Immediate Risk of Suicide and Cardiovascular Death After a Prostate Cancer Diagnosis: Cohort Study in the United States

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ARTICLE

Immediate Risk of Suicide and Cardiovascular Death After a Prostate Cancer Diagnosis: Cohort Study in the United States

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Background Receiving a cancer diagnosis is a stressful event that may increase risks of suicide and cardiovascular death, especially soon after diagnosis.

Methods We conducted a cohort study of 342 497 patients diagnosed with prostate cancer from January 1, 1979, through December 31, 2004, in the Surveillance, Epidemiology, and End Results Program. Follow-up started from the date of prostate cancer diagnosis to the end of first 12 calendar months after diagnosis. The relative risks of suicide and cardiovascular death were calculated as standardized mortality ratios (SMRs) comparing corresponding incidences among prostate cancer patients with those of the general US male population, with adjustment for age, calendar period, and state of residence. We compared risks in the first year and months after a prostate cancer diagnosis. The analyses were further stratified by calendar period at diagnosis, tumor characteristics, and other variables.

Results During follow-up, 148 men died of suicide (mortality rate = 0.5 per 1000 person-years) and 6845 died of cardiovascular diseases (mortality rate = 21.8 per 1000 person-years). Patients with prostate cancer were at increased risk of suicide during the first year (SMR = 1.4, 95% confidence interval [CI] = 1.2 to 1.6), especially during the first 3 months (SMR = 1.9, 95% CI = 1.4 to 2.6), after diagnosis. The elevated risk was apparent in pre–prostate-specific antigen (PSA) (1979–1986) and peri–PSA (1987–1992) eras but not since PSA testing has been widespread (1993–2004). The risk of cardiovascular death was slightly elevated during the first year (SMR = 1.09, 95% CI = 1.06 to 1.12), with the highest risk in the first month (SMR = 2.05, 95% CI = 1.89 to 2.22), after diagnosis. The first-month risk was statistically significantly elevated during the entire study period, and the risk was higher for patients with metastatic tumors (SMR = 3.22, 95% CI = 2.68 to 3.84) than for those with local or regional tumors (SMR = 1.57, 95% CI = 1.42 to 1.74).

Conclusion A diagnosis of prostate cancer may increase the immediate risks of suicide and cardiovascular death.

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Prostate cancer is one of the most common cancers and a leading cause of cancer death among men in the Western world (1). After the introduction of prostate-specific antigen (PSA) screening, the incidence of prostate cancer has increased substantially in the United States and other Western countries (2,3). The natural course of prostate cancer is highly variable, with high survival rates even without therapeutic intervention among men diagnosed with early-stage prostate cancer (4). The diagnosis itself may, however, represent a potent psychological stressor that, if strong enough, may increase risk of stress-related health outcomes, such as suicide and death from cardiovascular diseases, especially soon after diagnosis. In a recent nationwide Swedish study (5), we observed increased risks for suicide and cardiovascular events (both fatal and nonfatal) after a diagnosis of prostate cancer, especially during the first weeks after cancer diagnosis. The United States differs from Sweden in that it has adopted a higher level of PSA testing and so a greater risk of potential overdiagnosis of prostate cancer. Therefore, an association of prostate cancer diagnosis with suicide and cardiovascular events in the United States would be especially concerning. In this study, we explored whether these stress-related health outcomes are affected by a prostate cancer diagnosis also among men in the United States. We conducted a population-based cohort study by use of data from the Surveillance, Epidemiology, and End Results (SEER) Program.

Materials and Methods

Study Cohort

The SEER program of the National Cancer Institute collects uniformly reported data on patient demographics, month and year of diagnosis, tumor characteristics, treatment utilization, and mortality for all incident cancers from selected population-based cancer registries in the United States that covered 26% of the entire US population by 2000. We used SEER registry records for

CONTEXT AND CAVEATS

Prior knowledge

Receiving a cancer diagnosis is a stressful event and may increase risks of suicide and cardiovascular death, especially soon after diagnosis.

Study design

We used data from the Surveillance, Epidemiology, and End Results Program to conduct a cohort study of patients with prostate cancer to investigate associations between prostate cancer diagnosis and risk of suicide and cardiovascular death in the first year after diagnosis compared with those in the general US male population.

Contribution

During the first year after diagnosis, the mortality rate was 0.5 per 1000 person-years from suicide and 21.8 per 1000 person-years from cardiovascular diseases. Increased risk of suicide was found during the first year, in particular the first 3 months. The risk of cardiovascular death was slightly elevated during the first year, especially in the first month and particularly among those with metastatic disease.

Implications

Emotional counseling and support should be provided for patients with newly diagnosed cancer. These results add to the complex debate of pros and cons of extensive prostate-specific antigen testing and the many nonlethal prostate cancers thus detected.

Limitations

No cancer-free group was available as the reference. Data on physical or mental health status, other prevalent disorders or comorbid illness at diagnosis, and prostate cancer treatments were not available.

From the Editors

all men diagnosed with prostate cancer in the nine original registries that have complete data on cancers diagnosed from January 1, 1979, through December 31, 2004 (San Francisco-Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). A total of 345 384 patients with prostate cancer diagnosed as their first primary malignancy were identified. We excluded 2788 (0.8%) of these patients who were first diagnosed at autopsy or identified from the death certificate only and 99 (0.03%) with missing information on birth year, leaving 342 497 patients in the final analyses.

Follow-up

SEER data were linked with data from the National Death Index to determine death and cause of death. Survival time, as recorded in months, started at the date of cancer diagnosis and ended at date of death, date last known to be alive, or end of follow-up (December 31, 2005), whichever came first. We assessed suicide and cardiovascular outcomes that occurred during the first 12 calendar months after a prostate cancer diagnosis. Because SEER data provide only information on year and month of prostate cancer diagnosis for individuals who died in the same month of diagnosis, we assigned an average survival time of 15 days by assuming a constant probability of prostate cancer diagnosis throughout each calendar month. We used the *International Classification of Diseases* (*ICD*) versions 9 and 10 to classify outcomes: death from suicide (*ICD-9* codes E950–E959 in 1979–1998 and *ICD-10* codes U03, X60–X84, and Y87.0 in 1999–2005) or cardiovascular diseases (*ICD-9* codes 390–448 in 1979–1998 and *ICD-10* codes I00–I78 in 1999–2005). Cardiovascular death was further subgrouped as disease of the heart (*ICD-9* codes 390–398, 402, 404, and 410–429 and *ICD-10* codes I00–I09, I11, I13, and I20–I51), cerebrovascular disease (*ICD-9* codes 430–438 and *ICD-10* codes I60–I69), and other cardiovascular disease.

Statistical Analysis

To estimate the relative risks of suicide and cardiovascular death among men with prostate cancer compared with the general population, we calculated standardized mortality ratios (SMRs; ie, the ratios of the observed numbers of suicides and cardiovascular deaths among the prostate cancer patients to the expected numbers in the general population). The numbers of expected events were calculated by multiplying mortality rates from suicide and cardiovascular death for age (10-year categories), calendar period (1979–1983, 1984–1988, 1989–1993, 1994–1998, and 1999–2005), and state of residence in the general US male population by the follow-up time accrued from the study cohort. For San Francisco-Oakland, Detroit, Seattle, and Atlanta, we used rates from the state of California, Michigan, Washington, and Georgia, respectively. We calculated 95% confidence intervals (CIs) of the standardized mortality ratios by assuming that the observed numbers of outcomes followed a Poisson distribution (6).

We performed separate analyses by various time periods after diagnosis to examine immediate and longer-term influences of cancer diagnosis. For cardiovascular deaths, we examined the standardized mortality ratio of cardiovascular death in the first month after prostate cancer diagnosis (ie, the month of prostate cancer diagnosis), calendar months 2–6 after diagnosis, and calendar months 7–12 after diagnosis. Given the smaller number of suicides, we examined calendar months 1–3 (ie, the month of prostate cancer diagnosis and the next 2 months) and calendar months 4–12 to ensure both sufficient statistical power and a possibility of showing the most immediate effect of prostate cancer diagnosis (ie, calendar months 1–3).

Since the introduction of PSA screening, a substantial increase in prostate cancer diagnosis has been observed (3). In part because of the long lead time achieved by PSA testing, the shift in distribution of tumor stage at diagnosis to earlier-stage disease, and the increase in diagnosis of indolent cases of prostate cancer, the prognosis of prostate cancer has improved dramatically. We therefore assessed the associations between the prostate cancer diagnosis and the risks of suicide and cardiovascular death during the following three calendar periods: pre-PSA era (1979–1986), peri-PSA era (1987–1992), and PSA era (1993–2004).

To explore the impact of other factors that may modify the associations between prostate cancer diagnosis and suicide or cardiovascular death, we conducted additional stratified analyses by use of the following variables: age at diagnosis (<70, 70–79, or ≥80 years for suicide; or <65, 65–69, 70–74, 75–79, or ≥80 years for cardiovascular death), calendar period of diagnosis (pre-PSA, peri-PSA,

or PSA era for suicide; or 1979–1983, 1984–1988, 1989–1993, 1994–1998, or 1999–2004 for cardiovascular death), marital status at diagnosis (single, married, separated or divorced, widowed, or unknown), race (white, black, or others), registry place, county-level education, and county-level poverty rates, tumor grade (well or moderately differentiated, poorly or undifferentiated, or unknown), and tumor stage (local or regional, metastatic, or unknown). Because individual data on educational level and household income were not available, we linked the data with 2000 US Census data to obtain county-specific average educational level (ie, the percentage of the county residents who were at age 25 years or older and had no high school education; categorized as <12%, ≥12% to <15%, ≥15% to <18%, ≥18%, or unknown) and poverty rates (ie, the percentage of families in the county with a household income that was below the poverty level; categorized as <7%, ≥7% to <9%, ≥9% to <12%, ≥12%, or unknown). Categorizations were decided approximately by the quartile distribution of the stratification variables. An approximate χ^2 test was used to examine potential difference or linear trend of the standardized mortality ratio estimates across the above-mentioned strata.

To allay potential concern that prostate cancer treatment rather than diagnosis caused excess risks of suicide and cardiovascular death, we conducted a sensitivity analysis by restricting the analysis to prostate cancer patients for whom no surgery was performed.

All *P* values were from two-sided statistical tests and were considered to be statistically significant at a *P* of less than .05. All the analyses were performed by use of SAS, version 9.1 (SAS Institute, Cary, NC). Because the present analyses used preexisting and deindentified registry data, the Partners Health Care Institutional Review Board granted an exemption from review.

Results

Characteristics of the study participants are shown in Table 1. Mean age at diagnosis was 70.2 years, with more than one-quarter (26.8%; n = 91 939) of the 342 497 men diagnosed with prostate cancer before age 65 years (18.6% [n = 10 604] in pre-PSA era, 18.3% [n = 14 774] in peri-PSA era, and 32.5% [n = 66 561] in PSA era). The annual number of patients diagnosed increased markedly during the study period from 6106 in 1979 to 17 688 in 2004. Most prostate cancer patients were married or living as married at the time of diagnosis and most were whites. More than half of the patients were diagnosed with a "well or moderately differentiated" tumor (58.4% [n = 33 307] in the pre-PSA era, 68.6% [n = 55 473] in the peri-PSA era, and 69.7% [n = 142 611] in the PSA era), whereas 9% (n = 30 679) were diagnosed with metastatic disease (18.2% [n = 10 358] in the pre-PSA era, 12.6% [n = 10 154] in the peri-PSA era, and 5.0% [n = 10 167] in the PSA era).

Suicides

We observed a total of 148 patients who died of suicide during the first year after prostate cancer diagnosis (mortality rate = 0.5 per 1000 person-years) compared with the expected 105.2 on the basis of age-, calendar period-, and state-matched rates from the general population (SMR = 1.4, 95% CI = 1.2 to 1.6). The risk was highest from calendar month 1 through calendar month 3 after prostate

Table 1. Characteristics of prostate cancer patients in the Surveillance, Epidemiology, and End Results database, 1979–2004*

Characteristic	No. (%)
Age group at diagnosis	
<65 y	91 939 (26.8)
65–69 y	65 342 (19.1)
70–74 y	71 760 (21.0)
75–79 y	58 405 (17.0)
≥80 y	55 051 (16.1)
Calendar period of diagnosis	
1979–1983	33 453 (9.8)
1984–1988	43 242 (12.6)
1989–1993	79 368 (23.2)
1994–1998	78 594 (23.0)
1999–2004	107 840 (31.5)
Marital status at diagnosis	
Single (never married)	25 361 (7.4)
Married (including common law)	246 418 (72.0)
Separated or divorced	17 734 (5.2)
Widowed	28 914 (8.4)
Unknown	24 070 (7.0)
Race	
White	284 663 (83.1)
Black	39 266 (11.5)
Others†	15 980 (4.7)
Unknown	2588 (0.8)
Registry place	
San Francisco-Oakland SMSA	50 528 (14.8)
Connecticut	47 111 (13.8)
Metropolitan Detroit	65 817 (19.2)
Hawaii	12 765 (3.7)
Iowa	42 785 (12.5)
New Mexico	21 191 (6.2)
Seattle	53 026 (15.5)
Utah	23 267 (6.8)
Metropolitan Atlanta	26 007 (7.6)
County-level education: men without high school education‡	
<12%	79 573 (23.2)
≥12% to <15%	84 837 (24.8)
≥15% to <18%	99 122 (28.9)
≥18%	69 615 (20.3)
Unknown	9350 (2.7)
County-level poverty rates: households with income below poverty level§	
<7%	91 696 (26.8)
≥7% to <9%	66 128 (19.3)
≥9% to <12%	94 461 (27.6)
≥12%	80 862 (23.6)
Unknown	9350 (2.7)
Tumor grade	
Well or moderately differentiated	231 391 (67.6)
Poorly or undifferentiated	79 497 (23.2)
Unknown	31 609 (9.2)
Tumor stage	
Local or regional	288 077 (84.1)
Metastatic	30 679 (9.0)
Missing	23 741 (6.9)

* Mean age at diagnosis was 70.2 y (SD = 9.4 y). SMSA = standard metropolitan statistical area.

† This category includes American Indian or Alaska native or Asian or Pacific Islander.

‡ Percentage of residents at age 25 y or older who had no high school education as reported in the 2000 US Census.

§ Percentage of households with income below poverty level as reported in the 2000 US Census.

cancer diagnosis (SMR = 1.9, 95% CI = 1.4 to 2.6) and was decreased but still elevated from calendar month 4 through calendar month 12 after cancer diagnosis (SMR = 1.3, 95% CI = 1.0 to 1.5) (Table 2). The excess risk of suicide from calendar month 1 through calendar month 3 was statistically significant in the pre- and peri-PSA eras but not in the PSA era (Table 2). Being single, separated or divorced, or widowed was associated with a higher risk of suicide than being married (*P* for difference = .01, for calendar months 1–3, and *P* for difference < .001, for calendar months 4–12). Having a diagnosis of metastatic prostate cancer was associated with a higher risk of suicide in calendar months 4–12 after diagnosis (*P* for difference < .001), but not in calendar months 1–3 after diagnosis (*P* for difference = .52), than having a diagnosis of local or regional prostate cancer, although estimates were based on a small number of events.

Cardiovascular Deaths

A total of 6845 cardiovascular deaths were recorded during the first year after prostate cancer diagnosis (mortality rate = 21.8 per 1000 person-years) compared with 6282.9 deaths expected (SMR = 1.09, 95% CI = 1.06 to 1.12). The excess risk peaked during the first month after diagnosis (SMR = 2.05, 95% CI = 1.89 to 2.22) and decreased during calendar months 2–6 (SMR = 1.16, 95% CI = 1.12 to 1.20), with a reduced risk during calendar months 7–12 (SMR = 0.92, 95% CI = 0.89 to 0.95) (Table 3). In all three periods of time since diagnosis, the relative risks of cardiovascular death

Table 2. Risk of suicide after prostate cancer diagnosis*

	Calendar months 1–3			Calendar months 4–12		
Characteristic	**Exp. No. of diagnoses**	**Obs. No. of diagnoses**	**SMR (95% CI)**	**Exp. No. of diagnoses**	**Obs. No. of diagnoses**	**SMR (95% CI)**
Overall	23.7	45	1.9 (1.4 to 2.6)	82.0	103	1.3 (1.0 to 1.5)
Age group at diagnosis						
<70 y	8.2	16	1.9 (1.1 to 3.2)	29.1	41	1.4 (1.0 to 1.9)
70–79 y	9.6	15	1.6 (0.9 to 2.6)	33.9	39	1.2 (0.8 to 1.6)
≥80 y	5.8	14	2.4 (1.3 to 4.1)	19.0	23	1.2 (0.8 to 1.8)
Calendar period of diagnosis						
Pre-PSA era (1979–1986)	4.6	11	2.4 (1.2 to 4.3)	15.8	32	2.0 (1.4 to 2.9)
Peri-PSA era (1987–1992)	6.7	21	3.2 (2.0 to 4.8)	23.1	25	1.1 (0.7 to 1.6)
PSA era (1993–2004)	12.4	13	1.0 (0.6 to 1.8)	43.1	46	1.1 (0.8 to 1.4)
Marital status at diagnosis						
Married or living as married	16.7	24	1.4 (0.9 to 2.1)	58.4	53	0.9 (0.7 to 1.2)
Others†	6.9	21	3.0 (1.9 to 4.6)	23.6	50	2.1 (1.6 to 2.8)
Race						
White	20.0	44	2.2 (1.6 to 3.0)	69.4	94	1.4 (1.1 to 1.7)
Black	2.5	1	0.4 (0.0 to 2.2)	8.6	5	0.6 (0.2 to 1.4)
Others‡	1.1	0	N/A	4.0	4	1.0 (0.3 to 2.6)
County-level education: men without high school education§						
<12%	5.7	11	1.9 (1.0 to 3.4)	19.9	19	1.0 (0.6 to 1.5)
≥12% to <15%	6.2	13	2.1 (1.1 to 3.6)	21.7	19	0.9 (0.5 to 1.4)
≥15% to <18%	6.2	12	1.9 (1.0 to 3.4)	21.5	33	1.5 (1.1 to 2.2)
≥18%	5.0	9	1.8 (0.8 to 3.4)	17.2	28	1.6 (1.1 to 2.4)
Unknown	0.5	0	N/A	1.6	4	2.4 (0.7 to 6.2)
County-level poverty rates: households with income below poverty level‖						
<7%	5.7	11	1.9 (1.0 to 3.4)	19.9	23	1.2 (0.7 to 1.7)
≥7% to <9%	5.0	12	2.4 (1.2 to 4.2)	17.4	18	1.0 (0.6 to 1.6)
≥9% to <12%	6.5	11	1.7 (0.8 to 3.0)	22.3	28	1.2 (0.8 to 1.8)
≥12%	6.0	11	1.8 (0.9 to 3.3)	20.6	30	1.4 (2.0 to 2.1)
Unknown	0.5	0	N/A	1.6	4	2.4 (0.7 to 6.2)
Tumor grade						
Well or moderately differentiated	15.6	29	1.9 (1.2 to 2.7)	54.9	65	1.2 (0.9 to 1.5)
Poorly or undifferentiated	5.6	12	2.2 (1.1 to 3.8)	19.1	25	1.3 (0.8 to 1.9)
Unknown	2.5	4	1.6 (0.4 to 4.2)	8.0	13	1.6 (0.9 to 2.8)
Tumor stage						
Regional or local	19.3	36	1.9 (1.3 to 2.6)	67.8	72	1.1 (0.8 to 1.3)
Metastatic	2.4	3	1.3 (0.3 to 3.7)	7.4	22	3.0 (1.9 to 4.5)
Unknown	2.0	6	2.4 (1.1 to 6.5)	6.8	9	1.3 (0.6 to 2.5)

* CI = confidence interval; Exp. = expected; N/A = not applicable; Obs. = observed; PSA = prostate-specific antigen; SMR = standardized mortality ratio.

† This group includes single, separated, divorced, widowed, or unknown.

‡ This group includes American Indian or Alaska native, Asian or Pacific Islander, or unknown.

§ Percentage of residents at age 25 y or older who had no high school education as reported in the 2000 US Census.

‖ Percentage of households with income below poverty level as reported in the 2000 US Census.

decreased consecutively over calendar periods (Table 3). The increased risk of cardiovascular death during the first month after diagnosis remained statistically significant during the entire study (SMR = 1.55, 95% CI = 1.35 to 1.77) in the PSA era (1993–2004). In contrast, the risk during calendar months 2–6 was elevated only in the pre-PSA (1979–1986) and peri-PSA (1987–1992) eras but decreased in the PSA era. The risk in calendar months 7–12 was only elevated in the pre-PSA era but decreased in the peri-PSA and PSA eras. Similar trends were noted for disease of the heart, cerebrovascular disease, and other cardiovascular disease (Table 3).

We next focused on the first month after prostate cancer diagnosis and conducted stratified analyses as shown in Table 4. Age at cancer diagnosis, race, geographic areas, or tumor grade did not alter the association of prostate cancer with cardiovascular deaths materially. The excess risk of cardiovascular death decreased monotonically during the study period (*P* for linear trend < .001). Patients with prostate cancer who were single, separated, divorced, or widowed had higher excess risk of cardiovascular death than patients who were married or living as married at the time of prostate cancer diagnosis (*P* for difference < .001). Patients with prostate cancer who were living in a county with lower educational level (*P* for linear trend = .01) or higher poverty rates (*P* for linear trend = .05) had higher relative risk of cardiovascular death than in those with higher educational level or lower poverty rates. Higher risk was also noted for men diagnosed with metastatic tumors (SMR = 3.22, 95% CI = 2.68 to 3.84) than for those diagnosed with local or regional tumors (SMR = 1.57, 95% CI = 1.42 to 1.74) (*P* for difference < .001) (Table 4). We noted a high relative risk of cardiovascular death among the patients with unknown tumor grade (SMR = 5.76, 95% CI = 5.08 to 6.51) than those with a tumor grade (Table 4); patients with unknown tumor grade were on average older, more likely to be African American, and unmarried at the time of prostate cancer diagnosis than those with a known tumor grade (data not shown).

Sensitivity Analysis

We performed a sensitivity analysis to allay potential concern that surgical treatment rather than prostate cancer diagnosis was the stressor causing excess risks of suicide and cardiovascular death. This analysis was confined to 165 966 (48.5%) of the 342 497 patients for whom no surgery was performed. We found five observed suicides during the first 3 months compared with 2.5 expected suicides (SMR for suicide = 2.0, 95% CI = 0.6 to 5.7) and observed 402 deaths from cardiovascular disease during the first month compared with 155.48 expected deaths (SMR for cardiovascular death = 2.59, 95% CI = 2.34 to 2.85). Thus, although with lower statistical power, the point estimates for both suicide and cardiovascular death remained similar in the subgroup of patients who were not treated surgically.

Discussion

In this large population-based study, we observed increased risks of suicide and cardiovascular death among men who were newly diagnosed with prostate cancer. The excess risks were higher in periods closer to cancer diagnosis and in earlier calendar years. However, the increased risk of cardiovascular death during the

Table 3. Risk of cardiovascular death after prostate cancer diagnosis by subgroup*

Group and characteristic	Calendar month 1			Calendar months 2–6			Calendar months 7–12		
	No. of diagnoses			No. of diagnoses			No. of diagnoses		
	Exp.	Obs.	SMR (95% CI)	Exp.	Obs.	SMR (95% CI)	Exp.	Obs.	SMR (95% CI)
Overall									
Overall cardiovascular death	302.32	620	2.05 (1.89 to 2.22)	2776.63	3224	1.16 (1.12 to 1.20)	3258.33	3001	0.92 (0.89 to 0.95)
Diseases of heart	236.11	507	2.15 (1.96 to 2.34)	2168.18	2541	1.17 (1.13 to 1.22)	2541.62	2369	0.93 (0.89 to 0.97)
Cerebrovascular diseases	45.94	56	1.22 (0.92 to 1.58)	422.55	474	1.12 (1.02 to 1.23)	498.36	452	0.91 (0.83 to 0.99)
Other cardiovascular diseases	20.26	57	2.81 (2.13 to 3.65)	185.90	209	1.12 (0.98 to 1.29)	218.35	180	0.82 (0.71 to 0.95)
Pre-PSA era (1979–1986)									
Overall cardiovascular death	79.51	222	2.79 (2.44 to 3.18)	711.55	1154	1.62 (1.53 to 1.72)	812.82	956	1.18 (1.10 to 1.25)
Diseases of heart	61.64	172	2.79 (2.39 to 3.24)	552.44	900	1.63 (1.52 to 1.74)	631.89	764	1.21 (1.12 to 1.30)
Cerebrovascular diseases	12.29	25	2.03 (1.32 to 3.00)	109.46	184	1.68 (1.45 to 1.94)	124.47	137	1.10 (0.92 to 1.30)
Other cardiovascular diseases	5.57	25	4.48 (2.90 to 6.62)	49.64	70	1.41 (1.10 to 1.78)	56.46	55	0.97 (0.73 to 1.27)
Peri-PSA era (1987–1992)									
Overall cardiovascular death	86.53	187	2.16 (1.86 to 2.49)	794.91	940	1.18 (1.11 to 1.26)	931.45	869	0.93 (0.87 to 1.00)
Diseases of heart	68.28	161	2.36 (2.01 to 2.75)	627.00	740	1.18 (1.10 to 1.27)	733.92	683	0.93 (0.86 to 1.00)
Cerebrovascular diseases	12.56	10	0.80 (0.38 to 1.46)	115.63	138	1.19 (1.00 to 1.41)	136.16	135	0.99 (0.83 to 1.17)
Other cardiovascular diseases	5.69	16	2.81 (1.61 to 4.57)	52.28	62	1.19 (0.91 to 1.52)	61.37	51	0.83 (0.62 to 1.09)
PSA era (1993–2004)									
Overall cardiovascular death	136.27	211	1.55 (1.35 to 1.77)	1270.18	1130	0.89 (0.84 to 0.94)	1514.07	1176	0.78 (0.73 to 0.82)
Diseases of heart	106.19	174	1.64 (1.40 to 1.90)	988.73	901	0.91 (0.85 to 0.97)	1175.81	922	0.78 (0.73 to 0.84)
Cerebrovascular diseases	21.09	21	1.00 (0.62 to 1.52)	197.46	152	0.77 (0.65 to 0.90)	237.73	180	0.76 (0.65 to 0.88)
Other cardiovascular diseases	8.99	16	1.78 (1.02 to 2.89)	83.99	77	0.92 (0.72 to 1.15)	100.52	74	0.74 (0.58 to 0.92)

* CI = confidence interval; Exp. = expected; Obs. = observed; PSA = prostate-specific antigen; SMR = standardized mortality ratio.

Table 4. Risk of cardiovascular death within the first calendar month after prostate cancer diagnosis*

Characteristic	No. of diagnoses		SMR (95% CI)
	Exp.	Obs.	
Overall	302.32	620	2.05 (1.89 to 2.22)
Age group at diagnosis			
<65 y	16.44	31	1.89 (1.28 to 2.68)
65–69 y	34.55	51	1.48 (1.10 to 1.94)
70–74 y	40.55	85	2.10 (1.67 to 2.59)
75–79 y	79.70	96	1.20 (0.98 to 1.47)
≥80 y	131.08	357	2.72 (2.45 to 3.02)
Calendar period of diagnosis			
1979–1983	49.30	135	2.74 (2.30 to 3.24)
1984–1988	54.84	144	2.63 (2.21 to 3.09)
1989–1993	78.37	164	2.09 (1.79 to 2.44)
1994–1998	58.79	94	1.60 (1.29 to 1.96)
1999–2004	61.01	83	1.36 (1.08 to 1.69)
Marital status at diagnosis			
Single (never married)	19.78	62	3.14 (2.40 to 4.02)
Married (including common law)	198.01	362	1.83 (1.64 to 2.03)
Separated or divorced	12.08	25	2.07 (1.34 to 3.06)
Widowed	49.30	137	2.78 (2.33 to 3.29)
Unknown	23.16	34	1.47 (1.02 to 2.05)
Race			
White	255.97	525	2.05 (1.88 to 2.23)
Black	31.06	66	2.12 (1.64 to 2.70)
Others†	13.45	29	2.16 (1.44 to 3.10)
Unknown	1.84	0	N/A
Registry place			
San Francisco-Oakland SMSA	44.34	78	1.76 (1.39 to 2.20)
Connecticut	40.91	100	2.44 (1.99 to 2.97)
Metropolitan Detroit	63.77	121	1.90 (1.57 to 2.27)
Hawaii	9.96	27	2.71 (1.79 to 3.94)
Iowa	46.38	121	2.61 (2.16 to 3.12)
New Mexico	15.17	33	2.17 (1.50 to 3.05)
Seattle	43.58	71	1.63 (1.27 to 2.06)
Utah	17.55	41	2.34 (1.68 to 3.17)
Metropolitan Atlanta	20.65	28	1.36 (0.90 to 1.96)
County-level education: residents without high school education‡			
<12%	66.58	108	1.62 (1.33 to 1.96)
≥12% to <15%	72.53	144	1.99 (1.67 to 2.34)
≥15% to <18%	86.99	195	2.24 (1.94 to 2.58)
≥18%	68.44	148	2.16 (1.83 to 2.54)
Unknown	7.78	25	3.21 (2.08 to 4.74)
County-level poverty rates: households with income below poverty level§			
<7%	79.05	140	1.77 (1.49 to 2.09)
≥7% to <9%	56.64	113	2.00 (1.64 to 2.40)
≥9% to <12%	85.15	180	2.11 (1.82 to 2.45)
≥12%	73.70	162	2.20 (1.87 to 2.56)
Unknown	7.78	25	3.21 (2.08 to 4.74)
Tumor grade			
Well or moderately differentiated	183.18	262	1.43 (1.26 to 1.61)
Poorly or undifferentiated	74.54	101	1.35 (1.10 to 1.65)
Unknown	44.59	257	5.76 (5.08 to 6.51)
Tumor stage			
Regional or local	231.88	365	1.57 (1.42 to 1.74)
Metastatic	38.78	125	3.22 (2.68 to 3.84)
Missing	31.66	130	4.11 (3.43 to 4.88)

* CI = confidence interval; Exp. = expected; N/A = not applicable; Obs. = observed; PSA = prostate-specific antigen; SMR = standardized mortality ratio; SMSA = standard metropolitan statistical area.

† This group includes American Indian or Alaska native, or Asian or Pacific Islander.

‡ Percentage of residents at age 25 y or older who had no high school education as reported in the 2000 US Census.

§ Percentage of households with income below poverty level as reported in the 2000 US Census.

first month after prostate cancer diagnosis was observed throughout the study period.

Psychological stress has been associated with various hazardous health outcomes. Heart stunning or reversible left ventricular dysfunction with high levels of corticosteroids has been reported in a series of individuals without previous coronary disease who suffered from acute emotional stress (7). In epidemiological studies, severe stressful life events, including loss of a child due to death (8,9), experience of natural (eg, earthquake) (10,11) or social (eg, war) disasters (12), and even watching a world cup match (13), have been associated with higher risks of cardiovascular events and mortality. Whether a diagnosis of prostate cancer represents a similar stressful event is open to question. However, earlier studies have also reported an increased risk of suicide among patients with cancer of the breast (14), prostate (15), or other sites (16–18), and some studies (17,18) indicated that the risk may be highest during the first months or years after diagnosis.

The concentration of the highest relative risks of suicide and cardiovascular death to the first weeks after the prostate cancer diagnosis and subsequent reduction in risk elevations during the first year after diagnosis is similar to our earlier findings (5) in a large population of prostate cancer patients in Sweden in 1961–2004. In that study, we observed the highest relative risks of suicide and cardiovascular events (fatal and nonfatal combined) during the first week after diagnosis, followed by the first month and the first year after diagnosis. In the SEER data, both prostate cancer diagnosis and survival time after diagnosis were recorded in months, precluding the possibility to examine outcomes by weeks after diagnosis. If we assume that prostate cancer diagnoses were evenly distributed across a calendar month, the first calendar month should represent an average follow-up of approximately 15 days.

In the present study, we observed an elevated risk of suicide in the pre-PSA and peri-PSA eras but not in the PSA era. This finding contrasts with our previous finding (5) in Sweden, in which the risk elevation remained relatively stable during the entire study period. The reason for this discrepancy is unclear. However, the large number of indolent prostate cancers diagnosed in the United States with PSA screening during recent times and possible differential access to emotional support may have caused less emotional despair in men who were more recently diagnosed with prostate cancer in the United States. Although the risk of cardiovascular death during the first month remained elevated during the entire study period in this study, the relative risk declined in calendar months 2–6 and was decreased in the PSA era. The risk in calendar months 7–12 was only elevated in the pre-PSA era and decreased thereafter. In contrast, in the Swedish study, we found that although the relative risk of cardiovascular events also decreased over time, the risk has remained 20% elevated since the late 1980s.

The finding of a lower risk of cardiovascular death, especially during calendar months 7–12 after prostate cancer diagnosis in the peri-PSA and PSA eras was surprising. A plausible explanation might be that men with better health consciousness and medical surveillance were more likely to undergo PSA screening, which would lead to a higher recorded incidence of prostate cancer in otherwise healthier men. The discrepant findings among the pre-PSA, peri-PSA, and PSA eras lend further evidence to this

interpretation. Alternatively, men may change health behavior and other lifestyle factors after a prostate cancer diagnosis because of the diagnosis itself or as a result of a more intense contact with medical professionals. Smoking cessation, for example, can rapidly reduce cardiovascular risk within months of cessation (19). Also, it is possible that, among men at high risk for cardiovascular events, the stress induced by a prostate cancer diagnosis facilitates the occurrence of cardiovascular death, which would otherwise have happened later. This possibility could also support the decreased risk of cardiovascular death as the time after prostate cancer diagnosis increases. In addition, we cannot rule out that these findings were the result of a chance finding or of residual confounding. Nevertheless, the statistically significantly increased risk of cardiovascular death during the first month after a prostate cancer diagnosis throughout the study period supports the hypothesis that the immediate psychological stress induced by prostate cancer diagnosis results in cardiovascular death.

In our study, prostate cancer patients who were not married at the time of diagnosis had higher relative risks of both suicide and cardiovascular death than married patients. Having someone close to confide in might alleviate the psychological stress experienced from receiving a cancer diagnosis. Patients with prostate cancer who were living in a county with higher average level of education or lower poverty rates had lower relative risk of cardiovascular death than patients who were living in counties with lower average educational level and more poverty. This result might reflect different social and community support available to newly diagnosed cancer patients. We also observed a clear trend between higher relative risks for suicide and cardiovascular death among patients diagnosed with a metastatic tumor, which clearly would be more stressful than diagnosis of a clinically localized tumor. This finding might further explain the decreasing excess risks that have been observed in the PSA era, in which the proportion of advanced tumors was small (ie, 18.2% metastatic tumors in the pre-PSA era and 5.0% in the PSA era).

Strengths of our study include the large population-based sample of individuals diagnosed in various regions across the United States and the complete follow-up. In addition, the availability of tumor characteristics allowed us to assess the association between the tumor stage and the outcomes of interest.

Several limitations should also be noted. First, the SEER data only include information on cancer patients, precluding the possibility of having a cancer-free group as the reference. Although we carefully controlled for age, calendar time, and state of residence in the standardized mortality ratio calculation, other potential confounders (such as physical or mental health status or presence of comorbid illness) could not be addressed. However, the fact that the increased risks of suicide and cardiovascular deaths were concentrated in the first month after diagnosis mitigates such a concern. Second, in this analysis, we did not have data on other prevalent disorders among the prostate cancer patients before cancer diagnosis. One might speculate that incidental prostate cancer may be identified in men undergoing evaluation for cardiovascular disease, which could possibly explain the association we found. However, if this were the case, we would expect a stronger association in the PSA era. Our observation of fewer cardiovascular deaths after a prostate cancer diagnosis in the PSA era argues against this possibility. In fact, in our Swedish study (5), men with prevalent cardiovascular diseases had a lower relative risk of cardiovascular death after a prostate cancer diagnosis than other groups of men, perhaps because of protection from ongoing treatment for the cardiovascular disease (eg, use of beta-blockers). In addition, we used the state-level incidences of suicide and cardiovascular death for four metropolitan areas (San Francisco, Detroit, Seattle, and Atlanta), and it is possible that the actual incidences in these metropolitan areas might differ from the corresponding state-level incidences. However, the increased risk of cardiovascular death was observed consistently in all registry areas. In addition, concerns have been raised about the accuracy of cause of death information in death certificate data (20). However, there is little reason to believe that prostate cancer patients would be more likely than patients without prostate cancer to be incorrectly classified as dying from suicide or cardiovascular disease.

Finally, it is possible that prostate cancer treatments, such as hormonal therapy or surgery, might cause excess cardiovascular events. For example, hormone therapy has been associated with an increased risk of incident cardiovascular disease (21), shorter time to fatal myocardial infarction (22), and increased cardiovascular mortality in a subset of older men who underwent prostatectomy (23). Several post hoc analyses of randomized controlled trials that ascertained cardiovascular mortality, however, have not observed an increase in cardiovascular mortality associated with hormone therapy or with longer vs shorter duration of hormone therapy (24–28). Nevertheless, it is unlikely that hormonal treatment could have played a role in the risk elevation already during the first calendar month after prostate cancer diagnosis. The similar results observed in the additional analysis excluding patients who underwent a surgery on the other hand partially allay the concern about surgery.

In summary, findings of this study support those from our previous study (5) that prostate cancer diagnosis is associated with increased risks of suicide and cardiovascular death, especially during the immediate period after diagnosis. Because of the potentially lower degree of stress associated with the diagnosis of indolent prostate cancer, the relative risk of these adverse outcomes, particularly suicide, has decreased during the PSA era. Further studies are needed to shed light on whether these findings also apply to patients diagnosed with other cancers. We believe that suicide and cardiovascular death reflect only the tip of the iceberg of anxiety, mood disturbance, and perhaps other mental illness (or suffering) after a prostate cancer diagnosis. Hence, our study suggests the potential importance of providing emotional counseling and support for patients newly diagnosed with cancer. It also adds to the increasingly complex scenario of pros and cons of extensive PSA testing, which entails detection of large numbers of nonlethal prostate cancers.

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