

# Prostate Cancer Mortality in Areas With High and Low Prostate Cancer Incidence

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**Background** The effect of prostate-specific antigen (PSA) screening on prostate cancer mortality remains debated, despite evidence from randomized trials. We investigated the association between prostate cancer incidence, reflecting uptake of PSA testing, and prostate cancer mortality.

**Methods** The study population consisted of all men aged 50 to 74 years residing in eight counties in Sweden with an early increase in prostate cancer incidence and six counties with a late increase during two time periods. Incidence of metastatic prostate cancer was investigated in the period from 2000 to 2009, and prostate cancer-specific mortality and excess mortality were investigated in the period from 1990 to 1999 and the period from 2000 to 2009 by calculating rate ratios for high- vs low-incidence counties and rate ratios for the period from 2000 to 2009 vs the period from 1990 to 1999 within these two groups. All statistical tests were two-sided.

**Results** There were 4528 134 person-years at risk, 1577 deaths from prostate cancer, and 1210 excess deaths in men with prostate cancer in high-incidence counties and 2471 373 person-years at risk, 985 prostate cancer deaths, and 878 excess deaths in low-incidence counties in the period from 2000 to 2009. Rate ratios in counties with high vs low incidence adjusted for time period were 0.81 (95% confidence interval [CI] = 0.73 to 0.90) for prostate cancer-specific mortality and 0.74 (95% CI = 0.64 to 0.86) for excess mortality, and the rate ratio of metastatic prostate cancer was 0.85 (95% CI = 0.79 to 0.92).

**Conclusions** The lower prostate cancer mortality in high-incidence counties reflecting a high PSA uptake suggests that more-intense as compared with less-intense opportunistic PSA screening reduces prostate cancer mortality.

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The use of prostate-specific antigen (PSA) screening for detection of prostate cancer remains controversial. Two large, population-based, randomized clinical trials—the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Göteborg trial—demonstrated 21% to 44% statistically significant decreases in prostate cancer-specific mortality after 11 to 14 years of follow-up in screened vs unscreened men (1,2). In contrast, the prostate arm of the US Prostate, Lung, Colorectal, and Ovarian cancer screening trial (PLCO) found no benefit from systematic screening compared with opportunistic screening (3).

Thus, a controversy on PSA screening still remains, and in 2012 the US Preventive Services Task Force recommended against screening, stating “there is moderate to high certainty that the benefits of PSA-based screening for prostate cancer [in terms of reduced prostate cancer mortality] do not outweigh the harm [in terms of overdiagnosis]” (4). This recommendation has been criticized (5–7), and more data on the association between PSA screening and prostate cancer mortality are needed.

In addition to extended data from ERSPC and the Göteborg trial and the awaited results from the ongoing UK ProtecT trial, carefully designed and conducted observational population-based studies may provide valuable information on the association between PSA testing, early diagnosis, and treatment and prostate cancer mortality (8,9). Results from previous observational studies have been inconsistent; some studies have shown decreased prostate cancer mortality in areas with high PSA testing (10,11), whereas others have found no such difference (12,13).

In Sweden, as in many other Western countries, the introduction of PSA testing in the 1990s resulted in an increase in prostate cancer incidence. Except for a randomized trial on systematic screening conducted in the city of Göteborg, the introduction of PSA testing was in the form of opportunistic screening (14). Among the 24 Swedish counties, there were large differences in prostate cancer incidence, with an estimated fourfold variation in the proportion of men undergoing PSA testing despite a uniform, equal-access health-care system (15).

To capitalize on this natural experiment, we retrieved outcome data from three nation-wide, population-based registries in Sweden and assessed the incidence of metastatic prostate cancer, prostate cancer-specific mortality, and excess mortality in counties with an early increase in the incidence of prostate cancer and in counties with a late increase, reflecting differences in uptake of PSA testing, to investigate the association between PSA testing and prostate cancer mortality.

## Methods

### The Swedish Cancer Register, Cause of Death Register, and National Prostate Cancer Register

Swedish law mandates and regulates the registration of incident cancer cases in the Swedish Cancer Register and deaths in the Cause of Death Register. The Cancer Register contains each patient's 10-digit personal identity number, date of diagnosis, county of residence, and cancer site. The Cause of Death Register contains the personal identity number, date of death, and underlying and contributory causes of death. Since 1998, approximately 98% of all incident prostate cancer cases in the Swedish Cancer Register were also registered in the National Prostate Cancer Register, including the reason for the work-up that led to diagnosis, tumor stage, Gleason score, serum PSA at time of diagnosis, and primary treatment (16,17).

### Identification of Prostate Cancer Case Patients and Endpoints

We used the Swedish Cancer Register to identify prostate cancer case patients diagnosed from January 1, 1980, to December 31, 2009, and linked by personal identity numbers (18) to the National Prostate Cancer Register to obtain information on metastases at the time of diagnosis, evidenced by radiographic evaluation (bone scans) for the large majority of men or serum PSA levels greater than 100 ng/mL (16). We obtained date and cause of death by linkage to the Swedish Cause of Death Register for death attributed to prostate cancer when it was coded as "underlying cause of death." The study was approved by the Research Ethics Board at Umeå University Hospital.

### Statistical Analysis

We calculated the predicted prostate cancer incidence—that is, the incidence that would be expected if no PSA testing had occurred. Because PSA testing was introduced in clinical practice in Sweden in the 1990s, the prediction for each year up to 2009 was based on the observed incidence for the period from 1980 to 1990. We used a linear regression model with a common slope for calendar year but separate intercepts for each county. Age-adjusted prostate cancer incidence for men aged 50 to 74 years was calculated by direct standardization with weights from the Swedish population census of 2000 (19). We then calculated the cumulative difference between the observed and predicted age-adjusted prostate cancer incidence in men aged 50 to 74 years starting from 1995 and found a range of -126 per 100 000 to 1634 per 100 000. We used this difference to categorize counties as having high, intermediate, or low prostate cancer incidence and chose the cutoffs of 100 per 100 000 between low- and intermediate-incidence counties and 800 per 100 000 between intermediate- and high-incidence counties.

We used two measures of prostate cancer mortality—prostate cancer-specific mortality, which was based on the underlying cause of death

given in the Cause of Death Register (20,21), and excess mortality (22), based on the excess number of deaths (observed minus expected) regardless of cause of death among men with prostate cancer. We calculated the expected number of deaths as the product of person-years among the incident prostate cancer case patients and the total mortality rate in the population, calculated per year and per attained age in groups of 5 years. We determined prostate cancer mortality during two calendar periods, 1990 to 1999 and 2000 to 2009. We calculated incidence-based mortality for each of the mortality measures based on deaths among men diagnosed with prostate cancer during the study period (20,21). In addition, we calculated the 2000 to 2009 incidence of metastatic prostate cancer (23). To determine incidence and mortality rates, we used person-years based on population statistics by year and by 5-year age group. All rates were measured at the population level (with the male population, not the number of men with prostate cancer as denominator).

We calculated rate ratios (RRs) for high- vs low-incidence counties and the rate ratios for the period from 2000 to 2009 vs the period from 1990 to 1999 within these two groups. Finally we also determined rate ratios for high- vs low-incidence counties adjusted for time period by dividing by the corresponding rate ratio in the period from 1990 to 1999. We calculated rate ratios for men aged 50 to 74 years and the subgroup aged 55 to 69 years, which was the core age group in the ERSPC study (24). We based confidence intervals (CIs) on the assumption of a Poisson distribution of the number of events and calculated variances using the delta method on the logarithm of the estimates followed by normal approximation (25).

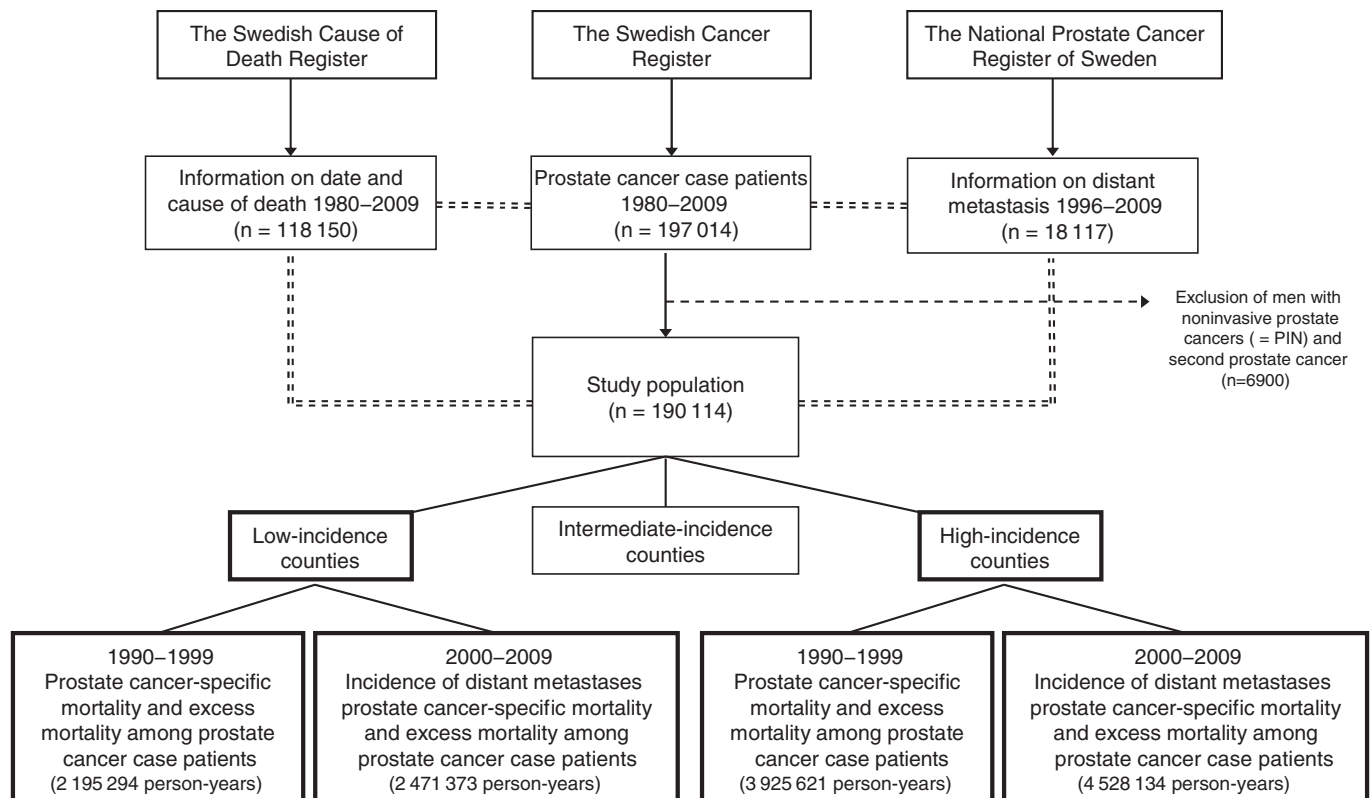
## Results

Between 1980 and 2009, 197 014 Swedish men aged 50 to 74 years were diagnosed with prostate cancer, and of those, 6900 men with noninvasive or secondary prostate cancers were excluded from the study. Figure 1 presents a flow chart of the study cohort.

There were 4 528 134 person-years at risk, 1577 deaths from prostate cancer, and 1210 excess deaths in men with prostate cancer in high-incidence counties and 2 471 373 person-years, 985 prostate cancer deaths, and 878 excess deaths in low-incidence counties in the period from 2000 to 2009. A rapid increase in prostate cancer incidence began in some counties in 1990 but not until 10 years later in other counties (Figure 2A). Figure 2B shows the cumulative difference between observed and predicted prostate cancer incidence in each county from 1995 to 2009. The difference in incidence between the high- and low-incidence counties was largest in 2005 and decreased thereafter, disappearing in 2009 (Supplementary Figure 1, available online).

In the period from 2000 to 2009, the cumulative incidence of metastatic disease, prostate cancer-specific mortality, and excess mortality was statistically significantly lower in high-incidence counties than in low incidence counties (Figure 3, A–C), with rate ratios of 0.85 (95% = 0.79 to 0.92) for metastatic disease, 0.87 (95% CI = 0.81 to 0.95) for prostate cancer-specific mortality, and 0.75 (95% CI = 0.66 to 0.86) for excess mortality (Figure 4A).

In high-incidence counties, prostate cancer-specific mortality and excess mortality were statistically significantly lower during the period from 2000 to 2009 than during the period from 1990 to 1999, and we observed similar, albeit somewhat weaker differences in low-incidence counties (Figure 4B). When taking



**Figure 1.** Flow chart of linkages between the Swedish Cancer Register, the Swedish Cause of Death Register, and the National Prostate Cancer Register of Sweden and final study population. \* Distant metastasis defined as M1 and/or prostate-specific antigen  $\geq 100$  ng/mL. ===== indicates registry linkage.

both county group and time period into consideration, the differences in cancer-specific mortality and excess mortality between high- vs low-incidence counties remained statistically significant (Figure 4C). The rate ratios adjusted for time period for high- vs low-incidence counties were 0.81 (95% CI = 0.73 to 0.90) for prostate cancer-specific mortality and 0.74 (95% CI = 0.64 to 0.86) for excess mortality, and the rate ratios for the subgroup of men aged 55 to 69 years were similar. The estimated rate ratio of prostate cancer specific mortality of 0.81 would correspond to an annual absolute reduction at 0.23 per 1000 men when applied to the Swedish prostate cancer mortality year 2000 in the age group 55 to 79 years.

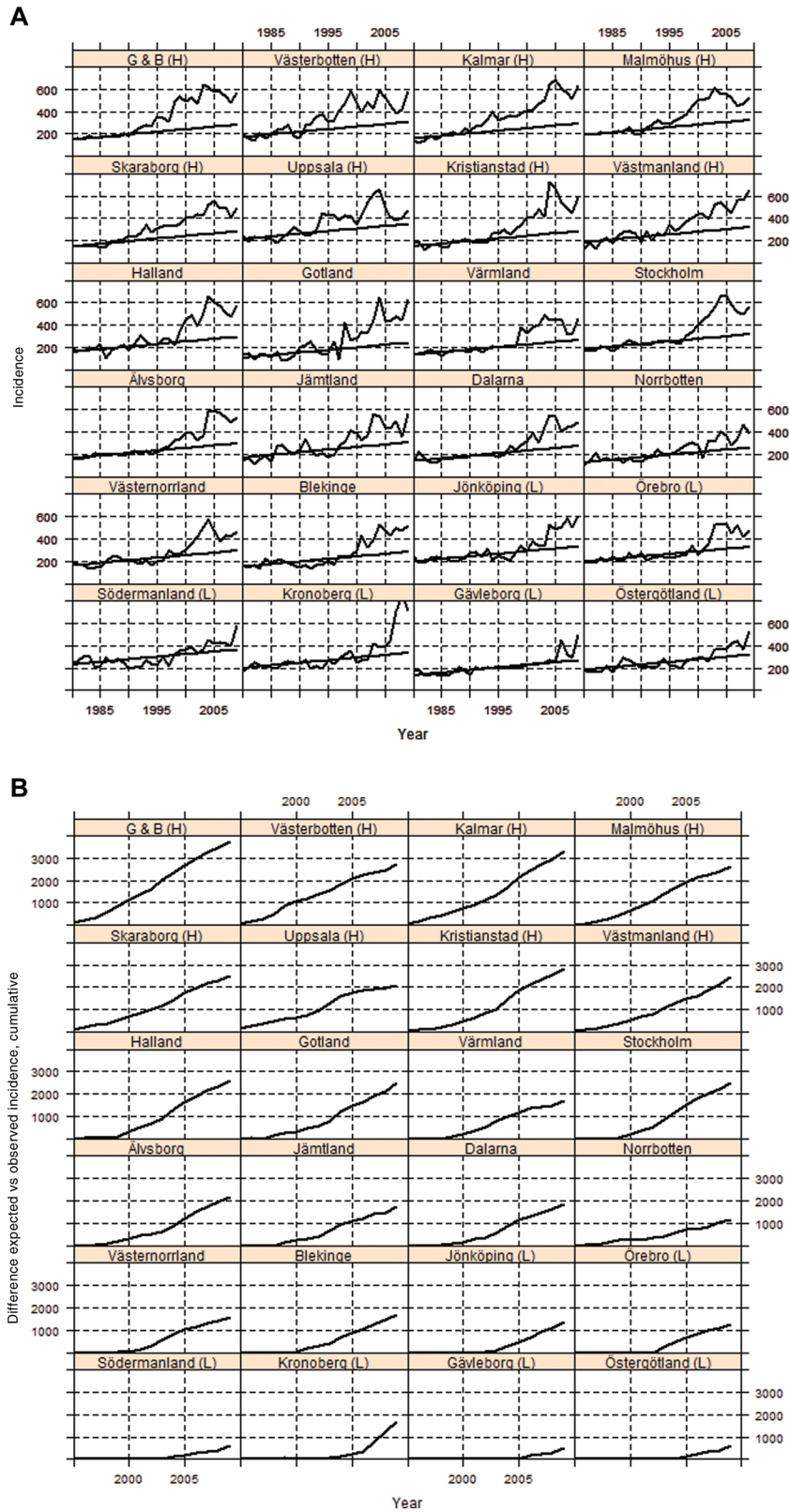
Data in the National Prostate Cancer Register from 2000 to 2009 indicated that diagnostic and therapeutic activity was higher in high-incidence counties than in low-incidence counties (Table 1). In the high-incidence counties, median age at diagnosis was lower, a higher proportion of men had low-risk cancer (clinical stage T1–T2, Gleason score 2–6, and PSA < 10 ng/mL at diagnosis), a higher proportion underwent radical prostatectomy, and median serum PSA at diagnosis was lower. The difference between high- vs low-incidence counties in diagnostic PSA levels was largest in 2000 (10.0 vs 17.6 ng/mL) and decreased steadily after that (Supplementary Table 1, available online). The use of radiotherapy and radical prostatectomy showed similar temporal trends with the highest use in high-incidence counties and with a

decreasing difference over time (Supplementary Figure 2, available online).

## Discussion

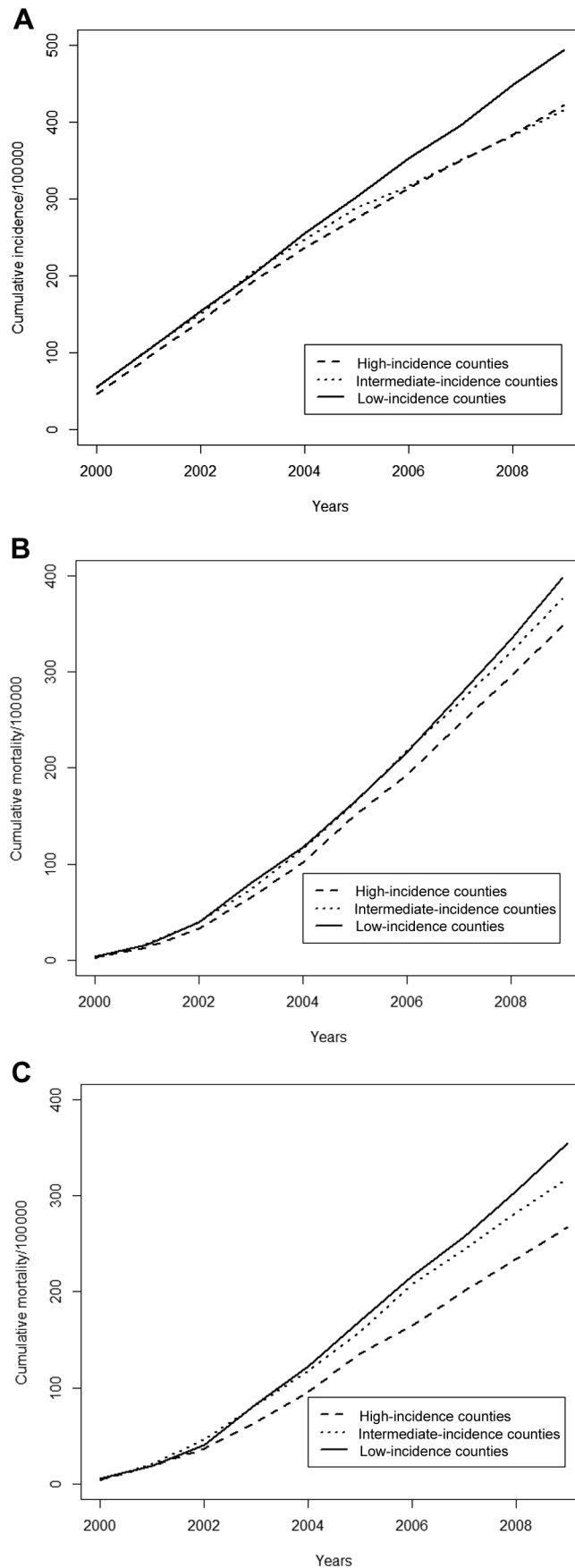
In this register-based, population-based study in Sweden, incidence of metastatic prostate cancer was 15% lower, and prostate cancer-specific mortality and excess mortality adjusted for time period were 19% and 26% lower, respectively, in counties with high vs low incidence of prostate cancer, reflective of early vs late uptake of PSA testing. These results suggest that opportunistic PSA screening decreases prostate cancer mortality.

The strength of our study lies in its population-based design, its magnitude, the completeness of the registers, and the equal access health care in the two study groups. It covered nearly 7 million person-years at risk and 2562 prostate cancer deaths registered between 2000 and 2009 and had the power to detect moderately strong associations between PSA testing and prostate cancer death. Furthermore, PSA testing is likely to be particularly effective in Sweden because prostate cancer mortality is higher in Sweden than in other countries, with a lifetime risk of prostate cancer death of 5% to 6%, so Swedish men with prostate cancer are at high risk of disease progression (26). Other strengths of our study were the use of incidence-based mortality, which enabled us to avoid diluting risk estimates by including deaths among men diagnosed before



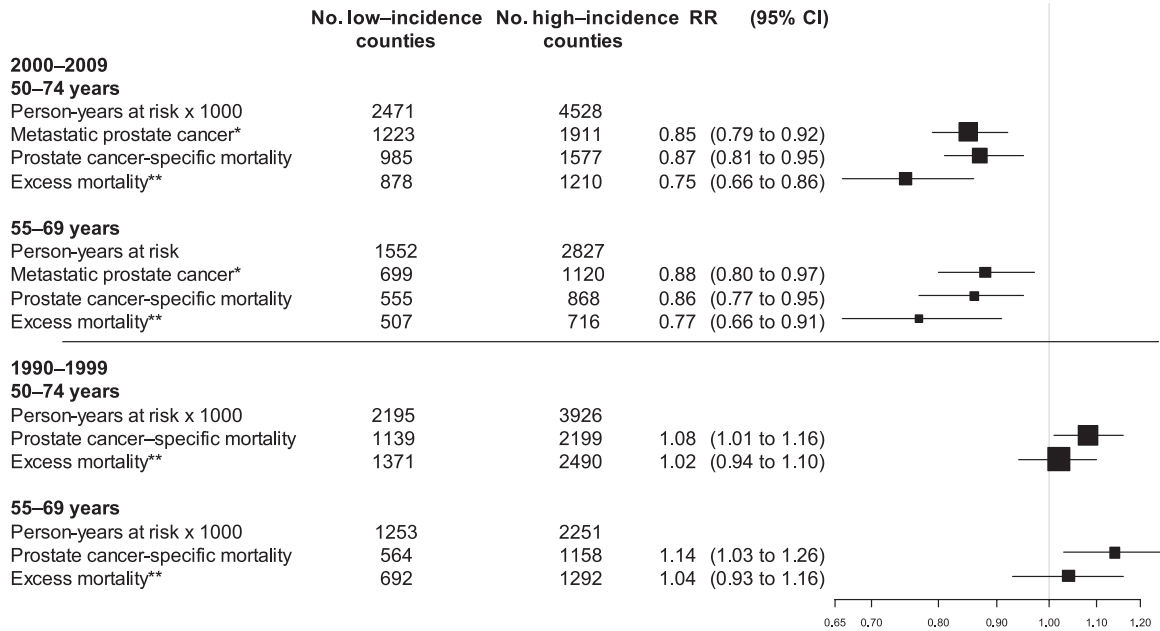
**Figure 2.** Counties ranked by the cumulative difference between observed and predicted prostate cancer incidence per 100 000 from 1995 through 2002. **A)** Observed and predicted age-standardized prostate cancer incidence in men aged 50–74 years in 24 Swedish counties during the period from 1980 to 2009. **Steady line** is predicted incidence, and **undulating line** is observed incidence. **B)**

Cumulative difference between observed and predicted incidence of prostate cancer during the period from 1995 to 2009. Negative differences resulting from the predicted incidence being higher than the observed incidence in low-incidence counties were set to zero. G & B = Göteborg and Bohus county; H = high-incidence county; L = low incidence county.

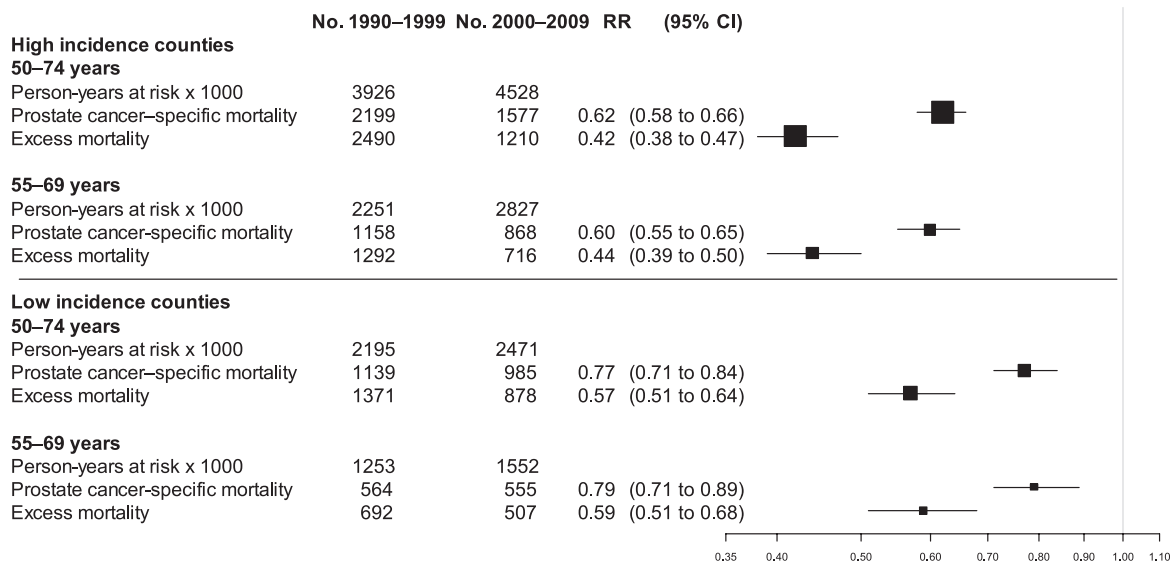


**Figure 3.** Prostate cancer incidence and mortality in men in Sweden aged 50 to 74 years, 2000 to 2009. **A)** Cumulative incidence of metastatic disease. **B)** Prostate cancer-specific mortality. **C)** Excess mortality.

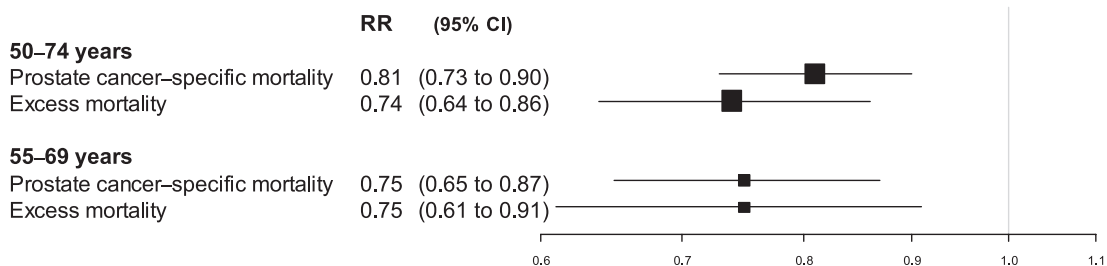
A



B



C



**Figure 4.** Risk of prostate cancer mortality according to county of residency (in groups of counties with high and low incidence) and time period in groups of counties with high, intermediate and low incidence of prostate cancer **A** Rate ratio (RR) of incidence of metastatic prostate cancer, prostate cancer-specific mortality, and excess mortality in high- vs low-incidence counties. **B** Rate ratio of prostate cancer-specific mortality

and excess mortality in the period from 2000 to 2009 vs the period from 1990 to 1999. **C** Rate ratio for high- vs low-incidence group adjusted for time period. \* Metastatic prostate cancer defined as M1 and/or prostate-specific antigen  $\geq 100$  ng/mL at diagnosis. \*\* Excess mortality defined as the excess number of deaths (observed minus expected), regardless of cause of death among men with prostate cancer. CI = confidence interval.

**Table 1.** Characteristics of men aged 50 to 74 years with prostate cancer in the National Prostate Cancer Register of Sweden, 2000 to 2009\*

Characteristic	County Incidence		
	High (n = 33 780)	Intermediate (n = 37 624)	Low (n = 16 377)
Age at diagnosis, y			
Median (IQR)	70 (63–77)	70 (63–77)	72 (65–79)
Mean (SD)	70.0 (9.3)	70.2 (9.2)	71.7 (9.1)
Serum PSA level, ng/mL			
Median (IQR)	10.8 (6.0–27.0)	12.0 (6.6–32.0)	15.0 (7.6–43.0)
No. missing (%)	506 (1.5)	1114 (3.0)	385 (2.4)
Mode of detection, No. (%)			
PSA testing as a part of health check-up	10 684 (31.6)	10 101 (26.8)	3646 (22.3)
Lower urinary tract symptoms	10 533 (31.2)	10 668 (28.4)	5793 (35.4)
Other symptoms/unknown	12 563 (37.2)	16 855 (44.8)	6938 (42.4)
Planned treatment, No. (%)†			
Surveillance	8937 (26.5)	8613 (22.9)	4079 (24.9)
Radical prostatectomy	8444 (25.0)	8425 (22.4)	2419 (14.8)
Radiation therapy	4198 (12.4)	4891 (13.0)	2501 (15.3)
Hormonal therapy	10 931 (32.4)	12 600 (33.5)	6620 (40.4)
Other/missing	1270 (3.8)	3095 (8.2)	758 (4.6)
Risk category, No. (%)‡			
Low risk	9874 (29.2)	9593 (25.5)	3366 (20.6)
Intermediate risk	8651 (25.6)	8997 (23.9)	3867 (23.6)
High risk	7908 (23.4)	9917 (26.4)	4570 (27.9)
Regionally metastatic	2097 (6.2)	2735 (7.3)	1407 (8.6)
Distant metastases	4524 (13.4)	5158 (13.7)	2891 (17.7)
Missing	726 (2.1)	1224 (3.3)	276 (1.7)

\* IQR = interquartile range; PSA = prostate-specific antigen; SD = standard deviation.

† Initiated or planned within the 6 months after diagnosis.

‡ Risk groups according to modification of the National Comprehensive Cancer Network. Low risk: T1 to 2, Gleason score 2 to 6, and PSA < 10 ng/mL. Intermediate risk: T1 to 2, Gleason score 7, and/or PSA 10 to <20 ng/mL. High risk: T3, and/or Gleason score 8 to 10, and/or PSA 20 to <50 ng/mL. Regionally metastatic disease: T4 and/or N1 and/or PSA 50 to <100 ng/mL in the absence of distant metastases (M0 or Mx). Distant metastases: M1 and/or PSA ≥ 100 ng/mL.

the introduction of PSA testing, and the use of three separate end-points—incidence of metastatic prostate cancer, prostate cancer-specific mortality, and excess mortality.

The Swedish Cancer Register captures 96% of all cancer diagnoses, and the capture rate is particularly high for solid tumors and in subjects aged less than 70 years (27). The validity of the Cause of Death Register is high for prostate cancer. For example, in the Göteborg screening trial, there was a 96% agreement between a chart review of death certificates and the Cause of Death Register (28), and in another study with a wider range in stage and grade, the agreement was 86% (29). Besides prostate cancer-specific mortality, we also investigated the incidence of metastatic prostate cancer, which was the first indication of the efficacy of PSA screening in the European trials (1,2). We assessed the occurrence of metastatic disease at date of diagnosis by use of data on the presence of bone metastases or a serum level greater than 100 ng/mL available from 2000 in the National Prostate Cancer Register.

Our study also had some limitations because we were unable to directly measure the extent of PSA testing in the population. Instead, we used the difference between the observed and predicted cumulative incidence of prostate cancer under the assumption that a high incidence indicated an early introduction and a high prevalence of PSA testing with ensuing early prostate cancer diagnosis and treatment. This assumption was corroborated by data in the National Prostate Cancer Register on distribution of risk categories with lower median serum PSA levels at diagnosis, higher proportion of clinically

localized low-risk cancers, higher proportion of curative treatments, and a lower age at diagnosis in high- vs low-incidence counties.

Geographical comparisons can be hampered by differences in baseline risk, and prior observational studies comparing high and low prostate cancer incidence areas in the United States reported no difference in prostate cancer mortality (12,13). In the first time period of our study, prostate cancer-specific mortality was higher in high-incidence counties than in low-incidence counties, showing that the subsequently lower prostate cancer mortality in high-incidence counties was not simply the result of differences in baseline risk. Temporal comparisons can be hampered by changes in diagnostic criteria over time and thus can also be affected by bias. To address these issues, we made separate geographical and temporal comparisons and used a combined approach as well, including adjustment for time periods in the analysis of geographical differences.

Our risk estimates were affected by other sources of bias. The decrease in excess mortality was consistently larger than the decrease in prostate cancer-specific mortality. Excess mortality likely overestimates the benefit of screening because it reflects a lower mortality from causes other than prostate cancer. There may be selection bias for healthy Swedish men with a long life expectancy who undergo PSA testing and early detection, as suggested in a previous study in the National Prostate Cancer Register, which showed lower 10-year all-cause mortality among men with low- and intermediate-risk prostate cancer compared with the background population, indicating a healthy screenee effect (30). In contrast, prostate cancer-specific mortality underestimates the risk reduction because it

is affected by attribution bias; death from an uncertain cause is more likely attributed to prostate cancer in men with a prostate cancer diagnosis than in other men (31). Furthermore, our follow-up time was 10 years at maximum, which is likely too short a time to reap the full effect of early detection. Finally, confounding by unknown factors cannot be ruled out. Despite these shortcomings, a higher incidence of prostate cancer was consistently associated with lower risk estimates in all 18 risk analyses.

The ERSPC study, the largest randomized screening trial to date with 761 prostate cancer deaths, showed virtually the same reduction (21%) in mortality observed after 11 years of follow-up as our study (1). In the Göteborg screening trial in Sweden, based on 122 prostate cancer deaths, a larger reduction in mortality was observed (44%), likely because of the longer median follow-up of 14 years. Speculatively, the larger effect in the Göteborg trial compared with our observations may, in addition to a longer follow-up, also be because of a more stringent work-up of men with elevated serum PSA in a trial setting and to a superior diagnostic and therapeutic level of care in a high-volume setting as compared with our results that were based on routine clinical practice among all health-care providers in 14 Swedish counties.

Our results from a population-based, real-life study indicate that more-intense as compared with less-intense opportunistic PSA screening decreases prostate cancer mortality, which reconciles the findings of the two largest trials on PSA screening to date, namely ERSPC (organized vs no screening) and PLCO (organized vs opportunistic screening) and is congruent with the reduction of prostate cancer mortality that has occurred in the United States during the last decades, during which time period early diagnosis and early treatment has increased drastically (32).

However, opportunistic screening as it is currently implemented in real life is inefficient and is implemented too frequently in the wrong age groups. In a recent Swedish study, 6% of men aged 40 to 49 years, 16% of men age 50 to 59 years, 27% of men aged 60 to 69 years, 30% of men aged 70 to 79 years, and 23% of men age 80 to 89 years had an annual PSA test (33), whereas in the United States, 45% of men aged 75 years and older have a yearly PSA test (34). The frequent PSA testing of older men leads to overdetection and overtreatment, and to maximize the benefits while at the same time minimizing the adverse effects of screening and ensuing treatment, risk-stratified screening with regular but infrequent PSA testing of middle-aged men holds promise (35).

In conclusion, in our population-based study we observed lower incidence of metastatic prostate cancer, lower prostate cancer-specific mortality, and lower excess mortality in counties with high vs low incidence of prostate cancer, reflecting PSA uptake. This indicates that more-intense as compared with less-intense opportunistic PSA screening reduces prostate cancer mortality.

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