Original Article

Trends in Incidence and 5-Year Mortality in Men With Newly Diagnosed, Metastatic Prostate Cancer—A Population-Based Analysis of 2 National Cohorts

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BACKGROUND: Early detection has increased prostate cancer (PCa) incidence. Randomized trials have demonstrated that early detection reduces the incidence of de novo metastatic PCa. Concurrently, life-prolonging treatments have been introduced for patients with advanced PCa. On a populations-based level, the authors analyzed whether early detection and improved treatments changed the incidence and 5-year mortality of men with de novo metastatic PCa. **METHODS:** Men diagnosed with PCa during the periods 1980 to 2011 and 1995 to 2011 were identified in the US Surveillance, Epidemiology, and End Results (SEER) program and the Danish Prostate Cancer Registry (DaPCaR), respectively, and stratified according to period of diagnosis. Age-standardized incidence rates were calculated. Five-year mortality rates for de novo metastatic PCa were analyzed using competing risk analysis. **RESULTS:** Totals of 426,266 and 47,024 men were identified in SEER and DaPCaR, respectively. Of these, 29,555 and 6874 had de novo metastatic PCa. The incidence of de novo metastatic PCa decreased (from 12.0 to 4.4 per 100,000 men) in the SEER cohort (1980-2011), whereas it increased (from 6.7 to 9.9 per 100,000 men) in the DaPCaR cohort (1995-2011). Five-year PCa mortality in the SEER cohort was stable for men diagnosed with de novo metastatic PCa from 1980 to 1994 and increased slightly in the latest periods studied ($P < .0001$), whereas it decreased by 16.6% ($P < .0001$) in the DaPCaR cohort. **CONCLUSIONS:** Despite earlier detection, de novo metastatic PCa remains associated with a high risk of 5-year disease-specific mortality. The reduced 5-year PCa mortality in the Danish cohort is largely explained by lead-time. Early detection strategies do indeed decrease the incidence of de novo metastatic PCa, as observed in the SEER cohort. This achievement, however, must be weighed against the unsolved issue of overdetection and overtreatment of indolent PCa. [See editorial on pages 000-000, this issue.] ***Cancer* 2018;000:000–000.** © *2018 American Cancer Society.*

KEYWORDS: epidemiology, incidence, mass screening, metastatic, mortality, prostate-specific antigen, prostatic neoplasms.

INTRODUCTION

Patients with de novo metastatic prostate cancer (PCa) have a high risk of disease-specific mortality.[1,2] An important rationale for the early detection of PCa is to reduce the incidence of de novo metastatic disease as a preliminary step toward a reduction in PCa-specific mortality. The rising incidence of PCa observed in western countries has mainly been driven by an increased use of prostate-specific antigen (PSA) testing.[3] In the United States, PSA-based early detection of PCa increased during the late 1980s, and PSA screening was recommended from the 1990s until 2012.[4,5] In Denmark, PSA-based early detection programs have never been recommended; however, laboratory data and trends in the incidence of PCa suggest that the use of PSA testing increased in the early 2000s.[6,7] Although the effect of PSA-based early detection on PCa-specific mortality is still under debate, early detection has significantly increased the number of men diagnosed with localized and locally advanced disease.[8-10] Randomized clinical trials (RCTs) investigating PSA-screening have demonstrated a reduction in the incidence of de novo metastatic PCa, but this has not been investigated in large, population-based studies.[11]

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See editorial on pages 000-000, this issue.

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TABLE 1. Baseline Characteristics of Men With De Novo Metastatic Prostate Cancer Included in Survival Analysis

	No. of Men (%)					
Year of diagnosis	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2009[a]
Total no.						
SEER	5910	6593	5668	3481	3121	2657
DaPCaR				1518	2204	2411
SEER						
Age: Median [IQR], y	73.0 [67.0-80.0]	74.0 [67.0-80.0]	74.0 [68.0-81.0]	74.0 [67.0-81.0]	75.0 [66.0-82.0]	76.0 [65.0-83.0]
DaPCaR						
Age: Median [IQR], y				74.2 [67.4-79.2]	73.8 [67.3-79.6]	73.2 [66.1-79.3]
PSA: Median [IQR], ng/mL				320 [76-676]	179 [57-500]	146 [46-500]
SEER						
GS[a]	n (%*)	n (%*)	n (%*)	n (%*)	n (%*)	n (%*)
≤7	1872 (45.4)	2239 (43.6)	1994 (35.2)	950 (38.5)	501 (23.5)	107 (6.1)
7-10	—	—	—	—	710 (33.3)	1660 (93.3)
≥8	2251 (54.6)	2895 (56.4)	2458 (43.4)	1515 (61.5)	919 (43.1)	—
NA	4123 (30.2)	1459 (22.1)	1216 (21.5)	1016 (29.2)	991 (31.8)	890 (33.5)
DaPCaR[a]						
GS[a]				n (%*)	n (%*)	n (%*)
≤6				162 (15.9)	333 (16.4)	161 (6.8)
7				366 (35.9)	630 (30.9)	595 (25.1)
≥8				491 (48.2)	1073 (52.7)	1618 (68.2)
NA				499 (32.9)[b]	168 (7.6)[b]	37 (1.5)[b]
PSA, ng/mL[c]				n (%***)	n (%***)	n (%***)
≤20				27 (8.3)	115 (10.3)	167 (12.7)
20 to ≤100				62 (19.1)	326 (29.1)	381 (28.9)
>100				235 (72.5)	678 (60.6)	772 (58.5)
NA				1194 (78.7)	1085 (49.2)	1091 (45.3)

Abbreviations: DaPCaR, Danish Prostate Cancer Registry; GS, Gleason score; IQR, interquartile range; NA, not available; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology, and End Results program of the National Cancer Institute; SD standard deviation.
[a] Data are from SEER 2005-2008).
[b] Data are from those who had a valid GS.
[c] Data are from those who had a valid PSA.

The main objective of the early detection of PCa is to decrease PCa-specific mortality. Concurrent with the dramatic changes in the incidence of PCa, life-prolonging treatment options for men with metastatic and castration-resistant PCa have been introduced.[12,13] Moreover, an optimized use of androgen-deprivation therapy and chemotherapy, better palliation, and improved management of comorbidities must be expected to improve the survival of contemporary men diagnosed with de novo metastatic PCa compared with their historic counterparts.[14-16]

To investigate the impact of changes in early detection strategies and improved PCa care on incidence and mortality in men with de novo metastatic PCa, we analyzed data in 2 population-based cohorts from Denmark and the United States.

MATERIALS AND METHODS

All incident cases of PCa (International Classification of Diseases code 61.9), census population estimates, and survival data for the period from 1980 to 2011 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) 9-registries (SEER 9) database.[17] Patients were followed from 1980 until death or December 31, 2013. Because the Danish population is comprised of 93.8% native white Danes, and most non-native Danes originate from Western European or Middle Eastern countries, the SEER data were restricted to include white men only, of which SEER 9 covers an estimated 8.7% of the total US population.[18,19] From the Danish Prostate Cancer Registry (DaPCaR), all Danish men diagnosed with PCa in the period from 1995 to 2011 were identified. Patients were followed from 1995 until death or April 28, 2015.[20] To calculate incidence rates, age-specific population figures were retrieved from Statistics Denmark.[18] Age, Gleason score (GS), PSA level (DaPCaR only), and tumor stage at diagnosis were retrieved for all patients diagnosed with de novo metastatic disease. In SEER, TNM classification was derived using several editions (depending on the period of diagnosis) of the TNM staging manual in the SEER*Stat tool (version 8.3.2; SEER Program, National Cancer Institute, Bethesda, MD) (Supporting Table 1). In the DaPCaR, tumors were classified as localized, regionally advanced, or distant metastatic until 2004. Since then the TNM (International Classification of Diseases, 10th

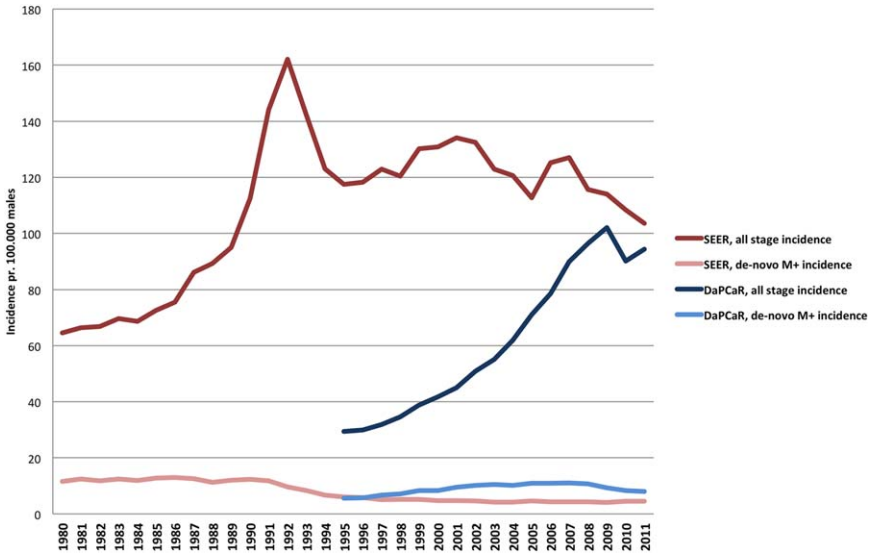

Figure 1. Age standardized incidence rates are illustrated. DaPCaR indicates Danish Prostate Cancer Registry; M+, metastatic; SEER, Surveillance, Epidemiology, and End Results program of the National Cancer Institute.

Edition) classification system has been used as previously described.[20] All men were stratified in 5-year to 7-year intervals according to the year of diagnosis. Trends in the age-standardized (World Health Organization world population) incidence rates of de novo metastatic and other-stage PCa from both cohorts were analyzed.

One-way analyses of variance and chi-square tests were used to compare numerical and categorical baseline data, respectively. Median overall survival (OS) was calculated using Kaplan-Meier estimates and compared using the log-rank test. Fine and Gray 5-year cumulative PCa-specific and other-cause mortality were calculated in a competing risk setting with PCa-specific and other-cause death treated as competing events. For complete 5-year follow-up, the SEER and DaPCaR cohorts were truncated in 2008 and 2009 (year of diagnosis), respectively. IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY) and RStudio (version 3.0.2; RStudio Inc, Boston, MA) were used for analysis.[21] This study was approved by the Danish National Data Protection Agency (file 2012-41-0390), the Danish Health and Medicines Authority (file 3-3013-858/1/), and the ethical committee of the Capital Region of Denmark (protocol H-4-2014-FSP).

RESULTS

In total, 426,266 and 47,024 men diagnosed with PCa were identified in the SEER 9 and DaPCaR databases, respectively. Among these, 29,555 men in SEER and 6874 in DaPCaR had de novo metastatic disease.

Baseline characteristics are provided in Table 1. In the SEER cohort, the median age at diagnosis of de novo metastatic PCa increased over time from 73.0 years (interquartile range [IQR], 67.0-80.0 years) to 76.0 years (IQR, 65.0-83.0 years; $P < .0001$). In the DaPCaR cohort, the median age at diagnosis decreased from 74.2 years (IQR, 67.4-79.2 years) to 73.2 years (IQR, 66.1-79.3 years; $P = .052$). In the DaPCaR cohort, when PSA levels were available, the median PSA level at diagnosis decreased from 320 ng/mL (IQR, 75-675 ng/mL) to 145 ng/mL (IQR, 46-500 ng/mL; $P < .0001$). Also in the DaPCaR cohort, there was a significant increase in the relative proportion of men diagnosed with GS $\geq$8 disease (from 48.2% to 68.2%) (Table 1) was observed. In the SEER cohort, there may have been a similar trend, but variations in the reporting of GS made it less certain. In total, 255 men (0.9%) in the SEER cohort and 48 (0.8%) in the DaPCaR cohort (with de novo metastatic PCa) underwent radical prostatectomy, and 4860 patients with de novo metastatic PCa (16.4%) in the SEER cohort received external-beam radiation, including palliative radiation of bony metastases. Data regarding nonsurgical treatment were unavailable in the DaPCaR database.

Incidence of De Novo Metastatic PCa

Over time, the overall incidence of PCa increased significantly in both cohorts (Fig. 1, Table 2).[7] The proportion of men diagnosed with de novo metastatic PCa relative to the overall incidence decreased substantially in both

TABLE 2. Yearly Incidence and Prostate Cancer-Specific Mortality Rates

Variable	Yearly Incidence and Mortality					
	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2011
Incidence per y						
SEER, total count	6626	9017	15,758	14,529	16,173	16,536
DaPCaR, total count				1498	2307	4000
SEER, as	67.2	83.7	136.8	121.9	128.2	115.2
DaPCaR, as				32.9	50.9	88.9
M+ incidence per y						
SEER, total count	1182	1319	1134	696	624	683
DaPCaR, total count				304	441	450
SEER, as	12.0	12.3	9.7	5.5	4.5	4.4
DaPCaR, as				6.7	9.7	9.9
PCa-specific mortality rate per y, %						
USA[a]	17.8	18.8	20.3	17.4	14.2	14.5
Denmark[b]				19.6	19.7	18.4

Abbreviations: as, age-standardized incidence rates per 100,000 males (World Health Organization world standard population); DaPCaR, Danish Prostate Cancer Registry; M+, metastatic; PCa, prostate cancer; SEER, Surveillance, Epidemiology, and End Results program of the National Cancer Institute.
[a] Rates are for white men (World Health Organization world population age standardized).
[b] Rates are based on data from NORDCAN (World Health Organization world population age standardized; see Engholm 2016[7]).

TABLE 3. Five-Year Mortality in Men Diagnosed With De Novo Metastatic Prostate Cancer

Period of Diagnosis	5-Year PCa-Specific Mortality (95% CI)		5-Year Other Cause Mortality (95% CI)		5-Year Overall Mortality (95% CI)	
	SEER	DaPCaR	SEER	DaPCaR	SEER	DaPCaR
1980-1984	54.4 (53.1-55-6)	—	25.6 (24.5-26.7)	—	80.0 (78.9-81.0)	—
1985-1989	56.1 (54.9-57.3)	—	24.4 (23.3-25.4)	—	80.4 (79.5-81.4)	—
1990-1994	54.2 (52.9-55.5)	—	23.3 (20.2-22.9)	—	77.4 (76.3-78.5)	—
1995-1999	57.0 (55.4-58.7)	73.4 (71.2-75.6)	21.5 (20.2-22.9)	11.3 (9.7-12.9)	78.5 (77.2-79.9)	84.8 (82.9-86.6)
2000-2004	59.2 (57.5-60.0)	65.4 (63.4-67.4)	20.8 (19.4-22.2)	14.6 (13.1-16.0)	80.0 (78.6-81.4)	80.0 (78.3-81.6)
2005-2009[a]	61.0 (59.2-62.9)	56.8 (54.8-58.8)	19.4 (17.9-20.9)	16.4 (15.0-17.9)	80.5 (78.9-82.0)	73.2 (71.4-75.0)
Entire cohort	56.5 (55.9-57.1)	64.0 (62.8-65.2)	22.9 (22.4-23.4)	14.5 (13.6-15.4)	79.4 (78.9-79.9)	78.5 (77.4-79.5)

Abbreviations: CI, confidence interval; DaPCaR, Danish Prostate Cancer Registry; PCa, prostate cancer; SEER, Surveillance, Epidemiology, and End Results program of the National Cancer Institute.
[a] Data are from SEER (2005-2008).

cohorts, from 17.8% to 4.1% ($P < .0001$) in the SEER cohort and from 20.3% to 11.3% ($P < .0001$) in the DaPCaR cohort. Although the age-standardized incidence rate of men diagnosed with de novo metastatic PCa decreased by 7.6 per 100,000 in the SEER cohort, it increased by 3.2 per 100,000 in the DaPCaR cohort. Age-standardized mortality rates from the United States and Denmark are listed in Table 2.

Survival and Mortality

The median OS for all patients diagnosed with de novo metastatic PCa during the study periods was similar in the 2 cohorts (SEER: median OS, 24.0 months; 95% confidence interval [CI], 23.6-24.4 months; DaPCaR: median OS, 26.0 months; 95% CI, 25.2-26.8 months) (Supporting Table 2).

The 5-year overall mortality (OM) after diagnosis of de novo metastatic PCa was 79.4% (95% CI, 78.9%-79.9%) and 78.5% (95% CI, 77.4%-79.5%) in the SEER and the DaPCaR cohorts, respectively (Table 3). In the US cohort, 5-year OM decreased in patients who were diagnosed during 1980 through 1994 and subsequently increased in recent periods. Throughout the period studied, 5-year OM decreased in the Danish cohort (Table 3).

In the SEER cohort, 5-year PCa-specific mortality was stable for patients who were diagnosed during 1980 through 1994 and increased from 54.2% (95% CI, 52.9%-55.5%) to 61.0% (95% CI, 59.2%-62.9%) when comparing patients who were diagnosed during 1990 through 1994 with those who were diagnosed during 2005 through 2008 ($P < .0001$) (Table 3, Fig. 2). In the DaPCaR cohort, 5-year PCa-specific mortality significantly

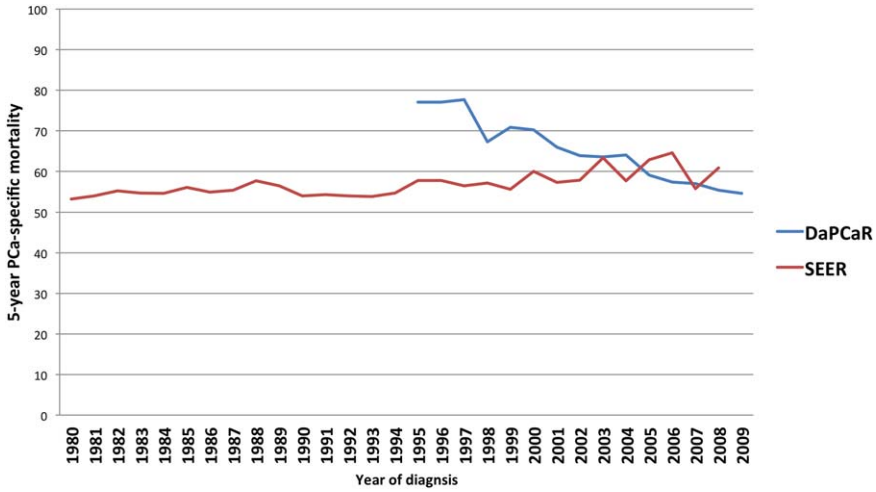

Figure 2. Five-year prostate cancer (PCa)-specific mortality is illustrated for patients with de novo metastatic prostate cancer. DaPCaR indicates Danish Prostate Cancer Registry; SEER, Surveillance, Epidemiology, and End Results program of the National Cancer Institute.

decreased from 73.4% (95% CI, 71.2%-75.6%) to 56.8% (95% CI, 54.8%-58.8%; $P < .0001$) over the period studied.

DISCUSSION

We compared changes in PCa incidence and 5-year mortality rates among men who were diagnosed with de novo metastatic PCa in 2 population-based cohorts subjected to different diagnostic strategies. In the United States, the incidence rate peaked within a few years of approval of PSA for screening, resulting in the detection of prevalent and small incident cancers.[4] After the peak, the incidence rate was stable for 2 decades before slightly decreasing in the latest periods of the study (Fig. 1). The Danish approach to early PSA-based detection has been more conservative, and official guidelines have recommended against population-based screening.[22] Nonetheless, the incidence of PCa in Denmark displays a pattern similar to that observed in the United States, although it trails by 15 to 17 years.

In the SEER data, the incidence of de novo metastatic PCa was relatively constant until 1994. The rather dramatic decrease of 63% during 1995 through 1999 likely reflects the long-term impact of PSA-based early detection strategies producing stage migration (Fig. 1, Table 2).[11] This is further supported by findings from a large PSA screening trial (the European Randomised Study of Screening for Prostate Cancer [ERSPC] trial), in which the incidence rate ratio was reduced for de novo metastatic PCa (0.60) with PSA screening.[23] However, this reduction has been accompanied by a dramatic increase in the numbers of men diagnosed with low-stage PCa, a large proportion of which have been low-risk to intermediate-risk cancers with very limited lethal potential, thereby fueling the concerns of overdiagnosis and overtreatment.[24,25]

If the patterns of the temporal trends in Danish incidences continue to mimic the American patterns, then we anticipate a future decrease in the incidence of de novo metastatic PCa in Denmark within a few years. The marked decrease in the median PSA level at diagnosis of de novo metastatic PCa supports this expectation. The median OS in men with de novo metastatic was comparable in the SEER and DaPCaR cohorts (24.0 vs 26.0 months, respectively), although with increased survival from 2000 and later in the Danish cohort (Supporting Table 2). This could be a consequence of lead time introduced during the initial phases of early detection. Still, the short median OS in both cohorts confirms that patients with de novo metastatic PCa have very poor outcomes. This median OS was lower than that in RCTs investigating patients with de novo metastatic PCa but was comparable to the OS in a Swedish population-based study.[2,14,15,26] These differences in OS illustrate the impact of patient selection in the outcomes of RCTs.

Parallel to an increase in OS, both 5-year OM and PCa-specific mortality among men with de novo metastatic PCa decreased in Denmark despite a relative increase in the number of patients with poorly differentiated tumors. This decrease is in contrast to the almost stable 5-year PCa-specific mortality rate observed in the SEER data and may reflect the more aggressive detection

strategies used in the United States before the PSA era (Table 3, Fig. 2). The improvement in 5-year PCa-specific mortality may be explained by several factors. Lead time, as proposed by others and supported by the observed decreases in age and median PSA levels at diagnosis, is likely the primary reason.[1] Other factors (including improved management of comorbidities, improved palliation, more frequent and refined use of androgen-deprivation therapy, and the introduction of docetaxel in 2004 of 2005) may have contributed to the reduction in 5-year PCa-specific mortality.[13,16] It should be noted that the last patients to be included in the 5-year mortality analyses were diagnosed in 2008 and 2009, respectively; and although, some might have benefitted from second-line chemotherapy, very few have received novel, life-prolonging treatment regimens such as abiraterone, enzalutamide, and early chemotherapy.[12,14,15]

In the SEER data, a significant reduction in the incidence of de novo metastatic PCa was observed from 1995 onward (Fig. 1, Table 2). Somewhat paradoxically, during that time, the 5-year PCa-specific mortality increased (Table 3). There are several possible explanations for this worsening in 5-year mortality. A portion of this change is attributable to length-time bias, in which "would-be" patients who have de novo metastatic PCa with a more indolent natural history were detected before they developed metastatic disease and thus are removed from the de novo metastatic category. Early detection strategies are more prone to detect cancers with less aggressive features, because they grow slowly with a consequent longer time "at risk" for detection; whereas more aggressive tumors grow fast and are more likely to become advanced before detection.[27] Therefore, it may be open to speculation whether a long-standing early detection strategy results in a de novo population in which the least aggressive PCa tumors are removed, leaving behind a population of patients who have more aggressive cancers with a higher risk of PCa mortality. This observation is further supported by the DaPCaR data, in which the relative proportion of patients harboring GS $\geq$8 disease has increased in more recent years in parallel with increased early detection. Unfortunately, a similar analysis of temporal changes in risk categories based on GS was not possible in the SEER data, because GS was grouped into risk categories in early years and only recently was recorded as the actual score on a case basis. In addition, over time, there have been shifts in how Gleason scoring is practiced by pathologists; however, most of the men included harbor GS $\geq$8 disease, for which the histologic interpretation has changed very little.[28]

In the DaPCaR data, we observed that the incidence of de novo metastatic PCa increased over time, probably as a consequence of increased awareness of PCa stimulated by opportunistic screening and increased use of surgery and radiation therapy during the study period. Because more individuals have undergone diagnostic workup, more patients with low metastatic burden have been diagnosed with metastatic disease. The lower metastatic burden at diagnosis corresponds with and likely explains the observed reduction in 5-year PCa-specific mortality in Denmark and the reduction in age and median PSA level at diagnosis. Therefore, the improvement in PCa-specific mortality in Denmark in more recent years is likely caused in large part by lead-time bias.

In the SEER data, the decreased incidence of de novo metastatic PCa parallels the decrease in PCa-specific mortality after 1995 (from 20.3 per 100,000 during 1990-1994 to 14.2 per 100,000 during 2000-2004), and it is logical to speculate whether the reduced mortality is caused directly by fewer men having metastases at diagnosis (Table 2). Although this explanation is likely, other causes (such as better treatments for localized and/or locally advanced disease and refined therapy/management of advanced disease) could account for some of the improvements in mortality. However, efforts to model PCa mortality patterns in the United States strongly suggest that screening and early detection, with a subsequent decrease in de novo metastatic PCa, account for much of the improvement in mortality.[29]

The strength of our study is its population-based design. The 2 large populations were retrieved from validated registries.[30] However, this is a retrospective analysis with obvious limitations. Except for information in both cohorts about the use of radical prostatectomy, data on the use of both radiotherapy and pharmacologic agents are missing. Also, the cause of diagnosis (screening, symptoms, other), metastatic burden at diagnosis, and PSA data (in SEER) were unavailable. More exact knowledge could strengthen the conclusions regarding the impact of PSA-based early detection strategies. Moreover, in the early years of the study, imaging modalities to detect metastatic disease were restricted to bone x-ray, conventional bone scintigraphy, and computerized tomography scans of the abdomen and chest. Newer and more sensitive imaging modalities (18F-sodium fluoride–positron emission tomography, magnetic resonance imaging, etc) have been used in more recent years, resulting in the diagnosis of more patients who have metastatic disease with fewer and smaller metastases (ie, oligo-metastatic disease). This may have introduced lead-time bias in more recent years

in patients with de novo metastatic PCa. Although we do not have exact figures available, it is likely that new and more sensitive imaging modalities have been introduced into the diagnostic workup earlier in the United States. The relatively high incidence of de novo metastatic PCa during the early periods of the study may in part be a reflection of this. However, if M-classification in the United States remains more sensitive than the classification used in Denmark, then the finding that the US de novo metastatic incidence is one-half that of the Danish incidence only strengthens our conclusion that the reduction over time in de novo metastatic disease is indeed a consequence of early detection.

Conclusions

We investigated the incidence and survival of patients with de novo metastatic PCa over time and acknowledge that the diagnosis of metastatic disease and survival depend on the frequency and sensitivity of metastatic workup. Very likely, lead-time, length-time, and stage migration biases affect the composition and outcomes of this population. Data from SEER reveal marked reductions in the number of men presenting with de novo metastatic PCa and in PCa mortality after the widespread introduction of PSA-based early detection, strongly suggesting that the diagnostic strategy used led to decreased de novo metastatic disease and mortality. In Denmark, decreases in mortality and in the number of men with de novo metastatic PCa have not been observed. However, strong trends in Denmark, including a marked decrease in the median PSA level at diagnosis of de novo metastatic PCa, strongly suggest that there is an impending stage shift in Denmark, likely because of lead time caused by the increased use of PSA testing. A comparison of the US and Danish populations with novo metastatic disease reveals an increasing similarity in epidemiology, suggesting that a decline in PCa-specific mortality in Denmark is imminent.

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CONFLICT OF INTEREST DISCLOSURES

John T. Helgstrand reports travel, accommodation, and registration expenses from Janssen Pharmaceuticals, Ipsen Pharma, and Astellas Pharma and personal fees from Janssen Pharmaceuticals. Martin A. Røder reports travel, accommodation, and registration expenses from Janssen Pharmaceuticals and Astellas Pharma and personal fees from Janssen Pharmaceuticals, Astellas Pharma, Sanofi-Aventis, and Eli-Lilly. Nina Klemann reports travel, accommodation, and registration expenses from Janssen Pharmaceuticals, Ipsen Pharma, and Astellas Pharma. Klaus Brasso reports travel, accommodation, and registration expenses from Sanofi and Astellas Pharma and personal fees from Sanofi-Aventis, Bayer Pharma, Astellas Pharma, and Janssen Pharmaceuticals. Peter Iversen reports travel, accommodation, and registration expenses covered by Astellas Pharma, Janssen Pharmaceuticals, Bayer Pharma, and Ipsen and personal fees from Astellas Pharma, Medivation, and Janssen Pharmaceuticals. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

John T. Helgstrand: Funding acquisition, conceptualization and design, writing–original draft, data collection, data analyses, interpretation of data, and project administration. **Martin A. Røder**: Conceptualization and design, writing–review and editing, supervision, data collection, interpretation of data, and project administration. **Nina Klemann**: Writing–review and editing, data collection, and interpretation of data. **Birgitte G. Toft**: Writing–review and editing, data collection, and interpretation of data. **Daphne Y. Lichtensztajn**: Writing–review and editing, data collection, data analyses, and interpretation of data. **James D. Brooks**: Writing–review and editing, supervision, data collection, and interpretation of data. **Klaus Brasso**: Conceptualization and design, writing–review and editing, supervision, interpretation of data. **Ben Vainer**: Writing–review and editing, supervision, data collection, and interpretation of data. **Peter Iversen**: Conceptualization and design, writing–review and editing, supervision, and interpretation of data. John T. Helgstrand had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final article and the decision to submit it for publication.

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