

## Interpreting Trends in Prostate Cancer Incidence and Mortality in the Five Nordic Countries

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**Trends in incidence and mortality rates of prostate cancer were analyzed using data from the national cancer registries of Denmark, Finland, Iceland, Norway, and Sweden. Joinpoint regression models were used to quantify temporal trends for the period from 1980 to 2004. Incidence rates were increasing and similar in the Nordic countries during the 1980s. Around 1990, a more rapid incidence increase began in all Nordic countries except Denmark, where an increase was seen 5 years later. In 2001, incidence rates in Denmark were half of those seen in the other Nordic countries, but mortality rates varied only marginally among countries. Mean annual declines in prostate cancer mortality of 1.9% (95% CI = 0.4% to 3.3%) and 1.8% (95% CI = 0.5% to 3.0%) were observed from 1996 to 2004 in Finland and Norway, respectively. During the same period, mortality rates leveled off in Iceland and Sweden but continued to increase in Denmark. The rapid increase in incidence during the early 1990s coincided with the introduction of the prostate-specific antigen (PSA) test and conveys little information about the occurrence of potentially lethal disease. Mortality rates, however, have recently stabilized or declined in countries where PSA testing and curative treatment have been commonly practiced since the late 1980s. Although other explanatory factors may be in operation, these trends are consistent with a moderate effect of increased curative treatment of early diagnosed prostate cancer and improved treatment of more advanced disease.**

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The difficulties in interpreting temporal trends in prostate cancer incidence and mortality are well known (1–4). Many microscopic prostate cancers remain asymptomatic during the entire lifespan (5), and the recorded incidence of prostate cancer is highly dependent on the likelihood of detecting nonlethal cancers. The effect of changes in diagnostic intensity on prostate cancer incidence and survival was observed several decades ago (6), and with the introduction of widespread testing with prostate-specific antigen (PSA) to detect asymptomatic cancers the relationship of diagnostic intensity to incidence rates has become all the more apparent.

Close-to-complete coverage of cancer incidence is achieved in the registries of the five Nordic countries, because they rely on reporting from multiple sources and can be matched to a unique national identification number. Using the registry data in the five

Nordic countries, this study had three objectives: 1) to clarify whether there were appreciable differences in the temporal trends in prostate cancer incidence and mortality across the Nordic countries, 2) to study the extent to which the recorded incidence rates of prostate cancer were associated with the introduction of PSA testing, and 3) to assess the possible impact of early diagnosis and treatment with curative intent on mortality rates in each country.

Prostate cancer incidence data were obtained from national cancer registries in the Nordic countries for the following periods: Denmark (1943–2001), Finland (1953–2004), Iceland (1955–2004), Norway (1953–2004), and Sweden (1958–2004) by year of diagnosis and 5-year age group (7). Corresponding national mortality data were similarly obtained for the following periods: Denmark (1951–2001), Finland

(1953–2004), Iceland (1955–2004), Norway (1953–2004), and Sweden (1961–2004) (7). Person-years at risk among men were based on year- and age-specific population data from the national vital statistics offices. For comparative purposes, we obtained US National Cancer Institute Surveillance, Epidemiology, and End Results incidence data for US white males for the period 1973–2003 and national US mortality data, also for US whites, for the period 1973–2004 (8,9).

Cumulative risk was calculated to provide an estimate of the current lifetime risk of occurrence of, or death from, prostate cancer. We defined a lifetime as between the ages of 0 and 74, and an absence of other competing causes of death across the age span was assumed (10). Age-adjusted incidence and mortality rates of prostate cancer (for all ages) were calculated using the age distribution in the Nordic population in 2000. To describe the long-term trends in the observed rates in the Nordic countries, 3-year aggregated data were used to remove some of the random variability in the annual rates. Five-year aggregates were used for Iceland due to small

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## CONTEXT AND CAVEATS

### Prior knowledge

Previous studies concerning the relation between the intensity of prostate-specific antigen (PSA) testing and mortality from prostate cancer have been inconsistent.

### Study design

Trends in prostate cancer incidence and mortality rates in the Nordic countries were analyzed using joinpoint regression models fitted to quantify linear changes with time.

### Contribution

The temporal trends of prostate cancer incidence and mortality in the Nordic countries were found to be consistent with a moderate effect of early diagnosis and improved treatment of prostate cancer on mortality.

### Implications

Incidence rates of prostate cancer in the Nordic countries are closely related to the extent of PSA testing and convey little information about the occurrence of potentially lethal disease. It will be important to closely monitor future trends in prostate cancer incidence and mortality alongside population-based data documenting the use of PSA and different treatment modalities.

### Limitations

Population-based data on trends in PSA testing and the use of curative treatment are limited. Therefore, the relationships between these factors and changes in incidence and mortality were difficult to quantify.

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numbers of incident cases. Joinpoint regression models were fitted to identify changes in prostate cancer incidence and mortality trends (11,12). To emphasize recent trends, the joinpoint analysis was restricted to the years 1980–2004. Due to small numbers, this analysis was not performed on the Icelandic data.

Incidence rates were increasing and similar in the Nordic countries during the late 1970s and the 1980s but diverged thereafter (Fig. 1). A more rapid increase in incidence began around 1990 in all Nordic countries except in Denmark, where an increase was seen about 5 years later. This contrasts with the doubling in incidence among US whites from 1986 to 1992, followed by a decline until 1995. At the beginning of the 21st century, the risk of being diagnosed with prostate cancer

before the age of 75 in Denmark was about one-third of that in Finland, Norway, and Sweden (Table 1). In 2001, the variation in incidence rates between the Nordic countries was ten times higher than the variation in mortality rates. Statistically significant and continuous annual declines in mortality of around 2% were observed in Finland and Norway from 1996, about 5 years after the start of the decreases observed among US whites (Table 2). In the same period, mortality rates in Iceland and Sweden stabilized, whereas in Denmark a slow but continuous increase was observed.

The observed increase in incidence in all countries before 1990 is most likely due to an increasing awareness of prostate-related symptoms, better access to health care, and the more frequent use of surgical treatment for benign prostate hyperplasia (BPH) (6). Increased use of transurethral resection of the prostate (TURP) is considered to be the primary reason for the observed increase in incidence rates of prostate cancer in the United States from 1973 to 1986 (14,15). In Sweden, TURP procedures increased from around 1500 annually in 1972 (6) to a peak of 14000 in 1991, declining thereafter to around 7000 by 2001 (16). In Denmark, after the introduction of TURP the number of prostatectomies increased by 43% from 1977 to 1983 (17).

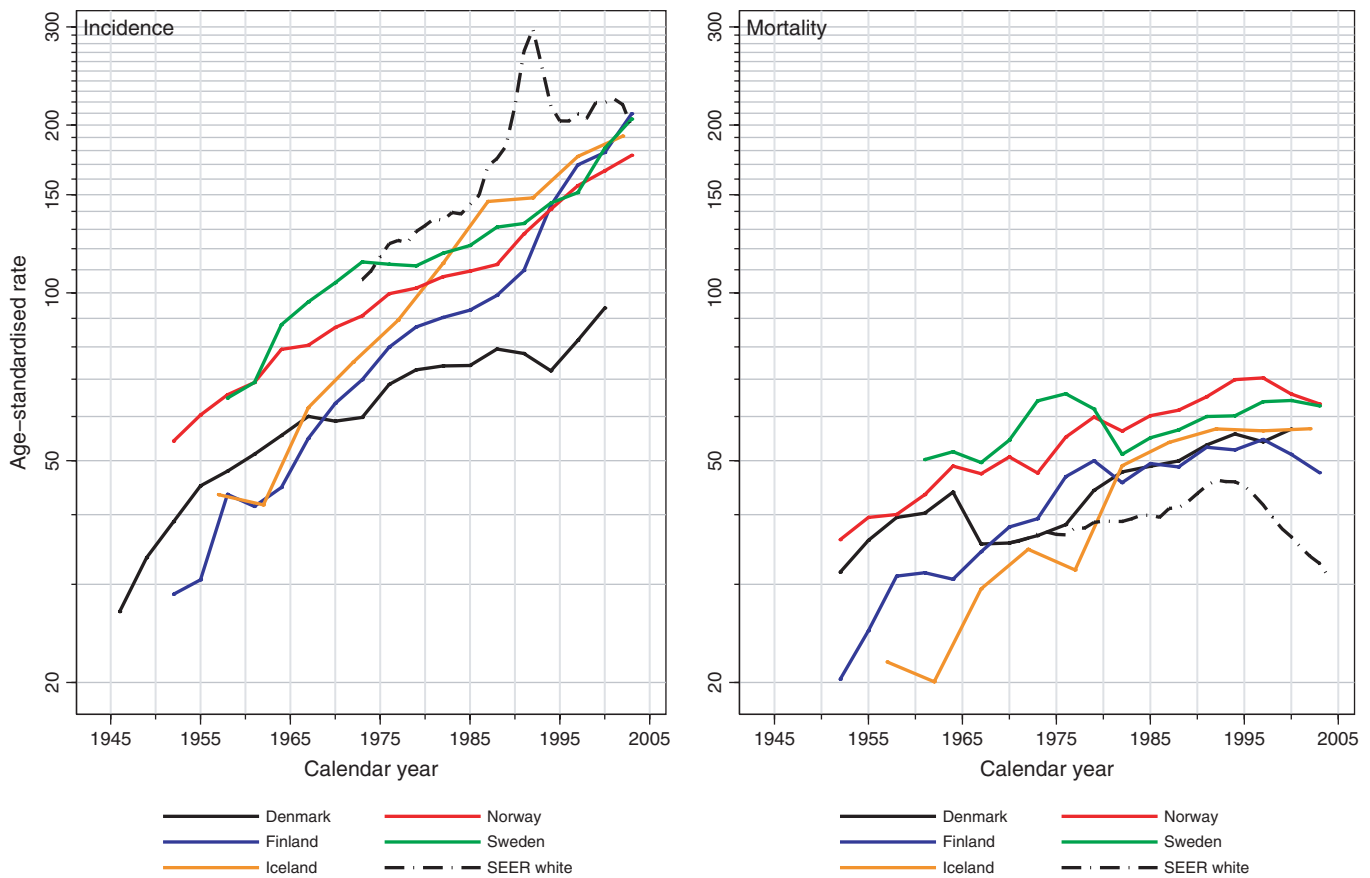
The impact of PSA testing on incidence was first reported in the United States (2), where it was associated with a doubling in rates of prostate cancer from 1986 to 1992 (Fig. 1). Likewise, after PSA became available in the Nordic countries around 1990, rapid increases in PSA testing (18,19) were associated with sharp increases in prostate cancer incidence (Fig. 2). These trends occurred despite recommendations of national authorities that advised against opportunistic PSA screening (20,21). PSA testing in Denmark, available since the mid 1980s (22), remained limited until around 1995, perhaps due to recommendations that advised against its use in asymptomatic men (23). The distribution of these restrictive recommendations plus less surgical treatment for BPH (24) may explain the decline in the recorded incidence in Denmark from 1991 to 1995. The total number of TURP procedures in Denmark decreased by more than 20% from 1991 to 1995 (25) and by 23% in patients with BPH

between 1993 and 1995 (26). The incidence trend after 1995, however, suggests an increasing level of diagnostic activity in Denmark as well (27).

When we compared the Norwegian and Swedish incidence rates and the number of PSA tests in the countries, a close relation between the use of PSA and cancer incidence was revealed (Fig. 2). In 1996, the rate of PSA tests per 1000 men was almost 80 in Norway and around 40 in Sweden, consistent with the more rapid increase in incidence observed in Norway during the early 1990s. In 2001, recommendations advising against PSA testing in asymptomatic men were distributed to all general practitioners and urologists in Norway (18). The decline in the incidence rates between 2000 and 2002 in Norway corresponded to a decline in PSA testing around this time, and the transience of both trends suggests that the recommendations had only a temporary effect on PSA testing and prostate cancer incidence. By 2002, the rates of PSA testing were similar in Norway and Sweden.

It is well documented that PSA screening entails detection of prostate cancer in many men who would not have been diagnosed during their lifetime in the absence of screening (28,29). Because no molecular marker can yet separate cancers that require treatment from those that will remain asymptomatic (30), overdiagnosis implies a considerable risk of overtreatment. Even before the PSA era, Tretli et al. (31) commented on the possibility of unnecessary treatment, given considerable variations in incidence yet small differences in mortality between the Nordic countries. Previous descriptive studies concerning the relation between the intensity of PSA testing and mortality from prostate cancer have been inconsistent (32–35), and whether increased diagnostic efforts result in a mortality reduction remains uncertain and hotly debated (36,37). Results from ongoing randomized screening trials in the United States (Prostate, Lung, Colorectal, and Ovarian cancer screening trial) and Europe (European Randomized Study on Screening of Prostate Cancer) designed to address the impact of PSA screening on prostate cancer mortality, are not yet available (38).

Feuer et al. (3) concluded that the rise and fall in prostate cancer mortality in the United States that was observed following



**Fig. 1.** Observed age-standardized rates (Nordic standard 2000) of prostate cancer incidence and mortality in the Nordic countries and the United States (all ages).

the introduction of PSA testing was consistent with the hypothesis that a constant proportion of US prostate cancer patients who die of other causes may have been misclassified as dying of prostate cancer (attribution bias). Attribution bias may have contributed to an observed increase in mortality in the Nordic countries. However, in contrast to what occurred in the United

States, the mortality reduction in Finland and Norway occurred while incidence was increasing.

Etzioni et al. (4) reported that PSA testing was unlikely to entirely explain the mortality decline in the United States since 1991. In their analyses, the authors found that only the shortest mean lead time (average time that diagnosis is advanced by

screening) considered—i.e., 3 years—was consistent with a major impact of PSA testing on mortality, given that the downturn occurred earlier than would be predicted by most estimates of lead time (29,39). Based on a model of the natural history of screen-detected localized prostate cancer, Parker et al. (40) described the lead time as dependent on Gleason score and suggested

**Table 1.** Prostate cancer incidence and mortality in the Nordic countries: observed numbers and age-standardized rates in 2001 and cumulative risk for the latest year available, all ages

Country	Male population (millions)	Number of incident cases	Number of deaths	Age-standardized rates*			Cumulative risk	
				Incidence (RR†)	Mortality (RR†)	I:M ratio‡	Incidence§	Mortality§
Denmark	2.64	1997	1126	94.6 (1)	58.7 (1)	1.6	4.9 (2001)	1.8 (2001)
Finland	2.53	3593	790	183.2 (1.9)	51.5 (0.9)	3.6	13.7 (2004)	1.3 (2004)
Iceland	0.14	199	44	210.5 (2.2)	55 (0.9)	3.8	11.4 (2003  )	1.5 (2003  )
Norway	2.24	2890	1039	158.6 (1.7)	62.4 (1.1)	2.5	12.0 (2004)	1.7 (2003)
Sweden	4.40	7732	2460	183 (1.9)	62.8 (1.1)	2.9	14.5 (2004)	1.8 (2004)

\* Age-standardized rate using the Nordic standard 2000; EAPC = Estimated annual percentage change; RR = rate ratio; I = incidence; M = mortality; CI = confidence interval.

† Rate ratio of age-standardized Nordic rates using Denmark as the baseline.

‡ I:M ratio of age-standardized Nordic rates using Denmark as the baseline.

§ Cumulative lifetime risk, with lifetime defined as within the age range 0–74 and estimated by adding together rates over each year of age. Calculation assumes constant rates within age groups of 5 years and an absence of competing causes of death.

|| Midyear, calculation based on the period 2002–2004.

**Table 2.** The estimated annual percentage change and 95% confidence intervals within the specified linear segments identified via joinpoint regression of the age-standardized (Nordic 2000) rates (all ages)\*

Country	Joinpoints (incidence)		Joinpoints (mortality)	
	Segment	EAPC (95% CI)	Segment	EAPC (95% CI)
Denmark	1980–1991	0.7 (0.8 to 1.4)	1980–2001	1.0 (0.7 to 1.3)
	1991–1994	−3.5 (−12.3 to 6.1)		
	1994–2001	4.7 (3.4 to 5.9)		
Finland	1980–1990	1.4 (0.8 to 2.0)	1980–1996	1.0 (0.4 to 1.7)
	1990–1996	8.7 (7.3 to 10.1)	1996–2004	−1.9 (−3.3 to −0.4)
	1996–2002	2.0 (1.0 to 3.0)		
	2002–2004	11.0 (7.1 to 15.1)		
Norway	1980–1988	1.0 (−0.2 to 2.1)	1980–1996	1.5 (1.0 to 2.0)
	1988–1999	3.9 (3.2 to 4.6)	1996–2004	−1.8 (−3.0 to −0.5)
	1999–2002	−3.5 (−10.5 to 4.0)		
	2002–2004	14.8 (7.2 to 22.9)		
Sweden	1980–1996	1.6 (1.2 to 2.1)	1980–1999	1.1 (0.7 to 1.5)
	1996–2004	5.0 (4.0 to 6.0)	1999–2004	−0.6 (−2.9 to 1.9)

\* Incidence and mortality data analyzed for the period 1980–2004 or, Denmark, for 1989–2001 (1980–2001). The models were estimated using the weighted least squares method with the weights proportional to the inverse of the variance of the annual age-adjusted rates. We obtained these variances from the Poisson approximation of the binomial variation of the age-specific rates (13). Computation of the joinpoints—i.e., calendar years for which significant changes in the overall linear trend were detected—were based on the best fit of the regression models allowing 0, 1, 2, and 3 joinpoints. The trend over time was quantified as the estimated annual percentage change in each joined line segment, and its associated 95% confidence interval was used to characterize the major trends. Because multiple tests were performed, the statistical significance level of each test was adjusted to control the overall type I error at a specified  $\alpha$  level of 0.05. EAPC = estimated annual percentage change; CI = confidence interval.

that the effect of radical treatment on overall survival was strongest in men with high-grade disease. Screen-detected cancers with unfavorable prognostic factors (e.g., high Gleason scores) might have shorter lead times than the majority of screen-detected cancers and, provided that some of these were cured, would contribute to a mortality reduction earlier than would be expected for the majority of cancers. It is therefore possible that in Finland and Norway some men will have had PSA-detected cancers associated with an unfavorable prognosis and shorter lead times than the average 5–6 years previously estimated for prostate cancers with Gleason scores greater than 7 (40).

Taking into account these considerations, three observations are compatible with a contributory effect of PSA testing on the mortality trends in the Nordic countries: 1) mortality rates declined or leveled off since the mid 1990s in countries with extensive PSA testing (Finland, Iceland, Norway, and Sweden), 2) mortality decreased from 1996 in those countries in which the most rapid increases in incidence were seen during the early 1990s (Finland and Norway), and 3) the time lag between the rapid rise in incidence rates and the subsequent reduction in mortality was approximately 5–8

years in Norway, Finland, and the United States, with the shortest time lag in the United States and Finland, countries for which the most rapid increase in incidence was observed after the introduction of PSA testing. However, the fraction of patients treated with curative intent in Norway increased only moderately in the early 1990s, from 3% in the period 1985–1989 to 6% in the period 1990–1994 (R. Kvåle: unpublished data). Although the length of the lead time in an opportunistic screening setting is unknown, the small change in frequency of curative treatment during the early 1990s would suggest that the contribution of PSA testing and early radical treatment to the declines in mortality rates observed from the mid 1990s must be small. Moreover, it is difficult to separate a possible PSA testing effect on mortality from the impact of a general improvement in treatment in the very same countries and calendar periods for which the PSA test came into widespread use.

Changes in the management of prostate cancer, including an increasing use of treatment with curative intent for localized disease before the PSA era, may have contributed to a mortality reduction. A survey among departments of urology and general surgery in the Nordic countries from 1990 showed that clinical policies for managing

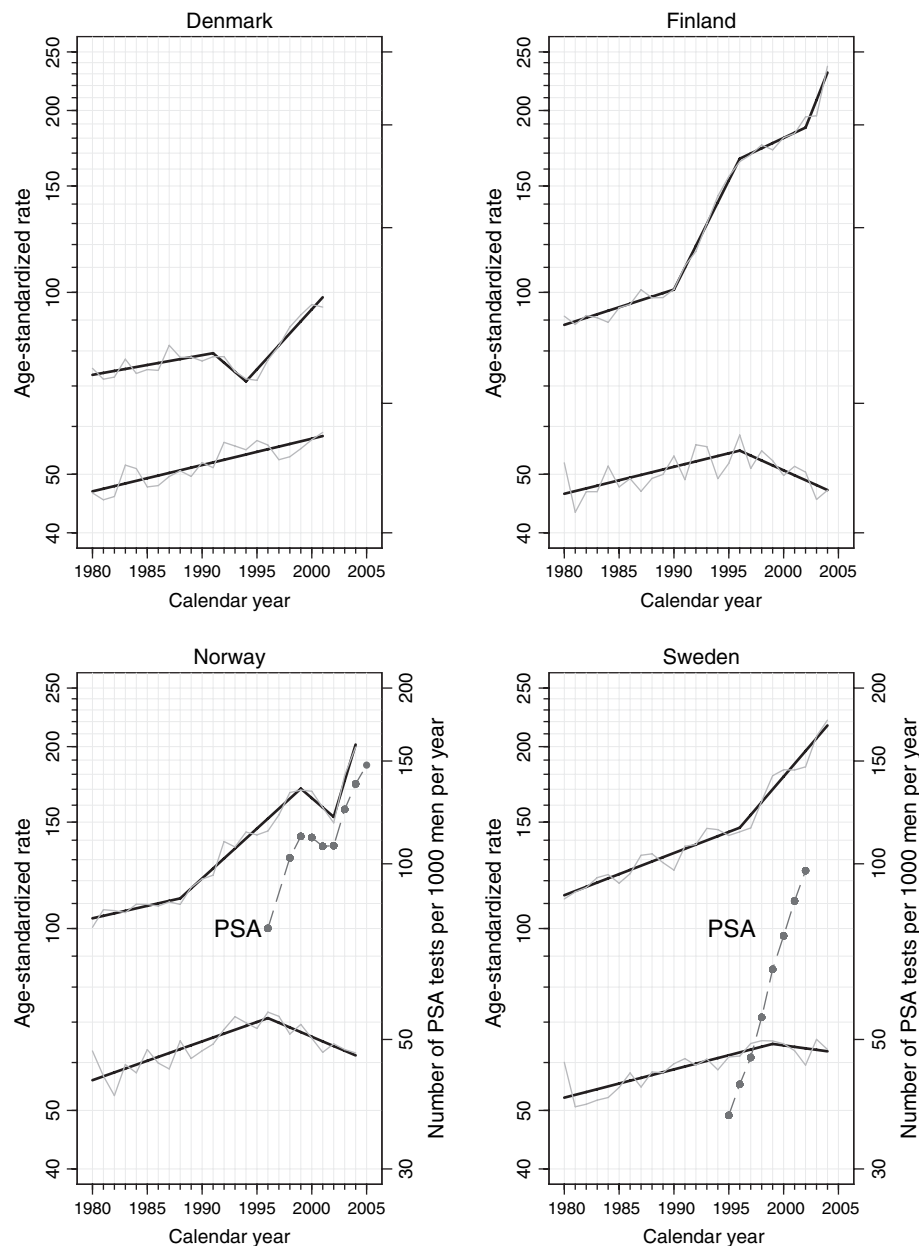
early prostate cancer were most conservative in Denmark and that treatment with a curative intent was used most extensively in Finland and Norway (41). In Denmark, the traditional therapeutic approach has primarily been to treat late-stage patients (42), and radical prostatectomy was not introduced until 1995 (43). Radical prostatectomy was, however, infrequently used throughout the Nordic countries before the mid 1990s. To illustrate this point, in the period from 1990 to 1994, radical prostatectomy was performed in only 3.0% and 3.3% of all patients diagnosed with prostate cancer in Norway (R. Kvåle: unpublished data) and Sweden (16), respectively.

We estimated the expected numbers of deaths based on the trends in mortality rates from 1996 to 2003 and the deaths expected if the age-specific increase from 1986 to 1995 continued linearly until 2003. We found that about 500 deaths from prostate cancer in Norway may have been avoided during the period 1996–2003. A Nordic study in which patients were randomly assigned to radical prostatectomy or watchful waiting for early prostate cancer showed that radical prostatectomy had to be given to 19 patients to prevent one prostate cancer death within 10 years (44). Combining these results with an estimated number of 3000 persons having been treated with curative intent (i.e., radiotherapy or surgery) from 1980 to 1999 in Norway (R. Kvåle: unpublished data) suggests that radical treatment may explain approximately one-third of the decline in prostate cancer mortality, or approximately 160 of the 500 deaths prevented. These estimates, although subject to substantial uncertainty, suggest that factors other than radical treatment have contributed to the reductions in prostate cancer mortality observed from 1996 onward.

Three studies of patients treated with radiotherapy and who had at least one disease characteristic predictive of poor prognosis (locally advanced disease, high Gleason grade, or node-positive disease) have compared outcomes of those patients randomly assigned to also receive adjuvant medical or surgical castration or hormonal therapy that was deferred until progression (45–47). These studies showed statistically significant advantages of immediate hormonal therapy with respect to overall survival. The introduction of gonadotropin-releasing hormone



**Fig. 2.** Fitted trends from joinpoint regression (**bold lines**) versus the observed age-standardized rates (Nordic standard 2000) of prostate cancer incidence and mortality in four of the five Nordic countries for all ages. The estimated national number of prostate-specific antigen tests (PSA) per 1000 men (**dashed lines**) is shown for Norway (1996, 1998–2005) and Sweden (1995–2002), based on an aggregated laboratory sample comprising approximately 80% (62% for 1998) and 100% of the PSA analyses performed in Norway and Sweden (19), respectively. PSA data for Norway were provided through Norwegian quality improvement of primary care laboratories in Bergen (S. Sandberg: personal communication, July 2007). We obtained samples of PSA data from Iceland and Denmark but had an insufficient gauge of the correct denominator over time to estimate the numbers of tests per 1000 men. From Icelandic data comprising the number of tests at 6 major laboratories covering 75% of the male population by 2002, the crude number of tests in 2002 was 12323, up from 891 tests in 1990 (T. Thorgeirsson, E. Ö. Jonsson, E. J. Olafsdottir, J. G. Jonasson, E. Jonsson, L. Tryggvadottir: unpublished data, July 2007). For Denmark, data from Copenhagen General Practitioners Laboratory comprising samples from general practitioners in the greater Copenhagen area, representing approximately 21% of the Danish population, indicated that there were 2361 PSA tests in 1995 compared with 14686 by 2003 (P. Felding: personal communication, July 2007).



agonists and antiandrogens occurred at about the same time as that of PSA testing and may have contributed to the mortality declines in the United States (48). Increased use of hormonal treatment, which, in intermediate- to high-risk patients, has recently been given in combination with dose-escalated radiotherapy (49,50), may also have contributed to the stabilization or decline in mortality rates in the Nordic countries. A Nordic report from 1992 described that the total use of endocrine therapy was most frequent in Norway and Finland (51). From 1995 to 2000, the annual sales of defined daily doses of antiandrogens plus gonadotropin-releasing hormone analogs

doubled in Sweden (52) and tripled in Norway (H. Strøm: personal communication) and Finland (53).

There are limitations to this study. In particular, changes in routines of the National Statistics offices may have influenced the mortality statistics. For example, the peak in prostate cancer mortality in Sweden around 1975 was likely a result of prostate cancer frequently being classified as the underlying cause of death among men diagnosed within a few years before they died (54). Another change in institutional practice that may have influenced mortality statistics is the introduction of the International Classification of Diseases,

Eighth Revision, which coincided with the apparent drop in prostate cancer mortality in Denmark in the late 1960s, although this may not be the only explanation for the decrease. In addition, it would have been beneficial to comprehensively assess the incidence and mortality trends alongside concomitant population-based data on PSA testing and the use of curative treatment; however, such data were only available in selected Nordic countries.

We conclude that the incidence rates of prostate cancer are closely related to the introduction of the PSA test. The recent stabilization or declines in prostate cancer mortality rates observed in four of

the five Nordic countries are consistent with a modest effect of increased curative treatment of early diagnosed prostate cancer and improved treatment of more advanced disease. However, the individual contribution of the different factors to the observed reduction in mortality remains uncertain.

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