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Homogeneous Prostate Cancer Mortality in the Nordic Countries Over Four Decades

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Abstract

Background—Incidence of prostate cancer (PCa) has greatly increased in the Nordic region over the past two decades, following the advent of prostate-specific antigen (PSA) screening. Consequently, interpreting temporal trends in PCa has become difficult, and the impact of changes in exposure to causal factors is uncertain.

Objective—To reveal geographic differences and temporal trends in PCa in the Nordic countries. Because the recorded incidence of PCa has been profoundly influenced by PSA screening, we focused our analyses primarily on PCa mortality.

Design, setting, and participants—We analyzed national PCa incidence and mortality data from Denmark, Finland, Norway, and Sweden from 1965 to 2006 using the PC-NORDCAN software program and the online NORDCAN database.

Measurements—Cumulative incidence and cumulative mortality from PCa were calculated for selected calendar years during four decades, along with age-standardized mortality rates. Incidence

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data in NORDCAN come from individual countries' cancer registries, and mortality data come from national mortality registries.

Results and limitations—From 1965 to 2006, 172 613 deaths from PCa were reported in the four Nordic countries. A substantial rise in incidence was observed across the region, with some geographic variation, since the late 1980s. In contrast, both disease-specific mortality rates and cumulative risk of PCa mortality lacked consistent temporal trends over the same period. Cumulative risk of PCa mortality ranged between 3.5% and 7.5% in the region over four decades, whereas cumulative incidence jumped from about 9% to >20%. Mortality has remained fairly constant among the countries, with a minimally lower risk in Finland.

Conclusions—Unlike most malignancies, the occurrence of lethal PCa showed minimal geographic variation and lacked consistent temporal trends over four decades. These findings may guide our search for important causes of PCa, a malignancy with etiology that is still largely unknown.

Keywords

Cancer trends; Mortality; Nordic region; Prostate cancer

1. Introduction

Monitoring and interpreting trends in cancer incidence is central to cancer control and prevention. For prostate cancer (PCa), however, the recorded incidence across most Western countries has been profoundly affected by prostate-specific antigen (PSA) screening, challenging the interpretation of temporal trends. In the United States, PCa incidence more than doubled between the mid-1980s and the 1990s [1], with similar trends in the Nordic countries appearing several years later [2,3]. Consequently, little is known about true trends in disease rates that would have occurred in the absence of PSA screening and that would reflect changes in exposure to causal factors during the last half of the 20th century.

Although mortality rates are an alternative source of information in detecting disease trends, they can be influenced by changes in survival and cure rates due to therapeutic advances. Among human malignancies, PCa remains an exception because treatments with curative intent—initially radical prostatectomy and, later, local radiation—were not developed until the 1980s. Although first utilized in most Nordic countries during the mid-1980s, curative treatments were not widely adopted until the 1990s [4]. Hence, temporal trends in PCa mortality may adequately reflect trends in incidence with limited confounding by changes in treatment patterns over time.

We undertook a nationwide analysis of PCa mortality in the Nordic countries, where reliable data have existed since the mid-20th century. Our goal was to assess temporal trends as well as geographic differences in mortality because such data may provide important clues about the causes of PCa, which is the most common malignancy in men but has poorly understood etiology [5].

2. Methods

The five Nordic countries encompass a population of nearly 25 million people. Because estimates are unstable for the population of 317 000 residing in Iceland [6], we restricted our analysis to Denmark, Finland, Norway, and Sweden, with comprehensive, nationwide registries of causes of death. To minimize uncertainty due to possible misclassification of death, particularly underdetection of PCa as a cause of death, we restricted our analyses to the period from 1965 to 2006, when all four countries had established nationwide cancer registries. National mortality data were obtained from the NORDCAN database, which details cancer

incidence and mortality rates among the Nordic countries through incorporation of data from national cancer and mortality registries. Nearly all PCa diagnoses are captured through linkage with national personal identification numbers. The PC-NORDCAN software program (v.2.4) was utilized to identify trends in PCa mortality in the Nordic countries at local and national levels from 1972 to 2006 [7]. We incorporated data from the publicly available NORDCAN database (v.3.5), which contains country-level statistics, from 1965 to 2006 [3]. To illustrate trends in PCa incidence and mortality during the last several decades, we examined age-specific and summary trends. Cumulative risk was calculated to provide an estimate of the lifetime risk of death from PCa by time period. We defined *lifetime* as between the ages of 0 and 84, and the absence of other competing causes of death across the age-span was assumed. Age-standardized incidence and mortality rates of PCa (per 100 000 person-years) were calculated for men between the ages of 0 and 84, to be consistent, using the age distribution in the Nordic population in 2000 as the standard to best reflect the age distribution in the region. Mean age at death from PCa for a selected year was estimated by multiplying the number of deaths per 5-yr age group by the median age and dividing that sum by the total number of PCa deaths in a given year. The median for the oldest age group (≥ 85) was chosen as 87 yr.

3. Results

We analyzed 172 613 deaths from PCa recorded between 1965 and 2006 in Norway, Sweden, Finland, and Denmark. Mean age at death from PCa across all countries and time periods was 76.6 yr, with country-specific data for selected years provided in Table 1.

We analyzed cumulative mortality from PCa in five selected years (1965, 1975, 1985, 1995, and 2006) spaced evenly throughout the period 1965–2006. For comparison, we also report cumulative incidence during the same years (Table 1). During the period 1965–2006, the cumulative incidence of PCa by age 84 in the Nordic countries (combined) increased more than two-fold on average, ranging between 8.7% and 21.5%, with variation by country and time period. In contrast, cumulative mortality from PCa by age 84 in all countries combined remained seemingly constant, ranging between 4.9% and 6.6%, with largely overlapping curves in all ages and time periods.

We next examined cumulative PCa mortality by age 84 separately by country (Fig. 1). Over four decades, cumulative mortality from PCa remained fairly stable in each country, between 3.5% and 7.5%. The decrease in disease-specific mortality in Sweden around 1980 may be attributed to changes in the registration of causes of death. There is evidence of a slight increase over time in all four countries until 1995, followed by a slight decrease, which is most pronounced in Finland and Norway. Variation among countries was small and inconsistent, with minimally lower PCa mortality in Finland than in the other three countries.

The cumulative incidence of PCa has risen steadily in all age groups since 1965 and varies noticeably among countries (Fig. 2). Cumulative incidence plots show a substantial increase in risk starting in the 1980s in Norway, Sweden, and Finland, whereas Denmark experienced a sizable surge in risk only within the last 10 yr. However, similar trends in the cumulative risk of PCa mortality are not evident (Fig. 3). In contrast to graphs of cumulative incidence, the shape of the curve for PCa mortality stays remarkably similar across time periods and among countries. The lifetime risk of dying from PCa by age 70 has remained low throughout recent years, at about 0.6%, although it increases sharply to nearly 6% by age 85.

Age-standardized PCa mortality rates in the Nordic countries have remained fairly stable across age groups since the 1980s. Rates are somewhat unstable before 1980, a finding that may be due to differences in reporting among the countries. Although rates were increasing slightly, albeit in a similar fashion, among countries through the mid-1990s, there is evidence of a small

recent decline (Fig. 4). However, a clear temporal trend in mortality rates is not apparent. The greatest reduction in mortality since the mid-1990s occurred in Norway and Finland, where PCa mortality rates have declined >21% since 1996 (from 50.6 and 39.0 per 100 000 person-years, respectively, in 1996 to 38.2 and 30.8 per 100 000 person-years in 2006). Sweden experienced an approximate 11% decrease over the same time period, whereas mortality rates in Denmark declined about 7%. The lack of a significant temporal trend in mortality rates echoes that seen in cumulative mortality across the Nordic region: Rates have generally been stable across time periods and among countries. Despite some variability in PCa mortality rates over time, the magnitude of variation does not equal the increase in PCa incidence rates observed across the region since the mid-1960s, ranging from approximately three-fold in Denmark to five-fold in Finland.

4. Discussion

Our analysis of four Nordic countries for PCa mortality generated two salient findings: (1) reasonable homogeneity in cumulative mortality from PCa among the countries and (2) lack of any strong overall temporal trend. This lack of a trend in mortality is notwithstanding a concomitantly large increase in cumulative incidence.

The findings of homogeneity and lack of a trend in PCa mortality are unique in cancer epidemiology. Virtually every malignant disease shows geographic variation in incidence among these countries; the variation is often substantial, and for PCa, it is about two-fold—highest in Sweden and lowest in Denmark. Furthermore, few cancers show such stable mortality rates over extended periods of time, and we have not previously observed largely overlapping cumulative risk curves.

Theoretically, we conceive at least three possible interpretations of our findings. First, according to the interpretation we consider most plausible, true incidence rates of lethal PCa have changed little over the studied time period. The corollary to this interpretation is that the dramatic temporal trends and geographic variation we observe in recorded incidence of PCa are attributable to differences in diagnostic intensity [8] and overdiagnosis of nonlethal disease [2,9]. Because few tools exist to accurately distinguish lethal PCa from nonlethal PCa, overtreatment may occur in some cases. This potential explanation has important implications for an informed debate about the interpretation of incidence trends, the optimal management of PCa, and the challenges and economic consequences of PSA testing [10]. Furthermore, it is also relevant in our search for factors that cause malignant transformation of the prostate and promote further progression to a lethal phenotype.

Second, the lethal consequences of a growing number of incident cancers might have been counteracted by earlier diagnosis through PSA screening among asymptomatic men, in combination with more frequent treatment for early PCa with a curative intent. The prevalence of PSA screening in the Nordic countries has increased greatly since the introduction of screening around 1990, with the most extensive screening conducted in Finland, Norway, and Sweden, despite a lack of national screening recommendations [2]. The extent to which these changes in PCa management affected mortality rates in 1990s and later continues to be debated, particularly in the United States [11]. Conflicting results from the European Randomized Study of Screening for Prostate Cancer and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial in the United States have fueled further discussion of whether regular PSA screening reduces PCa mortality [9,12]. In addition, radical prostatectomy was shown to reduce relative disease-specific mortality rates following diagnosis with early stage PCa in comparison to watchful waiting in Scandinavian men, although the absolute difference was small [13]. In the Nordic countries, however, treatment with curative intent, whether surgical or radiotherapeutic, was not extensively adopted until the mid-1990s [2]. Based on data from the

Swedish randomized trial, we would not expect to see a large impact from curative treatment on mortality for about 10 yr [13] and thus do not expect changes in treatment to considerably explain our findings. Patients diagnosed due to PSA testing experience a considerable lead time during which, by definition, no disease-specific mortality takes place [9,12,14]. For these reasons, concealment of underlying trends due to confounding by treatment is unlikely. Finally, it would be surprising if screening followed by curative treatment managed to compensate for increasing incidence to keep mortality constant.

Third, the incidence of lethal PCa might be stable over four decades, with no appreciable geographic variation while, simultaneously, the incidence of nonlethal disease might have increased dramatically, although at different absolute levels, in the four countries. This scenario would arise if incidence increases, but probability of progression to a lethal phenotype decreases over time; however, we are unaware of any empirical data supporting such a phenomenon for PCa. It also seems inconceivable that these two phenomena would balance each other to keep cumulative mortality constant.

What is the message to cancer epidemiologists and all those concerned with the prevention of lethal PCa if this disease is equally frequent in four Nordic countries with no substantial temporal trends over at least 40 yr? If lethal disease has remained constant over time, this implies that changes in the prevalence of exposure to causal risk factors for PCa over the last several decades have had no appreciable effect on disease-specific mortality. Conversely, it is possible that the decreasing prevalence of suspected contributors to PCa mortality, such as smoking [15–17], may be balanced by the increasing prevalence of other risk factors, such as obesity [18], resulting in an essentially null effect on mortality. If the downward trend in smoking is similar in magnitude to the upward trend in obesity, this could explain part of the static trend in PCa mortality.

The slight decrease in PCa mortality from 1995 to 2006 observed in Finland and Norway deserves mention because a similar pattern was not observed in Sweden and Denmark. Certain practices of screening, treatment, and classification of disease that vary among countries, including more frequent use of antiandrogens, may have led to this discrepancy. Because PSA screening has likely affected Norway and Sweden similarly [2], it is also possible that misclassification of causes of death may contribute to some of the slight variation in mortality curves. Similar discrepancies have been reported in the United States, where disease-specific mortality declined after 1994, in comparison to the United Kingdom [19], where both PSA screening and reductions in mortality were less pronounced.

5. Conclusions

Our analysis of PCa mortality in four Nordic countries has shown that the cumulative risk of death from PCa is nearly identical among the countries, with no visible temporal trend over the last four decades. These observations contrast with the substantial surge in incidence that occurred over the same time period, indicating that recent trends in incidence may be the result of overdiagnosis of nonlethal disease due to PSA screening and not an underlying shift in the distribution of causal factors [20]. Our findings apply directly to Scandinavian men and may not be generalizable to countries where PCa characteristics may vary. If corroborated, these findings may have important implications for future research and management of PCa.

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Prostate Mortality: Cumulative Risk age (0-84)

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Fig. 1.
Cumulative risk of prostate cancer mortality among men in the Nordic countries, NORDCAN 1965–2006. Reproduced with permission of the Association of the Nordic Cancer Registries [3].

Fig. 2. Cumulative risk of prostate cancer incidence in Finland, Denmark, Norway, and Sweden by age group, NORDCAN 1965–2006.

Fig. 3.
Cumulative risk of prostate cancer mortality in Finland, Denmark, Norway, and Sweden by age group, NORDCAN 1965–2006.

Prostate Mortality: ASR (World) age (0-84)

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Fig. 4. Age-standardized prostate cancer mortality rates (per 100 000) in four Nordic countries, NORDCAN 1965–2006. Reproduced with permission of the Association of the Nordic Cancer Registries [3].
ASR = age-standardized rate.

Table 1

Prostate cancer (PCa) in the Nordic countries during five specific years, NORDCAN 1965–2006

	Yr	Country				Nordic countries*
		Denmark	Finland	Norway	Sweden	
PCa deaths, No.	1965	561	212	485	1113	2376
	1975	547	359	640	1761	3325
	1985	820	504	917	1784	4057
	1995	1050	704	1064	2280	5128
	2006	1179	817	1039	2473	5547
Mean age at PCa death, yr	1965	75.2	74.1	76.0	75.9	75.6
	1975	75.3	74.9	76.3	76.6	76.1
	1985	76.1	75.4	76.4	76.4	76.2
	1995	76.8	76.4	78.2	77.6	77.4
	2006	77.8	77.4	79.3	79.2	78.6
Cumulative incidence, %	1965	6.4	5.4	9.7	10.5	8.7
	1975	7.5	9.0	11.1	13.0	10.8
	1985	8.7	11.0	12.6	13.6	12.0
	1995	8.3	17.2	15.8	16.2	14.7
	2006	15.5	20.8	20.8	21.4	19.9
Cumulative mortality, %	1965	5.0	4.1	6.0	5.5	5.3
	1975	4.1	5.0	5.9	7.1	5.8
	1985	5.5	4.8	7.2	6.0	5.9
	1995	6.2	5.6	7.0	6.5	6.3
	2006	6.1	4.7	5.9	6.2	5.8

* Denmark, Finland, Iceland, Norway, and Sweden combined.