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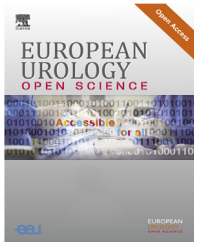

European Association of Urology

Prostate Cancer

Changes in Characteristics of Men with Lethal Prostate Cancer During the Past 25 Years: Description of Population-based Deaths

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Abstract

Background: Attempts to reduce prostate cancer (PC) mortality require an understanding of temporal changes in the characteristics of men with lethal PC.
Objective: To describe the diagnostic characteristics of and time trends for a nationwide population-based cohort of Swedish men who died from PC between 1992 and 2016.
Design, setting, and participants: Men with PC as the underlying cause of death from 1992 to 2016 according to the Swedish Cause of Death Register were included in the study. Characteristics at diagnosis were collected via links to other nationwide registries using personal identity numbers.
Outcome measurements and statistical analysis: Data on disease duration, age at death, and risk category were analyzed. Missing data for risk categories for men with an early date of PC diagnosis were imputed according to the method of chained equations.
Results and limitations: Between 1992 and 2016, age-standardized PC mortality decreased by 25%. Median PC disease duration increased from 3.3 yr (interquartile range [IQR] 1.6–6.3) to 5.9 yr (IQR 2.5–10.3) and the median age at death from PC increased from 78.9 yr (IQR 73.3–84.2) to 82.2 yr (IQR 75.2–87.5). The proportion of men with localized disease at diagnosis who died from PC increased from 34% to 48%, while the rate of distant metastases at diagnosis decreased from 56% to 42%. The rate of distant metastases at diagnosis was highest among the youngest men. Treatment trajectories could not be described owing to the large proportion of missing data before the start of registration in the National Prostate Cancer Registry.
Conclusion: Age-standardized PC mortality has decreased substantially since 1992. However, there is still a high proportion of men who die from PC who had localized

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disease at diagnosis, which indicates that more attention is needed to identify the underlying causes to prevent disease progression. Since the proportion of men with distant metastases at diagnosis remains high, early detection of lethal tumors is essential to further reduce PC mortality.

Patient summary: We investigated the characteristics of men who died from prostate cancer in Sweden between 1992 and 2016. We found that men with lethal prostate cancer live longer and are older when they die today in comparison to men who died at the beginning of the study period. However, the proportion of men with distant metastases at diagnosis remains high, which is why early detection of lethal tumors is essential to reduce mortality.

1. Introduction

Prostate cancer (PC) is prevalent in the majority of men older than 70 yr and owing to increasing life expectancy, more men will live long enough to die from PC [1]. Age-standardized PC mortality has decreased in many countries during the past two decades. This decrease is often interpreted as a consequence of earlier detection leading to a shift towards more favorable disease at diagnosis, alongside improvements in disease management [2].

A key factor in further reducing PC mortality is a better understanding of the temporal changes in diagnostic characteristics of men with lethal PC. The aim of the present study was to describe the1992–2016 time trends for diagnostic characteristics in a nationwide population-based cohort of men who died from PC.

2. Patients and methods

2.1. Data collection and design

Data for all men diagnosed with PC according to the Swedish Cancer Registry from 1970 and/or the National Prostate Cancer Register of Sweden (NPCR) from 1987 who were alive on January 1, 1992 were used to calculate the PC prevalence on January 1 every year from 1992 to 2016. Among PC cases we identified men with PC as the underlying cause of death from 1992 to 2016 according to the Cause of Death Register. Data on the size of the male Swedish population were retrieved from Statistics Sweden to calculate the age-standardized number of deaths using the age distribution in 2016 as reference. The number of counties in Sweden registering data in NPCR has gradually increased over time. The earliest four counties started registration in 1987. In 1996, 16 out of 21 counties registered information on PC. Virtually complete registration for all counties was achieved in 1998 [3]. We also used the link to the Longitudinal Integration Database for Health Insurance and Labor Market Studies, a nationwide database of socioeconomic factors. Linkage between the registers was made via unique personal identity numbers in the same way as for the PCBaSe database, as previously described [3]. Educational level was categorized according to years of schooling: low, $\leq$9 yr; middle, 10–12 yr; and high, $\geq$13 yr.

2.2. Imputation models

Disease severity was divided into five risk categories according to a modified version of the National Comprehensive Cancer Network guidelines: low risk: stage T1–2, Gleason score $\leq$6, and prostate specific antigen (PSA) <10 ng/ml; intermediate risk: stage T1–2, Gleason score 7, and/or PSA 10–20 ng/ml; high risk: stage T1–3, Gleason score 8–10, and/or PSA 20–50 ng/ml; regional metastases: stage T4 and/or N1 and/or PSA 50–100 ng/ml, and M0; and metastases: M1 and/or PSA $\geq$100 ng/ml [4]. The degree of completeness of data on factors needed to determine risk category has gradually increased with time. The method of chained equations was used in cases with data missing for risk category, resulting in ten imputation data sets [5]. Owing to the gradual increase in completeness of the data, we used three separate imputation models for men diagnosed in 1970–1986, 1987–1995, and 1996–2016. Further details are as previously reported [6].

In the earliest period, clinical data on PC were not available for any men. Therefore, the imputation had to be based on complete data from a later calendar period. Men with known risk stage who were diagnosed in 1987–1991 were used to impute data for men diagnosed in 1970–1986. These complete cases were selected on the assumption of a similar very low rate of opportunistic screening with PSA.

For men diagnosed in 1987–1995 we had a limited number of complete cases. To increase the number of complete cases, we also included complete cases diagnosed between 1996 and 2005 in low-incidence counties excluding men with stage T1c disease [7].

The imputation model for men diagnosed in 1996–2016 included TNM stage, Gleason score, World Health Organization (WHO) grade, serum PSA, risk category, age at and year of diagnosis, marital status, county of residence, mode of detection, comorbidity, concomitant cancer, primary treatment, survival since diagnosis, and cause of death. The analyses were performed using R [8].

3. Results

3.1. Characteristics of the cohort

The characteristics of the cohort are presented in Table 1. We identified 54 645 men with PC as the underlying cause of death and categorized the dates of death into four different time periods: 1992–1997, 1998–2004, 2005–2010, and 2011–2016. During the whole study period, the proportion of men older than 85 yr among those who died from PC increased from 28% to 31%. The proportion who lived with PC for 8–16 yr and for >16 yr before death from PC increased from 15% to 31%, and from 2% to 7%, respectively.

3.2. Prevalence and mortality rate

As shown in Fig. 1, the prevalence of PC in Sweden increased steadily from 25 873 in 1992 to 105 564 in 2016. During the same time period, the number of men older than 40 yr in

Table 1 – Characteristics of the study population at date of death

Parameter [a]	Prostate cancer deaths by period				
	1992–1997 (*n* =14 844)	1998–2004 (*n* = 13 724)	2005–2010 (*n* = 13 380)	2011–2016 (*n* = 12 697)	1992–2016 (*n* = 54 645)
Median age at death, yr (IQR)	78.9 (73.3–84.2)	80.4 (74.6–85.3)	81.3 (75.0–86.3)	82.2 (75.2–87.5)	80.6 (74.4–85.8)
Age at death, *n* (%)					
<65 yr	688 (4.6)	652 (4.8)	667 (5.0)	645 (5.1)	2652 (4.9)
65–69 yr	1231 (8.3)	1013 (7.4)	1149 (8.6)	1112 (8.8)	4505 (8.2)
70–74 yr	2195 (14.8)	1792 (13.1)	1810 (13.5)	1838 (14.5)	7635 (14.0)
75–79 yr	3266 (22.0)	2837 (20.7)	2611 (19.5)	2516 (19.8)	11 230 (20.6)
80–84 yr	3319 (22.4)	3159 (23.0)	2987 (22.3)	2711 (21.4)	12 176 (22.3)
85–89 yr	2543 (17.1)	2596 (18.9)	2413 (18.0)	2211 (17.4)	9763 (17.9)
≥90 yr	1602 (10.8)	1675 (12.2)	1743 (13.0)	1664 (13.1)	6684 (12.2)
Educational level, *n* (%)					
High	1206 (8.1)	1560 (11.4)	2015 (15.1)	2243 (17.7)	7024 (12.9)
Low	7036 (47.4)	7324 (53.4)	6831 (51.1)	5891 (46.4)	27 082 (49.6)
Middle	2995 (20.2)	3772 (27.5)	4253 (31.8)	4425 (34.9)	15 445 (28.3)
Missing	3607 (24.3)	1068 (7.8)	281 (2.1)	138 (1.1)	5094 (9.3)
Median disease duration, yr (IQR)	3.3 (1.6–6.3)	3.9 (1.8–7.3)	4.7 (2.1–8.6)	5.9 (2.5–10.3)	4.3 (1.9–8.1)
Disease duration, *n* (%)					
0–1 yr	2187 (14.7)	1780 (13.0)	1407 (10.5)	1130 (8.9)	6504 (11.9)
1–2 yr	2647 (17.8)	2064 (15.0)	1708 (12.8)	1387 (10.9)	7806 (14.3)
2–4 yr	3644 (24.5)	3175 (23.1)	2705 (20.2)	2210 (17.4)	11 734 (21.5)
4–8 yr	3874 (26.1)	3810 (27.8)	3806 (28.4)	3264 (25.7)	14 754 (27.0)
8–16 yr	2161 (14.6)	2492 (18.2)	3171 (23.7)	3873 (30.5)	11 697 (21.4)
≥16 yr	331 (2.2)	403 (2.9)	583 (4.4)	833 (6.6)	2150 (3.9)
Civil status at year of death, *n* (%)					
Married	9218 (62.1)	8368 (61.0)	8023 (60.0)	7351 (57.9)	32 960 (60.3)
Not married	2485 (16.7)	2439 (17.8)	2621 (19.6)	2793 (22.0)	10 338 (18.9)
Widower	3139 (21.1)	2916 (21.2)	2735 (20.4)	2551 (20.1)	11 341 (20.8)
Unknown	2 (0.0)	1 (0.0)	1 (0.0)	2 (0.0)	6 (0.0)
Registered in NPCR, *n* (%)					
Yes	2762 (18.6)	8941 (65.1)	11 549 (86.3)	11 988 (94.4)	35 240 (64.5)
No	12 082 (81.4)	4783 (34.9)	1831 (13.7)	709 (5.6)	19 405 (35.5)
Risk category, *n* (%)					
Low	44 (0.3)	195 (1.4)	418 (3.1)	692 (5.5)	1349 (2.5)
Intermediate	305 (2.1)	729 (5.3)	1234 (9.2)	1631 (12.8)	3899 (7.1)
High	3469 (23.4)	4484 (32.7)	4279 (32.0)	3855 (30.4)	16087 (29.4)
Regionally metastatic	3202 (21.6)	2291 (16.7)	1731 (12.9)	1542 (12.1)	8766 (16.0)
Metastatic	7824 (52.7)	6025 (43.9)	5718 (42.7)	4977 (39.2)	24 544 (44.9)

IQR = interquartile range; NCPR = National Prostate Cancer Register of Sweden.
[a] Educational level was classified according to years of education (low, ≤9 yr; middle, 10–12 yr; high, ≥13 yr). The category "not married" includes men who were never married or divorced.

Sweden increased from 1 969 106 to 2 488 962. The crude PC-specific mortality was stable during the study period, while the age-standardized number of PC deaths decreased by 25%, from 2807 to 2089.

3.3. Median disease duration

Fig. 2 shows the disease duration during the study period for men who died from PC, which increased from a median of 3.3 yr (interquartile range [IQR] 1.6–6.3) in 1992 to 5.9 yr (IQR 2.5–10.3) in 2016.

3.4. Age distribution at death from PC

The median age at death from PC during the study period increased from 78.9 yr (IQR 73.3–84.2) in 1992 to 82.2 yr (IQR 75.2–87.5) in 2016 (Fig. 3).

3.5. Distribution of risk categories at diagnosis by year of PC death

The distribution of risk categories at diagnosis by year of PC death and the distribution within quartiles of age are presented graphically in Fig. 4. Among all men who died from PC, the proportion diagnosed with low-risk PC during 1992–2016 increased from 5% to 6%, while the proportions diagnosed with intermediate-risk and high-risk PC increased from 7% to 14%, and from 22% to 28%, respectively. The proportion of men diagnosed with regionally metastatic disease did not change and remained at 11%, while the proportion who were diagnosed with metastases decreased from 56% to 42%.

The proportion of men with metastases at diagnosis decreased with increasing age at PC death. During the study period, the proportion of men diagnosed with metastases decreased from 60% to 55% in the lowest age quartile and from 45% to 37% in the highest quartile.

4. Discussion

4.1. Principal findings

Against a background of a 25% decrease in age-standardized PC mortality, the median disease duration among men who died from PC increased by 2.5 yr. The median age at death increased by more than 3 yr during the study period. The proportion of men who had localized disease at diagnosis and then died of PC increased during the study period, while

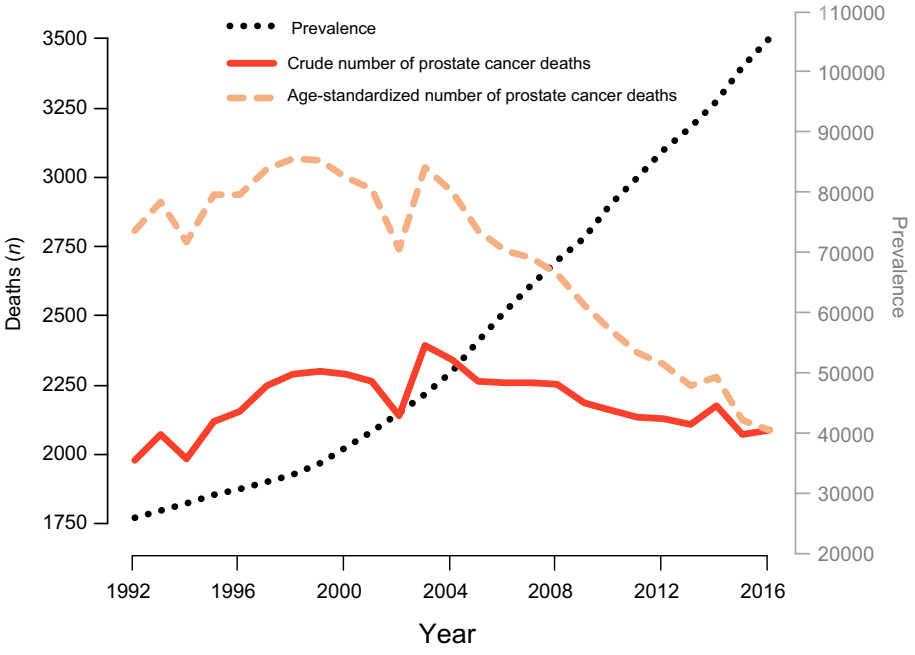

Fig. 1 – Prevalence of prostate cancer and raw and age-standardized numbers of prostate cancer deaths.

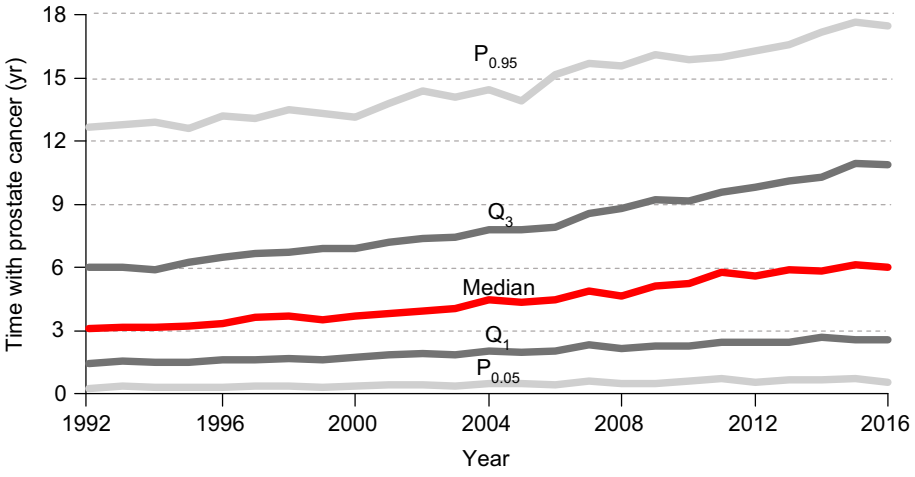

Fig. 2 – Disease duration during the study period for men who died from prostate cancer. Duration was defined as the time between date of prostate cancer diagnosis and date of death. P = percentile; Q = quartile.

the proportions with regional and distant metastases decreased. The proportion of those with distant metastases at diagnosis who died from PC was highest among the youngest men.

4.2. Age-standardized mortality and median disease duration among those who died from PC

The age-standardized PC mortality has steadily decreased over the past two decades. We found an age-standardized mortality decrease of 25% during the study period. In a study of global patterns in PC incidence and mortality, mortality declined or stabilized in recent years in most of the countries examined, a trend that was more pronounced in high-income countries [2]. The median disease duration before PC death in our study increased from 3.3 yr in 1992 to 5.9 yr in 2016. The decrease in age-standardized mortality and the increase in disease duration before PC death can be explained by a number of factors. Greater use of PSA testing [9–11] results not only in leadtime effects but also in survival benefits because of early diagnosis. Significant improvements in both local and systemic

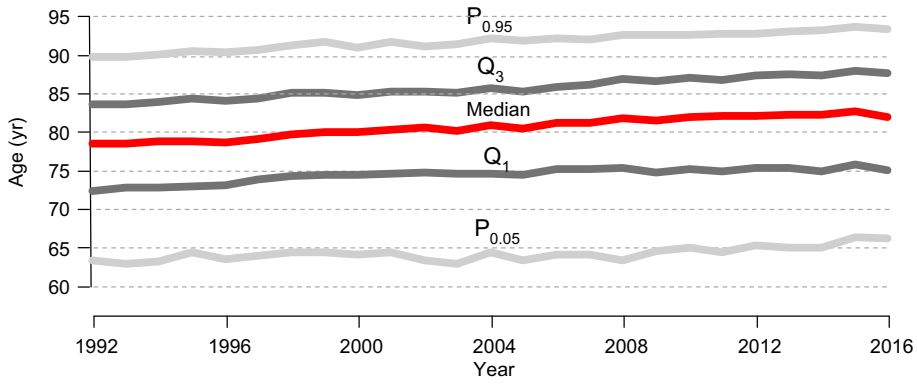

Fig. 3 – Age at death from prostate cancer during the study period. P = percentile; Q = quartile.

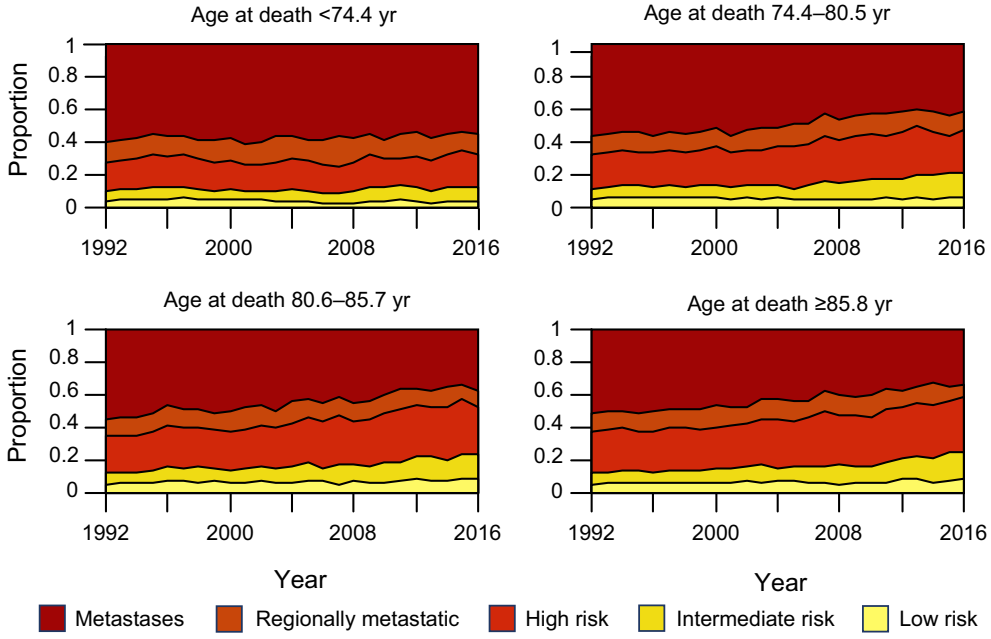

Fig. 4 – Distribution of risk categories at diagnosis by year of prostate cancer death within quartiles of age at death. The risk group classification was based on a modification of the National Comprehensive Cancer Network categorization: low risk: clinical stage T1–2, Gleason score 2–6 and prostate-specific antigen (PSA) <10 ng/ml; intermediate risk: clinical stage T1–2, Gleason score 7, and/or PSA 10–20 ng/ml; high risk: clinical stage T1–3, Gleason score 8–10, and/or PSA 20–50 ng/ml; regionally metastatic: clinical stage T4 and/or N1 and/or PSA 50–100 ng/ml, and M0/Mx; distant metastases: stage M1 and/or PSA ≥100 ng/ml.

treatments during this time period have prolonged survival in more advanced disease; examples include the addition of curative treatment for locally advanced disease, early chemotherapy, and new androgen deprivation therapies such as abiraterone and enzalutamide [12–16].

4.3. Median age at death increased among those who died from PC

Median age at PC death increased by 3.3 yr during the study period, from 78.9 to 82.2 yr. This can probably be explained by improved treatment strategies as described above, as well as an increase in the population of healthy elderly individuals with fewer competing risks of death than previously. The life expectancy for the male population in Sweden increased by 4.5 yr (from 75.6 to 80.1 yr) during the same time period. As a corollary, more men with a PC diagnosis live long enough for PC to spread and become lethal, while escaping death from other causes. Old age remains the most important risk factor for both PC diagnosis and PC death.

4.4. Risk category at diagnosis among men who died from PC

The proportion of men who had localized disease at diagnosis among those who died from PC increased during the study period, while the proportion of men with regional and distant metastases at diagnosis decreased. The men who died from PC despite early diagnosis constitute an

important group requiring further research to establish the cause of disease progression and underline the need for prognostic and predictive markers identifying a subset of localized PC cases that warrant aggressive treatment. Our results cannot reveal whether men who died after an early diagnosis had their life prolonged or if they were just aware of their disease for longer without any benefit. The shift in risk categories could also indicate some instances of a missed opportunity for treatment. For example, the shift was more prominent among older than younger men, and recommendations to not pursue curative treatment for older men have been based on age rather than actual health status. However, treatments received during the disease trajectory could not be evaluated in our study. Furthermore, a recently published Swedish nationwide study suggests misclassification of cause of death among older men with localized PC in the Swedish Causes of Death Register, resulting in an inflated proportion of older men with PC as the cause of death, which could add to the shift observed [17].

4.5. Proportion of men with metastases at diagnosis was highest in the youngest group among those who died from PC

Among those who died from PC, the proportion of men with metastases at diagnosis was highest in the youngest group, with 55% in the first age quartile compared to 37% in the fourth age quartile at the end of the study period. In a Danish study of men who died from PC between 1995 and 2013, the median age at diagnosis for men diagnosed with metastatic disease decreased from 74.8 yr in 1995 to 73.6 yr in 2013 [18]. The relatively low proportion of men with metastasis at diagnosis among the oldest group might be partly explained by misclassification of the cause of death among older men with localized disease described above. The fact that relatively young men are diagnosed with incurable disease stresses the importance of early detection. However, this is not uncomplicated, as higher diagnostic activity using traditional modes of detection (such as PSA testing) among the youngest men will result in overdiagnosis of low-risk disease with overtreatment as a consequence. This highlights the need for effective methods for diagnosing significant tumors, such as the evolution of biomarkers and genetic information in combination with magnetic resonance imaging to identify tumors at a curable stage, which could help in further reducing the number of men who have metastatic disease at diagnosis [19–22].

4.6. Strengths and limitations

The main strength of our study is the high rate of data capture for the registers. NPCR currently captures 98% of all men with PC in the Swedish Cancer Registry, to which recording is mandated [23]. The accuracy of the underlying cause of death in the Cause of Death Register has been estimated as 96% [24]. Men with PC as the underlying cause of death in the Cause of Death Register but without a diagnosis of PC according to the Swedish Cancer Registry were not included, a proportion previously reported to be <2% [23]. The major limitation is that we could not describe the treatment trajectory owing to a large proportion of missing data before the start of NPCR registration. Another limitation is the use of imputation models, leading to a degree of uncertainty regarding the classification of risk categories among men with an earlier date of diagnosis. Notably, major changes in the classification system occurred during the study period. A transition from the WHO grading system to the Gleason system in the NPCR occurred in the years following 2000, which had to be accounted for in the imputation models. In addition, the Gleason system underwent major revisions by the International Society of Urological Pathology (ISUP) in 2005 and in 2014, resulting in upgrading and stage migration. This poses a problem for all studies of temporal trends. However, we believe that this is a minor issue in the present study as it only affects those diagnosed after the first revision and who died due to PC before 2016. In addition, the new ISUP classification mostly affects the balance between the low and intermediate risk categories and the number men in our study diagnosed in either of these two categories after 2006 and who died before 2016 is limited (n = 284) [25,26].

5. Conclusions

Our results reflect the synergistic effects of early PC detection (which contains elements of both lead time and true survival benefits), improvements in PC management, and increasing life expectancy during the past two decades. Two observations underline—also from the perspective of characterizing those who died of PC—the pressing need to find better tools to characterize the biological behavior of PC. First, the high proportion of men with localized disease at diagnosis who still die from PC highlights that more effort is needed to identify which men in the low-risk groups require measures to prevent disease progression. Second, the proportion of men with distant metastases at diagnosis has decreased but remains high, so methods for early detection of lethal tumors that avoid overdiagnosis are essential in the drive to reduce PC mortality.

Author contributions: Oskar Bergengren had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lycken, Garmo, Westerberg, Axén, Stranne, Holmberg, Bill-Axelson.
Acquisition of data: Lycken, Garmo, Westerberg, Axén, Stranne, Holmberg, Bill-Axelson.
Analysis and interpretation of data: Lycken, Bergengren, Drevin, Garmo, Westerberg, Axén, Stranne, Holmberg, Bill-Axelson.
Drafting of the manuscript: Lycken, Bergengren, Garmo, Westerberg, Axén, Stranne, Holmberg, Bill-Axelson.
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