Conditional Relative Survival and Competing Mortality of Patients with Prostate Cancer in Korea: A Nationwide Cohort Study

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ABSTRACT

Background: Conditional relative survival (CRS) and competing mortality are important survivorship issues after cancer treatment. We aimed to investigate them among patients with prostate cancer treated by various modalities.

Methods: Using a nationwide population-based database, we calculated 5-year CRS conditioned on 1 through 5 years survival after diagnosis. These rates were stratified by age, sex, socioeconomic status, comorbidities, and treatment received. Cause of death and estimated cause-specific mortality were also described and considered with competing risks.

Results: A total of 81,773 patients newly diagnosed with primary prostate cancer from 2007 to 2013 were identified. The 5-year CRS was 81.1% at baseline, but increased gradually up to 95.4% at 4 years and exceeded 100% at 5 years after diagnosis, suggesting no excess mortality compared with the general population. However, this pattern differed by treatment received. Patients who underwent androgen deprivation therapy showed 5-year CRS of only 88.4% at 5 years after diagnosis, implying persistent excess mortality. Prostate cancer constituted around one-third of deaths, while other cancers were the main cause of death within <2 years after diagnosis. Noncancer-related deaths, including cardiovascular disease and respiratory disease, increased with time since diagnosis.

Conclusions: CRS rates for patients with prostate cancer improved over time and exceeded that of the general population at 5 years. Other cancers were the main cause of death in the earlier survivorship phase, and deaths from noncancer causes gradually increased over time.

Impact: Our findings will help patients and clinicians make evidence-based decisions on the basis of a patient's dynamic risk profile.

Introduction

Prostate cancer is the second most common cancer in men worldwide; it accounts for 13.5% of all male cancers and 6.7% of all male cancer-related deaths (1). As of 2019, prostate cancer is the most common male cancer, with 174,650 new cases, and the second most common cause of cancer-related deaths in the United States (2). Prostate cancer is the fourth most common male cancer and the most common urologic malignancy in Korea, with 12,797 new cases reported in 2017 (3).

Survival statistics are of great interest to patients with cancer and their clinicians who must make important life and healthcare decisions based on estimates. However, conventional survival (represented by cumulative 5-year survival) is calculated from the time of diagnosis and such estimate becomes less meaningful as time progresses (4). Conditional survival (CS) estimates can directly address this issue by only considering individuals who have survived a certain period after being diagnosed with cancer, and may represent the best tool to assess dynamic changes in prognosis (5). Furthermore, conditional relative survival (CRS) can reveal excess mortality among patients with cancer compared with cancer-free individuals at a given time after diagnosis (6, 7).

As a result of earlier diagnosis and advances in treatment, survival of patients with prostate cancer has improved greatly, and the number of prostate cancer survivors has increased substantially (8). With improved survival of prostate cancer, more patients are at risk of death from causes other than prostate cancer. For example, older patients with prostate cancer and significant comorbidities have a higher chance of dying from competing causes other than prostate cancer. Prior studies based on Western populations have examined causes of death in patients with prostate cancer (9–11) and showed changing trends in competing mortality (12, 13). However, no major study about non-prostate cancer mortality is available in Asia, where the epidemiology of prostate cancer and other diseases differs from those of Western countries. Understanding patterns in the cause of death over time is a key to predict the healthcare needs of a growing population and developing a public health strategy.

The usefulness of CS and CRS analyses is shown in large population-based or tumor-specific cohorts of patients with cancer (14–22), while a limited number of studies has investigated CS among patients with prostate cancer (19–21, 23–25). Notably, CS estimates of patients with prostate cancer were assessed in general cancer registry cohorts, including other cancers (19–21), or in very specific settings, such as

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stage IV prostate cancer (23), metastatic prostate cancer (24), and when patients were treated with surgery only (25). In addition, CRS estimates among patients with prostate cancer were reported only in one U.S. study (20). To the best of our knowledge, no study has investigated the changes in 5-year CRS rates and competing mortality among patients with prostate cancer undergoing various available treatments, as seen in real clinical practice. Therefore, this study uses nationwide healthcare data in Korea to investigate CRS among patients with prostate cancer stratified by age, socioeconomic status, comorbidities, and various primary treatments. In addition, causes of death among patients with prostate cancer were analyzed with consideration of competing mortality.

Materials and Methods

Data source and study population

Our retrospective cohort was based on the Korean National Health Insurance Service (KNHIS) database. KNHIS is the single government payer that runs public health insurance in Korea. Subscription is mandated for the entire Korean population (∼50 million people), except for people with the lowest income levels (∼3% of total population, covered by Medical aid). In Korea, healthcare providers are reimbursed for their medical services mainly by a fee-for-service scheme. Providers must submit information on disease codes, diagnostic tests, procedures, and other medical treatments performed. The KNHIS database has been widely used in various epidemiologic studies, including those investigating CRS (26), and its background and data composition are described in detail elsewhere (27).

From the KNHIS database, a total of 81,773 patients newly diagnosed with prostate cancer [International Classification of Diseases version 10 (ICD-10), code C61] from January 1, 2007 to December 31, 2013 were selected. The study population was followed from date of diagnosis to death or until December 31, 2015, whichever came first. Vital status was linked to mortality and cause of death data from the National Statistical Office of Korea. This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center [Seoul, Republic of Korea (South), IRB no. SMC 2019-01-159-001]. The requirement for informed consent was waived, as this study used deidentified secondary data.

Variables

Income level was categorized into four groups by insurance premium level (in Korea, insurance premium is determined by income status, not health risk), and medical aid was combined into the lowest income group. Comorbidities at baseline were defined by diagnostic codes (on the basis of ICD-10) and prescription of relevant medications in the year prior to diagnosis: hypertension (I10–I11 and antihypertensive medication), diabetes mellitus (E10–E14 and antidiabetic medication), dyslipidemia (E78 and lipid-lowering agent), cardiovascular disease [includes ischemic heart disease (I20–25) and stroke (I63 or I64)], and chronic obstructive pulmonary disease (COPD, J40–47).

Treatment was defined by procedure code after prostate cancer diagnosis, and those who did not receive active treatment, such as surgery, androgen deprivation therapy (ADT), or radiotherapy, were considered as the active surveillance/watchful waiting (AS/WW) group (28). Treatment types were categorized as (i) AS/WW, (ii) surgery, (iii) surgery + ADT, (iv) radiotherapy + ADT, (v) ADT only, and (vi) radiotherapy only. ADT included orchiectomy, luteinizing hormone-releasing hormone agonist, antiandrogen, combined androgen blockade, and estrogen therapy.

Statistical analysis

Relative survival was calculated as the observed survival among patients with cancer divided by the expected survival of the general population with the same period and age (14, 29). Population lifetables used to calculate expected mortality rates in the general population were obtained from Statistics Korea. CRS, defined as the probability of surviving an additional y years on the condition that a patient had already survived x years, was calculated by dividing the relative survival at $(x + y)$ years by the relative survival at x years:

$$\textit{Conditional relative survival } (y|x) = \frac{\textit{relative survival } (x + y)}{\textit{relative survival } (x)}$$

We calculated the 5-year relative survival at baseline and 5-year CRSs conditioned on 1 through 5 years already survived after the diagnosis. Survival estimates were stratified by age group (<40, 40–65, 65–75, and ≥75 years), income status, place of residence (metropolitan, city, and rural), comorbidities (cardiovascular disease, COPD, hypertension, diabetes mellitus, and dyslipidemia), year of diagnosis (2007–2010 vs. 2011–2013), and treatment received (six groups as defined above).

Causes of death were analyzed with broad categories (e.g., diseases of circulatory system, code I00-I99) and selected specific disease subcategories (e.g., ischemic heart disease, code I20–I25) defined by ICD-10 (30). Number and proportion for each cause of death were tabulated according to survival time from diagnosis to date of death (<1, 1–2, 3–5, and ≥5 years) and patient characteristics.

Because prostate cancer–specific and other-cause mortality are competing events, which eliminates the possibility of the primary event of interest, cause-specific mortality was modeled with consideration of competing risk by Fine and Gray semiparametric proportional hazards model (31, 32). Incidence of mortality by major causes of death (prostate cancer, other cancers, cardiovascular, and respiratory) was depicted by cumulative incidence function considering the competing risk.

All statistical analyses were conducted using SAS version 9.1 (SAS Institute), and $P < 0.05$ was considered significant.

Results

Baseline characteristics

Mean age (SD) was 68.5 (9.4) years. The prevalence of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, and COPD was 52.9%, 20%, 21.5%, 10.3%, and 26.8%, respectively. Among study subjects, 27.6% had surgery only, 8.1% had surgery +ADT, and 28.1% had ADT only, while 33.2% did not receive any active treatment (AS/WW; **Table 1**).

Relative survival and CRS

For all patients with prostate cancer, 5-year relative survival was 81.1%. Five-year relative survival rates conditioned on having already survived 1, 2, 3, and 4 years were 89.5%, 92.4%, 94.1%, 95.4%, and at ≥5 years, it exceeded that of general population (102.6%; **Fig. 1A**; **Table 2**). Five-year CRS rates of all patients with prostate cancer and those according to age group, income status, preexisting comorbidities, and treatment received are depicted in **Fig. 1B–I**. Detailed estimates are presented in **Table 2**.

Patients had lower 5-year relative survival when they were diagnosed at younger (<40 years) or very old (≥75 years) age. However, those differences in CRS rates decreased over time, and were then similar to those of the middle age groups at 3 years after diagnosis.

Table 1. Baseline characteristics of study participants.

N	81,773
Age	
Mean, SD	68.5 ± 9.4
<40	363 (0.4)
40–65	24,223 (29.6)
65–75	35,627 (43.6)
≥75	21,560 (26.4)
Income status	
Rank 16–20 (highest)	19,367 (23.7)
Rank 11–15	14,482 (17.7)
Rank 6–10	19,277 (23.6)
Rank 1–5 (lowest) + medical aid	28,647 (35.0)
Place of residence	
Metropolitan	48,638 (59.7)
City	21,849 (26.8)
Rural	10,932 (13.4)
Comorbidities	
Hypertension	43,269 (52.9)
Diabetes mellitus	16,359 (20.0)
Dyslipidemia	17,574 (21.5)
CVD	8,447 (10.3)
COPD	21,938 (26.8)
Treatment, combination	
(AS/WW)	27,110 (33.2)
Surgery	22,561 (27.6)
Surgery + ADT	6,639 (8.1)
RT	794 (1.0)
RT + ADT	1,682 (2.1)
ADT	22,987 (28.1)

Abbreviations: ADT, androgen deprivation therapy; AS/WW, active surveillance/watchful waiting; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; RT, radiotherapy; SD, standard deviation.

Relative survival at baseline was worse in the lower income group, and the gap in CRS persisted over time up to 5 years.

Patients with cardiovascular disease had markedly lower relative survival at baseline (51.3% vs. 84.5%), but this gap decreased with time. Lower relative survival with COPD (72.2% vs. 84.3%) or diabetes mellitus (72.2% vs. 83.3%) at baseline persisted even with longer survival. Meanwhile, patients with prostate cancer with dyslipidemia showed better CRS, compared with those without dyslipidemia. Patients diagnosed in 2011–2013 showed slightly higher 5-year relative survival than those who were diagnosed in 2007–2010 (82.5% vs. 80.0%).

By treatment type, the AS/WW group had lower relative survival (64.3%) at baseline compared with the general population, but CRS exceeded 100% at 5 years after diagnosis. In contrast, patients who received surgery only had nearly the same survival as the general population (98.8%), and it soon exceeded 100% at 1 year after diagnosis. The surgery + ADT group showed slightly lower 5-year relative survival, and 5-year CRS was more than 100% after 4 years. Those who received ADT only showed much lower 5-year relative survival (77.1%), but 5-year CRS gradually increased over time, up to 88.4% after 5 years.

Cause of deaths and competing mortality

During the follow-up period, 32.2% (n = 26,353) of the study population had died. Among 10,946 deaths observed within 1 year of diagnosis, other cancers (n = 7,961; 72.7%) was the predominant cause of death, followed by prostate cancer. After 1 year, other cancers and prostate cancer were leading causes of death, with similar proportions. Deaths from cardiovascular, respiratory, and other causes of death gradually increased with time elapsed since diagnosis. At ≥5 years after diagnosis, deaths from noncancer causes (42.1%) exceeded deaths from prostate cancer (29.6%) or other cancers (27.5%; **Table 3**; Supplementary Fig. S1).

Younger patients were more likely to die from other cancers, while older patients were more likely to die from prostate cancer. Patients with cardiovascular disease or COPD were more likely to die from other cancer or comorbidities, while those without cardiovascular disease or COPD were more likely to die from prostate cancer. Patients who were diagnosed in 2011–2013 showed slightly lower proportion of prostate cancer–related deaths than those diagnosed in 2007–2010 (**Table 4**).

Kaplan–Meier curves for each cause of death are also shown in **Fig. 2**, stratified by age (**Fig. 2A–E**) and treatment group (**Fig. 2F–J**). When stratified by age group, higher cumulative mortality from all cause, prostate cancer, other cancers, cardiovascular disease, and respiratory disease was observed in the older group, except for high incidence of other cancer–related deaths in the very young group (age < 40 years). When stratified by treatment received, the highest cumulative mortality from prostate cancer, cardiovascular, and respiratory causes was observed in the ADT group, and the lowest mortality was observed in the surgery only and surgery + ADT groups. Mortality in earlier years was highest in the AS/WW group, which had the highest incidence of other cancer–related deaths.

Discussion

We have demonstrated changes in CRS and competing mortality over time among patients with prostate cancer using a large population–based cohort including >81,700 subjects. To the best of our knowledge, this is the first study to investigate changes in the CRS and competing mortality among patients with prostate cancer according to various primary treatments.

Our data clearly show that 5-year CRS in patients with prostate cancer improved with every additional year survived. If a patient with prostate cancer survived for 5 years after diagnosis, he can expect to have a higher relative survival rate than the general population. This is consistent with the findings from a U.S. study of the Surveillance Epidemiology and End Results database (based on the largest data, N = 204,472), which showed the increasing tendency of CRS over time. In addition, the study showed that 5-year relative survival probability after having already survived 5 years with localized/regionally staged prostate cancer reached 100% (20). Notably, this differs from the findings in many other cancers, in that CRS after 5 years usually does not reach the survival rate of the general population (20).

Cancer survivors often think of survival estimates at the time of diagnosis as static, as they are usually not updated on CS after treatment. Many patients have higher fear of recurrence and show negative coping behaviors, which is at least partially because of lack of updated prognostic information. Therefore, we believe that our CRS data will provide useful information to patients with prostate cancer. We suggest that clinicians should make efforts to successfully communicate this changing risk profile to their patients.

Both the youngest (<40 years of age) and oldest (>75 years of age) groups showed lower relative survival than other age groups. A French study also showed that younger patients with prostate cancer (15–55 years of age) have a higher probability of death, especially in their earlier years (21). This is probably because most aggressive prostate cancers occur in earlier ages (33). Lower CRS in the oldest

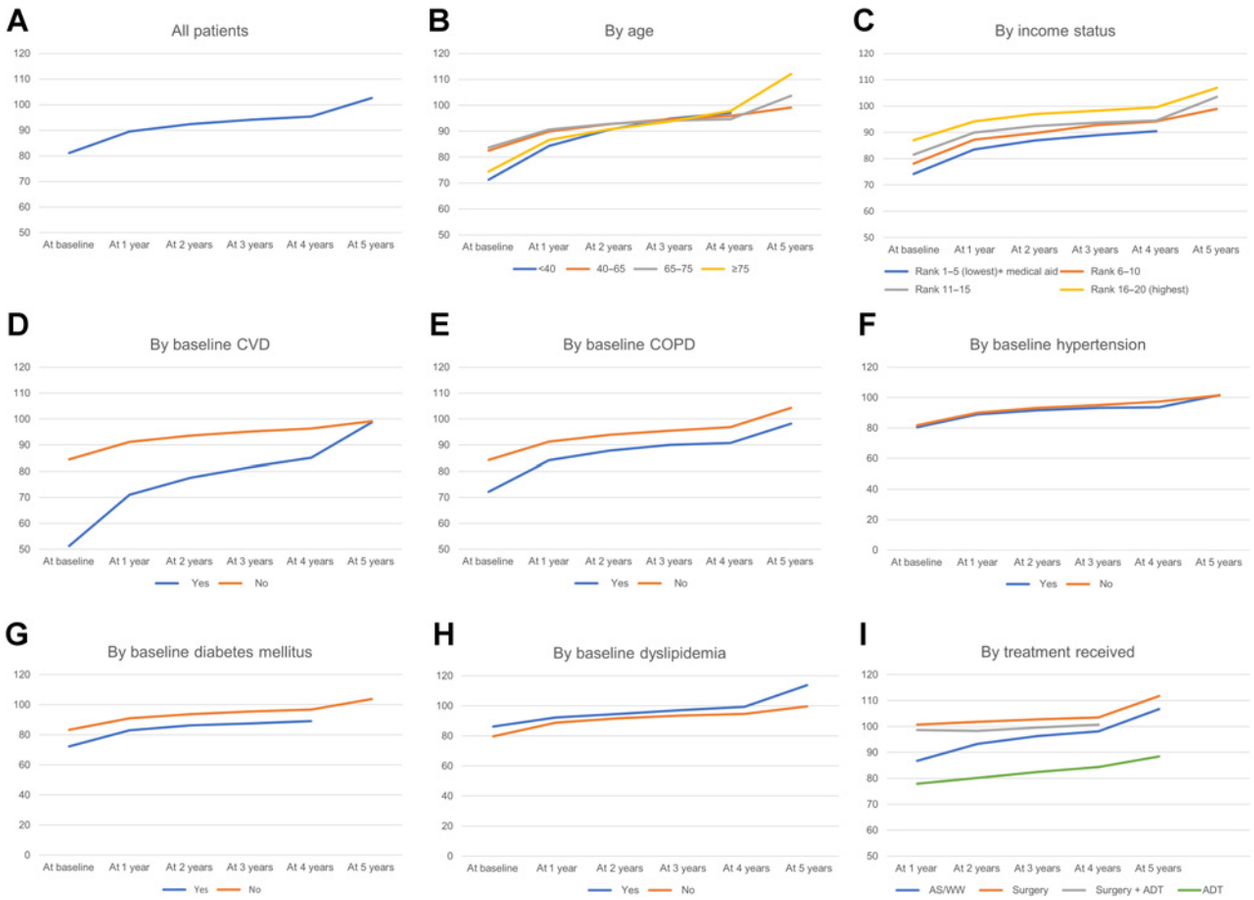

Figure 1.

Five-year relative survival at baseline and CRS of patients with prostate cancer. All patients (**A**), by age (**B**), by income status (**C**), by baseline cardiovascular disease (CVD; **D**), by baseline COPD (**E**), by baseline hypertension (**F**), by baseline diabetes mellitus (**G**), by baseline dyslipidemia (**H**), and by treatment received (**I**).

group during the earlier survivorship period has not been reported, as previous studies limited their study population to <70 or <75 years of age (21, 22). The reason for lower CRS in the oldest group is not certain, but it could be due to poorer endurance of cancer treatment toxicity.

We also showed that CRS continues to be higher in patients with higher income level. This might be due to generally lower mortality in the higher income group, as CRS is calculated by comparison with the general population in the same age group. It is also likely that higher income groups are more likely to have screen-detected cancer than lower income groups, as PSA screening in Korea is more commonly consumed by wealthier people through private health screening programs (34).

The CRS rates were lower in patients with prostate cancer and cardiovascular disease in earlier years, but the gap decreased with additional time survived and became similar at 5 years. Cardiovascular disease risk was highest in earlier years (e.g., during the first 6 months of ADT), and then became similar to a comparison cohort (35). Therefore, cardiovascular risk management is especially important in the period from diagnosis through early survivorship. CRS rates remained persistently lower in patients with prostate cancer with COPD or diabetes mellitus, implying continued excess mortality because of the comorbidity. Differences in CRS rates by hypertension were not large, as it is generally not fatal. The finding that patients with prostate cancer with dyslipidemia showed better CRS and fewer deaths due to cardiovascular disease may probably be because dyslipidemia is often detected by routine screening tests without symptoms and it reflects better cardiovascular disease management.

Importantly, we found significant differences in CRS depending on primary treatment. Several studies have assessed CRS estimates as a whole prostate cancer group without stratifying various primary treatment methods because these studies were based on general cancer registry cohorts without detailed treatment information (19–21). Patients undergoing surgery only can expect CRS > 100% even at 1 year after diagnosis. Because surgery is a curative option for men with early-stage prostate cancer, the surgery group is more likely to participate in preventive healthcare measures and seek healthier lifestyle patterns than the general population, consequently leading to higher CRS rates (36). The CRS rate of patients receiving ADT, which is commonly used as a palliative treatment for advanced prostate cancer, was around 77% at baseline, but gradually increased over time. This result indicates that patients who have good response to ADT can expect a gradual increase in CRS rates over time, although it was lower than that of the general population even after 5 years (88.4%).

Interestingly, AS/WW patients had relatively low 5-year CRS in earlier years (1–2 years after diagnosis), but had CRS exceeding 100% at 5 years after diagnosis. We suggest that the AS/WW groups

Table 2. Five-year relative survival at baseline and conditioned on 1–5 years of survival.

	5-year survival (95% CI)		Conditional relative 5-year survival (95% CI)									
	At baseline		At 1 year		At 2 years		At 3 years		At 4 years		At 5 years	
All patients	81.1	(80.7–81.5)	89.5	(89.0–90.0)	92.4	(91.8–92.9)	94.1	(93.4–94.9)	95.4	(94.3–96.6)	102.6	(101.3–103.8)
Age												
<45	71.3	(66.1–75.8)	84.3	(79.4–88.2)	90.7	(84.7–94.6)	94.9	(88.7–98.0)	97	(90.2–99.5)	NA	NA
40–65	82.6	(82.0–83.1)	89.9	(89.3–90.5)	92.7	(92.0–93.3)	94.6	(93.8–95.3)	95.9	(94.7–97.0)	99.1	(97.8–100.2)
65–75	83.7	(83.1–84.3)	90.6	(90.0–91.3)	92.9	(92.1–93.7)	94.1	(93.0–95.1)	94.6	(92.7–96.3)	103.7	(101.7–105.6)
>75	74.5	(73.3–75.7)	86.7	(85.1–88.2)	90.8	(88.8–92.8)	93.8	(91.0–96.6)	97.8	(93–102.5)	112.1	(106.6–117.4)
Income status												
Highest	87	(86.3–87.7)	94.2	(93.4–95.0)	97	(96.0–97.9)	98.2	(97.0–99.4)	99.6	(97.6–101.4)	106.9	(104.9–108.9)
Middle-high	81.5	(80.7–82.4)	89.9	(89.0–90.9)	92.4	(91.2–93.6)	93.7	(92.1–95.2)	94.5	(92.0–96.8)	103.5	(100.8–105.9)
Middle-low	78.1	(77.1–79.1)	87.2	(86.1–88.3)	89.7	(88.4–91.1)	92.7	(91.0–94.4)	94.2	(91.4–96.8)	98.9	(96.0–101.5)
Lowest	74.2	(73.3–75.1)	83.5	(82.4–84.5)	86.9	(85.6–88.1)	88.9	(87.2–90.6)	90.4	(87.6–92.9)	NA	NA
Place of residence												
Metropolitan	84.4	(83.9–84.9)	91.9	(91.3–92.5)	94.5	(93.8–95.2)	96.2	(95.3–97.1)	97.1	(95.6–98.6)	99	(97.4–100.4)
City	77.6	(76.8–78.5)	86.5	(85.5–87.4)	89.8	(88.7–91.0)	91.9	(90.4–93.4)	94.2	(91.8–96.4)	106	(103.3–108.4)
Rural	73.3	(72.1–74.6)	84.2	(82.7–85.7)	86.5	(84.6–88.4)	87.7	(85.2–90.1)	89.2	(85.4–92.7)	93.8	(89.9–97.4)
Comorbidities												
CVD												
Yes	51.3	(49.9–52.7)	71	(69.1–72.9)	77.5	(75.1–79.9)	81.7	(78.5–84.7)	85.1	(80.4–89.4)	98.8	(93.5–103.6)
No	84.5	(84.1–84.9)	91.2	(90.7–91.6)	93.6	(93.0–94.2)	95.2	(94.4–95.9)	96.3	(95.1–97.5)	99.2	(97.9–100.4)
COPD												
Yes	72.2	(71.4–73.1)	84.2	(83.2–85.2)	87.8	(86.5–89.0)	90.1	(88.4–91.7)	90.8	(88.1–93.4)	98.2	(95.2–100.9)
No	84.3	(83.8–84.8)	91.3	(90.8–91.9)	93.9	(93.2–94.5)	95.5	(94.6–96.3)	96.9	(95.6–98.2)	104.3	(102.9–105.7)
Hypertension												
Yes	80.5	(79.9–81.1)	89.0	(88.3–89.7)	91.6	(90.7–92.4)	93.2	(92.1–94.3)	93.6	(91.8–95.4)	101.7	(99.7–103.6)
No	81.7	(81.2–82.3)	90.1	(89.4–90.7)	93.2	(92.4–94.0)	95.1	(94.1–96.0)	97.3	(95.7–98.7)	101.5	(99.9–102.9)
Diabetes mellitus												
Yes	72.2	(71.2–73.2)	83	(81.8–84.2)	86.2	(84.7–87.6)	87.6	(85.6–89.5)	89.2	(86.0–92.2)	NA	NA
No	83.3	(82.8–83.7)	91	(90.5–91.5)	93.7	(93.1–94.4)	95.5	(94.7–96.3)	96.7	(95.4–98.0)	103.7	(102.3–105)
Dyslipidemia												
Yes	86.2	(85.3–87.1)	92.3	(91.2–93.3)	94.7	(93.4–95.9)	97.1	(95.4–98.7)	99.4	(96.7–101.9)	113.7	(110.6–116.4)
No	79.7	(79.2–80.2)	88.8	(88.2–89.3)	91.8	(91.2–92.4)	93.5	(92.7–94.3)	94.6	(93.3–95.9)	99.7	(98.3–101.0)
By diagnosis year												
2007–2010	80.0	(79.5–80.6)	89.0	(88.4–89.6)	92.2	(91.6–92.8)	94.1	(93.4–94.9)	95.4	(94.2–96.6)	102.6	(101.3–103.8)
2011–2013	82.5	(81.8–83.3)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
By treatment												
AS/WW	64.3	(63.6–65.1)	86.8	(86.0–87.7)	93.3	(92.3–94.2)	96.3	(95.1–97.5)	98.1	(96.3–99.8)	106.7	(104.8–108.5)
Surgery	98.8	(98.3–99.3)	100.7	(100.1–101.3)	101.8	(101–102.5)	102.7	(101.6–103.7)	103.5	(101.7–105.1)	111.8	(109.9–113.5)
Surgery + ADT	99.2	(98.2–100.2)	98.7	(97.4–99.9)	98.3	(96.7–99.8)	99.6	(97.6–101.5)	100.7	(97.4–103.5)	NA	NA
RT	74.8	(68.2–80.7)	81.4	(68.0–92.3)	97.3	(80.2–109.0)	108.7	(87.7–120.4)	130.3	(99.5–141.3)	NA	NA
RT + ADT	98.7	(95.1–101.8)	103.8	(100.0–107.-)	99.4	(62.1–116.9)	82.9	(23.2–117.8)	95.9	(24.6–134.2)	NA	NA
ADT	77.1	(76.2–78.0)	77.9	(76.8–78.9)	80.2	(78.9–81.5)	82.5	(80.8–84.1)	84.4	(81.7–86.9)	88.4	(85.6–91.0)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; NA, not available; RT, radiotherapy.

include two different groups, that is, a no treatment group due to other health conditions and a low-risk localized cancer group. The first group would have higher mortality within a few years after diagnosis mainly from other cancers or cardiopulmonary conditions. The second group is likely to be screen-detected prostate cancer, and would otherwise have good health condition, showing no excessive mortality compared with the general population. Our finding is likely due to the mixture of two different patient populations.

The cause of death should be considered as a part of a physician's surveillance algorithm to afford more accurate management. We found that prostate cancer–related deaths constituted less than one-third of deaths throughout survivorship, while other cancers were the main cause of death in earlier years and noncancer-related deaths increased gradually over time. The finding that other cancers were the most common cause of deaths within 1 year might be interpreted as follows: (i) patients had been diagnosed with other cancers before and were found to have secondary prostate cancer during follow-up (e.g., through regular abdominal CT scan for follow-up for colorectal or stomach cancer or via prostate cancer screening by clinicians) and (ii) patients were diagnosed with prostate cancer and another more fatal cancer simultaneously or later, and the prognosis was determined by the latter. The risk for second primary cancer after first prostate cancer diagnosis was similar to or even lower than that of the general population (37). However, other cancers still comprised around 30% of deaths after 5 years, and secondary primary cancer was the main determinant of death in patients with prostate cancer and secondary primary cancer (38), suggesting the need for continued surveillance for second primary cancer. The relative contribution

Table 3. Causes of death in patients with prostate cancer by year since diagnosis.

Years since diagnosis	<1 year	1–2 years	3–5 years	>5 years
Number of deaths	10,946	8,733	4,206	2,468
Cause of death				
Prostate cancer (C61)	1,985 (18.1)	3,163 (36.2)	1,540 (36.6)	730 (29.6)
Other cancers	7,961 (72.7)	3,793 (43.4)	1,301 (30.9)	679 (27.5)
Lung cancer (C33–C34)	2,171 (19.8)	895 (10.3)	300 (7.1)	169 (6.9)
Liver cancer (C22)	1,039 (9.5)	363 (4.2)	166 (4.0)	68 (2.8)
Colon cancer (C18–C20)	724 (6.6)	549 (6.3)	166 (4.0)	86 (3.5)
Stomach cancer (C16)	986 (9.0)	460 (5.3)	139 (3.3)	60 (2.4)
Cardiovascular	249 (2.3)	517 (5.9)	400 (9.5)	312 (12.6)
Respiratory	154 (1.4)	330 (3.8)	267 (6.3)	216 (8.8)
Others	519 (4.7)	877 (10.0)	671 (16.0)	511 (20.7)
Unknown	78 (0.7)	53 (0.6)	27 (0.6)	20 (0.8)
Specific details of cause of death				
Prostate cancer (C61)	1,985 (18.1)	3,163 (36.2)	1,540 (36.6)	730 (29.6)
Certain infectious and parasitic diseases (A00–B99)	43 (0.4)	58 (0.7)	55 (1.3)	48 (1.9)
Neoplasm (C00–D48), except for prostate cancer (C61)	7,961 (72.7)	3,793 (43.4)	1,301 (30.9)	679 (27.5)
Diseases of the blood and blood-forming organs and certain disorders involving immune mechanism (D50–D89)	7 (0.1)	9 (0.1)	7 (0.2)	6 (0.2)
Endocrine, nutritional, and metabolic diseases (E00–E88)	48 (0.4)	92 (1.1)	67 (1.6)	52 (2.1)
Mental and behavioral disorders (F01–F99)	7 (0.1)	21 (0.2)	18 (0.4)	23 (0.9)
Diseases of the nervous system (G00–G98)	23 (0.2)	57 (0.7)	47 (1.1)	54 (2.2)
Diseases of the circulatory system (I00–I99)	249 (2.3)	517 (5.9)	400 (9.5)	312 (12.6)
Ischemic heart diseases (I20–I25)	77 (0.7)	159 (1.8)	98 (2.3)	86 (3.5)
Cerebrovascular diseases (I60–I69)	108 (1.0)	203 (2.3)	176 (4.2)	117 (4.7)
Diseases of the respiratory system (J00–J98)	154 (1.4)	330 (3.8)	267 (6.4)	216 (8.8)
Pneumonia (J12–J18)	45 (0.4)	129 (1.5)	126 (3.0)	121 (4.9)
Chronic lower respiratory diseases (J40–J47)	77 (0.7)	135 (1.6)	75 (1.8)	57 (2.3)
Diseases of the digestive system (K00–K92)	62 (0.6)	84 (1.0)	55 (1.3)	46 (1.9)
Liver disease (K70–K76)	42 (0.4)	37 (0.4)	21 (0.5)	14 (0.6)
Diseases of the musculoskeletal system and connective tissue (M00–M99)	4 (0.0)	15 (0.2)	15 (0.4)	3 (0.1)
Diseases of the genitourinary system (N00–N98)	35 (0.3)	48 (0.6)	50 (1.2)	35 (1.4)
Other noncancer causes (eye/ear/skin disorders, pregnancy, congenital)	2 (0.0)	4 (0.1)	7 (0.2)	3 (0.1)
Unknown	78 (0.7)	53 (0.6)	27 (0.6)	20 (0.8)

of noncancer causes, which includes cardiovascular disease and respiratory disease, increased with time after diagnosis. Thus, meticulous management of other comorbidities is crucial in prostate cancer survivors, especially when the proportion of prostate cancer as a cause of death is decreasing, as in recent years (39).

United Kingdom data showed that prostate cancer, other cancers, cardiovascular disease, and other causes comprised 49.8%, 11.6%, 17.8%, and 20.7% (40) of deaths, respectively. The same values for Swedish data were 56.7%, 5.9%, 20.4%, and 27%, respectively (for men with <5 years of follow-up; ref. 41), whereas the corresponding numbers in the United States were 36.5%, 15%, 27.2%, and 21.3%, respectively (41). While direct international comparison is not easy due to different clinicodemographic profiles, follow-up duration, and PSA screening and treatment practices, our data are similar to that of the United States, where PSA screening is commonly performed. However, our data show lower cardiovascular disease mortality, reflecting the lower incidence of cardiovascular disease in the Asian population.

Older people generally had a higher cumulative probability of death from all causes, prostate cancer, other cancers, and noncancer causes. This is understandable as they showed higher prostate cancer–specific mortality, mainly due to diagnosis with high-risk prostate cancer and receipt of fewer curative treatments (42), and also higher death rates from other causes. In our study, the most intriguing findings were those of the youngest patients with prostate cancer, who had early disease onset. They showed more prostate cancer–related deaths than middle-aged patients immediately after diagnosis, and the highest cumulative mortality even when compared with the oldest patients. We found that the early-onset group had worse CRS than middle-aged and older men (**Table 2**). Patients with early-onset prostate cancer were more likely to have poorly differentiated adenocarcinoma, and demonstrated poor survival rates (43). Early-onset prostate cancer could be a component tumor of Lynch syndrome or BRCA mutation (44). In addition, a Swedish study showed that risk of second primary cancer showed U-shaped patterns, indicating higher RR in both young (age < 60 years and RR = 5.70) and very elderly patients (age ≥ 90 years and RR = 3.71) compared with the general population (38). This study also showed that the proportion of deaths from second primary cancers in prostate cancer survivors with second primary cancers was higher in the younger age group than their older counterparts (e.g., 68.3% for age < 60 vs. 20.4% for age ≥ 90). In line with these findings, we found that the early-onset group in our study had the lowest proportion of prostate cancer–related deaths, which reflects more deaths from other cancers, as shown in **Table 4**.

Table 4. Causes of death in patients with prostate cancer who underwent various treatments for prostate cancer by patient characteristics.

	Prostate cancer	Other cancer	Cardiovascular	Respiratory	Others	Unknown
All patients	7,418 (28.2)	13,734 (52.1)	1,478 (5.6)	967 (3.7)	2,578 (9.8)	178 (0.7)
Age						
<45	14 (13.5)	90 (86.5)	0 (0)	0 (0)	0 (0)	0(0)
40–65	1,024 (20.0)	3,589 (70.1)	121 (2.36)	44 (0.86)	304 (5.9)	39 (0.8)
65–75	2,726 (27.1)	5,402 (53.6)	566 (5.62)	316 (3.14)	988 (9.8)	78 (0.8)
>75	3,654 (33.1)	4,653 (42.1)	791 (7.16)	607 (5.49)	1,286 (11.6)	61 (0.6)
Income status						
Rank 16–20 (highest)	2,446 (29.9)	3,968 (48.6)	517 (6.3)	359 (4.4)	842 (10.3)	40 (0.5)
Rank 11–15	1,719 (28.2)	3,234 (53.1)	326 (5.4)	191 (3.1)	582 (9.6)	36 (0.6)
Rank 6–10	1,282 (26.8)	2,638 (55.1)	237 (5.0)	159 (3.3)	447 (9.3)	24 (0.5)
Rank 1–5 (lowest) + medical aid	1,971 (27.0)	3,894 (53.3)	398 (5.5)	258 (3.5)	707 (9.7)	78 (1.1)
Place of residence						
Metropolitan	4,021 (28.3)	7,321 (51.5)	825 (5.8)	504 (3.6)	1,429 (10.1)	115 (0.8)
City	2,158 (28.1)	4,008 (52.2)	429 (5.6)	296 (3.9)	748 (9.7)	45 (0.6)
Rural	1,202 (27.9)	2,326 (54.0)	215 (5.0)	162 (3.8)	389 (9.0)	16 (0.4)
Comorbidities						
CVD						
Yes	821 (16.4)	3,214 (64.3)	330 (6.6)	184 (3.7)	415 (8.3)	33 (0.7)
No	6,597 (30.9)	10,520 (49.3)	1,148 (5.4)	783 (3.7)	2,163 (10.1)	145 (0.7)
COPD						
Yes	1,777 (19.7)	5,360 (59.3)	489 (5.4)	503 (5.6)	859 (9.5)	57 (0.6)
No	5,641 (32.6)	8,374 (48.4)	989 (5.7)	464 (2.7)	1,719 (9.9)	121 (0.7)
Hypertension						
Yes	4,044 (27.4)	7,366 (49.9)	1,073 (7.3)	560 (3.8)	1,620 (11.0)	86 (0.6)
No	3,374 (29.1)	6,368 (54.9)	405 (3.5)	407 (3.5)	958 (8.26)	92 (0.8)
Diabetes mellitus						
Yes	1,477 (23.1)	35,10 (54.8)	397 (6.2)	187 (2.9)	793 (12.4)	40 (0.6)
No	5,941 (29.8)	10,224 (51.3)	1,081 (5.4)	780 (3.9)	1,785 (9.0)	138 (0.7)
Dyslipidemia						
Yes	1,311 (28.3)	2,153 (46.5)	391 (8.5)	167 (3.6)	571 (12.3)	34 (0.7)
No	6,107 (28.1)	11,581 (53.3)	1,087 (5.0)	800 (3.7)	2,007 (9.2)	144 (0.7)
By diagnosis year						
2007–2010	4,773 (29.3)	7,979 (48.9)	1,035 (6.35)	659 (4.0)	1,743 (10.7)	113 (0.7)
2011–2013	2,645 (26.3)	5,755 (57.3)	443 (4.41)	308 (3.1)	835 (8.3)	65 (0.7)
By treatment						
AS/WW	698 (5.6)	10,061 (80.7)	467 (3.9)	302 (2.4)	846 (6.8)	91 (0.7)
Surgery	151 (5.9)	1,759 (68.9)	178 (7.0)	81 (3.2)	365 (14.3)	20 (0.8)
Surgery + ADT	334 (40.7)	266 (32.4)	66 (8.1)	27 (3.3)	123 (15.0)	4 (0.5)
RT	12 (4.9)	208 (84.2)	6 (2.4)	9 (3.6)	11 (4.5)	1 (0.4)
RT + ADT	140 (62.0)	52 (23.0)	12 (5.3)	7 (3.1)	14 (6.2)	1 (0.4)
ADT	6,083 (60.6)	1,388 (13.8)	749 (7.5)	541 (5.4)	1,219 (12.1)	61 (0.6)

Abbreviations: CVD, cardiovascular disease; RT, radiotherapy.

Patients diagnosed in recent years had higher relative survival than those diagnosed before 2010, consistent with findings from the Korea Central Cancer Registry (3). In Korea, PSA screening has increased, and it is likely that earlier diagnosis due to PSA screening might have contributed to the increase in survival rates (45). However, our analyses of the influence of calendar year was limited as recruitment only spanned 7 years to assess changes, and follow-up of recent patients was not enough to calculate CS.

Our study has several limitations. First, because we used administrative claims data, we had insufficient clinical information, such as cancer stage and Gleason score. However, our treatment information is more likely to largely reflect such conditions, as treatment decisions are often based on disease severity. Second, our data might not be generalizable to other countries because practice patterns in prostate cancer screening, diagnosis, and treatment vary depending on the country (46). In Korea, prostate cancer screening by PSA testing is becoming more common in private health screening programs, although its clinical utility remains controversial (47). Third, cause of death data are generally subject to inaccuracy, and our cause of death data list only one cause of death. Nevertheless, it is the official cause of death listed by the National Death Registry and is the most probable cause that contributed to the death of the patient among multiple causes.

In conclusion, overall CRS rates for patients with prostate cancer improved over time and exceeded that of the general population at 5 years after diagnosis. However, significant differences in CRS existed depending on the primary treatment; patients undergoing surgery only had CRS > 100% at 1 year after diagnosis, while patients receiving ADT did not reach the level of the general population even after 5 years. Prostate cancer–related deaths constituted around one-third of the causes of deaths, while other cancers were the main cause of deaths in earlier years and

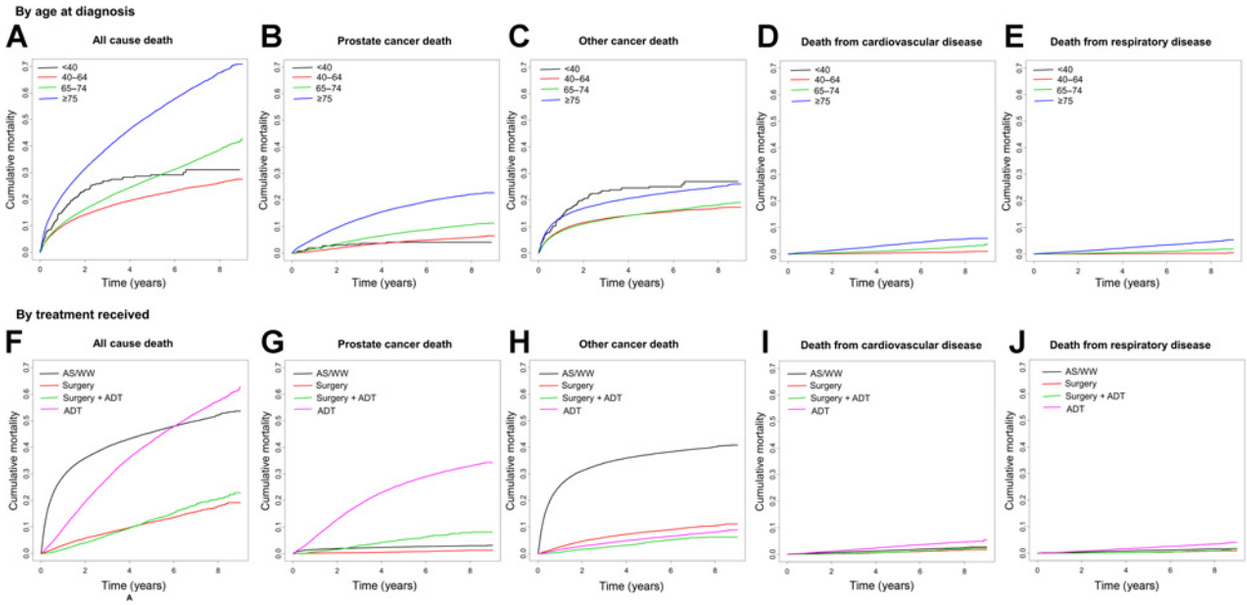

Figure 2.

Cumulative mortality, stratified by age at diagnosis (upper) and by treatment received (lower), from all causes (**A, F**), prostate cancer (**B, G**), other cancer (**C, H**), cardiovascular disease (**D, I**), and respiratory disease (**E, J**) among patients with prostate cancer.

noncancer-related deaths gradually increased over time. Our results provide valuable prognostic information to physicians and patients planning for life after treatment and suggest the need for second primary cancer screening and management of noncancer comorbidities.

Authors' Disclosures

No disclosures were reported.

Disclaimer

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Authors' Contributions

J. Park: Conceptualization, investigation, visualization, methodology, writing–original draft. **K. Han:** Data curation, software, formal analysis. **D.W. Shin:** Conceptualization, supervision, investigation, methodology, project administration, writing–review and editing. **S.H. Park:** Data curation, software, formal analysis. **H.B. Shin:** Supervision, validation, writing–review and editing.

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