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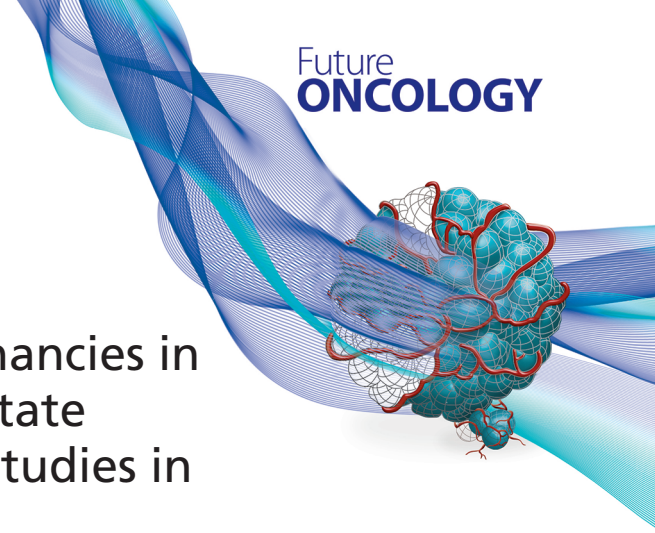

Incidence of second primary malignancies in metastatic castration-resistant prostate cancer: results from observational studies in three countries

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Aim: This reports some of the first incidence rate (IR) estimates of second primary malignancies (SPMs) in men with metastatic castration-resistant prostate cancer (mCRPC) in three countries. **Patients & methods:** Claims data from the German Pharmacoepidemiological Research Database; registry data from the Prostate Cancer Data Base Sweden; and combined registry-claims data from the US Surveillance, Epidemiology and End Results-Medicare database were analyzed to obtain overall survival and incidence of SPMs in men with mCRPC. **Results:** SPMs occurred in 308 German (n = 2360), 273 Swedish (n = 2849) and 172 US (n = 2234) men with mCRPC. IRs of SPMs were 79.0 (95% CI: 70.4–88.4), 101.7 (95% CI: 90.3–114.5) and 59 (95% CI: 50–68) per 1000 person-years in German, Swedish and US cohorts, respectively. **Conclusion:** These studies report some of the first IR estimates of SPMs in men with mCRPC, providing a historical risk estimate of SPM in this patient population.

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Keywords: healthcare data • prognosis • prostate cancer • risk estimate • second primary malignancies

Prostate cancer (PC) is the second most common form of cancer in men with approximately 1.3 million incident cases globally in 2018, accounting for 7.1% of all incident noncutaneous malignant neoplasms [1]. At diagnosis, higher Gleason grade, higher nuclear grade and larger tumor volume have been shown to be predictors of death in prostate cancer [2]. The morbidity and mortality of PC are also strongly associated with its propensity to metastasize to the bone, which occurs in approximately 90% of men with advanced PC [3,4,5]. The growth and spread of prostate tumors are promoted by androgen signaling via the androgen receptor (AR) [6,7]. When bound to androgen ligands, this intracellular receptor drives growth, differentiation and survival of cancer cells [7,8]. The AR can be activated in the absence of native ligand by growth factors, like IGF-I, cytokines or kinases [6,7,8].

Owing to the androgen sensitivity of PC, hormone ablation via medical androgen deprivation therapy (ADT) or surgical castration is the cornerstone of treating advanced PC [9,10]. Although hormone ablation has a high initial response rate, patients generally experience disease progression within 1–3 years as the PC becomes androgen independent [11]. Tumors resistant to ADT are termed castration-resistant prostate cancer (CRPC) [11].

Most patients eventually develop metastases, thus progressing into the metastatic castration-resistant prostate cancer (mCRPC) disease state [12]. The most common site of metastases is the bone, which is associated with a substantial decrease in life expectancy for men with PC. 1- and 5-year survival rates have been estimated at 87.0% (95% CI: 86.5–87.4) and 55.8% (95% CI: 54.9–56.7), respectively, for those without bone metastases, compared with 47.4% (95% CI: 44.1–50.6) and 2.7% (95% CI: 2.2–3.4), respectively, for those with bone metastases [13].

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Table 1. Comparison of data sources used in the three studies.

	Type of data source	Population covered	Representativeness of country population
GePaRD (Germany)	Claims database	~20% of the German general population across all regions of the country	Representative of the German general population with regard to age, sex and region of residence [33,34]
PCBaSe (Sweden)	Prostate cancer registry linked to other nationwide registries†	Covers 98% of all newly diagnosed cases of prostate cancer in Sweden [45]	Representative of all men diagnosed with prostate cancer in Sweden [31]
SEER-Medicare (USA)	Cancer registry-claims database	~94% of the US population aged ≥65 years [46]	Broadly representative of the general US population aged ≥65 years [32]

†Linked registries comprising the PCBaSe include the Swedish Cancer Register, National Patient Register, Swedish Prescribed Drug Register, Cause of Death Register and Population Register.
GePaRD: German Pharmacoepidemiological Research Database; PCBaSe: Prostate Cancer Data Base Sweden; SEER: US Surveillance, Epidemiology and End Result.

Population-based studies in several tumor types, including PC, have shown that patients with metastatic disease are at increased risk for the development of second primary malignancies (SPMs). With the development of novel agents that extend overall survival, including abiraterone, cabazitaxel, enzalutamide, radium-223 and sipuleucel-T [14,15,16,17,18], patients with mCRPC may be at an increased risk for developing SPMs; however, data from patients with mCRPC are limited [19,20,21,22]. Moreover, the treatments patients receive for prostate cancer may have unintended side effects, including SPMs after radiation therapy [19,20,21,22]. Information on the incidence of SPMs in this patient population are important for informing future monitoring and management.

The objective of this report is to summarize the results from three distinct population-based, observational cohort studies that assessed the overall incidence of SPMs, site-specific incidence of the SPMs and overall survival among German, Swedish and US men with mCRPC. The three cohort studies were similar in design and were conducted contemporaneously with the common goal of obtaining representative rates of SPMs in three distinctive databases, healthcare systems and geographies [23].

Patients & methods

Data sources

Secondary claims data from the German Pharmacoepidemiological Research Database; registry data from the Prostate Cancer Data Base Sweden [24], which includes data from the National Prostate Cancer Register of Sweden linked with other national health registers (i.e., the Swedish Cancer Register, National Patient Register, Swedish Prescribed Drug Register, Cause of Death Register and Population Register); and combined registry-claims data from the US Surveillance, Epidemiology and End Results (SEER)-Medicare linked database administered by the US National Cancer Institute (NCI) were analyzed (Table 1). Full description of these sources and data quality is provided in the 'Supplementary methods' section in Supplementary Materials. The three studies described here adhered to the Guidelines for Good Pharmacoepidemiology Practices by the International Society for Pharmacoepidemiology.

Cohort enrollment in the German study was from 1 January 2004 to 31 December 2011, with follow-up ending 31 December 2013. For the Swedish study, the time period of 1 January 1998 to 31 December 2011 was used to identify men with PC, with follow-up ending 31 December 2013 [25]. Because information on drug purchases in Sweden is only available from 1 January 2006 onward, only data from 1 January 2007 to 31 December 2011 were used in identifying mCRPC to ensure ≥1 year of history before enrollment and ≥2 years of potential follow-up time per patient. For the US study, SEER data on PC diagnoses was available through 2011, so PC was identified during the time period from 1 January 2000 to 31 December 2011 [26]. Linked Medicare data was used for follow-up to 31 December 2013.

Cohort entry dates for the German and Swedish cohorts were the dates of first observed bone metastasis; for the US cohort, the cohort entry date was the date on which the patient first received a therapy representing a second-line systemic treatment for PC after ADT [25,26]. Follow-up ended at the occurrence of an SPM, the end of the study period, when registry-tracked insurance coverage lapsed (i.e., for emigration, death or discontinuation of Medicare Parts A or B coverage [USA] or when insurance coverage ended due to any reason including death [German cohort]).

Cohort study objectives

The primary objective for each of the three studies was to estimate the incidence of any SPM among men with mCRPC. Secondary objectives were to estimate the incidence of site-specific SPMs and to evaluate the overall survival of men with mCRPC.

Patient eligibility criteria

Eligible patients for all studies were men with a primary diagnosis of PC, which was coded as C61 in the German and Swedish cohorts (International Classification of Diseases, 10th Revision [ICD-10]) and as Code C61.9 with behavior code '/3' (malignant) in the SEER database for the US cohort (ICD for Oncology, Third Edition [ICD-O-3]). In the German and Swedish cohorts, only men with PC and a history of bone metastases (ICD-10 Code C79.5) were included; they were required to have data available for ≥1 year before the first diagnosis of bone metastasis.

Men in the US cohort were required to be enrolled in both Medicare Parts A and B for ≥1 year before the cohort entry date and continuously between the date of initial diagnosis of PC and the cohort entry date. Unlike the German and Swedish studies, the US study only used the initiation of second-line systemic therapy after ADT to define the included population (i.e., history of bone metastasis was not an explicit inclusion criterion). Because metastases occurring after diagnosis do not impact the amount of reimbursement to the Medicare provider, metastases are less likely to be completely captured and accurately coded [27]. Therefore, using ICD-9 codes in the SEER-Medicare data to identify patients with metastatic disease occurring after the initial cancer diagnosis will result in an incompletely and inaccurately classified cohort, and such use was not permitted by the NCI reviewers of the US study design. Although the US study differed from the others in not requiring the presence of bone metastases as a criterion for inclusion, it was found that 84.5% of the men in the US study had either a history of bone metastases recorded in their claims data or were prescribed second-line, bone-targeting therapy (a proxy for bone metastases), or both [26]. Therefore, the investigators concluded that most men in the US cohort had evidence of bone metastases (i.e., mCRPC) and thus could be comparable to the German and Swedish studies.

For identification of castration resistance in all studies, men must have undergone surgical castration or received medical ADT after PC diagnosis and had evidence that the PC was resistant to surgical castration or ADT, as previously published for the US study [26]. Resistant disease was indicated by starting one of the following second-line systemic therapies: abiraterone, cabazitaxel, docetaxel, enzalutamide, estramustine (German cohort only), ketoconazole (German and Swedish cohorts only), mitoxantrone or sipuleucel-T. For the German and Swedish cohorts, resistant disease was also defined as initiation of ADT treatment, chemotherapy or mitoxantrone ≥1 month after surgical castration; discontinuation of ADT; or change of the agent or modality of ADT. For the German and Swedish cohorts, identification of resistant disease must have occurred any time before diagnosis of bone metastasis, or within 30 days after the diagnosis.

Exclusion criteria were having a first PC diagnosis later than 2 months after the diagnosis of bone metastases (German and Swedish cohorts); enrollment in a health maintenance organization (US cohort) during the year before cohort entry; having a diagnosis of any other cancer (except nonmelanoma skin cancer) on or before the cohort entry date (US study); or having any diagnostic code for metastases (other than bone or lymph node metastases) on or before the cohort entry date (US study). The use of any radiopharmaceutical for bone metastases (e.g., samarium, strontium, rhenium or radium) was also a key exclusion criterion in the German and Swedish studies.

Outcomes

Events of SPM were defined as diagnoses of incident malignancies after cohort entry. In the German and Swedish databases, SPM events (ICD-10 codes: C00-C76, C81-C96, excluding C61) were considered incident if the respective ICD-10 code – with accuracy of three digits – had not occurred before cohort entry (e.g., C16.1 was counted as a first record only if the same person had no history of C16 ICD-10 codes). This applied for both any SPM and the respective site-specific SPMs. In the German study, the date of the diagnosis was defined as the hospital admission date for inpatient diagnoses, or as the first coded diagnostic or therapeutic procedure from the diagnosing physician in the quarter of the outpatient diagnosis. An outpatient diagnosis had to be confirmed by an inpatient or a second outpatient diagnosis within 183 days. In the German and the Swedish studies, analyzed sites of SPM included the bladder, colon, lung and rectum; leukemia was also included. *In situ* neoplasms and neoplasms of uncertain or unknown behavior (ICD-10 codes D00-D09, D37-D48) were explicitly excluded.

In the US cohort, SPM events were identified through either SEER or Medicare records. In the SEER data, an SPM event was identified when there was a diagnosis of a nonprostate primary cancer after cohort entry. In the Medicare data, an SPM event was identified after cohort entry as an ICD-9-CM code for a primary malignancy (other than nonmelanoma skin cancer or PC) associated with one hospitalization or with two hospital outpatient visits or with two physician visits. The SEER-Medicare Data Use Agreement prohibits reporting cell counts <11 or providing information (e.g., event counts or incidence) that could allow the calculation of cell counts <11. To prevent such reporting, lower-frequency SPMs were grouped to yield reportable numbers. The cancer type categories analyzed were lung/bronchus; urinary bladder; colon/rectum; nonprostate, nonbladder genitourinary tract (including kidney, ureters, urethra and testis); noncolorectal GI tract (including esophagus, stomach, small intestine, liver, biliary tract and pancreas); non-Hodgkin lymphoma and myeloma; brain; meningeal, head, neck and endocrine; melanoma, breast and nipple; and miscellaneous or unspecified.

Statistical methods

Study population characteristics were described by summary statistics for categorical and continuous variables, respectively. Incidence of SPMs was reported as the incidence rate (IR) per 1000 person-years by dividing the number of incident cases by the accumulated person-time (per 1000 person-years) in the cohort (until SPM occurred or cohort exit, whichever came first). Corresponding 95% CIs of the IRs were calculated based on the substitution method assuming a Poisson distribution of the cases [28]. The survival function was estimated by the Kaplan–Meier method.

Sensitivity analyses

In both the German and Swedish cohorts, several identical sensitivity analyses were conducted. For the first of these sensitivity analyses, in addition to the other previously defined inclusion criteria, chemical castration, surgical castration, radical prostatectomy, CRPC treatment or mCRPC treatment served as a proxy for initial PC diagnosis; denosumab, clodronate or other parenterally administered bisphosphonates initiated after PC diagnosis served as an additional proxy for bone metastasis diagnosis; and, patients with ≥6 months since the first ADT and an indication of first metastatic PC (bone metastases diagnosis or proxy) were also included in the mCRPC population. In a second sensitivity analysis, the mCRPC population was defined as those individuals from a larger metastatic PC population who had received either CRPC or mCRPC treatment, with cohort entry date defined as the date of first purchase of one of these drugs. In the third and fourth sensitivity analyses, the mCRPC population was defined by excluding men with any other cancer or visceral metastases before cohort entry date.

In the German study, an additional sensitivity analysis was carried out by considering only inpatient diagnoses for the identification of SPMs. In the Swedish study, the analyses of any SPM and skeletal-related events were reperformed without censoring time after the first event, with only those cases that differed from earlier incidences counted as events [25].

In the US cohort, a sensitivity analysis was conducted to assess the effect on the estimated IRs by varying the criteria for identifying SPM, including counting only SPM events that were identified in the SEER data [29].

Results

Participants

In total, 7443 men with mCRPC were included in this analysis, with similar numbers of men included from each of the cohorts: German (n = 2360), Swedish (n = 2849) and US (n = 2234) (Table 2). The mean ages at the time of cohort entry were 72.9, 75.6 and 76.6 years for the German, Swedish and US populations, respectively (previously reported for the US study [26] and the Swedish study [25]). The mean time from the initial diagnosis of PC to progression to mCRPC was 3.4 ± 2.0, 5.8 ± 3.0 and 3.5 ± 2.7 years in the German, Swedish and US populations, respectively. Other patient characteristics from each study are shown in Table 2.

Incidence of SPM

The overall IRs of SPM were 79.0 (95% CI: 70.4–88.4), 101.7 (95% CI: 90.3–114.5) and 59 (95% CI: 50–68) per 1000 person-years in the German, Swedish and US cohorts, respectively (Table 3). IRs were similar across age categories, and no trend was observed when IRs were compared across age categories in any of the cohorts.

Sensitivity analyses in the German cohort yielded slightly lower IRs (per 1000 person-years) when mCRPC treatments were used as sole proxies to define the mCRPC cohort (69.9; 95% CI: 58.9–82.3), when using the

Table 2. Patient characteristics in the three studies.

	German cohort (GePaRD) n = 2360	Swedish cohort (PCBaSe) n = 2849	US cohort [26] (SEER-Medicare) n = 2234
Age at cohort entry, years			
Mean (SD)	72.9 (7.8)	75.6 (8.1)	76.6 (6.2)
Age group, years, n (%)			
<65	315 (13.3)	291 (10.2)	N/A[†]
65–69	478 (20.3)	359 (12.6)	297 (13.3)
70–74	563 (23.9)	515 (18.1)	625 (28.0)
75–79	514 (21.8)	679 (23.8)	595 (26.6)
80–84	336 (14.2)	644 (22.6)	451 (20.2)
≥85	154 (6.5)	361 (12.7)	266 (11.9)
Time since first PC diagnosis, years			
Mean (SD)	3.4 (2.0)	5.8 (3.0)	3.5 (2.7)
Time since PC diagnosis, years, patient numbers (%)			
<1	209 (8.9)	66 (2.3)	340 (15.2)
1–2	915 (38.8)	243 (8.5)	502 (22.5)
>2	1236 (52.4)	2540 (89.2)	1392 (62.3)

[†]Data from the US study only included men aged ≥65 years at the cohort entry date.
GePaRD: German Pharmacoepidemiological Research Database; PC: Prostate cancer; PCBaSe: Prostate Cancer Data Base Sweden; SD: Standard deviation; SEER: US Surveillance, Epidemiology and End Result.

Table 3. Incidence rates of second primary malignancy in the three studies.

	German cohort (GePaRD)			Swedish cohort (PCBaSe)			US cohort (SEER-Medicare)		
	Events	Person-years	IR (95% CI) (per 1000 person-years)	Events	Person-years	IR (95% CI) (per 1000 person-years)	Events	Person-years	IR (95% CI) (per 1000 person-years)
Overall	308	3900	79.0 (70.4–88.3)	273	2686	101.7 (90.3–114.5)	172	2922	59 (50–68)
Age at SPM, years									
<65	42	460	90.7 (65.3–122.6)	33	295	112.0 (79.6–157.6)	N/A[†]		
65–69	56	700	80.6 (60.9–104.6)	34	443	76.7 (54.8–107.4)	30	551	54 (37–78)
70–74	79	1060	74.2 (58.8–92.5)	66	605	109.0 (85.6–138.8)	63	920	68 (53–88)
75–79	73	890	81.8 (64.1–102.9)	62	628	98.7 (76.9–126.6)	37	747	50 (35–68)
80–84	40	570	70.4 (50.3–95.8)	51	470	108.6 (82.5–142.9)	42	704	60 (43–81)[‡]
≥85	18	210	83.9 (49.7–132.5)	27	244	110.5 (75.8–161.1)			

[†]Data from the US study only included men aged ≥65 years at the cohort entry date.
[‡]Categories 80–84 years and ≥85 years were combined to avoid reporting a count <11, which is prohibited by the SEER-Medicare data use agreement.
CI: Confidence interval; GePaRD: German Pharmacoepidemiological Research Database; IR: Incidence rate; PCBaSe: Prostate Cancer Data Base Sweden; SEER: US Surveillance, Epidemiology and End Result; SPM: Second primary malignancy.

alternative three-step mCRPC definition (69.6; 95% CI: 63.2–76.4), when men who had ever been diagnosed with any SPM at cohort entry date were excluded from the mCRPC cohort (68.1; 95% CI: 56.0–82.1), or when men who had ever been diagnosed with any visceral metastasis at the cohort entry date were excluded from the mCRPC cohort (72.8; 95% CI: 64.2–82.2). When only inpatient SPM diagnoses were considered, the IR of SPM showed a notable decrease to 44.7 (95% CI: 38.5–51.7) per 1000 person-years.

Sensitivity analyses in the Swedish cohort yielded slightly lower IRs (per 1000 person-years) when using the alternative three-step mCRPC definition (95.8; 95% CI: 86.8–105.7), when mCRPC treatments were used as sole proxies to define the mCRPC cohort (87.5; 95% CI: 69.9–109.6), or when men who had ever been diagnosed with any SPM at cohort entry date were excluded from the mCRPC cohort (91.9; 95% CI: 78.2–108.1). When men

Table 4. Site-specific incidence of second primary malignancy.

n (%)	German cohort (GePaRD) n = 2360	Swedish cohort (PCBaSe) n = 2849	US cohort [26] (SEER-Medicare) n = 2234
Urinary bladder	40 (13.0%)	29 (10.6%)	22 (12.8%)
Lung	37 (12%)	16 (5.9%)	29 (16.9%)†
Colon	13 (4.2%)	15 (5.5%)	21 (12.2%)‡
Nonprostate, nonbladder genitourinary tract			18 (10.5%)
Noncolorectal GI tract			17 (9.9%)

†Includes lung and bronchus.
‡Includes colon and rectum.
GePaRD: German Pharmacoepidemiological Research Database; GI: Gastrointestinal; PCBaSe: Prostate Cancer Data Base Sweden; SEER: US Surveillance, Epidemiology and End Result.

Table 5. Estimated probability of survival at 1, 3 and 5 years in the three studies.

Study cohort	Estimated probability of survival, % (95% CI)		
	1 year	3 year	5 year
German cohort (GePaRD)	58 (56–60)	26 (24–28)	17 (15–18)
Swedish cohort (PCBaSe)	37 (35–38)	9 (8–10)	4 (3–5)
US cohort (SEER-Medicare) [26]	56 (54–58)	17 (15–18)	9 (7–11)

CI: Confidence interval; GePaRD: German Pharmacoepidemiological Research Database; PCBaSe: Prostate Cancer Data Base Sweden; SEER: US Surveillance, Epidemiology and End Result.

who had ever been diagnosed with any visceral metastasis at the cohort entry date were excluded from the mCRPC cohort, the respective overall SPM incidence was not different from that of the original analysis (100.5; 95% CI: 89.0–113.6). When time after the first event during follow-up was not censored, the estimated overall SPM incidence in the mCRPC cohort was slightly higher than that in the original analysis (104.1; 95% CI: 93.0–116.5).

The US study also assessed the effect of varying requirements for defining SPM, ranging from less restrictive (a single claim in any Medicare file or a SEER diagnosis) to more restrictive (a SEER diagnosis only) criteria [29]. Analysis using only SEER data to identify SPMs yielded a lower IR of SPM (9.7 [95% CI: 5.9–15] per 1000 person-years).

Site-specific incidence of SPM

Of all SPMs, the most commonly reported cancers in all three cohorts were those of the urinary bladder, lung and colon, as summarized in Table 4. Secondary solid tumors occurred with an incidence of 67.4 (95% CI: 59.2–76.5) and 96.6 (95% CI: 85.5–109.0) in the German and Swedish cohorts, respectively. In accordance with the NCI's Data Use Agreement, the counts and IRs of all secondary solid tumors are not reported for the US cohort to avoid reporting or prevent calculation of numbers <11 for the remaining SPMs.

For the two most common sites of SPM, bladder and lung, IRs per 1000 person-years were 10.3 (95% CI: 7.3–14.0) and 9.5 (95% CI: 6.7–13.0), 10.0 (95% CI: 6.97–14.4) and 5.5 (95% CI: 2.3–9.0), and 7.5 (95% CI: 4.7–11) and 9.9 (95% CI: 6.6–14), for the German, Swedish and US cohorts, respectively. Other nonprostate, nonbladder genitourinary tract SPMs, which were only reported collectively in the US study, occurred with an IR of 6.2 (95% CI: 3.7–9.7) per 1000 person-years.

The IRs of hematologic malignancies including leukemia were generally too low to be evaluated in all cohorts.

Overall survival

Median survival time in these studies was 1.3 years (95% CI: 1.2–1.4), 0.6 years (95% CI: 0.6–0.7) and 1.2 years (95% CI: 1.1–1.3) in the German, Swedish and US cohorts, respectively (previously reported for the US study [26] and the Swedish study [25]) (0ptFigure 1). Estimated survival probabilities at 1, 3 and 5 years are shown in Table 5.

Discussion

The results of these large population-based, observational cohort studies using high-quality registry and healthcare data from three countries fill an important scientific gap in knowledge about the incidence of SPM among men with mCRPC. Until recently, the standard of care for men with an initial diagnosis of metastatic PC was continuous medical ADT [30]. Use of second-line therapies, such as docetaxel or abiraterone, in combination with medical ADT, has only become common in the last 4–5 years, after large trials showed significant survival benefit in

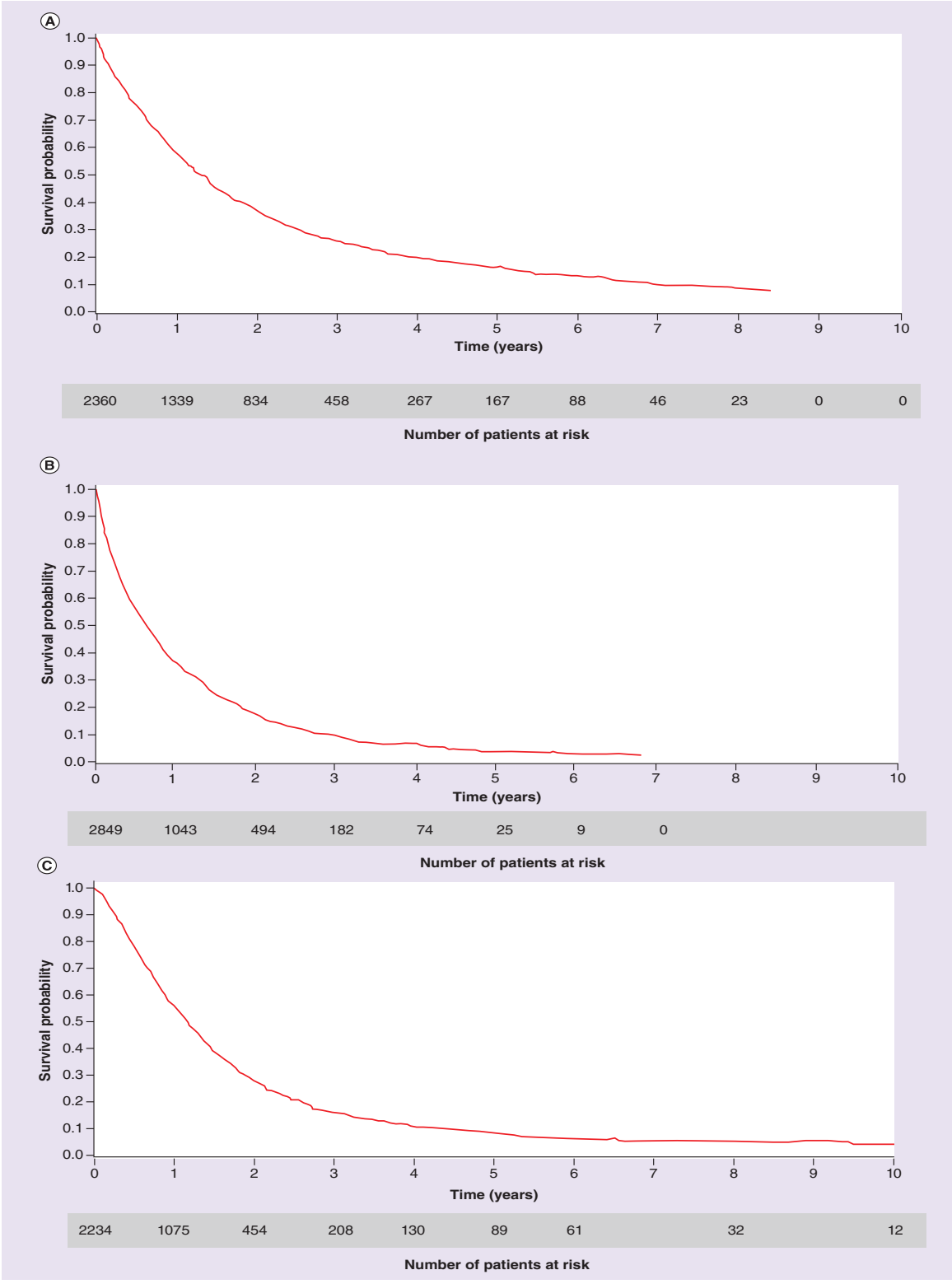

Figure 1. Kaplan–Meier estimates for overall mortality. (A) German cohort (**GePaRD**); **(B)** Swedish cohort (**PCBaSe**); **(C)** US cohort (**SEER-Medicare**). Note: Data on the number of subjects at risk for year 7 and year 9 were omitted to avoid reporting a count less than 11, which is prohibited by the SEER-Medicare data use agreement.
GePaRD: German Pharmacoepidemiological Research Database; PCBaSe: Prostate Cancer Data Base Sweden; SEER: US Surveillance, Epidemiology and End Result.

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Table 6. Summary of results from the three studies in men with metastatic castration-resistant prostate cancer.

	Summary
n (total)	7443
Mean ages	Ranges from 72.9 to 76.6
Overall SPM events	753
Median survival	<1.5 years
Overall IRs of SPM	Range from 59 to 101.7 per 1000 person-years
Most common SPMs	Bladder (ranging from 7.5 to 10.3 per 1000 person-years) Lung (ranging from 5.5 to 9.9 per 1000 person-years)

IR: Incidence rate; SPM: Second primary malignancy.

men with metastatic PC [30]. With the increased survival benefit from treatments such as abiraterone, cabazitaxel, enzalutamide, radium-223 and sipuleucel-T [14,15,16,17,18], patients with mCRPC may be at an increased risk for developing SPMs, making them important to characterize.

Data sources for these studies are representative of the populations of their respective countries: the Prostate Cancer Data Base Sweden is highly representative, and contains data on all men diagnosed with prostate cancer in Sweden [31]; the SEER-Medicare database is representative of the general US population aged 65 years or older [32]; and the German Pharmacoepidemiological Research Database comprises a large database of secondary (health claims) data from the general German population [33,34]. The epidemiological data presented here are some of the first, to our knowledge, to address the incidence of SPMs in men with mCRPC.

Rates of SPM were found to be highest in the Swedish cohort (101.7 [95% CI: 90.3–114.5] per 1000 person-years), and lowest in the US cohort (59 [95% CI: 50–68] per 1000 person-years). It cannot be ruled out that any of these IR values may have been overestimated due to the recording of false positive events. For example, urinary bladder and 'nonprostate, nonbladder genitourinary tract cancers could potentially be misclassified as SPMs rather than regional spread of PC, and it cannot be excluded that some physicians recorded these diagnoses instead of, or in addition to, the code for PC. It is, therefore, possible that misclassification could explain some of the IR differences among the three countries evaluated here.

Median survival times for men with mCRPC were similar in the German and US cohorts, and lower in the Swedish cohort. Estimates of median survival in each country were less than 1.5 years, which are in agreement with those reported in randomized trials of men with mCRPC (Table 6) [17,18]. Although therapeutic alternatives are evolving rapidly and several have shown survival benefit for men with mCRPC, the relatively short survival time of men with mCRPC should be taken into consideration when assessing the potential risks of new therapies that palliate symptoms or improve function for these patients [35].

Considering the IRs of different cancer types in the older general population (≥65 years), this study suggests that men with PC and bone metastases may have a substantially increased risk of SPMs (Table 6). For instance, SEER reports an age-adjusted IR of 3.84 per 1000 for primary cancers of the lung/bronchus in men aged 65 years and older in the US during the period 2011–2015 [36]; the studies reported here found IRs for lung/bronchus cancer as SPM ranging from 5.5 (95% CI: 2.3–9.0) to 13.2 (95% CI: 9.4–17.8) per 1000 in men with mCRPC.

Among cancer survivors in the general population, according to SEER data from 1992 to 2008, the most common sites of second malignancy were lung, colorectal, prostate and bladder, found in 18, 12, 9 and 8% of all cancer survivors, respectively [37]. Our analyses found that bladder and lung were the most common sites of SPMs in patients with mCRPC. Studies have shown prostate cancer patients might have an inherently increased risk of bladder cancer, especially after radiotherapy, which would support the difference seen from the general cancer survivor population [22].

Local specifics of the claims/registry data or the local healthcare system may have affected the observed IRs of SPM in the different geographies. Differences in the healthcare systems among these three countries (e.g., adjudication process for claims, universal coverage on medical expenditures, differences in out-of-pocket spending) might have differentially encouraged men to comply with follow-up appointments and could, therefore, have affected the detection of SPMs. In Germany, for example, information about patients with cancer may not be captured in hospital data – or only at a later stage-because centers often bill on an outpatient basis only. In contrast, outpatient cancer diagnoses may be recorded for suspected cancers, which may have contributed to the high IRs. Further investigations would be required to assess the validity of recorded outpatient SPM diagnoses. Moreover, there is

evidence implicating environmental factors in the progression of prostate cancer [38]. For instance, abnormalities in carbohydrate metabolism such as insulin resistance are commonly associated with the western lifestyle and obesity. Insulin resistance causes circulating levels of insulin and IGF-I to be high, which can activate the AR, leading to prostate cancer growth and progression [38]. The different geographies and lifestyles of the claims/registry data may help explain the differences seen in SPMs, and may limit its transferability to other populations.

Additionally, regarding the exclusion of men with previously diagnosed malignancies (other than nonmelanoma skin cancer) in the US study, it is likely that this criterion decreased the possibility of the misinterpretation of previous malignancies as SPMs during follow-up. However, it may have also contributed to the lower SPM rate observed in the SEER-Medicare cohort, as it is theoretically possible that men with a history of some other (nonprostate) cancer before developing CRPC might have a higher rate of yet another (i.e., a third) cancer than men who had no history of another cancer before developing CRPC.

A key limitation of these studies is that CRPC must be determined by proxy, as CRPC is a clinical diagnosis that is not recorded in a coded field within administrative health insurance or registry databases. Furthermore, information that is required to identify CRPC more definitively (serum testosterone levels, prostate-specific antigen measurements and results of imaging studies) is not available in the registries and Medicare claims data. Therefore, these investigations used a pragmatic approach and defined mCRPC based on administration of 'second-line' treatments, changing of medical ADT, or discontinuation of medical ADT after surgical or medical castration to indicate that progression had occurred despite castration. Although the use of additional medications (beyond ADT) was appropriate for identifying CRPC during the time period we studied, it will likely not be a valid approach hereafter because subsequent clinical trials have demonstrated a survival benefit for simultaneous treatment with docetaxel plus ADT or with abiraterone plus ADT as compared with ADT alone in selected subgroups of men with advanced PC and no previous ADT [39,40,41,42]. Similar results have also been reported recently for apalutamide and enzalutamide [43,44].

Another limitation of this report arises from the reporting of both registry and claims data. Although both collect data that can be used to monitor diagnosis, disease characteristics and treatment, it should be noted that the objective of the former is to provide data for quality assurance and improvement, whereas the objective of the latter is to collect data for billing and reimbursement. That these objectives are not the same could result in differences when comparing data from registry and claims databases. Indeed, in an exploratory analysis, we found that that the inclusion of *in situ* neoplasms and neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes (i.e., ICD-10 D-diagnoses) to identify SPM outcomes in the German and Swedish studies led to higher IRs than those reported here (~3.5- and 1.2-times higher, respectively). The observed elevation in IRs were unsurprising given that, if they were included, patients receiving D-diagnoses would constitute a large proportion (almost 30%) of mCRPC patients in the German study. We hypothesize that, because the German data come from a health claims database and the Swedish data come from a collection of registries, it is likely that D-diagnoses occur more frequently and/or earlier in the German dataset, which would, therefore, lead to a higher estimate of the IR of all SPMs in Germany than in Sweden. Future cancer epidemiologic studies comparing registry and claims data should keep these findings in mind to prevent the potential overestimation of SPM IRs.

Conclusion

The results of this report are based on large, high-quality registry and healthcare data from three countries: Germany, Sweden and the USA. These cohort studies are among the first to provide concurrent estimates of the IR of SPMs in men with mCRPC in three countries and to provide historical information that can be used as a reference for future analyses of SPMs in these patient populations.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0315

Author contributions

J Zong was responsible for the individual studies' conception and design. ZP Vassilev, M Soriano Gabarró, JA Kaye, CW Saltus, O Riedel, O Scholle, J Mehtälä, P Korhonen, E Garbe and J Zong were responsible for data acquisition and analysis, as well as drafting and revision of the manuscript.

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Disclaimer

The main results and sensitivity analyses of the US study have previously been published in references [26] and [29]. The main results and sensitivity analyses of the Swedish study have previously been published in reference [25].

Data & protocol sharing statement

Individual participant data that underlie the results reported in this article will not be shared. In Germany, use of personal data is protected by the Federal Data Protection Act, and particularly the use of claims data for research is regulated by the Code of Social Law. Researchers have to apply for a project-specific permit from the statutory health insurance providers as well as their governing authorities. The use of the data on which this publication is based was only allowed for BIPS employees within the framework of the specified project and limited to a predefined time span. Researchers who want to access the data on which this publication is based need to ask for new approval by the statutory health insurance providers and their respective authorities.

Individual participant data from the Swedish study cannot be directly shared per the data use agreement between EPID Research and Uppsala County Council. The Steering Group of the National Prostate Cancer Register coordinates research projects within the PCBaSe framework and can be contacted in order to submit a request for data. For further information, see http://npcr.se/npcr/medarbetare/

Individual participant data from the US study cannot be shared per the data use agreement between RTI-HS and NCI.

The three study protocols for each of the cohorts are publicly available in the EU PAS Register of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), under EU PAS Register numbers EUPAS12665 (GePaRD), EUPAS33448 (PCBaSe) and EUPAS13602 (SEER program).

Financial & competing interests disclosure

O Riedel and O Scholle are current employees and E Garbe is a former employee of the Leibniz Institute for Prevention Research and Epidemiology – BIPS; J Mehtälä and P Korhonen are employees of EPID Research Oy; and C Saltus and J Kaye are employees of RTI Health Solutions, all of which received funding from Bayer AG to conduct these studies. BIPS, EPID Research and RTI Health Solutions designed their respective studies, acquired the data, conducted the analyses, interpreted study results and decided to submit the article for publication with input from Bayer. Z Vassilev, J Zong and M Soriano-Gabarró are employees of Bayer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The authors state that the studies within this work were conducted using data from the GePaRD (Germany), PCBaSe (Sweden; with data use agreement on 28 November 2016) and NCI's SEER program (USA). Studies were guided by data use agreements between the statutory health insurance providers, the respective governing authorities and the Leibniz Institute for Prevention Research and Epidemiology – BIPS; between the PCBaSE and EPID Research Oy; and between NCI and RTI Health Solutions. According to the Ethics Committee of the University of Bremen, studies based on GePaRD are exempt from institutional review board review. Swedish and US studies were reviewed by their respective institutional review boards, receiving exemptions on 24 October 2016, and 23 February 2016.

Summary points

- With the development of novel agents that extend overall survival, patients with metastatic castration-resistant prostate cancer (mCRPC) may be at an increased risk for developing second primary malignancies (SPMs), making them important to characterize. However, data on SPMs from patients with mCRPC are limited.
- The results of this report are based on large, high-quality registry and healthcare data from three countries, including the German Pharmacoepidemiological Research Database, the Prostate Cancer Data Base Sweden and the US Surveillance, Epidemiology and End Results-Medicare, which are representative of the populations of their respective countries.
- SPMs occurred in 308 German (n = 2360), 273 Swedish (n = 2849) and 172 US (n = 2234) men with mCRPC.
- The overall incidence rates (IRs) of SPM were 79.0 (95% CI: 70.4–88.4), 101.7 (95% CI: 90.3–114.5) and 59 (95% CI: 50–68) per 1000 person-years in the German, Swedish and US cohorts, respectively.
- Bladder and lung SPMs were most common, with IRs per 1000 person-years of 10.3 (95% CI: 7.3–14.0) and 9.5 (95% CI: 6.7–13.0), 10.0 (95% CI: 6.97–14.4) and 5.5 (95% CI: 2.3–9.0), and 7.5 (95% CI: 4.7–11) and 9.9 (95% CI: 6.6–14) for the German, Swedish and US cohorts, respectively. Median survival was 1.3 (95% CI: 1.2–1.4), 0.6 (95% CI: 0.6–0.7) and 1.2 years (95% CI: 1.1–1.3) in the German, Swedish and US cohorts, respectively.
- These cohort studies are among the first to provide concurrent estimates of the IR of SPMs in men with mCRPC in three countries.
- The epidemiological data presented here provide historical information that can be used as a reference for future analyses of SPMs in these patient populations.

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