



Platinum Priority – Prostate Cancer

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Suicide Risk in Men with Prostate-Specific Antigen–Detected Early Prostate Cancer: A Nationwide Population-Based Cohort Study from PCBaSe Sweden

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Abstract

Background: The risk of suicide is increased among cancer patients including men with prostate cancer (PCa). However, whether this increased risk applies to men diagnosed subsequent to prostate-specific antigen (PSA) testing is not known.

Objective: To assess the risk of suicide among men diagnosed with PCa subsequent to PSA testing.

Design, setting, and participants: The Prostate Cancer Base Sweden (PCBaSe Sweden) database, the Swedish Cause of Death Register, and the Swedish census database were used. The PCBaSe Sweden is a merged database that includes data from the Swedish National Prostate Cancer Register (NPCR) for cases diagnosed between January 1, 1997, and December 31, 2006. The number of suicides registered for cases in the PCBaSe cohort was compared with the expected number of suicides in an age-matched general male Swedish population.

Measurements: Standardised mortality ratios (SMRs) with 95% confidence intervals (CIs) were calculated for different categories of cases.

Results and limitations: There were 128 suicides among the 77 439 PCa cases in the NPCR compared with an expected number of 85 (SMR: 1.5; 95% CI, 1.3–1.8). The risk of suicide was not increased for the 22 405 men with PSA-detected T1c tumours (SMR: 1.0; 95% CI, 0.6–1.5), whereas the 22 929 men with locally advanced nonmetastatic tumours (SMR: 2.2; 95% CI, 1.6–2.9) and the 8350 men with distant metastases (SMR: 2.1; 95% CI, 1.2–3.6) had statistically significant increased SMRs for suicide. Potential effects of comorbid medical and psychiatric conditions could not be investigated.

Conclusions: No increased risk of committing suicide was observed among men with PCa diagnosed subsequent to PSA testing, whereas the risk was twice as high among men with locally advanced or metastatic disease, compared with an age-matched male population.

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1. Introduction

The introduction of prostate-specific antigen (PSA) testing as a screening tool for early detection of prostate cancer (PCa) in the beginning of the 1990s drastically increased the detection of PCa and widened the gap between incidence and mortality [1]. Although there is no official PSA screening program in Sweden, the proportion of men diagnosed with low-risk, early stage PCa due to testing of serum PSA has increased yearly. In 2005, >40% of all men diagnosed with PCa in Sweden were diagnosed with nonpalpable tumours on the basis of PSA testing as compared with <10% in 1996 [2]. Early detection of PCa by means of PSA testing increases the risk of overdiagnosis and results in no or a small survival benefit [3,4].

Today, multiple lines of evidence indicate the risk of suicide is increased in cancer patients including men with PCa [5–8]. It is unknown, however, whether this heightened risk exists for all stages of PCa including early nonpalpable PCa, detected by PSA testing.

Although depression is a major risk factor for suicide, other factors also play a role, such as family discord, lack of social support, and functional limitations, especially among the elderly [9]. We hypothesised that a diagnosis of a low-risk PCa detected subsequent to PSA testing may increase the patients' risk of suicide due to psychological reactions associated with a cancer diagnosis [10,11]. We also examined the risk of suicide in relation to tumour characteristics and time since diagnosis.

2. Methods

2.1. Study population

This study was performed within the Prostate Cancer Base Sweden (PCBaSe Sweden), a database in which a number of different registers are merged [12]. PCBaSe Sweden includes all cases registered in the National Prostate Cancer Register (NPCR) of Sweden following a diagnosis of PCa from January 1, 1997, to December 31, 2006. NPCR was started in 1996 in four of the six health care regions in Sweden, and from 1998 on, all regions have participated. The NPCR contains data on tumour characteristics and primary treatment with a 98% capture rate compared with the Swedish Cancer Register to which registration is compulsory and regulated by law. Urologists report details about all incident PCa cases to the NPCR, including the diagnosing unit, personal identity number, date of diagnosis, reason for cancer detection (symptomatic, health control, other), serum levels of PSA at diagnosis, tumour stage according to the TNM classification [13], tumour differentiation according to the World Health Organisation (WHO) grading system [14] or by use of the Gleason score (from 2000 on, almost exclusively on the basis of the Gleason score [15]) as well as treatment decision within 6 mo from date of diagnosis.

2.2. Study design

The personal identity number, which is individually unique, allowed cross-linkage between patients registered in the NPCR (Table 1) with the Cause of Death Register, containing information on the underlying cause of death, on contributing cause or causes of death, on whether an autopsy was performed, and on the surgical procedures used within 4 wk of death. The Cause of Death Register includes all deceased persons who

were residents of Sweden at the date of death [16]. We were able to identify deaths recorded as certain suicides (International Classification of Diseases [ICD]-10 codes X60–84) as well as uncertain suicides (ICD-10 codes Y10–34), a category used when it is not possible to decide if the death was accidental or intended.

Socioeconomic characteristics were determined by record linkages to the 1960, 1965, 1970, 1980, 1985, and 1990 census databases and were based on a commonly used socioeconomic status (SES). This indicator is founded on occupational group and stratified into *lower* (including blue-collar and low-level white-collar workers), *higher* (intermediate- and high-level white-collar workers and self-employed), and *unknown or missing* [17]. We used the last registered SES for each person because many men were retired at the time they were diagnosed with PCa. The study was approved by the Central Ethics Committee at Umeå University.

2.3. Statistical analysis

By using chronological 5-yr age categories (eg, 30–34, 35–39, 80–84) from age 30 to ≥85 yr and annual calendar periods from 1997 through 2006, we created a contingency table of the observed number of suicides in the study cohort. Similarly, accumulated person-time for the corresponding age groups and calendar periods were calculated. The expected number of suicides was calculated by multiplying the age and time-specific person-times with the corresponding incidences of suicides in the general Swedish population. Standardised mortality ratios (SMRs) were calculated by dividing the observed number with the expected number of suicides; the 95% confidence intervals (CIs) for the SMRs were established by assuming that the observed cases had a Poisson distribution using Byar's normal approximation [18]. For trend and test of equality, Poisson regression models were employed using the observed number of cases as response and the logarithm of the expected number of cases as offset. All statistical analyses were performed using the statistical program package R [19].

3. Results

The PCBaSe Sweden database includes 77 439 men diagnosed with PCa between January 1, 1997, and December 31, 2006, with a mean follow-up time of 3.4 yr (Table 1). Among these men, we identified 128 certain suicides yielding a suicide rate of 48.3 per 100 000 person-years. The corresponding age and standardised suicide rate in the general population was 31.9 per 100 000 person-years, and the expected number of suicides was 84.6 in this cohort, resulting in an SMR of 1.5 (95% CI, 1.3–1.8) (Table 2).

Our main analysis focused on certain suicides, but we also analysed data including uncertain suicides. Including uncertain suicides did not statistically change the results significantly (data not shown). In accordance with the general pattern of suicides among Swedish men, the most common mode of self-harm was by hanging, followed by intentional self-poisoning and injuries inflicted by firearms.

3.1. Years since diagnosis and age at diagnosis

Compared with the background population, the risk of suicide was significantly increased during the first and second years (SMR: 2.2; 95% CI, 1.5–3.0) following diagnosis. The risk was increased in all ages (SMR range,

Table 1 – Patient characteristics and number of certain suicides

	Full PC cohort		Patient with death due to intentional self-harm	
Patients in study, No. (%)	77 439	(100.0)	128	(100.0)
Follow-up, mean (SD)	3.4	(2.5)	2.1	(1.8)
Age, yr, No. (%)				
<65	19 281	(24.9)	26	(20.3)
65–74	28 039	(36.2)	44	(34.4)
≥75	30 119	(38.9)	58	(45.3)
Year of PC diagnosis, No. (%)				
1997–1999	18 147	(23.4)	38	(29.7)
2000–2002	22 262	(28.7)	57	(44.5)
2003–2006	37 030	(47.8)	33	(25.8)
Mode of detection*, No. (%)				
Symptoms	33 834	(57.1)	61	(67.8)
Health control	14 248	(24.0)	9	(10.0)
Other reason	6316	(10.7)	10	(11.1)
Missing information	4894	(8.3)	10	(11.1)
T stage, No. (%)				
T1c	22 405	(28.9)	21	(16.4)
T0/T1ab	5804	(7.5)	8	(6.2)
T2	24 858	(32.1)	42	(32.8)
T3–4	22 929	(29.6)	53	(41.4)
Missing	1443	(1.9)	4	(3.1)
M stage, No. (%)				
M0	24 034	(31.0)	34	(26.6)
M1	8350	(10.8)	14	(10.9)
Mx/Missing	45 055	(58.2)	80	(62.5)
PSA, No. (%)				
PSA <4	4432	(5.7)	5	(3.9)
PSA ≥4–<10	22 725	(29.3)	31	(24.2)
PSA ≥10–<20	16 916	(21.8)	27	(21.1)
PSA ≥20–<100	20 968	(27.1)	42	(32.8)
PSA ≥100	10 307	(13.3)	19	(14.8)
Missing data	2091	(2.7)	4	(3.1)
Gleason score†, No. (%)				
2–4	7505	(9.7)	14	(10.9)
5–7	52 685	(68.0)	80	(62.5)
8–10	15 588	(20.1)	30	(23.4)
Missing data	1661	(2.1)	4	(3.1)
Planned initial treatment, No. (%)				
Expectancy	19 775	(25.5)	30	(23.4)
Treatment with curative intent	23 333	(30.1)	29	(22.7)
Treatment with hormonal therapy	32 232	(41.6)	57	(44.5)
Missing data	2099	(2.7)	12	(9.4)
Socioeconomic status				
High	37 660	(48.6)	56	(43.8)
Low	38 669	(49.9)	72	(56.2)
Not gainfully employed	306	(0.4)	0	(0.0)
Unclassified or missing	804	(1.0)	0	(0.0)

PC = prostate cancer; PSA = prostate-specific antigen; SD = standard deviation.

* Presented for subcohort with PC diagnosis after January 1, 2000.

† World Health Organisation grade converted to Gleason score in 18% of the cases using the rule G1 = 2–4, G2 = 5–7, and G3 = 8–10.

1.5–1.6), with no discernible difference between age groups.

3.2. Mode of detection, TNM stage, prostate-specific antigen at diagnosis, and Gleason score

Men who had their tumours reported as health control detected in the NPCR (the variable “mode of detection”) did not have an increased risk of suicide (SMR: 0.8; 95% CI,

0.4–1.5), whereas men who were detected due to workup of symptoms had a two-fold increase (SMR: 2.1; 95% CI, 1.6–2.7). The risk of suicide was not elevated in men with stage T1c tumours (nonpalpable PSA-detected tumours) or T2 tumours, but there was a two-fold increase in risk in patients with locally advanced tumours stages T3 and T4 (SMR: 2.2; 95% CI, 1.6–2.9). For patients with distant metastases (M1), there was a two-fold increase in risk of committing suicide (SMR: 2.1; 95% CI, 1.2–3.6). The risk was

Table 2 – Standardised mortality ratios with 95% confidence interval and number of observed deaths and expected number of deaths

	Intentional self-harm		
	ICD-10 codes X60–X84		
	SMR	(95% CI)	No. of Deaths/Exp
Full PC cohort	1.51	(1.26–1.80)	128/84.6
Follow-up since PC diagnosis			
0–6 mo	1.97	(1.40–2.71)	38/19.3
6–12 mo	1.33	(0.76–2.16)	16/12.0
1–2 yr	2.19	(1.53–3.05)	35/16.0
2–5 yr	1.05	(0.70–1.51)	29/27.6
≥5 yr	1.02	(0.49–1.88)	10/9.8
Age at PC diagnosis, yr			
<65	1.49	(0.98–2.19)	26/17.4
65–74	1.46	(1.06–1.96)	44/30.2
≥75	1.57	(1.19–2.03)	58/37.0
Year of PC diagnosis			
1997–1999	1.13	(0.80–1.55)	38/33.7
2000–2002	1.87	(1.42–2.43)	57/30.4
2003–2006	1.62	(1.11–2.27)	33/20.4
Mode of detection*			
Symptoms	2.09	(1.60–2.68)	61/29.2
Health control	0.81	(0.37–1.54)	9/11.1
Other reason	1.82	(0.87–3.36)	10/5.5
Missing information	1.98	(0.95–3.65)	10/5.0
T stage			
T1c	1.00	(0.62–1.53)	21/21
T0/T1ab	1.00	(0.43–1.96)	8/8.0
T2	1.40	(1.01–1.90)	42/29.9
T3–4	2.19	(1.64–2.86)	53/24.2
Missing	2.87	(0.77–7.34)	4/1.4
M stage			
M0	1.07	(0.74–1.50)	34/31.6
M1	2.13	(1.16–3.58)	14/6.6
Mx/Missing	1.72	(1.37–2.15)	80/46.4
PSA			
PSA <4	1.04	(0.34–2.44)	5/4.8
PSA ≥4–<10	1.36	(0.92–1.93)	31/22.8
PSA ≥10–<20	1.36	(0.89–1.97)	27/19.9
PSA ≥20–<100	1.65	(1.19–2.24)	42/25.4
PSA ≥100	2.04	(1.23–3.19)	19/9.3
Missing	1.66	(0.45–4.25)	4/2.4
Gleason score†			
2–4	1.08	(0.59–1.81)	14/13.0
5–7	1.44	(1.14–1.79)	80/55.5
8–10	2.08	(1.40–2.97)	30/14.4
Missing	2.42	(0.65–6.21)	4/1.7
Planned initial treatment			
Expectancy	1.15	(0.77–1.64)	30/26.2
Treatment with curative intent	1.28	(0.86–1.84)	29/22.6
Treatment with hormonal therapy	1.65	(1.25–2.13)	57/34.6
Missing data	9.62	(4.96–16.8)	12/1.2
Socioeconomic status			
High	1.35	(1.02–1.75)	56/41.6
Low	1.72	(1.35–2.17)	72/41.9
Not gainfully employed	0	NA	0/0.4
Unclassified or missing	0	NA	0/0.8

CI = confidence interval; Exp = expected number of deaths; ICD = International Classification of Diseases; NA = not applicable; PC = prostate cancer; PSA = prostate-specific antigen; SMR = standardised mortality ratio.

* Presented for subcohort with PC diagnosis after January 1, 2000.

† World Health Organisation grade converted to Gleason score in 18% of the cases using the rule G1 = 2–4, G2 = 5–7, and G3 = 8–10.

also elevated in men with unknown or missing data concerning metastases (SMR: 1.7; 95% CI, 1.4–2.2). The risk of suicide was elevated in men with PSA >20 ng/ml but not among patients with PSA <20 ng/ml.

Patients with tumours classified with a Gleason score 2–4 were not at increased risk of committing suicide. Men with a Gleason score of ≥ 5 had an increased risk (SMR: 1.44; 95% CI, 1.1–1.8), with the highest risk estimate found in men with a Gleason score of 8–10 (SMR: 2.1; 95% CI, 1.4–3.0).

A likelihood ratio test showed a statistically significant difference between risk for suicide depending on various modes of detection ($p = 0.009$). A post hoc trend test for increased risk with tumour severity described by nonmissing T category ($p = 0.002$), PSA-level group ($p = 0.03$), and Gleason score ($p = 0.05$) showed statistically significant risk increases with increasing severity.

3.3. Treatment within 6 months

Neither men who were registered as being planned for curative treatment within 6 mo after the time of diagnosis nor those who received no initial treatment (watchful waiting) were at increased risk of committing suicide. In contrast, a higher SMR was observed among men who received endocrine primary treatment (SMR: 1.6; 95% CI, 1.2–2.1). In the group with missing data for primary treatment, 12 men committed suicide compared with an expected number of 1.2, yielding an SMR estimate of 9.6 (95% CI, 5.0–16.8). Nine of these men committed suicide within 6 mo.

3.4. Socioeconomic status

Among men with high SES, 32.0% were diagnosed with T1c tumours and 27.2% had locally advanced tumours at diagnosis. Corresponding proportions for men with low SES were 26.1% and 31.8%, respectively. A significantly increased mortality in suicide was observed among men diagnosed with PCa in both SES groups (Table 2).

4. Discussion

In this nationwide population-based cohort study of men in PCBaSe Sweden, we found no evidence for an increased risk of suicide among men diagnosed with early nonpalpable PCa detected by PSA testing. The suicide rate, however, was twice as high among men diagnosed with locally advanced or metastatic disease compared with the general male population.

In contrast to our hypothesis, there was no increased suicide risk among men with early nonpalpable T1c tumour detected by means of PSA testing. Anxiety related to a crisis reaction may develop into a depression, and several studies have shown that there is a high anxiety level among screeners in various screening programs, especially among those who receive positive results regardless of whether the result is true or false. A negative result of a screening test delivered without explanation or advice may also result in unwanted effects [20]. However, as in most countries, men who underwent PSA testing in Sweden at the time represent

an opportunistic screening population and not a true population-based screening program by invitation. Therefore, they may have been more health conscious, less prone to develop depression, and more prepared to accept the potential side effects of curative treatment than the general population [21]. Men with high SES were more often diagnosed with T1c tumours than men with low SES, indicating a higher screening activity in the group of men with higher education and economic status. The risk to commit suicide was increased for men with high as well as low SES, and factors related to the disease itself and independent of SES probably contribute.

Our results indicate that the risk of suicide increases with severity of clinical stage at diagnosis, corroborating findings of Yousaf et al who studied the suicide risk among 564 508 Danish cancer patients diagnosed between 1971 and 1986. In this study, the highest risk of suicide was observed in patients with nonlocalised cancers and cancers with a perceived poor prognosis [8]. In the present study, the risk was elevated for men with locally advanced tumours, suggesting that not only symptoms associated with generalised disease such as pain, anaemia, and lack of strength may explain the excess risk. Waern et al found that older men have decreased tolerance for somatic symptoms and an increased risk of committing suicide compared with a randomly selected control population [22]. If they have a somatic disease and also experience pain, the risk of developing a depression increases five times, and depression is the major risk factor for suicide [23]. Although discomfort caused by local symptoms may be present, the increased risk observed in men with locally advanced disease may be a consequence of the perception that there is no cure, which could trigger a feeling of hopelessness as well as a crisis reaction followed by depression. Another possible explanation could be the early introduction of hormonal therapy with androgen deprivation in men without metastases but with locally advanced tumours. In a study of quality of life on asymptomatic men with nonmetastatic PCa, Herr and O'Sullivan found that androgen deprivation therapy resulted in increased fatigue, decreased physical activity, greater emotional distress, and poorer general health after 6 mo and at 1 yr [24].

The risk of suicide in men with missing information on tumour characteristics such as mode of detection, TNM stage, PSA, and Gleason score was elevated and similar to that observed in men with advanced tumours. In the group of men without information on treatment, the risk of suicide was 10-fold higher than the background population. However, most of the men in this group committed suicide early, and therefore the expected number of suicides was very low and the SMR disproportionately high.

We could not document socioeconomic factors to be a confounder. A Swedish study from 2001 showed a socioeconomic gradient in suicide risk with the highest rates observed in men with low education [25]. Among the men that we studied, we found an increased suicide risk in both socioeconomic groups.

To the best of our knowledge, our study is the first report on a nationwide population-based study cohort on risk of

suicide for different categories of PCa cases. The strengths of this study include the population-based design with inclusion of approximately 98% of all men in Sweden diagnosed with PCa between 1997 and 2006. There are a number of limitations in the study: The number of suicides was small, only 128 men registered in PCBaSe committed suicide, and consequently, the CIs for our estimates are rather wide. We did not want to divide time from diagnosis in shorter time intervals because the low number of events would increase the risk of chance findings, and a small increased risk immediately after diagnosis could be undetected due to the dilution of the longer time intervals. Furthermore, the potential confounding role of comorbid, medical, and psychiatric conditions are not accounted for but are unlikely to change our conclusion. Our finding that men with PSA-detected PCa are not in danger of committing suicide can only concern the risk of suicide in men who actively choose to take their PSA and not be generalised to a population-based screening program offered by invitation.

5. Conclusions

We conclude that the increased suicide risk in men with PCa was not due to an increase in the suicide risk for men with PSA-detected tumours. There was an increased risk of suicide for men with advanced and metastatic disease, which is important to acknowledge in order to focus on the need to identify signs of depression and optimise treatment among this category of patients.

Author contributions: Anna Bill-Axelsson 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: Bill-Axelsson, Stattin (PCBaSe Sweden), Steineck, Garmo, Lambe.

Acquisition of data: Swedish urologists registering in NPCR and Stattin, Adolfsson, Garmo, and Lambe for merging databases for PCBaSe.

Analysis and interpretation of data: Bill-Axelsson, Garmo, Stattin, Bratt, Lambe, Steineck, Nyberg.

Drafting of the manuscript: Bill-Axelsson.

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