lies in their population size, lengths of follow-back and follow-up, amount of variables, and the ability to link to internal (medical record databases, registries) and external data. However, independent of the data source selected, broad expertise regarding the strengths and weaknesses of claims data is required to perform high-quality research based on this data source.

The future development of claims data research in Germany is intimately connected with the general chances and risks of digitalisation in healthcare systems. The technological revolution driven by big data is the main source for the transformation of information infrastructures in healthcare systems worldwide [102]. Big data technologies have enabled health services-related research to analyse data that were in the past not analysable due to their volume, velocity, and variety. This technological and social trend implicates new, powerful options in claims data analyses. Chances are characterised by the opportunity to systematically produce valuable information regarding treatment patterns, under- and overtreatment in specific diseases or the correlation between risk factors and the development of diseases. This could lead to increasing efficiency of healthcare systems by analysing real-world evidence, which would assist health policy makers. Important requirements to achieve this objective were identified in our literature review. First, our results have shown that equal chances to all researchers for access to claims data have to be implemented. The establishment of the DIMDI data pool is an important step in this direction. The data of all SHI funds in Germany is merged in this official database and access is possible for a broad number of institutions. However, the specific limitations of the DIMDI data pool have to be overcome to provide a comprehensive all-payer database, which is broadly accepted and used by researchers.

Second, other important data sources (e.g. pension fund data, laboratory results, regional data) have to be linked to SHI fund claims data to close the existing information gap. Similar to US claims data research, the information from EMR and registries could provide a deeper insight into real-life treatment and patient-relevant assessments, which could improve healthcare research. Therefore, data linkage will become of increasing relevance in claims data-based research in Germany. A first step in this direction is taken by the German National Cohort, which is currently implementing a comprehensive longitudinal healthcare database with the aim of examining the reasons for the development of chronic diseases in Germany in the future. This database will not only combine claims data from public and private social insurance agencies (e.g. health insurance funds, pension insurance) with information from different registries (e.g. mortality and cancer registries), but also include information from interviews, questionnaires, and physical examinations carried out

with participants. Further information contains geocoded environmental data [103].

Third, our study has shown that methodological guidelines and data validation algorithms have to be advanced. A sophisticated methodological framework considering the specific advantages and limitations of German claims data is an essential requirement to further increase the international acceptance and quality of claims data analyses. Data linkage and the improvement of methodological standards could increase the acceptance of claims data-based results in policy decision making and early benefit assessment.

Fourth, access to claims data has to be embedded in modern data protection law. Rising concerns regarding the permanent surveillance of the population describe a main risk factor in the age of big data. Health data includes particularly sensitive information, which has to be protected comprehensively by data protection regulations. On the other hand, protection of the right of informational self-determination of the individual has to be balanced with the right of freedom of scientific research because both are components of the German constitution. Current policy reforms of the European Union regarding data protection regulations of their member states should respect the importance to be considerate of these legal interests. Otherwise, the potential of this valuable data source will not be used entirely to optimise healthcare.

Finally, this review has some limitations as well. The selection of keywords used to establish the research strategy was challenging because of the lack of uniformity in the English translation and use of the German term for claims data from SHIs (*GKV-Routinedaten*). Of the wide range of terms found in the literature, we restricted our analyses to the most common keywords of 'claims data', 'administrative data', 'routine data', and 'secondary data'. Despite this wide search strategy, it cannot be ruled out that some relevant publications might have been omitted. However, with the objective of providing a comprehensive overview, we performed the systematic search in three databases and additionally conducted a manual search. Moreover, full text articles as well as chapters in edited books were included, resulting in 435 publications.

Another limitation of this review is that we recorded and calculated the time lag of publication based on full years, because in some journals the exact publication date was unavailable. Since the results may be biased, to show the central tendency of the values, we decided to quote the median instead of the mean, because the former is often more robust and unaffected by any single value. Another limitation concerning the development of the quality of journal articles over time is that for some publications, SJR indicators were not available. This might result in a slight distortion of the figure. The increase in the average SJR indicator might also possibly be due to an overall increase in SJR indicators instead of exclusively being attributed to articles published in higher-ranked journals. In sum, to our knowledge this is the first review examining the use of German claims data and analysing certain characteristics of the included publications between 2000 and 2014.

5. Conclusions

The current study focused on the status, development, and perspectives of German claims data for research purposes. From 2000 to 2014, we found a strong increase in the number of empirical and methodological publications dealing with German claims data. These studies provide an important source of information for healthcare stakeholders. However, we identified a lack of APCDs. A first step in the direction of comprehensive databases is taken by the implementation of the DIMDI database, but it comprises only information from SHI funds and has many limitations, which restrict significantly its use. Therefore, at the present, claims data from individual SHI funds are still the main option for access.

To ensure a positive future development of claims data research in Germany, equal chances for access to all researchers have to be implemented and methodological standards have to be improved. Furthermore, based on the role model of the US H-CUP, German claims data have to move in the direction of combining data from all, public and private payers, with equal chances of access for all researchers. Only then could this important data source develop its full potential to assist decision makers in creating high-performing healthcare systems.

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Conflict of interest statement

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.healthpol.2016.01.007.

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Modul 2

Access, use, and challenges of claims data analyses in Germany

Neubauer, Sarah

Kreis, Kristine

Klora, Mike

Zeidler, Jan

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Access, use, and challenges of claims data analyses in Germany

Neubauer, Sarah[1]

Kreis, Kristine[1]

Klora, Mike [1]

Zeidler, Jan[1]

[1] Leibniz Universität Hannover, Center for Health Economics Research Hannover (CHERH), Hannover, Germany

Corresponding author:

Sarah Neubauer

Gottfried Wilhelm Leibniz Universität Hannover

Center for Health Economics Research Hannover (CHERH)

Otto-Brenner-Str. 1

D-30159 Hannover

Tel: +49 (0) 511 762 14242

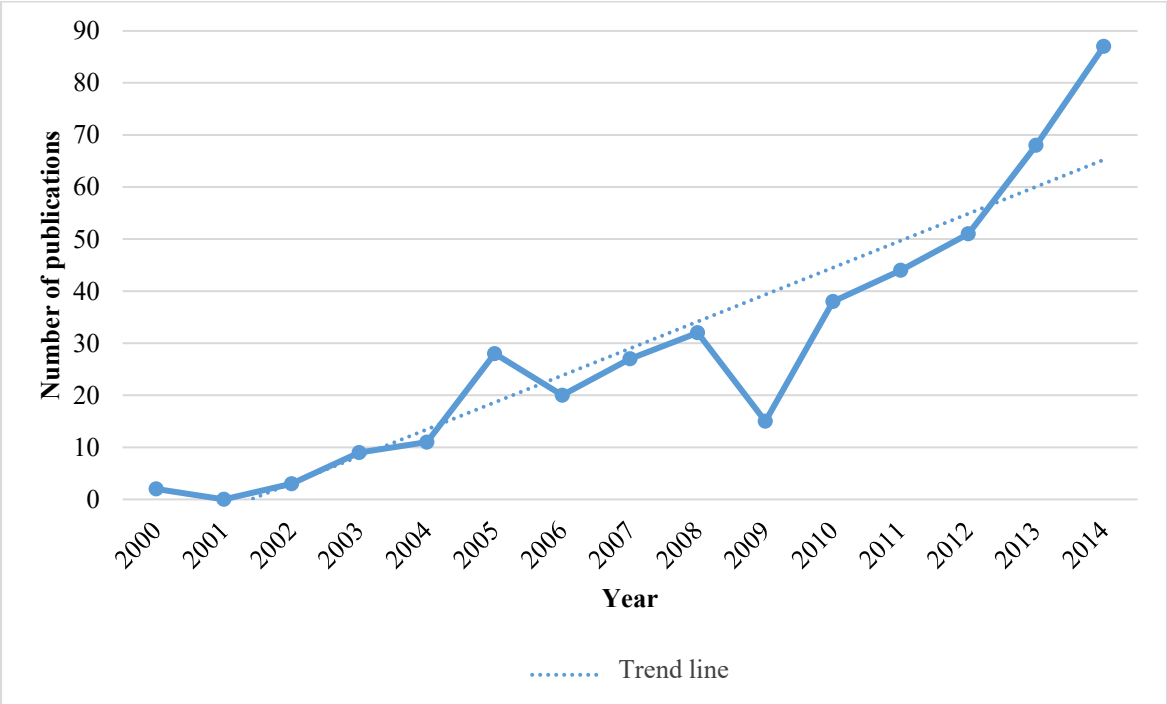
Fax: +49 (0) 511 762 5081

Mail: sn@cherh.de

Worldwide, information infrastructures have developed rapidly towards big data over the past few years. The evolution of powerful computers has made it possible to improve the data exchange process within the healthcare system [1]. This technological trend has also triggered new and powerful possibilities in health service related research (e.g., claims data analyses), because it now allows the analysis of more complex and larger data sets.

In this editorial, we focus on claims data analyses, because they are an important and powerful source of information to support the decision-making processes of healthcare stakeholders, researchers, and policy makers regarding various aspects of the healthcare system. A few years ago, the statutory health insurance (SHI) companies in Germany made their data available for research purposes, because they realized the comprehensive potential of these data for both rational allocation of resources and for health services research to optimize healthcare provisions. The German government increasingly supports and funds claims data research, thus confirming the growing relevance of such research. Furthermore, recently, this research field developed a sophisticated methodological framework for comprehensively analyzing and interpreting the data in the context of various research questions. The significant increase in the number of claims data studies (and frequency of policy-relevant research) confirms this trend [2, 3] (see Fig. 1).

Fig. 1 Number of publications dealing with German claims data on SHIs over time



Source: Based on Kreis et al. 2016.

Claims data studies mainly use the information stored in data warehouses of the SHI. As a form of administrative data, primarily collected for billing and reimbursement purposes, claims data belong to the category of secondary data. These data are transmitted directly from healthcare providers to

SHI funds, which include information on (all) cross-sector contacts between the insured and the healthcare system in their database. Compared with clinical trials, claims data analyses could reflect real-life healthcare provisions. Further advantages of this data source are the cost-efficient generation of data and a typically large study population compared with randomized controlled trials, which researchers often view as the gold standard for providing information on treatment efficacy and safety in a clinical setting. These data also help include groups that are typically more difficult to observe through primary data collection (e.g. children, severely ill individuals, dementia patients, or residents of nursing homes).

Over the last 15 years, almost one-third of the published claims data studies have focused on health economics [2]. Furthermore, due to its advantages, researchers have previously used this data source for health services research on treatment patterns, under- and overtreatment of specific diseases, epidemiology studies, and as an input factor for modeling studies [4]. The aim of all these studies was to increase transparency and efficiency of the healthcare system by analyzing real-world evidence.

Moreover, the latest national call for proposals confirms that there is both an increase in the importance of and positive development in claims data research. The German government and the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) established the 'Innovation Fund', which will provide funding of 75 million euros per year for projects dealing with health service research over a period of 4 years. In such projects, it is recommended to involve at least one health insurance fund. A recently published report stated that the ‘use and combination of administrative data to improve care’ was the second most popular subject field for project proposals [5]. Furthermore, the current policy reforms of the European Union regarding data protection regulations for member states have identified the potential of this valuable data source and, in contrast to commercial use, do not restrict the requirements for research purposes.

However, despite these advantages, SHI claims data also have specific limitations [6, 7] based on the specific purposes (i.e., billing and reimbursement) of collecting the data. A common restriction of retrospective analyses with German claims data is that detailed clinical data (e.g., disease activity, severity grades of a disease, symptom scores, clinical test results, quality of life data, and documentation of prescribed doses, i.e., ‘days of supply’) are mostly unavailable.

Moreover, one of the biggest challenges for healthcare scientists in Germany is to obtain equal access to claims data for research purposes. For historical reasons, SHI funds differ in the quantity and composition of their members (e.g., socio-economic composition of the insured persons), and not all SHI funds operate nationwide, reducing the comparability of the studied population across SHI members or even the entire German population. Therefore, the choice of the data source could

influence the study population and validity of the results. Moreover, access is often only possible with good relations with a health insurance fund, which does not provide equal chances to all researchers. Therefore, to provide equal access opportunities and increase the power and quality of data analyses, many scientific associations in Germany have requested to merge the data of all health insurance funds into one database.

As a first important step towards a merged database, the German Institute of Medical Documentation and Information (DIMDI) implemented a nationwide data pool in 2014. Based on the financial allocation mechanisms for social insurance funds (morbidity-oriented risk structure compensation scheme, hereinafter Morbi-RSA), which should decrease selection risk, this official database includes aggregated healthcare data from SHI funds. According to the German Social Security Code (§§303a to 303e SGB V), only institutions such as health insurance funds, the Federal Joint Committee G-BA, representations of patients, and service providers, as well as institutions for research and healthcare reporting, may use these aggregated data from the DIMDI data pool [8]. In contrast, single health insurance funds provide data at the individual level. Nevertheless, these are not open for commercial use. As the DIMDI data pool includes individual data for approximately 70.65 million German individuals, researchers could use the data for calculating treatment prevalence and performing representative evaluation studies for the publicly insured. Further advantages include analysis options for service providers, low user fees, central point of contact offered by the data pool, and the validation by the prior Morbi-RSA verification.

Thus far, the DIMDI Institute has received approximately 53 applications; of these, the institute granted delivery of aggregated results to 18 applications, and 29 are currently undergoing the review process. The institute rejected or researchers withdrew four applications for technical reasons. As of June 2016, two publications based on the DIMDI data pool have been published [9, 10].

Despite these improvements, in Germany, the data pool still has limitations. This concerns, for example, the limited amount of variables compared with the variables from single SHI funds. Additionally, the original data transmitted from the SHI funds for the Morbi-RSA do not include specific demographic information, such as insurance start and end (entry/leave) date, type of insurance, and date of death. Some of these are strongly aggregated data, so that some variables contain reduced information (e.g., only for a month or year). Moreover, there are restrictions on information on regional codes (e.g., place of residence and zip code), medical aids, rehabilitation, long-term care insurance, outpatient services, and medical procedures and operations. Furthermore, there are no institutional identifiers for hospitals or physicians. The data are available with a delay of approximately 4 years, and the processing time of project proposals is long and unpredictable.

We can conclude that the possibilities to conduct health services research using the DIMDI database are limited. However, the DIMDI data pool is undergoing continuous structural development, and its enhancement can further extend its importance in claims data analyses [2].

In the US or Canada, where claims data research has a longer history, a significant number of claims databases are accessible to scientists (i.e., those from the American Health Maintenance Organisations, the US Government, or Canadian Provinces) [11]. Moreover, certain research centers even provide free assistance to scientists in obtaining claims data (e.g., by assisting in preparation of requests), as well as in analyzing data sources (e.g., by conducting workshops and offering technical support) [12].

Apart from better access opportunities, the advantages of US and Canadian databases when compared with German claims data include larger population size, longer follow-back and follow-up periods, larger amount of variables, and the possibility to link claims data to internal and external data sources. Furthermore, although data from German SHIs and the DIMDI data pool include information solely on treatments financed directly by the SHI, in the US, all payer claims databases are available, including data derived from public and private payers [13, 14].

To extend the usability of claims data, we need equal chances for all researchers. This means less restriction in accessing claims data for all researchers and other healthcare stakeholders, longer observation period (extension of lengths of follow-back and follow-up), and higher amount of useful information for research purposes. Furthermore, we recommend that the data be available nationwide and the amount of variables be extended for the DIMDI data pool. The establishment of the DIMDI data pool is an important step in the direction of a comprehensive data source and increased transparency. Recently, both the importance and capability of linking claims data to internal data (medical record databases and registries) and external data have increased. However, the possibility of data linkage with other important data sources (e.g., pension fund data, laboratory results, and regional data) is also necessary to close the existing information gap.

As long as the government does not enforce development towards a comprehensive all-payer database, with less limitations and accessibility to researchers, data access in Germany will be inferior to that in most other European (and OECD) countries.

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Modul 3

Determinants of colorectal cancer screening in Germany: a claims data analysis

Pardey, Nicolas

Kreis, Kristine

Schmidt, Torben

Stahmeyer, Jona

Krauth, Christian

Zeidler, Jan

Zeitschrift für Gastroenterologie; 59(7): 644-656.

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2021

Modul 4

Healthcare costs associated with breast cancer in Germany: a claims data analysis

Kreis, Kristine

Plöthner, Marika

Schmidt, Torben

Seufert, Richard

Schreeb, Katharina

Jahndel, Veronika

Maas, Sylke

Kuhlmann, Alexander

Zeidler, Jan

Schramm, Anja

The European Journal of Health Economics; 21(3): 451-464.

DOI: 10.1007/s10198-019-01148-w.

2020

Healthcare costs associated with breast cancer in Germany: A claims data analysis

Kreis, Kristine[1]
Plöthner, Marika[1]
Schmidt, Torben[1]
Seufert, Richard[2]
Schreeb, Katharina[3]
Jahndel, Veronika[3]
Maas, Sylke[3]
Kuhlmann, Alexander[1]
Zeidler, Jan[1]
Schramm, Anja[2]

[1] Leibniz Universität Hannover, Center for Health Economics Research Hannover (CHERH), Hannover, Germany

[2] AOK Bayern - Die Gesundheitskasse, DLZ Versorgungsmanagement, Regensburg, Germany

[3] BioNTech AG, Mainz, Germany

Corresponding author:

Kristine Kreis

Gottfried Wilhelm Leibniz Universität Hannover
Center for Health Economics Research Hannover (CHERH)
Otto-Brenner-Straße 7
30159 Hannover

Tel: +49 511 762-17998
Fax: +49 511 762-5081
Email: kjk@cherh.de

Abstract

Purpose This study estimates the healthcare costs associated with breast cancer (BC) for different treatment phases (initial, intermediate, terminal) in Germany from the payer's perspective.

Methods The analysis uses claims data from the AOK Bayern covering 2011-2014 for continuously insured BC patients identified through inpatient and outpatient diagnoses. We calculate the healthcare costs attributable to BC using a control group design comparing the target population to a 1:2 matched control group adjusted for age, gender, and comorbidities. For incident and prevalent BC cases, we calculate age-standardized phase-specific incremental costs stratified by cost domain.

Results The initial, intermediate, and terminal phases comprise 3,841, 28,315, and 1,767 BC cases, respectively. BC-related incremental costs follow a u-shaped curve, with costs highest near diagnosis and death, and lower in between. With average costs of €33,237 per incident and €28,211 per prevalent case in the remaining 11 months before death, the highest BC-related incremental healthcare costs can be found in the terminal phase. In the initial phase, there were mean incremental costs of €21,455 the first 11 months after diagnosis. In the intermediate phase, incremental costs totaled €2,851 per incident and €2,387 per prevalent case per year. Healthcare costs decreased with age in most phases. The cost drivers depend on the treatment phase, with cytostatic drugs and inpatient treatment showing the highest economic impact in most phases.

Conclusion The study concludes that BC care costs impose a relevant economic burden on statutory health insurance and vary substantially depending on the treatment phase.

Keywords Breast cancer, Disease cost, Claims data, Joinpoint, Germany

Introduction

Breast cancer (BC) is the world's second most common type of cancer and the most frequent in women. It represents 12% of all new cancer cases and 25% of all cancers in women [1]. In 2014, the age-standardized rate of incidence for women was 114.6 per 100,000 people in Germany, representing 69,220 new BC cases. Between 1980 and 2004, the incidence rate increased by about 50% [2]. Moreover, 559,900 German women (10-year prevalence) were living with a BC diagnosis in 2014, and 17,670 of them died from the disease. However, the relative 5-year survival rate increased from 69% in 1980 to 81% in 2004 [3]. This improvement resulted from better treatment options (e.g., higher radiation doses [4]), new drug interventions [5], and earlier diagnoses (e.g., through mammography screening [6]).

The treatment and prognosis of BC are influenced by factors such as age, cancer stage, and tumor characteristics (status of estrogen receptor, progesterone receptor, human epidermal growth receptor 2, and the histologic grade) [7]. The disease stage (diseases stage 0-IV) influences disease-specific costs [8], which range from $60,637 (stage 0) to $134,682 (stage IV) per patient in the initial 12 months postdiagnosis. In the European Union, cancer incurred €126 billion of costs in 2009, €15 billion of which were attributable to BC. Accounting for 12% of total cancer costs, BC represents the second highest economic cancer burden [9]. Germany's costs of illness (COI) for BC were estimated at around 2169 million euros in 2015 [10]. Germany has Europe's highest BC healthcare costs per person [9].

Cost analyses are important for political decision-making concerning prioritization and allocation [11]. Economic studies on BC cost patterns [12] include few analyses of BC-attributable health expenditures in Germany [13,14]. Only two studies have reported the COI of BC using claims data from a statutory health insurance (SHI) in Germany [14,15] of which one was only published as a poster abstract [15]. The second study is based on highly aggregated data sets referring to the year 1999 and covering inpatient spending, medication costs and sickness benefits, thus neglecting further cost domains (i.e., outpatient care, remedies/medical aids, rehabilitation). Moreover, stratification by cost category did not take place [14]. Claims data from SHIs are well suited for cost analyses since they are routinely collected for billing and reimbursement. However, a detailed analysis of overall direct disease-related costs that identifies the cost-driving factors is required, because the extant studies differ substantially in their cost-calculation methods and cost domains considered.

Moreover, unlike US data [16], the German data have not been analyzed for cost patterns through a clinically meaningful phase-of-care approach in relation to diagnosis and death. The phases used by US studies are commonly divided into initial, intermediate and terminal care, and phase duration can be determined theoretically or empirically. This approach takes into account that costs may differ strongly across phases according to the need for treatment and healthcare costs are

expected to be highest near diagnosis and death [16]. This is the first study that estimates the BC-attributable health expenditures in Germany according to empirically determined treatment phases.

Methods

Data source and study population

AOK Bayern provided data on all services reimbursed. Its sickness fund covered almost 4.3 million insured individuals in 2011 [17]. The analysis includes costs for inpatient and outpatient care, medication/cytostatic drugs, remedies and medical aids, rehabilitation, sick leave, and travel expenses. Patient identification was based on the ICD-10-GM system with ICD codes C50.0 to C50.9. Inclusion in the study population required documentation for at least one inpatient diagnosis or secured outpatient BC diagnosis in 2012. For exclusive identification by outpatient diagnosis, a second secured outpatient diagnosis was required within the following three quarters (i.e., occurring in 2013). We used 2011 to differentiate between incident and prevalent cases. Patients were defined as "incident" if no C50 diagnosis (outpatient/inpatient) was documented in 2011. All sample patients had to be continuously insured from 2011 to 2014 or until death (whichever came first). Male patients and patients under 18 were excluded, as both groups require special treatment.

Study design

We calculated BC-attributable costs using a control group design with pairwise direct matching. We compared BC patients to a 1:2 matched control group adjusted for gender, age and comorbidities. Using the Elixhauser comorbidity score [18], we calculated comorbidities for both the intervention and control groups in 2011 on the basis of at least one inpatient/secured outpatient diagnosis. To avoid over-adjustment, BC diagnosis was excluded in the count. For matching, we used the nearest neighbor approach, allowing for a caliper of five years/points. The control sample consisted of females continuously insured by AOK Bayern from 2011 to 2014 without a BC diagnosis. Replacement of control group members was only allowed once.

Follow-up started for BC cases identified by hospitalization from the beginning of the month of the inpatient diagnosis. In German claims data, outpatient diagnoses are reported on a quarterly basis. Thus, within the quarter of each BC diagnosis, we defined the beginning of the month in which the first service date (according to the Uniform Valuation Scheme [EBM]) was documented as the approximate date of the index event. Follow-up ended in the latest 2 years following the index event or in the month of death, whichever came first. We ensured that all BC cases classified as "non-deceased" had not died within 6 months following the end of the observation. For controls, we considered follow-up periods analogously to the BC cases.

Following US studies [16,19-25], we divided the time after BC diagnosis into clinically relevant treatment phases: (1) initial phase, comprising the primary course of therapy (e.g., surgery, chemotherapy, radiation); (2) intermediate phase, including active surveillance and ongoing medication to prevent recurrence (e.g., hormone blockade) or treatment complications derived from the initial course of therapy; and (3) terminal phase, comprising (palliative) services provided in the last months before death. Lacking a scientific consensus on the duration of BC treatment phases, we first calculated the monthly BC-attributable costs and examined the average cost patterns from diagnosis to death. Using Trend Analysis Software from the National Cancer Institute [26], we applied joinpoint regression [22,27] to determine the length of the initial and terminal phase by assessing the points at which statistically significant changes occur in the cost slope. According to joinpoint regression analysis, there must be at least 12-16 data points (months) to receive two joinpoints. As the observation period's maximum was 24 months and BC cases showed different characteristics (e.g., incident vs. prevalent, alive vs. deceased), not all individuals underwent all phases of care. Therefore, to determine the length of the initial phase, we examined average cost patterns of newly diagnosed BC cases that were observable for 18-24 months. Similarly, definition of terminal phase length was based on prevalent BC cases that had died during the observation period and were observable for 18-24 months preceding death.

After determination of phase care length, individuals were assigned to phases of care. Following the literature [22,24], the observation period for BC cases who died was first assigned to the terminal phase of care. Any remaining time under observation, and all follow-up time for BC survivors, was then transferred to the initial treatment phase, and the most recent was assigned to the intermediate phase. In the initial and terminal phases, patients were excluded if they were not observable for the period determined by the joinpoint regression analysis. To be included in the intermediate phase, BC cases had to be observable for at least 12 months (costs are on an annual basis).

Calculation and presentation of healthcare costs

Copayments and out-of-pocket payments were not considered because costs were analyzed from the SHI perspective. Healthcare costs in euro were extracted from the database for both BC cases and controls. For each inpatient/rehabilitation stay and sick leave period, costs were divided by the length of stay/duration and calculated according to the start and end of each phase. Unfortunately, only annual outpatient care costs were available. To obtain monthly values, outpatient care costs were divided by the months under observation. To provide a better overview, the costs of cytostatic drugs and any remaining medication are reported separately. These medication costs include only

prescriptions for outpatient care. The costs of drugs administered during inpatient episodes are part of total inpatient costs.

By comparing the cost differences between BC cases and controls, we could calculate the BC-attributable costs differentiated according to care phase. To adjust for age differences between SHIs, we standardized costs according to the 5-year-age-structure of compulsory insured women in Germany for 2011 using data from the Federal Ministry of Health [17]. As the cases were few, we aggregated the costs of BC cases younger than 45 (initial and intermediate phase) and younger than 50 (terminal phase) before standardization. Sensitivity analyses were also conducted, calculating standardized healthcare costs by treatment type for the initial and terminal phase of care. Patient allocation to treatment types was based on clinical knowledge defining codes for surgery, radiotherapy and chemotherapy (see Appendix 1). Inclusion required at least one healthcare service. Data management and statistical analyses were performed with SAS 9.4.

Results

Study population

The inclusion criteria produced 36,033 BC patients (see Fig. 1). Of these, 32,058 were matched to 64,116 controls (1:2) and followed for a maximum of 2 years. After the matching, no significant differences were observed between BC cases and the controls concerning gender, age, or comorbidity score (see Table 1). Overall, 13% of BC cases were identified as incident, and 6% died within the follow-up period.

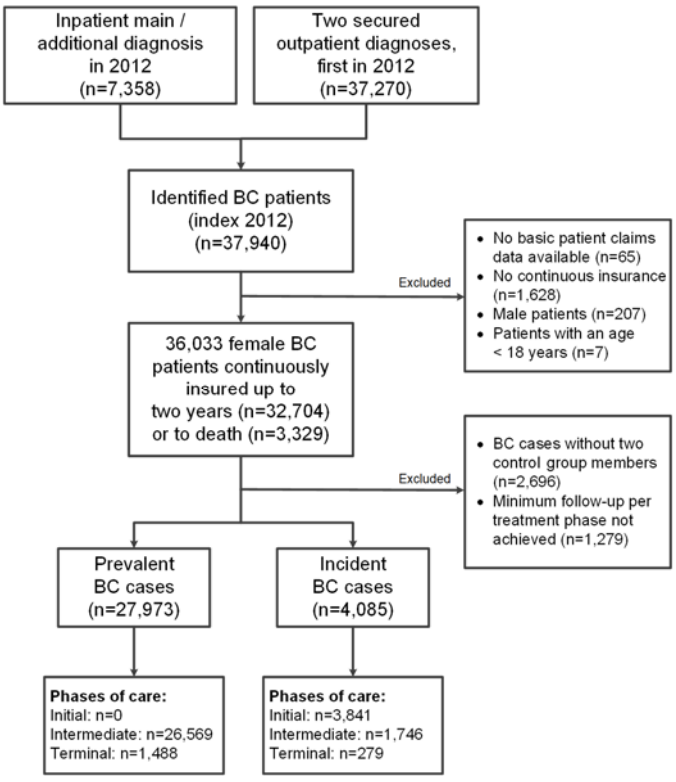

Fig. 1 Cohort selection

Through the joinpoint regression analysis, the initial treatment phase was defined as the month of diagnosis and the following 10 months. The terminal phase comprised the last 11 months of life, and the intermediate phase comprised all months between the initial and terminal phases. In the initial and terminal phase, the joinpoint regression analysis identified the points at which BC-related costs decreased significantly. BC cases were included in one (94%) or two (6%) phases of care. Survivors were followed for 23 months on average (SD = 1) and deceased individuals 17 months (SD = 4) on average.

Table 1 Demographic characteristics after matching

Group	Gender: female		Age		Elixhauser comorbidity score		n
	%	p[a]	Mean [SD]	p[b]	Mean [SD]	p[b]	
BC cases	100	1	67.12 [12.17]	0.99	5.93 [8.67]	0.99	32058
Controls	100		67.13 [12.16]		5.93 [8.67]		64116

SD standard deviation

[a] Ch-square test

[b] U test following Mann and Whitney

Concerning demographic characteristics, Table 2 shows that age at phase onset averaged around 67 in the initial phase, 67 (incident cases) versus 68 years (prevalent cases) in the intermediate phase, and 77 (incident cases) versus 76 years (prevalent cases) in the terminal phase. The mean Elixhauser Score was 4 points for BC cases in the initial phase, 4 (incident cases) versus 6 (prevalent cases) points in the intermediate phase and was highest for individuals assigned to the terminal phase (7 versus 13 points). Within each phase, prevalent cases had a significantly higher comorbidity score than incident individuals ($p < 0.001$; Mann–Whitney U test).

Table 2 Baseline characteristics of BC cases

Phase	Age (at phase onset)				Elixhauser comorbidity score				n
	Mean [SD]	Median	Min	Max	Mean [SD]	Median	Min	Max	
Initial									
Incident	66.78 [13.15]	68	21	101	3.99 [7.31]	1	-11	49	3841
Intermediate									
Incident	67.03 [13.12]	69	21	102	3.84 [7.29]	0	-10	49	1746
Prevalent	67.81 [11.83]	69	19	107	5.81 [8.57]	3	-14	58	26569
Terminal									
Incident	76.97 [13.35]	80	23	100	7.15 [8.42]	6	-7	39	279
Prevalent	76.49 [11.75]	78	37	100	13.35 [10.16]	12	-7	49	1488

SD standard deviation

Healthcare costs

The highest incremental BC costs are in the terminal phase, followed by the initial and intermediate phases. Tables 3 and 4 show the age-standardized healthcare costs in euro per cost component within each treatment phase for incident and prevalent patients.

As Table 3 shows, in the first 11 months following diagnosis, the average BC-related incremental costs totaled €21,455 per patient. At €11,220 per patient, cytostatic drugs represent more than half (52%) of initial phase costs, followed by inpatient care (23%), outpatient care (11%), and sick leave payments (8%). All remaining cost compounds are of minor importance. Subgroup analyses revealed that total initial phase costs varied substantially by treatment type (see Appendix 2). Incremental costs totaled €60,000 in patients treated with surgery, radiotherapy and chemotherapy whereas incremental costs of those treated with surgery alone (€7,874) or surgery and radiotherapy (€11,210) were much lower.

In the intermediate phase, there were €2,851 mean BC-related incremental costs for incident and €2,387 for prevalent patients per year. For incident BC cases, almost a third of the costs is attributable to outpatient care. Cytostatic drugs, inpatient care, and sick leave payments each accounted for 15 to 20% of incremental BC-related costs. In contrast, accounting for over half of incremental costs in prevalent cases, the highest cost drivers are cytostatic drugs, followed by outpatient care (18%), inpatient care (14%), and remedies/medical aids (9%). In both incident and prevalent cases, all remaining medication, rehabilitation, and travel expenses have limited effects on incremental costs.

In the terminal phase (11 months before death), mean BC-related incremental costs totaled €33,237 in incident and €28,211 in prevalent cases. In both incident and prevalent cases, nearly half of the costs were attributable to inpatient care, followed by cytostatic drug treatment (accounting for 29-34%). Differentiating phase costs by treatment type, subgroup analyses showed that total terminal care costs ranged between €11,608 in patients without active therapy (no claim for surgery, radiotherapy and chemotherapy) and €52,651 in those treated with radiotherapy and chemotherapy (see Appendix 3).

Several studies suggest that BC costs differ substantially by age [13,14]. Given the unstandardized costs stratified by 5-year age groups (see Appendices 4 and 5), incremental BC-related costs in the initial phase decreased substantially by age, with €56,169 in patients aged 30- 34 compared to €4,530 in patients aged 85 or older. Though not apparent in all 5-year age groups, this general trend is also evident in the intermediate and terminal phases.

Table 3 Age-standardized healthcare costs of incident BC cases in Germany (in €, mean [standard deviation])

Cost sector	Initial phase (11 months)			Intermediate phase (12 months)			Terminal phase (11 months)		
	BC cases	controls	Increment	BC cases	controls	Increment	BC cases	controls	Increment
Medication	12043 [24100]	495 [1723]	**11548** [24227]	1186 [7070]	491 [1516]	**695** [7237]	11971 [22320]	690 [3915]	**11281** [22696]
Cytostatic drugs	11224 [23676]	4 [165]	**11220** [23679]	577 [6769]	0	**577** [6769]	9805 [21863]	0	**9805** [21863]
Other medication	819 [2021]	491 [1702]	**328** [2637]	609 [1848]	491 [1516]	**118** [2383]	2166 [3529]	690 [3915]	**1476** [5389]
Remedies/medical aids	525 [1090]	231 [578]	**295** [1220]	573 [1144]	289 [767]	**283** [1368]	1247 [1685]	279 [837]	**969** [1817]
Outpatient care	3119 [2541]	765 [615]	**2353** [2626]	1736 [1620]	850 [642]	**886** [1761]	3528 [3065]	853 [751]	**2675** [3186]
Inpatient care	6141 [7111]	1160 [4254]	**4982** [8303]	1864 [4515]	1383 [4493]	**482** [6376]	16513 [14745]	1024 [2810]	**15488** [15125]
Rehabilitation	178 [734]	81 [513]	**97** [882]	118 [627]	94 [578]	**24** [850]	357 [1355]	91 [497]	**266** [1448]
Sick leave payments[a]	1862 [4421]	126 [1051]	**1736** [4483]	560 [2094]	111 [885]	**448** [2224]	1643 [4033]	61 [525]	**1581** [3909]
Travel expenses	508 [860]	64 [332]	**444** [923]	112 [392]	80 [398]	**32** [555]	1031 [1241]	55 [205]	**976** [1266]
Sum	24377 [29560]	2922 [5686]	**21455** [30297]	6149 [10186]	3298 [5889]	**2851** [11823]	36289 [30060]	3052 [6372]	**33237** [31236]

[a] If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance covering 70% of the gross salary for up to 78 weeks.

Table 4 Age-standardized healthcare costs of prevalent BC cases in Germany (in €, mean [standard deviation])

Cost sector	Intermediate phase (12 months)			Terminal phase (11 months)		
	BC cases	controls	Increment	BC cases	controls	Increment
Medication	1890 [10128]	568 [1642]	**1322** [10229]	12003 [23427]	643 [1982]	**11360** [23427]
Cytostatic drugs	1220 [9654]	7 [284]	**1213** [9657]	9698 [22836]	6 [359]	**9692** [22840]
Other medication	670 [1857]	561 [1610]	**109** [2427]	2306 [3460]	638 [1943]	**1668** [3959]
Remedies/medical aids	511 [890]	305 [856]	**206** [1208]	1238 [1542]	416 [1187]	**822** [1931]
Outpatient care	1295 [1191]	871 [716]	**424** [1376]	2876 [2557]	872 [710]	**2005** [2683]
Inpatient care	1684 [4539]	1353 [3556]	**330** [5711]	14914 [15460]	1885 [5466]	**13029** [16567]
Rehabilitation	95 [469]	92 [449]	**3** [638]	202 [906]	98 [547]	**103** [1056]
Sick leave payments[a]	214 [1166]	141 [936]	**73** [1479]	298 [1532]	139 [1339]	**158** [1978]
Travel expenses	105 [368]	77 [324]	**27** [481]	834 [1078]	99 [435]	**735** [1151]
Sum	5794 [12561]	3407 [5201]	**2387** [13443]	32365 [30141]	4153 [7752]	**28211** [30612]

[a] If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance covering 70% of the gross salary for up to 78 weeks.

Discussion

Cancer costs are typically first reported at the initial diagnosis, for a specific event like recurrence, or generally (for cancer survivors) in a specific year. However, costs may change over time when measured longitudinally starting from initial cancer diagnosis to long-term survival or death. In the US, phase-specific approaches are often used to analyze cancer cost patterns [16,25]. This study used claims data on real-life treatment to estimate the costs of BC care for Germany according to clinically relevant treatment phases. Using definitions of treatment phases according to joinpoint regression analysis, our study suggests that incremental BC-related costs differ substantially by care phase. Standardized BC-attributable costs were highest in the terminal phase (11 remaining months before death), averaging around €33,237 in incident cases and €28,211 in prevalent case. Initial care costs in the 11 months after diagnosis totaled €21,455. Costs of €2,851 for incident and €2,387 for prevalent cases were incurred each year in the intermediate phase. Average costs in the intermediate phase are significantly lower ($p < 0.001$; Wilcoxon rank sum test) than for the initial and terminal phase. Consistent with US BC studies, the costs follow a u-shaped curve, with costs highest near diagnosis and death, and lower in between. Comparing absolute costs with US data would be challenging due to differences in treatment structures and reimbursement schemes as well as methodological inconsistencies (e.g., in data sources, study populations, matching criteria, and phase selection methods).

European studies that have not applied a data-driven phase-of-care approach have also found that the economic burden of BC is highest in the periods following diagnosis and near death [13]. With standardized costs of €21,455 per person for the first 11 months after diagnosis, initial care costs in our study are much higher than are those in other studies. Based on German claims data, Damm et al. [15] reported that BC-attributable costs averaged around €4,300 per person in the first year after diagnosis. The 12-month costs of initial care have been reported to total around €8,553 for Sweden (converted from SEK to € with an average 2005 exchange rate of 9.2822 SEK/€) [28]) and €7,982 for Belgium [29]. However, studies differ in their data sources and cost calculation methods, as well as in the cost domains examined, leading to an underestimation of costs. Moreover, BC healthcare costs per case [30]/per person in the EU [9] are generally found to be more than two to three times higher in Germany than in Belgium or Sweden.

For the intermediate phase, annual direct BC-related healthcare costs were estimated at €2,851 for incident and €2,387 for prevalent cases. While Broekx et al. (2011) [29] reported much lower costs for the 2nd year following diagnosis (€1,317 per patient for Belgium), our results are in line with Lidgren et al.'s [28] finding that annual direct costs for the 2nd and following years after initial BC diagnosis /recurrence totaled €2,359 (converted from SEK to € with an average 2005 exchange rate of 9.2822 SEK/€). Moreover, our results indicate that incident cases result in a significant ($p < 0.001$;

Mann–Whitney U test) average cost impact of about €460 per year compared to prevalent cases. Given the proximity in time to the primary diagnosis, active surveillance and therapy for complications resulting from the initial course of therapy might be paramount. In prevalent cases, more than half of the costs are attributable to cytostatic drugs, indicating that our sample might include BC cases experiencing recurrent events. Although BC costs are generally higher near diagnosis and death, intermediate phase costs will become increasingly economically important, even if patients remain recurrence-free, as BC is showing increasing survival rates. Further examination of whether intermediate care costs will decline after initial diagnosis, as reported by Broekx et al. [29], is required.

Few studies have examined mortality costs. In the 11-month terminal phase of care, direct BC-related healthcare costs averaged €33,237 in incident cases and €28,211 in prevalent cases. The only German study that calculated BC costs in the terminal phase found, by applying the propensity score method and adjusting for age and comorbidities, incremental direct healthcare costs of €10,950 in the last year before death [15]. However, unlike our analysis, this study did not include all cost domains from the perspective of the SHI and performed one-to-one matching to balance patient characteristics between cases and controls. The choice of comparison cohort can strongly impact the net costs of cancer [31], but the scientific literature displays no broad consensus on the choice of comparison group in cancer cost estimation. As healthcare costs vary strongly, depending on comorbidities and resource consumption, one-to-two matching may lead to more robustness in estimation.

Concerning direct costs, most studies report inpatient care [13,15,32] or both inpatient care and drugs [9] as the greatest cost drivers in BC. Our results suggest that the cost-driving factors depend on the care phase. In the initial phase, cytostatic drug costs were the main driver, whereas in the terminal phase inpatient treatment was paramount. The impact of cytostatic drugs in the intermediate phase was greater for prevalent (51%) than for incident (20%) patients. Inpatient care costs contributed to 23% of costs in the initial phase and 14-17% in the intermediate phase. The differences in the economic relevance of inpatient care and medication might reflect the fact that cytostatic drug costs represent only outpatient prescriptions and that chemotherapy might also be administered during an inpatient episode and thus be included in inpatient costs.

Consistent with previous German studies [13,14], we found that direct BC-attributable costs decreased with age, particularly in the initial treatment phase (see Appendices 4 and 5). Older women might have a lower chance of receiving aggressive treatment due to comorbidities or lower expected long-term benefits, or because they reject chemotherapy. Similar to Gruber et al. [14], we found that, while 97% of healthcare costs were BC-attributable in 25-29-year-old women, the share decreased to 56% in women over 85. In the intermediate phase, the share decreased from 77% to 23% in incident and from 71% to 15% in prevalent cases. Younger women might be more likely to take time off from work after diagnosis and, as they receive more aggressive treatment, may also experience more lasting

effects from the initial therapy. Hence, if BC could be detected earlier or even prevented, especially among young women, the overall cost burden could be reduced.

This study is limited by the nature of its data source. First, as claims data are routinely collected for billing and reimbursement, they do not include information on clinical parameters, thus preventing cost stratification by cancer stage or tumor type. However, we differentiated between incident and prevalent patients as well as different treatment types. As patient allocation to treatment cohorts (subgroup analyses) was based exclusively on services reimbursed by SHI and some services / drugs are not indication-specific (e.g., methotrexate), some patients might not have been (adequately) captured. However, consulting a clinical expert, we developed an algorithm using a wide range of different classification systems. Moreover, with regard to the differentiation of incident and prevalent cases, using a lookback period of 1 year might overestimate incident BC cases. Nevertheless, when performing sensitivity analyses identifying BC cases in 2013 (n=37,824) and extending the lookback period from 1 to 2 years, we found a small decrease in the percentage of incident patients from 13.5% (1 year) to 12.0% (2 years).

Second, claims data lack information on cause of death. Hence, BC cases assigned to the terminal phase might have died from causes other than BC. Third, as only annual (calendar year) outpatient care cost data were available, monthly costs might not have been assigned adequately to the care phases. However, in the 12-month intermediate phase, more than 80% of the individuals started their phase in the first quarter of 2012, covering almost the full calendar year. Fourth, sick leave payments include exclusively SHI costs. German law requires that an employee will only receive sick leave payments from the health insurance (covering 70% of the gross salary for up to 78 weeks) if an illness lasts longer than 6 weeks. During the first 6 weeks of sickness the employer has to pay 100% of the salary. Fifth, we used data from one regional sickness fund. As the composition of health insurances differs (e.g., in terms of age, gender and social status [33,34]) our results' generalizability might be limited. The median age at diagnosis and death was about 3 and 5 years, respectively, above the median age reported in registry data [3], because the AOK Bayern included a higher proportion of insured women 70 or older and a lower proportion of insured women 30-70 relative to all statutory insured women in Germany in 2011 [17]. To address this issue and generalize costs, we standardized them according to gender and the 5-year age structure of the German health insurance population. We thus calculated BC-related incremental costs under real-life conditions, including all cost domains that might be relevant from the SHI perspective. Ours is the first study to calculate direct BC costs for Germany using an incidence-based phase-of-care approach.

Conclusion

The economic burden of BC represents a major challenge for the SHI. This study indicates that BC healthcare costs depend on treatment phase, with higher costs near diagnosis and death and lower costs in between. The greatest economic burden occurs in the first 11 months following diagnosis and the last 11 months before death, depends heavily on patient age, with cytostatic drugs and inpatient care accounting for three quarters of total costs. Although intermediate phase costs are lower than those in phases near diagnosis and death, they remain substantial. Future studies should stratify German BC care costs according to cancer stage and tumor characteristic by linking claims data with clinical information.

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Modul 5

Treatment-related healthcare costs of metastatic castration-resistant prostate cancer in Germany: a claims data study

Kreis, Kristine

Horenkamp-Sonntag, Dirk

Schneider, Udo

Zeidler, Jan

Glaeske, Gerd

Weißbach, Lothar

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ORIGINAL RESEARCH ARTICLE

Treatment-Related Healthcare Costs of Metastatic Castration-Resistant Prostate Cancer in Germany: A Claims Data Study

Kristine Kreis[1] · Dirk Horenkamp-Sonntag[2] · Udo Schneider[2] · Jan Zeidler[1] · Gerd Glaeske[3] · Lothar Weissbach[4]

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Abstract

Purpose Treatments for patients with metastatic castration-resistant prostate cancer (mCRPC) have expanded rapidly. They include the chemotherapies docetaxel and cabazitaxel, hormonal drugs abiraterone and enzalutamide, and best supportive care (BSC). Cabazitaxel has proven to be the last life-prolonging option, associated with a significant risk of serious adverse events. Given the lack of real-world evidence, we aimed to compare healthcare resource utilization (HRU) and costs in patients with mCRPC treated with cabazitaxel, docetaxel, abiraterone, enzalutamide, and BSC.

Methods We used 2014–2017 claims data from a large German statutory health insurance fund, the Techniker Krankenkasse, to identify patients with mCRPC. Patient allocation to individual therapy regimens was based on clinical knowledge and included therapy cycles, duration of therapy, and continuous treatment. The study period lasted from the first claim until death, the end of data availability, a drug switch, or discontinuation of therapy, whichever came first. Multivariate regression models were used to compare monthly all-cause and mCRPC-related HRU and costs across cohorts by adjusting for baseline covariates (including age and comorbidities).

Results The 3944 identified patients with mCRPC initiated treatment with cabazitaxel ($n = 240$), docetaxel ($n = 539$), abiraterone ($n = 486$), enzalutamide ($n = 351$), or BSC ($n = 2328$). In most domains, HRU was highest in the cabazitaxel cohort and lowest in the BSC group. Accordingly, the highest all-cause and mCRPC-related costs per month, respectively, were observed in patients receiving cabazitaxel (€7631/€6343), followed by abiraterone (€5226/€4579), enzalutamide (€5079/€4416), docetaxel (€2392/€1580), and BSC (€959/€438). Cost variations were mostly attributable to drugs, inpatient treatment, and sick leave payments.

Conclusion mCRPC treatment imposes a high economic burden on statutory health insurance. Cabazitaxel is associated with substantially higher expenses, resulting from higher drug costs and a greater need for inpatient treatment. As mCRPC continues to be incurable, decision makers and clinician leaders should carefully evaluate public access to innovative agents and optimal treatment strategies.

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✉ Kristine Kreis
kjk@cherh.de

[1] Center for Health Economics Research Hannover (CHERH), Gottfried Wilhelm Leibniz Universität Hannover, Otto-Brenner-Straße 7, 30159 Hannover, Germany

[2] Versorgungsmanagement, Techniker Krankenkasse, Bramfelder Straße 140, 22305 Hamburg, Germany

[3] Forschungszentrum Ungleichheit und Sozialpolitik, Universität Bremen - SOCIUM, Mary-Somerville-Str. 5, 28359 Bremen, Germany

[4] Gesundheitsforschung für Männer gGmbH, Muthesiusstr. 7, 12163 Berlin, Germany

Key Points for Decision Makers

Patients with metastatic castration-resistant prostate cancer (mCRPC) treated with cabazitaxel have more hospital admissions and substantially higher monthly treatment costs than patients treated with docetaxel, abiraterone, enzalutamide, and best supportive care.

In choosing a treatment, the clinical management of mCRPC should carefully weigh expected survival against potential adverse events and the financial burden resulting from healthcare resource utilization.

1 Introduction

Castration-resistant prostate cancer (CRPC) is an advanced form of cancer where the disease progresses despite medical or surgical treatments to lower androgens. Approximately 10–20% of patients with prostate cancer (PC) become hormone refractory within 5 years after diagnosis. At CRPC diagnosis, over 84% of patients have metastases. Of the remaining patients, one-third could expect metastasis diagnoses within 2 years [1, 2]. Although, in 2010, the median overall survival after metastatic CRPC (mCRPC) diagnosis was reported to be 9–13 months [1], new treatments have increased median survival to approximately 16–35 months, depending on the tumor burden [3]. In Germany, almost 14,000 men die every year from PC [4].

Although treatment for patients with mCRPC is limited to palliative care, several treatment options are available. Depending on clinical symptoms, performance status, pretreatment, and patient preferences, treatments include immunotherapy, hormonal therapy, chemotherapy, and supportive measures (best supportive care [BSC]) [5]. Treatment options improved with the introduction of docetaxel, which was the first drug to improve survival in patients with mCRPC and has been the standard first-line therapy since 2004 [6, 7]. Further life-prolonging drugs became available with the approval of cabazitaxel chemotherapy in 2010, followed by the hormonal drugs abiraterone and enzalutamide [5]. Cabazitaxel was designed to overcome docetaxel resistance. In the TROPIC phase III trial, cabazitaxel led to a significant increase in median overall survival compared with mitoxantrone (15.1 vs. 12.7 months) in patients pretreated with docetaxel [8]. Antineoplastic activity of cabazitaxel has also been shown in patients with progressing mCRPC pretreated with docetaxel and hormonal drugs (abiraterone or enzalutamide) [9]; however, as a first-line treatment, cabazitaxel did not demonstrate superiority over docetaxel in terms of overall and progression-free survival [10]. Cabazitaxel also raised some concerns as it induced a significantly higher risk of grade III/IV neutropenia compared with mitoxantrone (82 vs. 58%, respectively) [8]. Current German guidelines recommend cabazitaxel as second-line therapy for patients with mCRPC with disease progression during or after docetaxel treatment and a good performance status [11].

Although treatments have expanded rapidly, information on their financial impact is limited. In the EU, the total economic burden of PC was estimated to be €8.43 billion in 2009, of which €5.43 billion was attributable to direct healthcare costs. Germany has Europe's highest PC healthcare expenditure per person [12]. PC costs of illness (COI) in Germany were estimated at approximately €1.85 billion in 2015 [13]. Focusing on COI analyses in the field of mCRPC, a recently published worldwide review [14] reported a broad range of cancer-specific healthcare costs, depending on the characteristics of included patients. However, only few studies have stratified costs by treatment, with most focusing exclusively on selected treatments—for example, hormonal therapy [15–17]—only considering pharmacy costs [15, 18, 19], and/or estimating costs for a hypothetical patient population (literature-based cost analysis) [16, 20]. Since mCRPC healthcare costs have not previously been reported for Germany [14, 21] and the evidence for real-world outcomes of mCRPC stratified by contemporary treatment are limited, this study's purpose is to analyze the healthcare resource utilization (HRU) for patients with mCRPC and the costs of treatment with cabazitaxel, docetaxel, abiraterone, and enzalutamide in comparison with BSC. This can provide valuable information for decision makers and clinician leaders regarding public access to innovative treatments and optimal treatment decisions.

2 Methods

2.1 Perspective

This analysis was conducted to evaluate the economic burden of mCRPC in terms of statutory health insurance (SHI). Claims data were obtained from one of the largest sickness funds in Germany, the Techniker Krankenkasse, covering approximately 10 million individuals in 2017 [22]. The analysis includes HRU and pharmaceutical costs (ready-to-use drugs and cytostatic agents), outpatient and inpatient care, and sick leave payments. Copayments and out-of-pocket payments were not considered because costs were analyzed from an SHI perspective.

2.2 Study Population

Patient identification required documentation for at least one inpatient diagnosis, secured outpatient diagnosis, or hospital outpatient diagnosis for PC based on the *International Classification of Diseases, Tenth Revision, German Modification* (ICD-10-GM code C61) between 2014 and 2016. All male sample patients had to be continuously insured from 2014 to 2017 or until death (whichever came first). Identification of metastases was based on ICD codes C77, C78, and C79. To ensure the metastasis diagnosis was associated with PC (ICD codes do not include information on the primary tumor), patients were only included if ICD code C61 was documented in the same quarter. To ensure resources and costs were not influenced by additional cancer therapies, patients were excluded if further malignant neoplasms (ICD code 'C') were documented (in an inpatient or secured outpatient

diagnosis), with the exception of the following ICD codes: C20 (rectum), C41 (bone and articular cartilage of other and unspecified sites), C43/C44 (skin), C67 (bladder), C68 (other and unspecified urinary organs), C80 (malignancies without specification of side), and C85 (other and unspecified types of non-Hodgkin lymphoma). We allowed for malignancies that were judged by our clinical expert to be associated with locally advanced PC, for example malignant neoplasms of the bladder and rectum. Additionally, we did not exclude malignant neoplasms where the therapies did not compete with PC treatment (e.g., skin cancer).

Following current clinical practice guidelines for PC at the time of cohort selection [23–25], first-line therapy for maintaining castrate testosterone levels (androgen-deprivation therapy) was defined as at least one prescription of luteinizing hormone-releasing hormone (LHRH) agonists/antagonists identified through drug claims (L02AE01, L02AE02, L02AE03, L02AE04, L02BX01, L02BX02, and H01CA04). As regards second-line treatment, patients were categorized into five treatment groups: cabazitaxel, docetaxel, abiraterone, enzalutamide, and BSC. Patient allocation to cohorts was based on patients undergoing a first-line therapy who received either one of the second-line drugs or, for BSC, at least one of the selected outpatient/inpatient health services (e.g., pain therapy, radiotherapy, blood transfusion), as shown in Table 1 in the electronic supplementary material (ESM). As patients received multiple treatments (consecutively or in parallel), patient allocation to cohorts was based on clinical knowledge defining further criteria for continuous treatment. For inclusion in the cabazitaxel cohort, continuous treatment was defined as at least three cycles of chemotherapy within 90 days. For the docetaxel cohort, at least six cycles of chemotherapy were required, with three cycles given within 90 days. In the cabazitaxel and docetaxel cohorts, patients were excluded if they were not cabazitaxel naive and docetaxel naive, respectively, namely, if there was an initial drug prescription before the first-line index date. Reflecting clinical knowledge on the time period in which the first signs of resistance (i.e., prostate-specific antigen progression) can occur [26–28], in the abiraterone and enzalutamide cohorts, continuous treatment was defined as lasting at least 180 days, with at least six prescriptions within 180 days (with an average gap between pharmacy claims up to a maximum of 34 days). For the BSC cohort, we first restricted the potential pool of first-line therapy patients with mCRPC to those never having received cabazitaxel, docetaxel, abiraterone, or enzalutamide after first-line therapy. Inclusion in the BSC cohort required at least one BSC-specific healthcare service in addition to a PC diagnosis and an observation period of at least 180 days. In the hormonal cohorts and BSC, patients who received at least one cycle of chemotherapy (cabazitaxel or docetaxel) in the 3-month baseline period were excluded.

2.3 Study Design

The date of the first claim of chemotherapy/medication prescription or health service received (only in the BSC group) was defined as the index date. The study period spanned from that date until (1) death, (2) data cutoff (31 December 2017), (3) drug switch, or (4) discontinuation of therapy, whichever came first. In case (4), the observation period ended with the last claim plus 21 days (end of cycle) of cabazitaxel/docetaxel and plus 30/28 days (prescription length) in abiraterone/enzalutamide.

Complete claims data for patients meeting the eligibility criteria were extracted and the following baseline characteristics obtained: age at index date, duration of observation, and comorbidities. Patients' comorbidities were measured 1 year prior to the index date using the well-established pharmacy-based metrics (PBM) [29], which have been developed for risk adjustment in healthcare utilization. PBM include 32 binary indicators of chronic conditions identified by prescription claims data. Since diseases might not always be documented as ICD codes, filled prescriptions might reflect patients' perception of severe conditions that warrant treatment. To avoid overadjustment, PBM group 9 (including drug codes for malignancies) was discarded.

As the duration of observation differed between individuals, we calculated resource use and costs for the entire study period but reported them as monthly values. HRU was measured as the average number of drug prescriptions, outpatient visits, hospital outpatient visits, hospital admissions, hospital days, and days with sickness benefits. The number of outpatient visits was determined by adding up the number of invoiced services based on the uniform value scale per day and medical specialist [30].

Healthcare costs (€) were also extracted, but no adjustments were made to a common year of valuation. To identify cost drivers, costs were analyzed by type. For each inpatient stay and sick leave period, costs were divided by the length of stay/duration and calculated according to the start and end of observation. For inpatient stays where the discharge day occurred after the end of observation, only costs within the follow-up period were considered. To obtain outpatient care costs, we calculated average costs per quarter day [30] and multiplied them by the number of days under observation in that quarter. Moreover, overall healthcare costs were calculated as the sum of costs from all domains. Whenever possible, HRU and costs were reported separately for all mCRPC-related events (defined as mCRPC-related medication or claims with a PC diagnosis) and regardless of underlying medical reasons (all-cause HRU and costs).

2.4 Statistical Analyses

To compare baseline characteristics, we reported absolute and relative frequencies for categorical variables and summarized continuous variables using the mean, standard deviation, and median. Differences between cohorts regarding patient characteristics and outcomes were analyzed using Chi-squared tests or Fisher's exact tests (count <5) for categorical variables and Mann–Whitney *U* tests (two groups) and Kruskal–Wallis tests (more than two groups) for continuous variables. Significance was determined at the level of ≤ 0.05.

We conducted unadjusted and adjusted comparisons. The HRU and cost outcomes of patients treated with cabazitaxel, docetaxel, abiraterone, and enzalutamide were compared with those of the patients in the BSC cohort. Adjustments were made for the following covariates: age groups, further malignancies documented in patients with mCRPC, and comorbidities according to PBM. For adjusted comparisons of HRU, incidence rate ratios (IRRs) were estimated using Poisson-specified regression models with or without zero inflation (depending on the model fit). To address uncertainties, we applied bootstrap analysis with 1000 samples per model for calculating the confidence intervals (CIs). For cost prediction, we estimated two-part models for all cost categories where the dependent variable was zero for at least one observation. Thus, we split the analysis into two parts, i.e., first fitting the probability of observing a positive versus zero outcome and then analyzing positive costs using linear regression based on ordinary least squares or generalized linear models with a gamma distribution, and identity link function, depending on the model fit. While the cohort estimates are provided exclusively in the following tables and figures, the entire output for all-cause healthcare costs is provided in Table 4 in the ESM (as a check for robustness).

To compare our results with those from other studies, we converted costs to € using the average exchange rate of a given year as listed in Eurostat [31] and reported them as monthly costs. Data management and statistical analyses were performed with SAS 9.4 for Windows, SAS Institute Inc., Cary, NC, USA.

3 Results

3.1 Study Population

We identified 92,712 patients (see Fig. 1) with a PC diagnosis in 2014–2016 who were continuously enrolled until the end of 2017 or to death, whichever came first. Of the 8525 patients with metastases, 5771 received first-line treatment with LHRH agonists or antagonists. Using the study inclusion criteria concerning the number of prescriptions, continuous treatment, and pretreatment, patients were treated as follows: cabazitaxel ($n = 240$), docetaxel ($n = 539$), abiraterone ($n = 486$), enzalutamide ($n = 351$), and BSC ($n = 2328$).

Table 1 presents patient demographics and baseline characteristics. With an average age of 71 years, patients receiving cabazitaxel and docetaxel were significantly ($p < 0.0001$) younger (by approximately 3 years) than patients starting hormonal therapy or BSC. In the cabazitaxel and docetaxel cohorts, there was a larger proportion of individuals aged < 70 years and a smaller share of individuals in the oldest age group (≥ 80 years). The median duration of observation ranged between 4 months in the cabazitaxel cohort and 24 months in the BSC cohort. When considering comorbidities at baseline, patients in the cabazitaxel cohort had the highest mean number of PBM groups, and BSC patients had the lowest. As shown in supplementary Table 2, 16 of 31 PBM groups differed significantly between cohorts. Cardiovascular diseases, rheumatic conditions, acid peptic diseases, and pain/inflammation were the most frequent chronic conditions documented in the 12 months preceding the index date.

3.2 Healthcare Resource Use

In most types of all-cause healthcare consumption, average unadjusted and adjusted utilization rates were highest for the cabazitaxel and lowest in the BSC group (Fig. 2). Adjusted analyses show that patients in the cabazitaxel, docetaxel, abiraterone, and enzalutamide cohorts had significantly more all-cause drug prescriptions, outpatient visits, and hospital outpatient visits than those in the BSC cohort (reference category). Cabazitaxel treatment was associated with a significantly higher number of all-cause inpatient admissions per month (IRR 2.34; 95% CI 1.77–2.93), even in comparison with all other cohorts. Moreover, patients in the chemotherapy cohorts spent significantly more days in hospital per month (cabazitaxel: IRR 2.57 [95% CI 1.65–3.77]; docetaxel: IRR 1.71 [95% CI 1.09–2.32]), whereas IRRs in the antihormone cohorts did not differ significantly from those receiving BSC. No significant differences existed in adjusted HRU between abiraterone and enzalutamide groups.

With the exception of inpatient admissions, a similar trend was observed in mCRPC-related HRU (Fig. 1 in the ESM). After adjusting for baseline covariates, all treatment cohorts showed a significantly higher number of mCRPC-related inpatient admissions compared with the BSC cohort. The adjusted IRRs (95% CIs) were 3.02 (2.14–4.02) for cabazitaxel, 1.48 (1.14–1.92) for docetaxel, 1.40 (1.11–1.76) for abiraterone, and 1.34 (1.06–1.68) for enzalutamide.

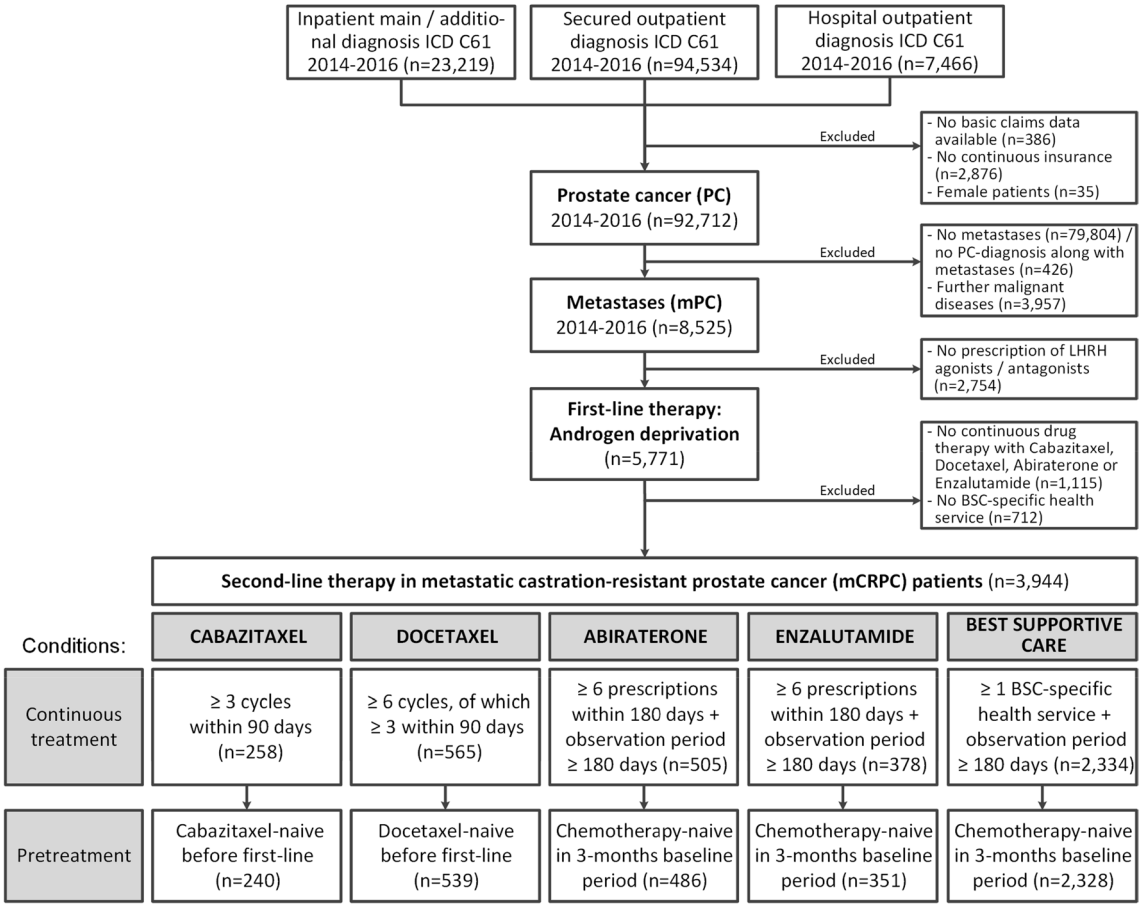

Fig. 1 Cohort selection. *BSC* best supportive care, *ICD* International Classification of Diseases, *LHRH* luteinizing hormone-releasing hormone, *mCRPC* metastatic castration-resistant prostate cancer, *mPC* metastatic prostate cancer, *PC* prostate cancer

3.3 Healthcare Costs

Adjusted monthly all-cause healthcare costs per patient (Fig. 3) totaled €7631 for cabazitaxel and were approximately three times higher than for docetaxel (€2392), 1.5 times higher than for abiraterone (€5226) and enzalutamide (€5079), and eight times higher than for BSC (€959). mCRPC-related healthcare costs accounted for 46–88% of monthly all-cause costs.

Except for hospital outpatient care, unadjusted cost analyses showed significant differences in healthcare costs among all cohorts (Table 3 in the ESM) and in most cost domains when considering cost differences compared with BSC (Table 2). Controlling for baseline covariates in mCRPC-related cost regression, Table 2 revealed that the probability of getting treatment did not differ significantly in all domains compared with BSC. However, if treatment occurred, costs associated with cabazitaxel or docetaxel treatment were significantly higher in almost all cost domains. Regarding cost distribution, variations were most prominent for pharmaceutical treatment, followed by inpatient care and sick leave payments. Compared with BSC, the adjusted differences (95% CI) in mCRPC-related monthly prescriptions and inpatient treatment were €4318 (4066–4428) and €417 (267–578), respectively, for cabazitaxel and €984 (914–1016) and €101 (38–170), respectively, for docetaxel. Thus, cabazitaxel-treated patients had significantly higher monthly drug and inpatient care costs when directly compared with those for patients receiving docetaxel. With respect to antihormonal therapy, the monthly burden of hospitalization in the abiraterone cohort was similar to that in the BSC cohort, and enzalutamide-treated patients did not differ with respect to hospital outpatient care and sick leave payments.

With regard to all-cause healthcare costs, adjusted differences showed a similar trend with drug prescription accounting for by far the majority of all-cause costs. No significant cost differences existed between abiraterone- and enzalutamide-treated patients in adjusted regression models.

In general, older age was associated with significantly lower all-cause monthly healthcare costs (Table 4 in the ESM). Compared with patients aged <65 years,

Table 1 Patient demographics and baseline characteristics

	Cabazitaxel	Docetaxel	Abiraterone	Enzalutamide	BSC
Age					
Years, mean ± SD	70.61 ± 7.7	70.46 ± 7.8	73.98 ± 7.7	74.72 ± 8.2	73.74 ± 8.6
Years, median	72	72	75	76	75
Age group, n (%)					
<65 years	48 (20.0)	122 (22.6)	63 (13.0)	43 (12.3)	317 (13.6)
65–69 years	40 (16.7)	108 (20.0)	53 (10.9)	43 (12.3)	314 (13.5)
70–74 years	62 (25.8)	126 (23.4)	121 (24.9)	72 (20.5)	528 (22.7)
75–79 years	70 (29.2)	121 (22.5)	132 (27.2)	94 (26.8)	616 (26.5)
≥80 years	20 (8.3)	62 (11.5)	117 (24.1)	99 (28.2)	553 (23.8)
Follow-up duration[a]					
Months, mean ± SD	4.5 ± 2.5	5.6 ± 2.9	16.2 ± 9.7	15.7 ± 7.9	26.3 ± 12.7
Months, median	4.2	4.5	12.7	13.4	24.2
Comorbidities[b]					
Mean ± SD	5.2 ± 2.3	4.6 ± 2.5	4.0 ± 2.4	4.4 ± 2.7	3.6 ± 2.5
Comorbidity classes[b], *n (%)*					
0	2 (0.8)	9 (1.7)	25 (5.1)	21 (6.0)	203 (8.7)
1–3	53 (22.1)	192 (35.6)	208 (42.8)	123 (35.0)	1028 (44.2)
4–6	123 (51.3)	219 (40.6)	182 (37.5)	128 (36.5)	806 (34.6)
7–9	51 (21.3)	103 (19.1)	64 (13.2)	67 (19.1)	247 (10.6)
≥10	11 (4.6)	16 (3.0)	7 (1.4)	12 (3.4)	44 (1.9)

Cohorts differ significantly ($p < 0.0001$) in all baseline characteristics. Differences were analyzed using Chi-squared tests for categorical variables and Kruskal–Wallis tests for continuous variables

BSC best supportive care, *SD* standard deviation

[a]Follow-up duration was measured as the time span from the index date until the end of observation (death, drug switch, discontinuation of therapy, or data cutoff, whichever came first)

[b]Comorbidities were assessed using a pharmacy-based metric with 32 classes. The redundant group of malignancies (group 9) was excluded

the gamma-specified regression model on all-cause costs showed a cost reduction of €316 for patients aged 65–69 years, €420 for patients aged 70–74 years, €329 for patients aged 75–79 years, and €286 for patients aged ≥80 years. The presence of the following chronic conditions significantly increased monthly all-cause costs (descending order): end-stage renal disease (€3633), HIV (€1003), pain (€458), anti-arrhythmics (€281), rheumatic conditions (€181), Parkinson's disease (€155), diabetes (€147), acid peptic disease (€101), and pain and inflammation (€88).

4 Discussion

This study provides insights into the HRU and costs of mCRPC for cabazitaxel, docetaxel, abiraterone, enzalutamide, and BSC in a real-world setting. It also contributes to an understanding of which factors drive costs. It highlights the high healthcare burden related to patients with mCRPC, especially those treated with cabazitaxel. Our analysis used claims data from one of the largest sickness funds in Germany, providing a greater sample size than most other COI studies on mCRPC [14, 32]. The participants' mean age (73 years) is similar to the previously reported mean age at CRPC diagnosis [1, 14]. Cabazitaxel- and docetaxel-treated patients were about 3 years younger than those in the other groups. At baseline, there were significant differences in the burden of disease across cohorts, with patients receiving cabazitaxel showing the highest mean number of comorbidities.

This study also revealed that HRU and costs highly depend on the treatment. Existing literature shows a wide range of healthcare costs in mCRPC [14, 32], but only few studies stratify costs by treatment. We found that, with few exceptions, adjusted IRRs were highest with cabazitaxel and lowest with BSC. Accordingly, cabazitaxel resulted in the highest healthcare costs by far, followed by abiraterone, enzalutamide, docetaxel, and BSC. Although we did not find any study analyzing healthcare costs by all the treatments used here, these cost proportions were also observed in studies comparing treatment with selected chemotherapies and hormonal therapies [18, 20, 33]. The higher economic burden with cabazitaxel was mainly due to higher drug costs and a greater need for inpatient treatment, even compared with docetaxel. As we detected large differences in CIs concerning hospitalization, further research should investigate

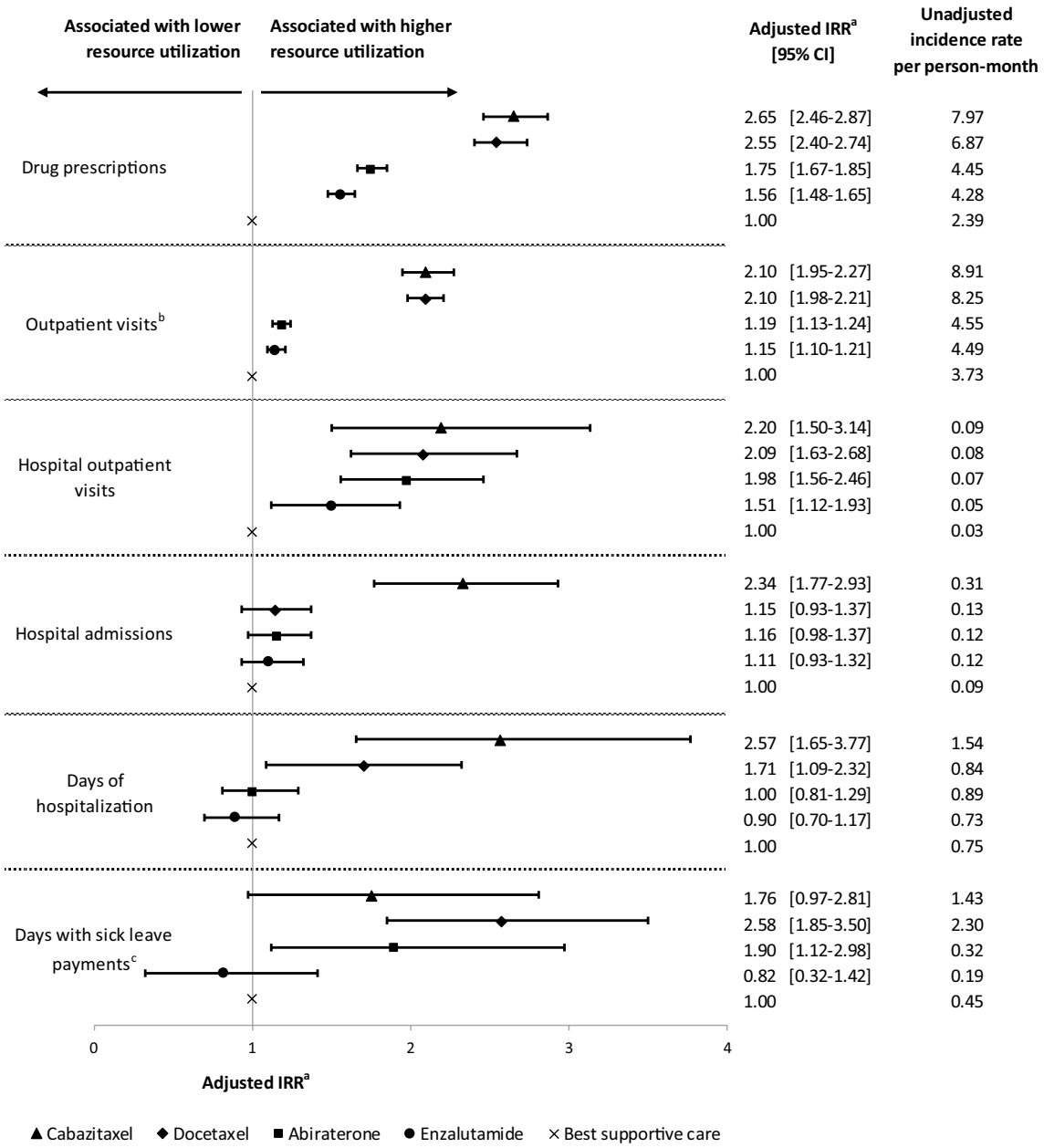

Fig. 2 Monthly all-cause health resource utilization by cohort. *CI* confidence interval, *IRR* incidence rate ratio. [a]IRRs were estimated using Poisson-specified regression models with or without zero inflation (depending on the model fit). Adjustments were made for the following baseline covariates: age groups, comorbidities (pharmacy-based classes), and further malignancies documented in patients with mCRPC. For calculation of CIs, a total of 1000 bootstrap samples were used. An estimate is statistically significant whenever the confidence interval does not include 1.0 (does not cross the vertical axis). [b]The unadjusted number of outpatient visits is underestimated. Flat-rate fees mean that not every outpatient consultation is documented in German claims data. [c]If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance covering 70% of the gross salary for up to 78 weeks

whether the increased number of hospital admissions might be due to planned hospitalizations to administer chemotherapy or the result of serious adverse events (e.g., febrile neutropenia) related to cabazitaxel. Controlling for baseline covariates, higher all-cause drug costs with cabazitaxel might stem from the fact that these patients are generally treated with more comedication to increase the safety and tolerability of chemotherapy than were the other mCRPC cohorts. Moreover, the higher sick leave payments in the chemotherapy cohorts might reflect the greater proportion of patients entitled to sickness allowance (employed individuals) combined with higher hospitalization rates.

Compared with existing literature on absolute cost values, our analysis revealed that, with €6343 for cabazitaxel and

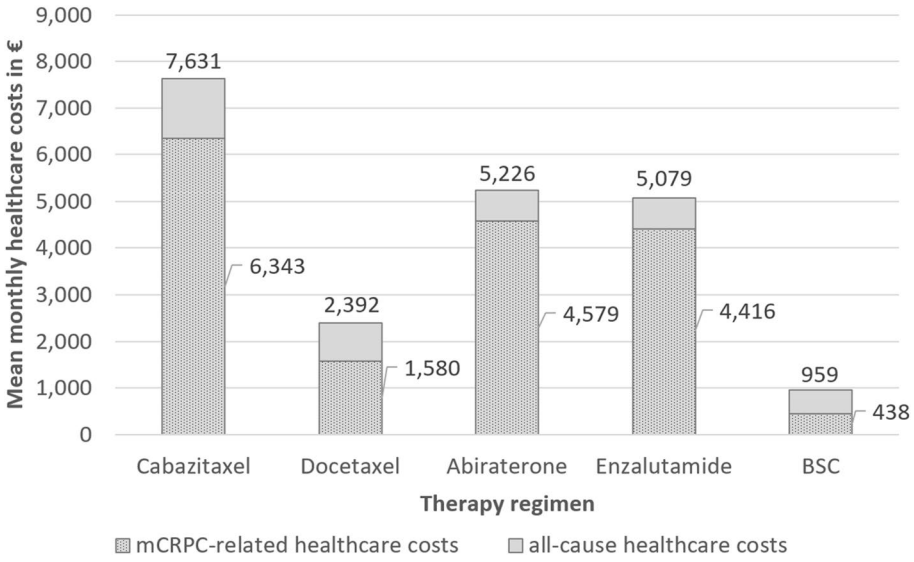

Fig. 3 Adjusted[a] mean monthly healthcare costs in patients with mCRPC by therapy. *BSC* best supportive care, mCRPC metastatic castration-resistant prostate cancer. [a]Adjusted models controlled for the following baseline covariates: age groups, comorbidities (pharmacy-based classes), and further malignancies documented in patients with mCRPC

€1580 for docetaxel, the monthly total mCRPC-related costs for chemotherapy seem to be slightly lower. In US/Canadian budget impact analyses/modelling approaches, monthly cabazitaxel treatment has been priced at €6182 (2013) for primary medication [18] and €9823–10,546 (2012) for drugs and administration [20]. The corresponding values for docetaxel were €566 (2013) for drugs [18]; €1310 (2014) for drugs, administration, concomitant medication, monitoring, and adverse events [33]; and €2817–3275 (2012) for docetaxel retreatment drug and administration [20]. However, variations might be explained by differences in healthcare system structure, reimbursement schemes, unit costs, and practice patterns [34].

Regarding antihormonal therapy, our analysis revealed monthly mCRPC-related healthcare costs of €4579 for abiraterone and €4416 for enzalutamide. Although abiraterone treatment monthly pharmacy costs are similar to those previously reported in US studies, averaging approximately €4500 (2012/2014/2017) [15, 17, 20], monthly total mCRPC-related costs are reported to be higher in most US studies, ranging from €5727 (2014) to €9715 (2017) [16, 17, 33]. However, some of these studies included additional cost domains (e.g., post-progression treatments and end-of-life care). Comparing enzalutamide to abiraterone, some US studies [15, 17, 33] considered its pharmacy costs to be higher but costs beyond drug acquisition (e.g., monitoring, adverse events, and end-of-life care [16, 17]) to be lower. By contrast, a recent claims data analysis [17] failed to show significant differences in total mCRPC-related healthcare costs. Controlling for baseline covariates, we did not find any significant differences in HRU and healthcare costs between these groups.

With monthly costs of €438, by far the lowest HRU and costs in most domains were observed with BSC. As its aim is to minimize symptom burden and maintain quality of life without directly affecting tumor activity, drug costs remain relatively low. As BSC covers a wide range of services, relevant drugs (e.g., cortisone) might have been neglected, thus underestimating costs. Since some health services (e.g., drugs) are not documented with an ICD diagnosis in German claims data, non-indication-specific medication is difficult to allocate to the underlying disease. However, consulting a clinical expert, we defined key treatment options in patients receiving BSC, including disease surveillance, pain therapy, radiotherapy, and blood transfusion. Further research is necessary to describe the BSC population and capture all kinds of supportive services.

Irrespective of the treatment, like previous studies [14, 17, 21, 35–37], our analysis highlights the financial impact of medication, followed by that of inpatient care (and partly sick leave payments) as the most important cost drivers in mCRPC. Moreover, across all cohorts, the youngest patients were the costliest per month. Although the age gradient has been a controversy discussed in PC treatment [36, 38, 39], it might be explained as follows: depending on their performance status, older men might receive a smaller dose of chemotherapy and thus have a lower risk of developing serious adverse events requiring intensive treatment.

Some limitations must be mentioned, most of which are inherent in the database (for an overview, see Kreis et al. [40] and Neubauer et al. [41]). First, patient allocation to treatment cohorts was based exclusively on services reimbursed by SHI. As claims data are routinely collected for billing and reimbursement, information on clinical parameters, such as cancer stage or tumor type, were not available for patient selection or cost stratification. Moreover, as already stated [32], we did not find a completely validated algorithm identifying patients with mCRPC in the literature.

Table 2 Difference in monthly healthcare costs (in €) compared with best supportive care

	Unadjusted cost differences[a]								Adjusted cost differences[b]								Model[c]
	Cabazitaxel vs BSC		Docetaxel vs BSC		Abiraterone vs BSC		Enzalutamide vs BSC		Cabazitaxel vs BSC		Docetaxel vs BSC		Abiraterone vs BSC		Enzalutamide vs BSC		
	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	Diff	*p* value	
All-cause costs																	
Drugs	6417	> 0.999	1420	> 0.999	4294	> 0.999	4160	> 0.999	6280	> 0.999	1336	> 0.999	4253	> 0.999	4107	> 0.999	Logit
		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	Gamma[d]
Outpatient care	162	< 0.001	108	< 0.001	− 9	0.277	0	0.982	130	< 0.001	109	< 0.001	− 2	0.690	4	0.535	Gamma[e]
Hospital outpatient care	31	0.002	31	0.082	4	0.528	15	0.851	22	< 0.001	23	0.006	6	0.614	12	0.730	Logit
		< 0.001		< 0.001		0.064		< 0.001		0.001		< 0.001		0.003		0.002	Gamma[d]
Inpatient care	385	0.004	90	< 0.001	84	0.062	95	0.147	237	< 0.001	38	< 0.001	40	0.004	59	0.003	Logit
		< 0.001		< 0.001		< 0.001		0.001		< 0.001		0.040		0.137		0.048	Normal[f]
Sick leave payments[g]	530	0.127	845	< 0.001	184	0.002	23	0.022	289	0.794	775	0.208	153	0.001	− 31	0.020	Logit
		< 0.001		< 0.001		0.013		0.804		0.023		< 0.001		0.009		0.703	Normal[f]
Total costs	7128	< 0.001	1707	< 0.001	4360	< 0.001	4249	< 0.001	6672	< 0.001	1432	< 0.001	4267	< 0.001	4120	< 0.001	Gamma[e]
mCRPC-related costs[h]																	
Drugs	4538	0.041	994	0.003	4074	> 0.999	3909	> 0.999	4318	0.127	984	0.006	4071	0.999	3906	0.999	Logit
		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	Gamma[d]
Hospital outpatient care	36	0.643	33	0.050	0	0.001	− 1	0.004	35	0.606	37	0.815	14	0.003	8	0.002	Logit
		0.006		< 0.001		0.912		0.881		< 0.001		< 0.001		0.002		0.064	Gamma[d]
Inpatient care	622	0.007	157	0.668	93	< 0.001	139	0.006	417	0.082	101	< 0.001	58	0.024	114	0.527	Logit
		< 0.001		< 0.001		0.040		0.006		< 0.001		0.004		0.172		0.013	Normal[f]
Sick leave payments[g]	540	0.145	862	< 0.001	197	0.004	58	0.018	277	0.720	783	0.145	169	0.002	− 4	0.014	Logit
		< 0.001		< 0.001		0.012		0.537		0.033		< 0.001		0.009		0.957	Normal[f]
Total costs	6116	> 0.999	1315	> 0.999	4192	> 0.999	4031	> 0.999	5904	> 0.999	1141	0.999	4141	0.999	3978	> 0.999	Logit
		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	Gamma[d]

Diff difference in monthly costs compared with BSC, *BSC* best supportive care, *mCRPC* metastatic castration-resistant prostate cancer

[a]Unadjusted models include therapy cohorts as explanatory variables

[b]Adjustments were made for the following baseline covariates: age groups, comorbidities (pharmacy-based classes), and further malignancies documented in patients with mCRPC

[c]Adjusted and unadjusted costs were estimated using two-part models for all categories where the dependent variable was zero for at least one observation. Positive costs were analyzed using linear regression based on ordinary least squares or generalized linear models with a gamma distribution, and identity link function, depending on the model fit. *p* values are shown for all parts of the models. As different regression models were used, adjusted cost differences cannot be summed up to total costs

[d]Two-part gamma model

[e]Gamma-specified model

[f]Two-part ordinary least squares model

[g]If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance, covering 70% of the gross salary for up to 78 weeks

[h]mCRPC-related drug costs were defined as any claim for cabazitaxel, docetaxel, abiraterone, enzalutamide and luteinizing hormone-releasing hormone. mCRPC-related hospital (outpatient) costs and sick leave payments were defined as any claim with a diagnosis of prostate cancer (*International Classification of Diseases* C61), including main/additional diagnosis in inpatient care

However, consulting a clinical expert, we developed an algorithm identifying patients with PC, metastasis, castration resistance, and second-line treatment, using a wide range of different classification systems for claims data. There is a strong likelihood that mCRPC in the final treatment cohorts was appropriately captured because inclusion required the prescription of (predominant) disease-specific drugs and evidence of continuous treatment.

Second, regarding HRU, the number of outpatient visits is underestimated. Flat-rate fees mean that not every outpatient consultation is documented in German claims data; for example, a patient may go to the doctor several times per quarter but be documented as a single treatment case [30]. Moreover, as only quarterly outpatient care cost data were available, costs might not have been assigned adequately depending on the varying treatment duration of drug groups. However, in a sensitivity analysis, we calculated costs by using the date of treatment in the database, confirming our main results. Third, similarly, mCRPC-related medication costs and consequently total mCRPC-related healthcare costs by treatment group are rather underestimated because the costs of comedication (e.g., antiemetics) and adverse events (e.g., nausea, stomatitis, and diarrhea) associated with the primary therapy were not considered in the analysis. Since drug claims are not linked with a diagnosis in German claims data, the assignment of costs from non-indication-specific drugs is challenging. However, we used a conservative approach to estimate mCRPC-related costs and calculated all-cause drug costs to report the maximum of healthcare costs.

Novel agents in the field of hormonal manipulation and chemotherapies are rapidly changing the available mCRPC treatments; therefore, patient allocation to cohorts represented a challenge, requiring further criteria for continuous treatment. To achieve the aims of palliative treatment, proper sequencing and effective combination of available agents becomes increasingly important for both clinicians and researchers. Although general guidelines on treatment options and algorithms exist [11, 23, 24], studies on the optimal choice, combination, and sequence of agents to maximize the clinical benefits (and minimize cross-resistance) [5, 42] or define thresholds for therapy changes are lacking.

5 Conclusion

This is the first study to assess all-cause and PC-related HRU and costs in patients with mCRPC stratified by five contemporary treatments reflective of real clinical practices. In Germany, mCRPC treatment represents a high economic burden for SHI. Our study observed substantial differences in age, HRU, and costs with cabazitaxel, docetaxel, abiraterone, enzalutamide, and BSC. Cabazitaxel- and docetaxel-treated patients were significantly younger than those receiving the other treatments. In most domains, cabazitaxel was associated with the highest HRU and healthcare costs because of the higher drug costs and inpatient care required. Future analyses should examine the reasons for this greater need for inpatient treatment and assess the financial impact with respect to survival time and adverse event rates. With expanding treatment options for patients with mCRPC resulting in an increased economic burden, public access to innovative agents and optimal therapeutic strategies should be carefully evaluated.

Author contributions All authors contributed to the study conception and design. Data validation, preparation, and analysis were performed by Kristine Kreis. Dirk Horenkamp-Sonntag and Udo Schneider offered access to claims data and were consulted on database specifics and statistical methods. Jan Zeidler provided expert oversight in the conception, implementation, and interpretation of the cost analysis and contributed throughout the manuscript. Lothar Weissbach initially developed the idea and provided clinical expertise during data analysis (by defining patient identification and cohort selection) and interpretation. Gerd Glaeske offered a drug-specific background in claims data-based healthcare research and focused on the structure of the paper. The first draft of the manuscript was written by Kristine Kreis, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The data that support the findings of this study are available from the Techniker Krankenkasse, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Compliance with Ethical Standards

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Conflict of interest KK, DHS, US, JZ, GG, and LW have no conflicts of interest that are directly relevant to the content of this study.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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Modul 6

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Kreis, Kristine

Horenkamp-Sonntag, Dirk

Schneider, Udo

Zeidler, Jan

Glaeske, Gerd

Weißbach, Lothar

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Safety and survival of docetaxel and cabazitaxel in metastatic castration-resistant prostate cancer

Kristine Kreis[1], Dirk Horenkamp-Sonntag[2], Udo Schneider[2], Jan Zeidler[1], Gerd Glaeske[3] and Lothar Weissbach[4]

[1]Center for Health Economics Research Hannover (CHERH), Leibniz Universität Hannover, Hannover, [2]Techniker Krankenkasse, Versorgungsmanagement, Hamburg, [3]Forschungszentrum Ungleichheit und Sozialpolitik, Universität Bremen - SOCIUM, Bremen, and [4]Gesundheitsforschung für Männer gGmbH, Berlin, Germany

Objectives

To investigate real-world haematological toxicity, overall survival (OS) and the treatment characteristics of docetaxel and cabazitaxel chemotherapy in metastatic castration-resistant prostate cancer (mCRPC).

Patients and Methods

This retrospective claims data study followed patients with mCRPC receiving cabazitaxel or docetaxel from their first chemotherapy infusion. Haematological toxicities were measured using treatment codes and inpatient diagnoses. OS was estimated using the Kaplan–Meier method. A multivariable Cox regression analysis was used to identify OS predictors.

Results

Data from 539 patients administered docetaxel and 240 administered cabazitaxel were analysed. Regarding adverse events, within 8 months of treatment initiation, some kind of treatment for haematological toxicity was documented in 31% of patients given docetaxel and in 61% of patients given cabazitaxel. In the same period, hospitalization associated with haematological toxicity was documented in 11% of the patients in the docetaxel cohort and in 15% of the patients in the cabazitaxel cohort. In the docetaxel cohort, 9.9% of patients required reverse isolation and 13% were diagnosed with sepsis during hospitalization. In the cabazitaxel cohort, the cumulative incidence was 7.9% and 15%, respectively. The median OS was reached at 21.9 months in the docetaxel cohort and, because of a later line of therapy, at 11.3 months in the cabazitaxel cohort. A multivariate Cox regression revealed that indicators of locally advanced and metastatic disease, severe comorbidities, and prior hormonal/cytotoxic therapies were independent predictors of early death.

Conclusion

Cabazitaxel patients face an increased risk of haematological toxicities during treatment. Together with their short survival time, this calls for a strict indication when using cabazitaxel in patients with mCRPC.

Keywords

cabazitaxel, claims data, docetaxel, metastatic castration-resistant prostate cancer, survival, toxicity

Introduction

With the introduction of novel agents during the past two decades, the treatment landscape for patients with metastatic castration-resistant prostate cancer (mCRPC) has expanded rapidly. The breakthrough came in 2004, with the approval of the taxane docetaxel, which has become the standard of care in chemotherapy [1]. Since then, further agents designed to increase life expectancy have been introduced. These include abiraterone, which blocks androgen biosynthesis, enzalutamide, which inhibits the androgen receptor signalling pathway, and alpha emitter Radium-223, which targets bone metastases [2]. One of the last life-prolonging options, cabazitaxel, another taxane, was approved as a second-line chemotherapy agent in 2010, after achieving a survival benefit of 2.4 months over mitoxantrone in patients pretreated with a docetaxel-containing regimen in the TROPIC trial [3]. Cabazitaxel also retained antitumour activity in patients who progressed after treatment with androgen receptor signalling targeted inhibitors [4]. However, in comparison with docetaxel, cabazitaxel was not convincing as a first-line therapy when it came to overall survival (OS). Febrile neutropenia, neutropenic infection, diarrhoea, and haematuria occurred more frequently among patients who received cabazitaxel [5]. According to the current

German guidelines [6], cabazitaxel therapy can be offered to docetaxel-pretreated patients with a good performance status, but careful monitoring is required.

Despite a wide range of life-prolonging treatment options, the optimal therapeutic sequencing, timing, and combinations of treatments for mCRPC patients remain unclear [7]. This makes it important to consider the patient's health status and adverse events when selecting an appropriate drug. While hormone manipulation is well tolerated, chemotherapy places a significant burden on patients. In terms of safety, the greatest risks posed by cabazitaxel are its myelosuppressive effects, in particular, neutropenia. This may result in dose modifications, treatment delays, premature discontinuation of therapy, or even death due to severe infection [8]. In the pivotal study of cabazitaxel, 82% of patients developed grade ≥ 3 neutropenia, 8% developed febrile neutropenia, 11% developed grade ≥ 3 anaemia, and 5% died from complications [3]. Due to the increasing use of granulocyte colony-stimulating factor (G-CSF), newer clinical studies have shown a lower incidence of neutropenia, although their results vary considerably [8]. However, real-world studies have reported comparatively high rates of haematological toxicity [9,10]. Given the strict eligibility criteria in clinical trials, participating patients may not be representative of a real-world population, since patients differ with respect to baseline variables and treatment. In real-life care, mCRPC patients had less favourable baseline prognostic factors, including older age, more aggressive disease, and a higher comorbidity burden [11,12].

Decision makers and clinical leaders are increasingly demanding real-world data to advance knowledge of effectiveness and safety in routine practice. Since health insurance claims data are routinely collected for billing and reimbursement, they provide an almost complete picture of healthcare utilization, and may be less affected by patient selection bias. The main objective of the present study therefore, was to use claims data to enhance knowledge of real-world clinical care in mCRPC patients treated with docetaxel or cabazitaxel by assessing patient and treatment characteristics, haematological toxicity, and OS. Since the two agents are used in different lines of therapy (cabazitaxel is approved for docetaxel-pretreated patients), this study has not compared the clinical endpoints of these therapies.

Patients and Methods

Data Basis and Patient Selection

This was a retrospective, observational cohort study based on claims data from the Techniker Krankenkasse which is one of the largest health insurance funds in Germany. Data obtained for the period from 2014 to 2017 covered sociodemographic information, drug claims, outpatient and inpatient care, and updated information on OS up to 30 September 2020.

The present analysis is based on a study population that was originally designed to evaluate the economic burden of treatment with docetaxel, cabazitaxel, abiraterone, enzalutamide, and best supportive care in mCRPC patients. Figure S1 summarizes the main inclusion criteria, applied stepwise. Details of the sample selection criteria can be derived from Kreis et al. [13]. As the present study analyses severe toxicities, we have restricted the population to patients treated with docetaxel and cabazitaxel.

The study population consisted of male insured persons with at least one inpatient and/or confirmed outpatient diagnosis of prostate cancer and (including metastases) at least one other diagnosis in the area of secondary malignant neoplasms, documented between 2014 and 2016. Analogous to the first-line therapy (in accordance with the guidelines valid at the time of the intervention) [14], patients identified by drug claims as having classic androgen deprivation therapy (ADT) were selected. Since claims data do not include clinical information, patients with mCRPC were allocated to further lines of therapy, based on the number of cycles, the duration of the therapy, and continuous treatment, as defined by clinical experts.

Study Design and Outcomes

Given its clinical importance, safety was assessed based on haematological toxicity. Adverse events were recorded while the patients were on chemotherapy. The patients were followed from the first administration of docetaxel/cabazitaxel (index date) until the earliest occurrence of one of the following events: therapy discontinuation, death, a drug switch during active treatment, or data cut-off (31 December 2017). In the first case, the end of the observation period was set to 21 days after the final drug administration. Given the lack of clinical information, haematological toxicity was operationalized by means of outpatient drug prescriptions (anatomical therapeutic chemical [ATC] codes) and operation and procedure (OPS) codes indicating treatment for haematological toxicity. OPS codes are part of the remuneration system for inpatient and outpatient treatment in Germany. All claim codes have been defined by medical experts; they are listed in Table S1. The time to each event was defined as the number of days from the index date to the earliest administration of G-CSF for the prophylaxis of neutropenia, blood transfusions for treating anaemia, or platelet concentrates for treating thrombocytopenia, as well as generally for any kind of haematological treatment. Using the same methodological approach, we also recorded hospitalizations with main or secondary diagnoses indicating medical complications that may arise from chemotherapy; the International Classification of Diseases (ICD) codes are listed

in Table S2. To explore whether the occurrence and treatment of haematological toxicities depends on the previous therapy, as a sensitivity analysis, within the cabazitaxel cohort we compared patients who received docetaxel during the previous 12 months with those who received it earlier in the course of treatment or never.

Treatment effectiveness was assessed in terms of OS, with the information on deaths updated until the end of September 2020. OS was measured as the period between the index date and death from any cause (German claims data do not include information on the cause of death).

We collected patient and treatment characteristics at the index date, during treatment follow-up, and in the case of death. Baseline patient characteristics included age, further malignancies, and general comorbidities, measured during the year prior to treatment initiation. Comorbidities were assessed using pharmacy-based metrics (PBMs) [15], which included 32 binary classes of chronic diseases, measured using drug claims. The advantage of a drug-based measurement over documented ICD codes is its likelihood of capturing conditions for which there is an actual need for treatment. Treatment characteristics included treatment history, the number of cycles, and information on the administration of cytotoxic drugs within the last 14 or 30 days before death. Regarding treatment history, the administration of the hormonal drugs abiraterone (ATC L02BX03, OPS 6-006.2) and enzalutamide (ATC L02BB04, OPS 6-007.6), and the cytotoxic agents docetaxel (ATC L01CD02, OPS 6-002.h) and cabazitaxel (ATC L01CD04, OPS 6-006.1) were recorded during the year prior to the index date.

Statistical Considerations

Descriptive analyses were carried out to summarize patient demographics and treatment characteristics. As docetaxel and cabazitaxel are administered in different lines of therapy, the treatments are not directly comparable. However, with regard to patient characteristics, we conducted chi-squared tests or Fisher's exact tests (count <5) for categorical variables and Mann–Whitney *U*-tests for continuous variables, in order to make valid statements about baseline conditions.

We assessed OS by the treatment cohort using the Kaplan–Meier method. Living patients were considered censored at the time of the last observation. An additional multivariable Cox regression model was used to identify predictors of OS. The following baseline covariates entered the regression model: age, further malignancies documented in mCRPC patients, comorbidities according to PBMs, and pre-treatment. All variables apart from age (metric, squared) were entered into the model as binary indicators. In the case of PBM-based comorbidities, we excluded the redundant group of malignancies (Group 9) from our analysis to avoid overadjustment. We tested the proportionality assumption; in case of a violation, we included the interaction of the covariate with time into the regression model [16]. Estimates were reported as hazard ratios (HRs) with 95% CIs, and the corresponding P values (P values ≤ 0.05 were taken to indicate statistical significance).

As when investigating haematological toxicities, multiple causes of failure were possible; we therefore performed competing-risk analyses. Our primary predictor was the type of chemotherapy, the failure event was the first occurrence of an adverse event, and the competing event was death. For all types of treatment with a sufficient number of events during the observation period, the time to the first adverse event was analysed using the cumulative incidence function. Statistical analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Patient and Treatment Characteristics

Given the inclusion criteria for continuous treatment (Figure S1), there were 539 and 240 patients in the docetaxel and cabazitaxel cohorts, respectively. As shown in Table 1, the patients had a median age of 72 years at baseline, and more than one-third of patients were 75 or more years old. In accordance with the course of the disease, patients in the docetaxel cohort had a significantly lower comorbidity burden than patients in the cabazitaxel cohort (four vs five PBM-based comorbidities; $P < 0.001$). Within the 12-month pre-index period, significant differences between docetaxel and cabazitaxel patients were visible in the following chronic conditions (in descending order): rheumatic conditions (78% vs 95%), acid peptic disease (52% vs 71%), congestive heart failure/hypertension (55% vs 63%), pain (25% vs 39%), epilepsy (7.1 vs 18%), anxiety and tension (4.5 vs 8.8%), and end-stage renal disease (1.1 vs 4.2%). Respiratory illness was more common among the docetaxel cohort (12% vs 6.7%). Table S3 provides a complete overview of all recorded comorbidities (online Supporting Information).

With regard to treatment characteristics, patients in the docetaxel cohort were followed up for a median of 4.5 months and received a median of eight cycles. Hormonal therapy during the previous year included abiraterone (26%) and/or enzalutamide (17%). During the 4.2 months of follow-up, patients in the cabazitaxel cohort received a median of six cycles of chemotherapy. As for their treatment history during the previous year, almost half of the patients received abiraterone (46%) and/or enzalutamide (45%) treatment. According to sequential therapy, 59% of patients in the cabazitaxel cohort had been treated with docetaxel during the previous 12 months.

TABLE 1 Patient and treatment characteristics by cohort.

	Docetaxel (*N* = 539)	Cabazitaxel (*N* = 240)	*P* *
Treatment follow-up, months	4.5 (4.2–6.1)	4.2 (2.8–5.4)	
Survival follow-up, months	21.9 (11.1–44.1)	11.3 (6.2–19.4)	
Patient characteristics			
Age at treatment initiation	72 (65–76)	72 (66–76)	0.7
Age group, *n* (%)			
< 65 years	122 (23)	48 (20)	0.16
65–69 years	108 (20)	40 (17)	
70–74 years	126 (23)	62 (26)	
75–79 years	121 (23)	70 (29)	
≥ 80 years	62 (12)	20 (8.3)	
Age at death[¶]	74 (68–78)	73 (67–77)	0.088
Comorbidities[†]	4 (3–6)	5 (4–7)	<0.001
Selected comorbidity[†] groups, *n* (%)			
Epilepsy	38 (7.1)	42 (18)	<0.001
Rheumatic conditions[‡]	418 (78)	228 (95)	<0.001
End-stage renal disease	6 (1.1)	10 (4.2)	0.006
Congestive heart failure / hypertension	296 (55)	151 (63)	0.037
Acid peptic disease	278 (52)	171 (71)	<0.001
Respiratory illness / asthma	63 (12)	16 (6.7)	0.032
Pain	134 (25)	93 (39)	<0.001
Anxiety and tension	24 (4.5)	21 (8.8)	0.018
Treatment characteristics			
Treatment cycles	8 (6–11)	6 (4–7)	–
Treatment cycle groups, *n* (%)			
3–5 cycles	–	104 (43)	
6–8 cycles	305 (57)	101 (42)	
9–11 cycles	115 (21)	18 (7.5)	
> 11 cycles	119 (22)	17 (7.1)	
Treatment history (1 year), *n* (%)			
Abiraterone	142 (26)	111 (46)	
Enzalutamide	89 (17)	109 (45)	
Docetaxel	12 (2.2)[§]	141 (59)	
Cabazitaxel	4 (0.7)	14 (5.8)[§]	
Chemotherapy before death[¶], *n* (%)			
14 days before death	5 (1.2)	10 (4.4)	
30 days before death	20 (4.9)	23 (10)	

*Estimates were given as median (interquartile range) or frequeny (percentage). *Due to the fact that docetaxel and cabazitaxel are administered in different lines of therapy, the therapies are not directly comparable. The P value is given in order to make statements about the baseline conditions. P values were calculated using Mann–Whitney U-tests for continuous and chi-squared tests for categorial variables. [†]Comorbidities were assessed using a pharmacy-based metric (PBM) with 32 classes. The group of malignancies (Group 9) was excluded due to redundancies. For clarity, this table includes only PBM groups with significant differences between cohorts. [‡]According to PBMs, corticosteroids for systemic use are part of the anatomical therapeutic chemical codes for the identification of rheumatic conditions. [§]As allocation to treatment cohort required continuous treatment with a minimum number of cycles, some individuals had received single doses before. [¶]At cut off-date, death had occurred in 411 patients in the docetaxel cohort and in 229 patients in the cabazitaxel cohort.*

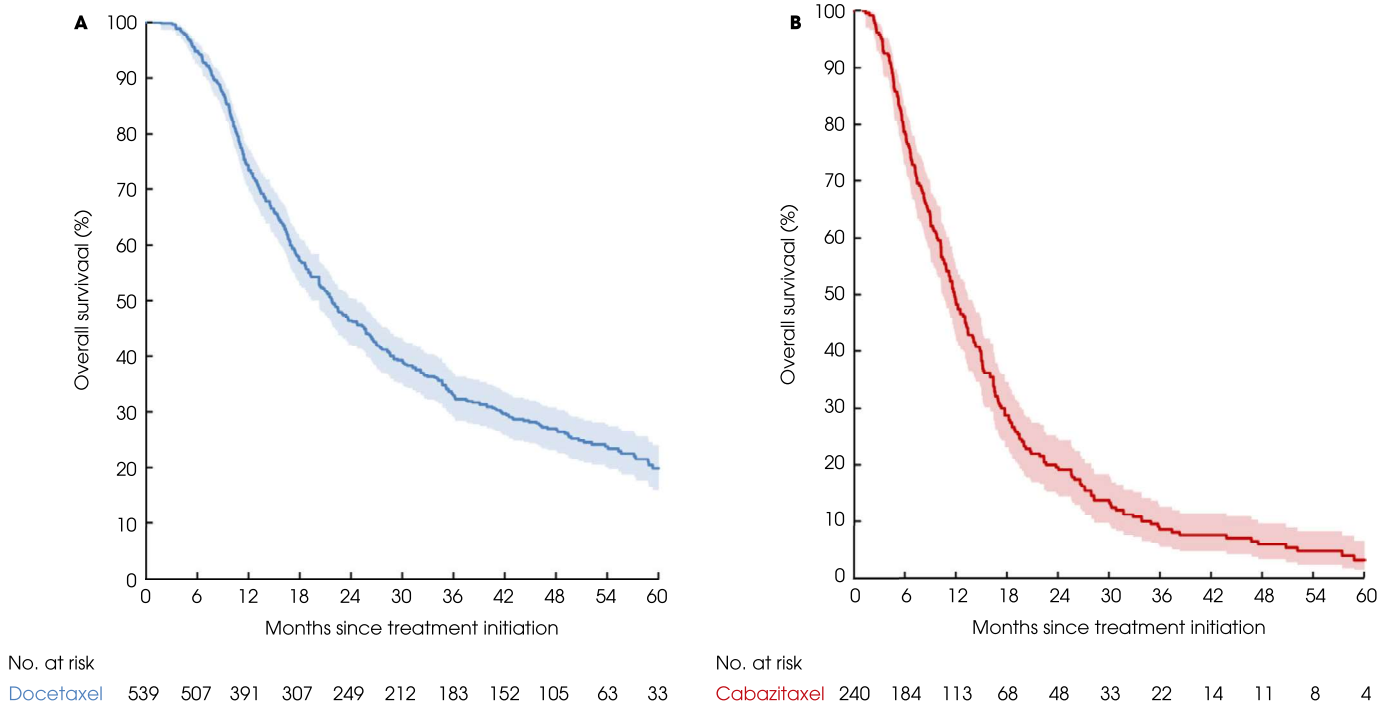
Overall Survival

At the cut-off date, death had occurred in 76% (n = 411) of the patients in the docetaxel cohort and in 95% (n = 229) of the patients in the cabazitaxel cohort (Table 1). Analogous to the therapy lines, patients in the cabazitaxel cohort were more likely to have received chemotherapy within a few weeks of death. Within 30 and 14 days of death, cytotoxic drugs were administered to 4.9% and 1.2%, respectively, of patients in the docetaxel cohort, and to 10% and 4.4%, respectively, of patients in the cabazitaxel cohort.

The Kaplan–Meier estimates are shown in Fig. 1. Patients in the docetaxel cohort had a median OS of 21.9 months. For cabazitaxel patients who had more progressed disease and were treated later, OS was 11.3 months. The 1-year, 2-year and 3-year survival rates were 73%, 46% and 35%, respectively, in the docetaxel cohort, and 48%, 15% and 6.3%, respectively, in the cabazitaxel cohort.

We also identified the predictors of OS (Fig. 2). The multivariate Cox regression showed that malignant neoplasms of the rectum (HR 2.01, 95% CI 1.05–4.14; P = 0.035) and bladder (HR 1.73, 95% CI 1.15–2.62; P = 0.009) were associated with diminished OS, while the presence of 'other malignant neoplasms of the skin' (ICD C44) was associated with a lower risk of all-cause death (HR 0.65, 95% CI 0.48–0.89; P = 0.007). Further comorbidities that increased mortality risk were end-stage renal disease (HR 1.83, 95% CI 1.05–3.18; P = 0.032), liver failure (HR 1.68, 95% CI 1.06–2.65; P = 0.027), acid peptic disease (HR 1.23, 95% CI 1.03–1.47; P = 0.026), and pain (HR 2.43, 95% CI 1.77–3.45;

FIG. 1 Overall survival (OS) in patients treated with A, docetaxel and B, cabazitaxel. Based on the criteria for continuous treatment, OS includes a minimum observation period of 49 days in the docetaxel cohort and a minimum of 39 days in the cabazitaxel cohort. As docetaxel and cabazitaxel are administered in different lines of therapy, the survival curves are presented separately and cannot be compared directly.



$P < 0.001$). Moreover, prior treatment with the hormonal agent abiraterone (HR 1.8, 95% CI 1.49–2.17; $P < 0.001$), and the cytotoxic agent docetaxel (HR 1.61, 95% CI 1.25–2.08; $P < 0.001$) and cabazitaxel (HR 1.94, 95% CI 1.16–3.25; $P = 0.012$) remained significantly associated with higher mortality risk.

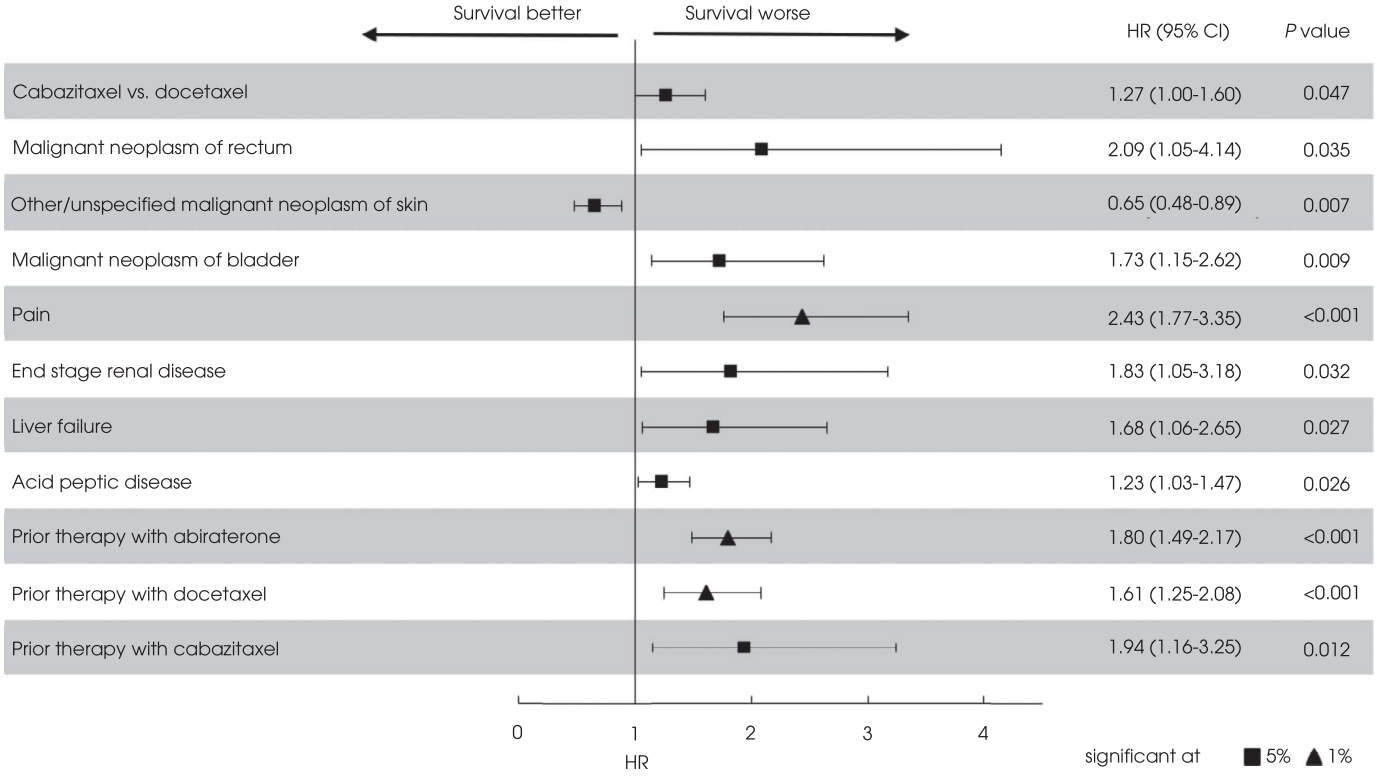
Haematological Toxicity

Within 8 months of treatment initiation, some kind of treatment for haematological toxicity, including neutropenia, anaemia, and thrombocytopenia, was documented in 31% of docetaxel-treated patients (Fig. 3A) and in 61% of cabazitaxel-treated patients (Fig. 3B). The most common drug administration occurred to prevent neutropenia, followed by the treatment of anaemia, while thrombocytopenia therapy played a minor role (not shown; numbers were too small to perform specific analyses).

Cumulative incidence plots showed that the time to the first event was shorter in patients treated with cabazitaxel. Regarding neutropenia, within 1 and 3 months of treatment initiation, 10% and 15% of the patients in the docetaxel cohort (Fig. 3C), and 25% and 32%, respectively, of patients in the cabazitaxel cohort (Fig. 3D) had received at least one administration of G-CSF. The incidence curve of the cabazitaxel patients showed a sharp increase approximately 3 and 6 weeks after therapy initiation and stabilized after approximately 3 months of therapy. Although treatment-emergent anaemia developed more slowly, a similar trend was evident between the treatment groups. Within 3 and 8 months after the index date, 8.2% and 17% of patients in the docetaxel cohort experienced treatment-emergent anaemia (Fig. 3E). In the cabazitaxel cohort, 16% and 33% of patients, respectively, experienced treatment-emergent anaemia (Fig. 3F). Regarding thrombocytopenia (not shown), within 8 months, treatment had occurred in only <1% of patients receiving docetaxel and in 3.4% of patients receiving cabazitaxel. Sensitivity analyses showed that, within the cabazitaxel cohort, the extent and treatment of haematological toxicities did not differ significantly according to whether patients had received docetaxel in the previous year or not.

Table 2 shows the cumulative incidence of patients with inpatient treatment associated with a medical complication. Within 8 months of treatment initiation, hospitalization associated with any kind of haematological toxicity was documented in 11% of patients in the docetaxel cohort and in 15% of patients in the cabazitaxel cohort. During the same period, reverse isolation was indicated in 9.9% of patients given docetaxel and in 7.9% of patients given cabazitaxel. Sepsis occurred in 13% of docetaxel-treated patients and in 15% of cabazitaxel-treated patients. Other common non-

FIG. 2 Significant predictors of overall survival in patients treated with docetaxel and cabazitaxel. The direct comparison of cabazitaxel and docetaxel was included to reflect the fact that both therapies are used in different lines of therapy. HR, hazard ratio.



haematological toxicities included fatigue (10% and 14%, respectively).

Discussion

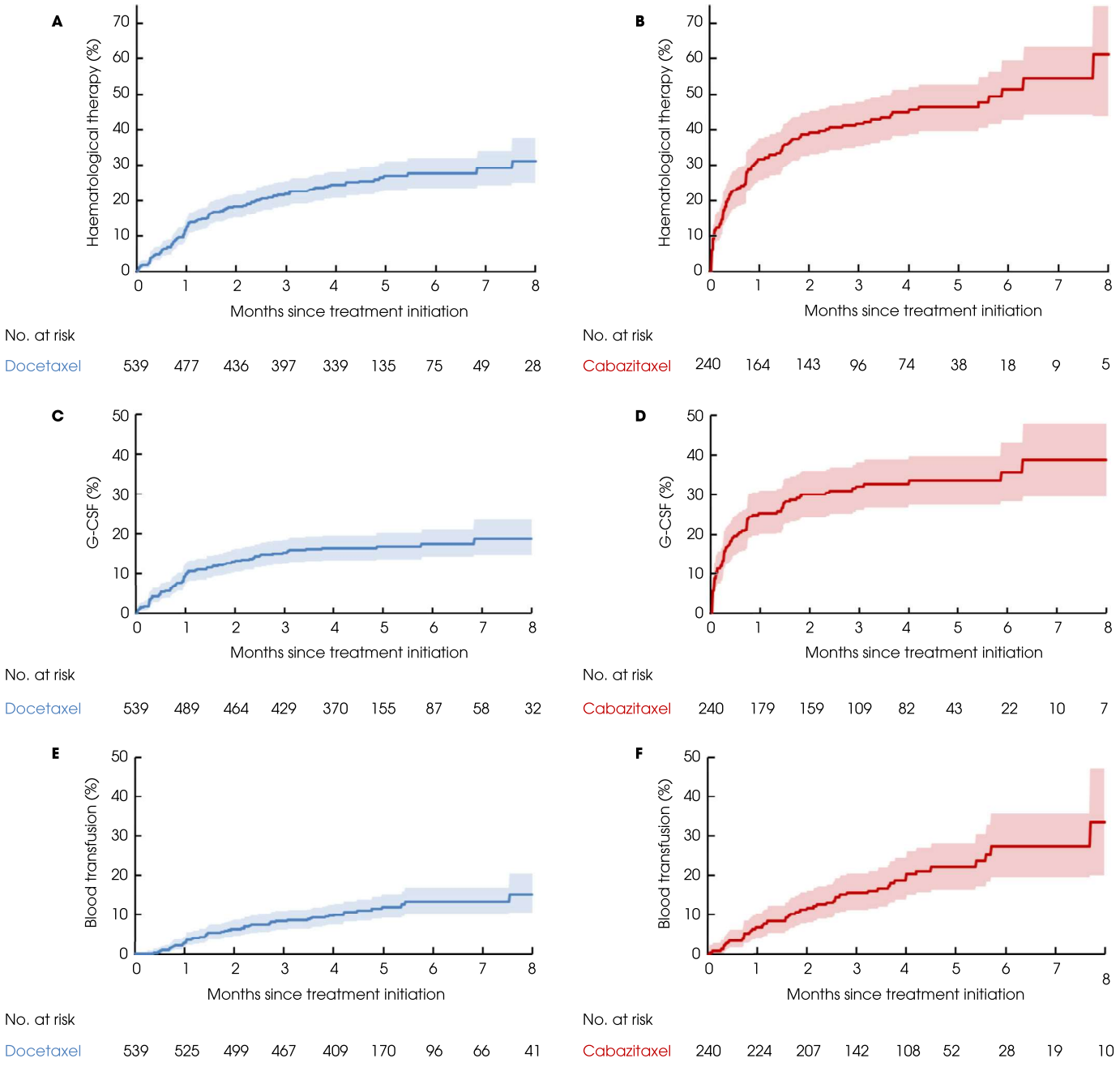
Given the increasing treatment options for mCRPC, the use of different agents must be carefully considered. This is particularly true for chemotherapies, where a short life extension may be associated with serious treatment-emergent health risks. To date, these issues have often been addressed using clinical trial data, in which participants may not fully represent real-life cancer care. To our knowledge, this is the first claims data study to assess haematological toxicity and OS in mCRPC patients treated with docetaxel and cabazitaxel. As one of the last treatment options, cabazitaxel is administered only when there is an advanced stage of disease in which other therapeutics are no longer effective.

At 11.3 months in the cabazitaxel cohort, the median OS of our patients was shorter than that in most clinical studies [8,12], but within the range of observational studies [10,12,17–19]. It ranged from 13.4 to 15.1 months in clinical trials [8,12], and from 9.6 to 12.9 months in routine clinical practice [10,12,17–19]. This may reflect the differing composition and prognostic baseline parameters of patients within and outside controlled clinical trials [11,12]. For example, our study population exhibited a high number of baseline comorbidities, and we did not exclude patients with end-stage liver or kidney disease. Regarding predictors of early death, the Cox regression showed that baseline indicators of locally advanced and metastatic prostate cancer (including pain), end-stage liver and kidney disease, and prior hormonal and cytotoxic therapy were associated with diminished survival. The inverse influence of life-extending pre-treatments may have reflected the fact that these patients had further progressed to cancer. Thus, they may be older, in a later stage and have a greater tumour load.

Even if the primary goal of chemotherapy is to prolong survival, treatment decisions must account for symptom improvement and good tolerability. Haematological toxicities are particularly important, as the risk of serious complications, including bleeding, neutropenic fever, and life-threatening infections, increases during phases with the lowest concentrations of erythrocytes, leukocytes and platelets. The results of the present study suggest that patients who receive cabazitaxel chemotherapy have an increased risk of needing treatment for haematological toxicities, including inpatient care.

According to the treatment guidelines [6,14], the prophylactic administration of G-CSF is not recommended during the first

FIG. 3 Treatment of haematological toxicities. Cumulative incidence function of time to first treatment of any haematological toxicity, first use of granulocyte colony-stimulating factor (G-CSF), and first blood transfusion since treatment initiation in patients treated with docetaxel (**A,C,E**) and cabazitaxel (**B,D,F**). As docetaxel and cabazitaxel are administered in different lines of therapy, the treatment curves are presented separately and cannot be compared directly.



chemotherapy cycle with cabazitaxel or docetaxel; however, it is indicated as a prophylactic measure in the case of severe symptomatic neutropenia in subsequent cycles. In general, however, with respect to cabazitaxel [4], primary prophylaxis with G-CSF should be considered for patients with clinical high-risk factors for serious complications (e.g. age > 65 years, poor general condition, previous episodes of febrile neutropenia). In the present study, sharp increases in the cumulative incidence plot of cabazitaxel-treated patients may reflect drug administration at the beginning of each conventional 3-week treatment cycle. Over the entire treatment period, administration rates of G-CSF (40%) were lower than those found in early access studies (≥ 60%) [9,20,21]; this may reflect greater risk avoidance through

TABLE 2 Inpatient stays associated with adverse events*.

Indication	Docetaxel			Cabazitaxel		
	1 month	3 months	8 months	1 month	3 months	8 months
Any kind of haematological toxicity	9 (1.7)	23 (4.3)	37 (11)	11 (5.0)	18 (8.4)	25 (15)
Neutopenia	5 (0.9)	15 (2.8)	24 (5.8)	7 (3.3)	11 (5.5)	16 (9.7)
Anaemia	4 (0.7)	9 (1.7)	16 (6.1)	4 (1.7)	8 (3.4)	12 (7.0)
Thrombocytopenia	0 (0)	1 (0.2)	2 (0.4)	2 (0.8)	4 (1.7)	8 (6.4)
Reverse isolation†	5 (0.9)	15 (2.8)	24 (9.9)	3 (1.7)	6 (3.2)	10 (7.9)
Sepsis	6 (1.1)	13 (2.4)	30 (13)	4 (1.7)	10 (4.4)	16 (15)
Fatigue	6 (1.1)	16 (3.0)	29 (10)	2 (1.3)	10 (4.8)	21 (14)
Nausea / vomiting	5 (1.1)	7 (1.5)	16 (7.1)	2 (0.8)	6 (2.6)	9 (4.7)
Diarrhoea /gastroenteritis	4 (0.7)	4 (0.7)	4 (0.7)	0 (0)	1 (0.4)	2 (5.8)

*Estimates are given as cumulative frequeny (cumulative percentage). *Cumulative incidence function of time to first admission with selected diagnoses (main or secondary diagnosis) within 1, 3 and 8 months after treatment initiation. †Admission to protect the individual from his surroundings.*

more intensive monitoring and early use in these studies. However, in line with other studies, the present study shows that, where treatment with G-CSF occurred, it was already in cycle 1 in half the cases [9,10,20,21]. By contrast, the administration of G-CSF in advanced cycles, as observed in the docetaxel cohort, may have been due to severe neutropenia in previous cycles.

A similar risk profile has emerged in the treatment of anaemia. According to the treatment guidelines [6,14], the administration of erythropoiesis-stimulating substances is only recommended for symptomatic anaemia, after careful consideration of the risks. The present study found that one-third of patients given cabazitaxel experienced treatment-emergent anaemia. Our results suggest that, under real-life conditions, crude rates of severe anaemia during treatment with cabazitaxel are higher than the rates of grade ≥ 3 anaemia reported in clinical studies, which were less than 12% [3,5,22]. Real-world studies [9,10,19,21,23] showed a much wider range, with a maximum of up to 27% [18].

To enhance the tolerability of cabazitaxel, several clinical trials have investigated different combinations of dose modifications and administration schedules [24]. When considering treatment-emergent adverse events, even in patients receiving low-dose cabazitaxel, the authors of an editorial [25] have explicitly pointed out the dangers of overtreatment, and called for precise patient selection, based on a comprehensive geriatric assessment (e.g. a G8 questionnaire). According to the guidelines developed for patients with prostate cancer aged > 70 years [26], treatment decisions should not depend primarily on age, but rather on patient health status, which affects both survival and the ability to tolerate adverse events. Aggressive treatment should only be administered to patients with reversible impairments (e.g. malnutrition). In this study, a substantial number of patients had severe underlying diseases, such as cardiovascular diseases or end-stage renal or liver failure.

Timing should also be considered when choosing an end-of-life therapy. Even if the patient's remaining life expectancy is difficult to predict and cabazitaxel represents one of the last options for tumour control, patients in the terminal phase can only benefit from chemotherapy when there is a genuine possibility of prolonging life or palliating symptoms. In the present study, one in 10 deceased patients in the cabazitaxel cohort received cytotoxic drugs in the last month of life. In the docetaxel cohort, only one in 20 patients received such drugs. In general, it has been demonstrated that cancer patients who receive tumour therapy very close to the end of life tend to have a higher symptom burden and poorer quality of life [27,28] than those who receive palliative care alone; the former often end their lives in acute care hospitals, [29] rather than entering hospices to receive appropriate palliative care. Regardless of the timing of therapy, a recent real-world study [13] has shown that, during active treatment, patients receiving cabazitaxel generally have a higher need for inpatient care than those receiving docetaxel (which is administered during earlier lines of therapy). Together with higher pharmaceutical costs, the monthly economic healthcare burden is three to four times higher for patients treated with cabazitaxel than for those receiving docetaxel.

The present study has some limitations. Because no ICD code for mCRPC exists, patients were identified using a combination of different classification systems (e.g. ICD and drug codes); however, as the purpose of treatment administration is not reported, some drugs may also be prescribed in a different setting. For example, in a clinical trial published in August 2015, the superiority of concomitant treatment with ADT plus docetaxel over ADT alone was demonstrated in terms of OS in patients with hormone-sensitive disease [30]. Depending on how quickly docetaxel was introduced into the therapeutic landscape, there might be a risk that patients with hormone-sensitive prostate cancer have been included. However, one-third of the patients in the docetaxel cohort had already started therapy before August

2015 and guideline implementation was only carried out in December 2016 [14].

Unfortunately, no information on the administered dosages was available in the claims data. In relation to adverse events, the number of patients with haematological toxicities was underestimated for two reasons: first, given the lack of clinical information in German claims data, patients were allocated to a treatment cohort based on a minimum number of therapy cycles, the duration of therapy, and continuous treatment. For example, patients who discontinued therapy after one or two cycles of cabazitaxel were excluded during patient selection, even though adverse effects or a poor response may have been of particular concern for these patients. Second, we were unable to differentiate between laboratory abnormalities and grade ≥3 adverse events. Nevertheless, drug code identification enabled us to record toxicities that were treatment-related in routine clinical settings. When reporting medical complications using inpatient diagnoses, it should be noted that these do not allow any conclusions to be drawn about the primary cause of hospitalization and that the causal relationship with prostate cancer or chemotherapy cannot be proven. However, as these are typical adverse events and competing oncological diseases were largely excluded in the course of patient selection [13], the probability of a correlation is high.

In conclusion, under real-life conditions, patients treated with cabazitaxel face an increased risk of haematological toxicities requiring treatment; in addition, their remaining lives are likely to be shorter than those reported in clinical studies. In some cases, cabazitaxel is administered shortly before death. With docetaxel as a reference, the treatment costs of cabazitaxel are also significantly higher, mainly due to higher drug costs and a greater need for inpatient treatment. In light of these findings, better guidelines are needed to establish criteria for the indication and timing of aggressive treatment at the end of life. Treatment choice requires a physician–patient discussion of the prognosis, which carefully considers the options for prolonging life, existing comorbidities, risks and the tolerability of adverse events and their treatment, as well as the patient's preferences for his remaining lifetime.

Conflicts of Interests

None declared.

Data Availability Statement

Claims data from the Techniker Krankenkasse were used under licence for the present study, and so are not publicly available.

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Correspondence: Kristine Kreis, Leibniz Universität Hannover, Center for Health Economics Research Hannover (CHERH), Otto-Brenner-Straße 7, 30159 Hannover, Germany.

e-mail: kjk@cherh.de

Abbreviations: ADT, androgen deprivation therapy; ATC, anatomical therapeutic chemical; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; ICD, International Classification of Diseases; mCRPC, metastatic castration-resistant prostate cancer; OPS, operation and procedure; OS, overall survival; PBM, pharmacy-based metric.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Sample selection flow chart.
Table S1. Claim codes indicating treatment for haematological toxicity.
Table S2. ICD codes for the identification of medical complications.
Table S3. Baseline comorbidities by cohort.

Modul 7

Treatment-related experiences and preferences of patients with lung cancer: a qualitative analysis

Aumann, Ines

Kreis, Kristine

Damm, Kathrin

Golpon, Heiko

Welte, Tobias

Graf von der Schulenburg, J.-Matthias

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Treatment-related experiences and preferences of patients with lung cancer: a qualitative analysis

Ines Aumann,*† Kristine Kreis,‡ Kathrin Damm,§ Heiko Golpon,¶** Tobias Welte†††‡‡ and J. Matthias Graf von der Schulenburg§§¶¶

*,‡Research Associate, §Senior Research Associate, §§Professor, Center for Health Economics Research Hannover (CHERH), Leibniz University of Hannover, Hannover, †,**,‡‡,¶¶Member, German Center for Lung Research (DZL), Hannover, and ¶Senior Physician, ††Professor, Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany

Correspondence
Ines Aumann
Center for Health Economics Research Hannover (CHERH)
Leibniz University of Hannover
Otto-Brenner-Str. 1
30159 Hannover
Germany
E-mail: ia@cherh.de

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Abstract

Background Lung cancer is one of the most common types of cancer worldwide, and it causes significant challenges for patients due to the poor survival rate and treatment-related side-effects. Because of lung cancer's great burden, identification and use of the patients' preferences can help to improve patients' quality of life.

Objective Interviews with patients who have lung cancer were used to ascertain a range of experiences and to make recommendations regarding the improvement of treatment based on these patients' preferences. Because chemotherapy is the common treatment option for lung cancer, we focused on this treatment. The interviews were audio-taped, verbally transcribed and evaluated via content analysis.

Setting and Participants A total of 18 participants (11 men and 7 women) with small or non-small-cell lung cancer who were receiving chemotherapy in one clinic were interviewed between June and July 2013.

Results Two main aspects with different subthemes were identified during the interviews. One main aspect focused on organizational context, such as the treatment day process, or experiences with different stakeholders, such as with the health insurance company or physicians. The other category referred to experiences that influenced psychosocial factors, including physical and mental experiences.

Discussion and Conclusion Patients reported different experiences concerning physical, psychological and organizational areas during chemotherapy. Nevertheless, some potential areas for improving care, and therefore the quality of life of patients with lung cancer, could be identified. These improvement measures highlighted that with small, non-time-consuming and inexpensive changes, the treatment for patients with lung cancer can be improved.

Introduction

Lung cancer is one of the most common cancers with 1.8 million cases worldwide in 2012, and it was the leading cause of cancer-related death.[1] In relation to other cancers, lung cancer has a poor 5-year survival rate. According to the different severities at diagnosis, the rate is between 2% for patients with distant metastases, 16% for patients with cancer in the lung and nearby lymph nodes and 49% for local lung cancer.[2]

Different types of treatment for lung cancer exist. Depending on the severity of the disease, surgery, chemotherapy or radiotherapy are potential treatment options. Nevertheless, chemotherapy is often undertaken either alone or in addition to surgery. The treatment causes a high burden for patients with cancer, including physical complaints about the disease itself, side-effects of the therapy, mental stress, and a lessening of family life and leisure activities. Other affected areas include professional limitations, financial worries, the need to apply for support services, the integration of inpatient and outpatient therapy treatment measures, and regular interaction with physicians and medical personnel.[3]

Corbin and Strauss pointed out that cancer diseases require a high degree of services from the private and medical setting of those affected.[4,5] Recent studies show that physicians often evaluate the needs and preferences of their patients in a different manner to the patients themselves.[6–8] Although the ramifications of the patient's perspective on their disease are not a new discovery, it still has a strong presence in recent studies. Most studies focus on quantitative analyses and include the use of a standardized questionnaire. For example, Mühlbacher *et al.* [9] used a discrete choice experiment to ascertain patient preferences in relation to treatment of non-small-cell lung cancer (NSCLC). They pointed out that patients prefer an increase in 'progression-free survival' and a reduction of 'tumour-associated symptoms' (e.g. cough, pain). With these instruments, it is difficult to assess the broad range of experiences and preferences that people have had with their treatment or disease because only some attributes can be evaluated. Furthermore, a qualitative approach can give broader insight and a more in-depth understanding of the experiences and preferences with chemotherapy. Qualitative studies of the burden and experiences of cancer patients with chemotherapy also exist but they mostly focus on cancer in general and only some studies integrated patients with lung cancer.[10–13]

Due to the great burden of the disease itself and the effects of the treatment, it is necessary to assess patients' treatment-related experiences to help optimize their quality of life. Therefore, this study focuses on the following two questions:

1. What is the particular burden for lung cancer patients with regard to treatment?
2. Which recommendations for improving treatment can be derived from the patients' preferences?

Methods

We conducted semi-structured, guideline-based, face-to-face interviews with patients suffering from NSCLC or small-cell lung cancer. The sample was recruited in cooperation with the oncology outpatient day clinic at the Hannover Medical School (MHH), Germany. The clinic covers the whole spectrum of medical treatments of a centre of supramaximal care with a total of 1518 beds and 452 783 patient contacts per year.

Patients were only included if they had undergone palliative chemotherapy at the time of the study and had experienced at least one cycle of chemotherapy. Patients who received adjuvant chemotherapy were excluded. The study nurse, who was not part of the treatment team, asked those patients to participate in the interviews. She provided information about the study's aim, the voluntary nature of consent, data collection and data processing. A confidential and anonymous handling of all personal data was promised. All information about the study and the declaration of consent was handed to the patients. To record different experiences, our maximum variation sample included patients

from various social backgrounds, ages and treatment methods. Some patients were accompanied by relatives during the interview. Owing to financial and time-related restrictions, the interviews were undertaken in the MHH's rooms. After written informed consent was obtained, most patients were interviewed in the time lag between the blood sample and chemotherapy in the oncology outpatient day clinic. All interviews were conducted between June and July 2013. A total of 18 patients with lung cancer were interviewed by a research assistant of the Center for Health Economics Research Hannover. The number of interviews was not predefined. We stopped conducting interviews after no new messages emerged. The study was approved by the MHH's Committee for Clinical Ethics.

The interviews were structured using a guideline based on information from the literature, which was developed in conjunction with an interdisciplinary group of researchers. Therefore, we conducted a systematic literature review from 12 electronic databases (e.g. EMBASE, MEDLINE), and included 20 qualitative and quantitative studies published between 2000 and 2012. This guideline was divided into four sections and contained open questions that encouraged patients to talk about their treatment-related experiences and preferences in their own words. First, patients were encouraged to describe an average treatment day in hospital. Second, patients were asked to talk about their expectations and experiences concerning chemotherapy in general, as well as the most harmful and burdensome side-effects. These questions targeted the experiences and effects of the chemotherapy on different areas, including physical or mental status, impact on daily living and contact with other patients. Third, patients were also encouraged to name ways of improving healthcare quality. The fourth section served as a way of potentially addressing an important topic for the patient. Additionally, some demographic data (e.g. age, or smoking and working status) were obtained before the interview. The interviews lasted 1–1.5 h and were audio-taped. Each interview was completely verbally transcribed and anonymized. As interviews were conducted in German, the citations were translated by two professional translators who are native speakers. Disparities were clarified bilaterally.

Data were analysed using qualitative content analysis methods with the additional inclusion of inductive categories.[14,15] To ensure the accuracy of the analysis process, two researchers (Kreis and Aumann) read the interviews and paraphrased the relevant text independently using the MAXQDA program. A codebook was also generated. The researchers analysed the text on the basis of deductive categories, which were derived from the questions in the guide. The inductive categories were developed directly from the text. In addition, some sections of the interviews were discussed by an interdisciplinary research group to identify further inductive categories.

To obtain an overall impression of the content, the transcripts were read and re-read. In subsequent discussions, the researcher checked the codes for consistency and agreement, and resolved any differences by an iterative process. The aim of a content analysis is to identify the cross-relationships, repetitions, commonalities, and differences of the statements to demonstrate a trend regarding the results. To achieve this, all interpretations and arguments are documented and supported by citations.

Results

Participants

A total of 18 patients (11 men and 7 women) with lung cancer completed the interviews. The average ages were 75 years for the men and 63 years for the women. Three of the 18 patients had a small-cell lung cancer diagnosis and 12 patients received additional radiation therapy. All patients were at a higher disease stage (>IIIA) due to their late diagnosis. Further demographics and cancer status are described in Table 1.

Table 1 Participant socio-demographics and clinical setting

Number	Age, Gender	Diagnosis	Stages	Radiation	Chemotherapy
1	75m	non-small	IV	yes	Second-line therapy, 9 cycles; intravenous
2	68m	Small	IV	no	Second-line therapy, 2 cycles; intravenous
3	61f	non-small	IV	yes	Third-line therapy, oral
4	63m	non-small	IV	yes	Second-line therapy, 2 cycles, intravenous
5	48f	non-small	IV	yes	First-line therapy, oral
6	74m	non-small	IV	no	First-line therapy, oral
7	59f	non-small	IV	yes	First-line therapy, 10 cycles; intravenous
8	70f	non-small	IV	yes	First-line therapy, oral
9	69m	non-small	IV	no	Fourth-line therapy, 2 cycles; intravenous
10	65m	Small	IV	no	First-line therapy, 1 cycle; intravenous
11	76f	non-small	IIIA	no	First-line therapy, 2 cycles; intravenous
12	65m	non-small	IV	yes	Second-line therapy, 2 cycles; intravenous
13	60m	non-small	IIIB	yes	Third-line therapy, 2 cycles; intravenous
14	72m	non-small	IV	yes	Third-line therapy, 7 cycles; intravenous
15	61f	non-small	IV	yes	Fifth-line therapy, oral
16	70m	non-small	IV	yes	Second-line therapy, 97 cycles; intravenous, maintenance therapy
17	75m	small	IIIB	yes	Second-line therapy, 2 cycles; intravenous
18	67f	non-small	IV	no	Second-line therapy, oral

f = female, m = male.

Themes

During the content analysis of the interviews, we identified four main themes. The first theme describes the chemotherapy-related experiences and preferences of patients with lung cancer in relation to the organizational aspects of their treatment, especially the day they receive chemotherapy. The second and third themes focus on experiences with different stakeholders (physicians and the health insurance company) and the last category contains treatment-related experiences and preferences that influence psychosocial factors, including physical and mental experiences, and changes in the patient's social environment.

Theme 1: Experiences and preferences during the treatment day

All patients described a very similar course of treatment, which is characterized by the collection of a blood sample, a consultation with the physician to discuss the blood values and to determine the next treatment steps, the collection of the chemotherapy substance at the pharmacy, and the subsequent chemotherapy. This treatment procedure was described by patients in a clear and factual language without many breaks. For some patients, it is an ordinary day of treatment due to the large number of therapy cycles and it is described as a natural process. Regarding the treatment day, some

patients also reported long waiting times, particularly between individual treatment steps.

> [. . .] and then, normally, a blood sample is first taken, two ampoules, and it is sent to the laboratory, then comes an appointment with the physician, in which the lab results are discussed once again, and he decides whether or not chemo will be performed, you understand? And yes, then comes another waiting period. One has to come down here and register, then wait, then the pharmacy delivers the chemo mixture and that can take a while and, oh well. (P9, 69m)

Nevertheless, the burden of waiting times was perceived differently among the patients. Those who had a long distance to travel to the hospital perceived the waiting time as a large burden because the driver had to allow time for the treatment and journey. This also limited the patients' flexibility and freedom, and ensured that the patients were dependent on others. Most patients mentioned the waiting times but accepted them and considered them to be unimportant, irrelevant, or a small problem compared to other problems. Thus, they approved of the waiting times and thought it impossible to accelerate individual treatment sections.

> Yes, but what the heck, because I think that [the waiting period] is all stuff that takes a back seat. In that respect, they can't possibly please everybody. (P4, 63m)

However, the patients did make suggestions for design improvements regarding the waiting times. First, patients wished for greater privacy during chemotherapy, such as through the provision of more treatment rooms, smaller rooms, or the inclusion of extra curtains. Second, patients requested more rooms so that no patient has to wait in the corridor before starting chemotherapy. Third, some patients wanted beds, or more rooms or comfortable chairs, while another patient would welcome the provision of headphones and music during chemotherapy. All these suggestions indicate that patients want to feel comfortable and need privacy.

> Perhaps they should [. . .] hand out earphones for music or something like that, don't you think? Then it wouldn't be so monotonous, one would get drowsy at the same time and doze a little, but with a little music in your ears, that's not a bad idea, is it? (P15, 61f)

Theme 2: Experiences with physicians:

As patients spend much time waiting for chemotherapy, meaning a highly stressful situation, they wanted to feel comfortable.

> I do not know [. . .], but you are nervous and you also have fears, isn′t it so? The clinic should be a place where you get the help to ignore the medical stuff and to relax. (P15, 61f)

Therefore, the organizational conditions, such as those mentioned above, and the personal relationship with the staff members, especially the physicians, must be suitable. Overall, the interviewed patients were very satisfied with the physicians. They trusted their physician regarding treatment decisions and felt unable to request improvements regarding the therapies.

> [. . .] the doctor already has to know how to improve that [the therapy]. (P11, 76f)

However, during the interviews, some patients expressed thoughts on improvements regarding the contact and communication with physicians. Patients wished for a certain level of continuity with the physicians and a frequent change of physicians was criticized because the patients had to build up confidence again.

> What I still regret is that one has just built up a rapport with a physician and he disappears overnight. (P2, 68m)

Chemotherapy is a tense situation. Routine and trust in physicians can help the patients to cope better with this situation. Patients often only knew the name of the senior physician, because other physicians frequently changed. Therefore, the confidence base of the patients that was given referred exclusively to the senior physicians. Patients know about the difficulties for a hospital to structure a treatment plan so that everybody always has the same contact person, but at least they wanted to be informed by the senior physician or another known staff member about any changes in the treatment

responsibility. Nevertheless, the frequency of physician changes should be kept to a minimum.

For patients who have regular contact with one physician, conversations are important to build up trust and reduce fears. Some patients mentioned that the physician took substantial time with them and created a very personal atmosphere during conversations.

> Well, as far as the physicians are concerned, they have a lot to do, they are really overworked, aren't they? But I must say that I am impressed with the physicians here. They have really taken their time and put in a lot of effort. Recently, I had an appointment with Dr. A, shortly before he left the clinic. He devoted more than an hour to me. Which physician allows more than one hour for a patient? (P3, 61f)

This personal atmosphere is an important prerequisite when it comes to the provision of information and its content. As patients are often overwhelmed by the range of information available from the internet, friends, and family, they need the help of a health-care professional like a physician to select correct and important information.

It was shown that patients generally feel well-informed by the physician about the treatment. Some patients, however, wanted more information about the handling and treatment of side-effects to acquire more security in dealing with disease specific situations. In particular, they were interested in whether the doctor was the right contact for the different side-effects and what therapies are available to combat them.

> With regard to the dermatological history, one should really know from the very beginning, who to turn to if eczema or something else really appears. (P18, 67f)

Likewise, regarding types of communication, patients had different desires. One patient did not wish to receive information via telephone. This patient feared a dispensation of personal contact and the possibility to talk about potential problems face-to-face. However, other patients preferred shorter methods of communication, because they had already experienced a long journey from their homes to the hospital and the side-effects of the chemotherapy cause high physical strain.

> I called today and said: Yes, the radiotherapy comes to an end tomorrow. What happens now? Should I have another CT and where? Here or there? What do I need to take with me? I was told: 'Yes, on Thursday – the day after tomorrow – here at the clinic. Then we can discuss it'. But that came from the office, not from the physician. Now, I ask myself, is that absolutely necessary. Because there are no facts available, absolutely nothing. If I came here and some tests had been done or a CT had meanwhile delivered a result, and they had wanted to discuss that with me face to face, then okay. I don't really think one wants to do that on the phone. But only so that you will probably be told: 'Yes, see to it that you get a referral for a CT from your GP and get the necessary blood tests for the CT done. And as soon as you have the results, come and see me again'. That would have been more logical in my opinion. (P1, 75m)

Altogether, this section shows that, besides organizational aspects, physicians also play an important role in giving patients a trustful atmosphere during chemotherapy and to make them feel comfortable. Therefore, they need a continuous contact person who is informed about the disease and treatment. Furthermore, new physicians should be introduced to the patients by the contact persons. The physician could improve the confidence by taking enough time for treatment discussions, asking patients how they want to get information, and to concentrate more on the patients′ individual needs and personality. This could create enough transparency to increase the acceptance of the organizational structure, such as waiting times, and reduce the patients' fears.

Theme 3: Experiences with health insurance

In terms of the organizational context, patients often had experiences with other stakeholders, especially regarding health insurance. For patients with lung cancer in particular, the absorption of travel costs was of great importance. As patients are not allowed to drive or they feel unable to drive to the therapy themselves, they need a taxi or a relative to drive them. Due to most patients being unable to

work, paying for a taxi is an additional financial burden. Because of this, patients can apply for reimbursement of taxi rides to the chemotherapy sessions using their health insurance. The interviews showed that most communication and settlement between the health insurance company and patients is simple and straightforward. In many cases, patients were supported by the applications made by hospital employees or physicians. Nevertheless, sometimes there were coordination problems with the health insurance companies, which were perceived as particularly troublesome by the patients. One patient reported that taxi rides for computer tomography (CT) were not approved as they were not part of the chemotherapy, and the patient would not 'beg for a benefit'.

> The taxi fares to chemo were covered, but those to CT, for example, were not, so I had to ask my girlfriend if she would drive me because I can't afford a taxi. Who can afford a taxi there and back? Hey? And if we have to come to the clinic twice a week, without receiving chemo or radiotherapy, who pays for that? (P3, 61f)

Equally, another patient was not compensated for the rides because of a treatment option available in another hospital, which was closer to the patient's home but not a certified centre. Another patient reported that the health insurance company had verbally confirmed they would finance the services, but subsequently refused until a new request was made. One patient reported problems completing the applications because she did not know whether the disease was chronic. As a result, she accidentally made false statements, consequently had to file an objection, and incurred considerable expenses. In addition, the long waiting time for the granting of support services through health insurance was criticized. Altogether, the patients who have had bad experiences with health insurance feel overwhelmed with the administrative burden because they never had in such an extend contact to the health insurance before, and so this situation is new for them. Without help from nurses and physicians, the situation for the patients would further deteriorate and, therefore, they wish to have support from the health insurance.

Theme 4: Treatment-related experiences and preferences of the patients that influence psychosocial factors

Besides the experiences with the organizational factors and stakeholders, the chemotherapy had an influence on the patients' psychosocial situation. The patients reported many physical side-effects, such as general sickness, low load capacity, and absence of appetite due to the chemotherapy. Problems with changes in their external appearance because of hair loss or skin rashes were also mentioned.

These side-effects caused great physical limitations resulting in lower performance levels and flexibility. As a result, patients reported a decrease in sporting and household activities. Additionally, patients often were unable to continue with their work. This situation occurred very suddenly and, thus, changed the patients' daily routines. Combined with their inability to work, some patients were worried about their financial security and economic existence, especially self-employed patients. Some of them even had to apply for early retirement due to their illness.

> Well, let me say this: I have been written off work and I suddenly have to spend the whole day at home. I have been ripped out of my environment, my professional life. (P5, 48f)

> Whether someone can afford it is an issue that relates to the economic situation, or if it is someone who is on the dole who gets cancer. That is actually another (unclear) aspect of this illness, that one is drained financially. So, if it causes us to lose our company now, which we feared at the beginning, that would be a disaster. (P4, 63m)

The changes in their daily life along with the fears resulting from the disease and the treatment cause psychological effects.

> Yes, I'm at the end of my strength. I can hardly move, can hardly walk, can hardly breathe. If I didn't have my girlfriend, I wouldn't be able to do anything, hey? (P3, 61f)

The psychological effects are characterized by different feelings. Patients differ between hopes and fears. On the one hand, the patients wish that the chemotherapy helped and extended their life but, on the other hand, they are afraid of physical disabilities, a lack of flexibility, and loss of independence. Due to these psychological strains, patients develop various strategies to deal with these limitations.

One group of patients took every opportunity to go for a walk and undertook specific breathing exercises. These patients wanted to actively take part in life and keep in touch with family and friends.

> I try to increase right now my walking distance so that I go out and walk around (P7, 59f)

Another group of patients stayed at home and cut themselves off from their external environment. These patients often reported changes in mood and that they sometimes behaved defensively and aggressively.

> It isn′t interesting anymore. I watch no news. It is all the same to me whatever happens anywhere in the world (P4, 63m)

Despite these differences between the two groups of patients, family is an important factor for both. They need support from the family to deal with the disease but they do not want to be a burden to their family. Nevertheless, patients report positively about the family growing closer together and building a better relationship, although the family was shocked about the diagnosis and it is difficult for them to deal with the situation.

> The family recognized if somebody does not feel well, then you must stick together. (P5, 48f)

There were, however, quite contradictory experiences concerning the circle of friends. Some patients distanced themselves from their friends and in some cases lied to them in order to avoid talking about their real problems.

> Well, the behaviour of friends that you spend time with is of course always a little/they said it again today, everyone always says 'Oh, you're looking good!' And then I think to myself: 'Oh! I don't want to hear that word again!' Because it's always such a poor little cancer patient, as though all of them walk around with bald heads or wigs, which constantly remind everyone of the situation. So one is/I am never free of the situation in that sense. (P18, 67f)

However, for patients without a family, their circle of friends was of great importance, providing household support or rides to hospital. For these patients, friends were indispensable. Altogether, chemotherapy leads to high physical and psychological strain for the patients. Strategies for dealing with these problems differ between the patient groups. Nevertheless, contact and support from family plays an important role for patients.

Discussion

Patients with lung cancer have had a variety of experiences that have affected their physical, psychological, and organizational areas of life. During the interviews, the patients with lung cancer sometimes directly reported their preferences to support and improve treatment. In addition, based on the patient-reported experiences, further recommendations can be derived. This section focuses on improvements to the treatment of patients with lung cancer, and distinguishes between patients' reported wishes and recommendations based on their reported experiences, in which some criteria mutually influenced each other. In other words, an improvement in organizational factors could, for example, enhance mental factors too.

First, some patients complained about long waiting times during chemotherapy and desired a more acceptable design of waiting times. This included greater privacy, such as through extra curtains or smaller treatment rooms. Other studies also identified the waiting time as an important aspect,[10,16,17] because patients get frustrated, angry, and irritated. Mitchell *et al.*'s results show that patients think that the 'delay in the clinic might be caused by adverse events, staff shortages and the general pressure of the throughput of patients'.[10] Conversely, in our study, patients expressed the opinion that the waiting time could not be reduced but, instead,

better shaped. Nevertheless, it could be an option to reduce the waiting time during chemotherapy by the family doctor taking a blood sample 1 day earlier so that the patients start the treatment day by directly discussing the treatment plan with the physician in the clinic. As the waiting time would be reduced, this could also improve the situation for the accompanying person.

Second, some patients reported problems communicating with their health insurance company concerning travel costs. Therefore the health insurance should optimize their quality and time of advice for these patient groups. Another option is to use and integrated these problems into the existing structure in the clinics. Although patients have the support of the physicians and nurses, this is not always sufficient. The capacity for so-called case managers, which are often located at the clinic, should be increased so that they have more time to go through the application documents together with the patients. However, a systematic review of the use of such measures to optimize cancer care pathways shows that case management is a black box, and it is not clear which areas contribute to an improvement of the pathways, due to different or unclear definitions.[18] Therefore, the case manager could have a gatekeeper function to optimize the treatment's structure, or the function of an advocate to answer labour and social law questions. It is also possible for the health insurance company to provide additional consultancy services that are specialized in treatment-related problems for patients with cancer using health insurance.

Third, the interviews showed the patients' general satisfaction with their physicians. Leydon *et al.* [19] confirmed this relationship of trust by patients with cancer. Frequently changing physicians in the clinic was perceived negatively by patients, and a German study reached the same conclusion.[20] To improve the patients' understanding of this situation, physicians should look for an open and honest conversation with patients and should respect their personality.

Fourth, patients with lung cancer reported different preferences regarding forms of communication. Some patients preferred personal contact with the physicians, while others favoured communication via telephone. In particular, those patients with a long distance to travel wanted to receive information via telephone. Thus, to communicate with patients in their preferred way, physicians should ask their patients at the beginning of the therapy which method of communication they want to use.

In addition, patients required more information about the treatment of side-effects. Comprehensive information about the chemotherapy itself existed, but there was a lack of clear treatment options for possible side-effects. Clinic staff should advise who the appropriate contact partners are for the patients. A further possibility would be to integrate patients into an interdisciplinary 'tumour board'. The National Cancer Institute defined a tumour board as a 'treatment planning approach in which a number of doctors who are experts in different specialties (disciplines) review and discuss the medical condition and treatment options of a patient.[21] This includes medical, surgical and radiation oncologists. Within such a meeting, patients could be truthfully informed about side-effects and treatment options by specialists. Better treatment of side-effects could also positively influence patients' abilities to participate in work and social life. This tumour board should be convened during the process of therapy decisions, as well as in the course of individual treatment steps, as patient-reported experiences might be relevant for the subsequent treatment steps.

Fifth, another fear that patients had was the financial burden, not only because of the inability to work, but also due to the indirect costs, for example those caused by searching for a driver to the clinic. This form of stress was associated with a high psychological burden for patients and their family. Timmons *et al.* [22] also confirm these results in a qualitative analysis of patients with breast, lung and prostate cancer. Thus, greater support in the household and subsidies for taxi expense could lessen this burden.

Limitations

Some study limitations need to be acknowledged. This study was conducted in one large clinic with a centre of supramaximal care, which limits the transferability of the organizational findings to other, especially smaller, clinics. Nevertheless, the organizational process of chemotherapy is largely standardized, particularly in centres with certification, which means that the organizational aspects may not be different in other clinics. Furthermore, some patients had prior experiences with other clinics. As this study only included patients from the German health-care system, the transferability of the experiences with the health insurances is limited. Additionally, the interviews were conducted in the rooms of the oncology outpatient day clinic. Patients may have answered questions incompletely or dishonestly. However, as the interviewer was not a member of the clinic, she may have been more likely to create an atmosphere of trust compared to a clinic member. Finally, a selection bias may have affected the results because we could not interview patients whose state of health did not allow study participation. This group of patients could have had other treatment-related experiences and different preferences for chemotherapy.

Conclusion

This study analysed the burden for patients with lung cancer caused by the treatment. Compared to other studies, we identified relevant experiences that influenced the atmosphere and well-being of patients with lung cancer during chemotherapy. Therefore, we identified that the experiences with organizational processes, health insurance, physicians, and physical and psychological side-effects influenced the patients' preferences. Furthermore, we used the identified experiences and preferences to derive recommendations about how the treatment can be modified. Based on their experiences, the following potential areas for improvement were defined: changing the waiting times, providing more information about the side-effects of the treatment options, making individual arrangements regarding communication methods between the physician and patient and improving information about the changing physicians during treatment. With these changes, patients could feel better during chemotherapy and have fewer fears so that their quality of life could be improved. They are also more likely to accept organizational limitations, such as waiting times.

Conflicts of interest

No conflicts of interest have been declared.

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