Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer among Canadian men, with the lifetime risk for being diagnosed approximately one in eight[1]. Such detection now occurs most commonly by use of Prostate-Specific Antigen (PSA) test. While the PSA test was introduced in Canada in 1986[2], its use did not become widespread until 1990-91, and then increased steadily over the next five years[2,3]. PSA testing is now common: the Canada Community Health survey conducted in 2000-2001 suggested that nearly half of Canadian men aged 50 years or older had received at least one PSA test in their lifetime[4]. Among the provinces/territories that asked respondents about PSA utilization in subsequent surveys, 49.8%, 50.9% and 49.9% of men over 35 years reported having at least one PSA test in their lifetime in 2007-08, 2009-10 and 2011-12, respectively[5].

Advocates assert that increased screening and subsequent diagnostic testing in Canada have led to reduced prostate cancer mortality[6,7]. We sought to describe secular changes in the Canadian epidemiology of prostate cancer – particularly aiming to describe the epidemiological relationship between PSA testing and prostate cancer mortality.

Methods

The number of cases of prostate cancer, number of deaths due to prostate cancer, age-specific and age-standardized incidence and mortality rates were obtained through the Public Health Agency of Canada's ORIUS database[8]. At the time of this analysis, the database contained extracts from the Canadian Vital Statistics Deaths Database[9] (1969-2009), as well as the National Cancer Incidence Reporting System (1969-1991) and the Canadian Cancer Registry[10] (1992-2007). Prostate cancer cases were identified using the International Classification of Diseases for Oncology, 3rd Edition topography code C61, excluding morphology codes 9050-9055, 9140, 9590-9992[11]. Deaths due to prostate

cancer were identified from the underlying cause of death, classified according to the International Statistical Classification of Diseases and Related Health Problems[12,13].

Data were categorised by 5-year age groups at diagnosis and death (45-49 years to 80-84 years), except men older than 85 years, who were grouped together. Incidence and mortality rates were calculated by dividing the number of cases or deaths by the male population estimate. Rates across all ages were standardized to the 1991 Canadian census population.

Data from the ORIUS database were imported into Microsoft Excel for data manipulation and visualization of incidence and mortality trends. The National Cancer Institute's Joinpoint Regression Program 4.0.1[14] was used to test changes in trends over time, via annual percent change (APC) for age-standardized and age-specific rates. This program fits straight-line segments on the log-linear scale to the incidence and mortality data, which meet at joinpoints. A segment was created between each statistically significant change in trend, and the APC was calculated for each segment. Monte Carlo permutation was used to test for significance. Statistical significance was set at $P < 0.05$[15].

Annual incidence and mortality rates by age were plotted to demonstrate their changes relative to changes in diagnosis, including the introduction of PSA testing in Canada. The PSA implementation period was defined as the five year period from 1991 to 1995 (based on reports of PSA use in Canada[3,16,17]). For comparison we present data for the earliest five year period: 1969 to 1973, 1986-1990 (just prior to widespread introduction of PSA testing), and the most recent five year period with complete data available for both incidence and mortality (2003-2007).

Results

The standardised incidence for prostate cancer doubled from 54.2 per 100,000 in 1969 to 103.9 in 2013 (Figure 1). Joinpoint analysis of the age-standardized incidence (Figure 2) demonstrates that this increase was gradual from 1969 to 1990 (APC 3.0%; increase from

52.2 to 125.8 cases per 100,000 respectively). From 1991 the prostate cancer incidence increased to a peak of 140.8 in 1993 (APC 12.8%), followed by a decline between 1993 and 1996 (APC 8.2%). Thereafter, incidence continued its upward trend at a rate similar to the pre-PSA period to a second peak in 2001 and then flattened out (APC -0.59%)

Incidence initially rose steadily, with a similar time trend for all age groups until 1988 (Figure 3 and Appendix Figure 3B). Thereafter, a more rapid increase in incidence was observed among men between 60 and 79 until overall incidence peaked in 1993. After a subsequent decrease among all age groups, incidence among younger men (<69 years) continued to increase from 1996, whereas incidence among men 75 years and older continued to decrease. Thus by 2007, incidence was similar for all age groups over 65 years.

Figure 4 shows that from 1969 to 1977 age-standardised mortality rate from prostate cancer was stable (APC -0.02%), then increased at an APC of 1.3% to peak in 1994, close to the 1993 incidence peak, then decreased at an APC of -3.3%. When analysed by age groups, prostate cancer mortality was consistently higher with increasing age across all years (Figure 5, and Appendix Figure 5B). However, mortality has decreased from its peak in approximately 1987 for younger men, and progressively later for older men - 1994 for the oldest (85+). For men aged 55 to 80 years, prostate cancer mortality in 2009 was 21 to 44% lower, depending on age group, than in 1969.

Prior to PSA testing, incidence rose substantially across all ages above 50 (Figure 6). Since the introduction of PSA testing, prostate cancer is now diagnosed much more frequently – and most cases are diagnosed in men aged <65 years. Changes in mortality have been much less pronounced than these changes in incidence.

Discussion

The apparent incidence of prostate cancer in Canada doubled in the 20 years before PSA testing was available, then increased substantially when PSA was made available for screening in 1991[18] to peak in 1993 at three times the initial level. The incidence

subsequently dropped, then resumed rising until 2001, and has levelled off since then. The rise, the peak and the subsequent drop in incidence occurred differentially by age groups. As a consequence of these changes in incidence, at 2009 rates one in eight men would be diagnosed with prostate cancer in his lifetime. The advance of diagnosis by more than 15 years suggested by these results is greater than other estimates of lead-time[19]. Mortality rates from prostate cancer were steady until 1977, rose until 1994 then dropped slowly, so the age-standardised rate is now about 20% less than in 1969. The greatest mortality reduction was 43.9% among men aged 70 to 74 years. The chance of dying from prostate cancer is much less than of being diagnosed: in 2009 it was 3.6%-one in 28 overall[1], but 75% of deaths occur among men over 75, and 56% over 80 years.

Comparison of secular changes in the incidence and mortality rates across the pre- and post-PSA implementation period suggests that PSA testing has influenced the apparent epidemiology of prostate cancer. The increased likelihood of diagnosis is unlikely to have occurred from a massive increase in the true incidence of prostate cancer in the population since 1969, when incident cases were usually identified on clinical grounds. Instead, prostate cancer is now being diagnosed at higher rates from among the large reservoir of undiagnosed prostate cancer[20,21], that would not develop into harmful disease in a man's lifetime (often termed overdiagnosis)[22] so the rise might be more properly called increase in discovered cancer. Before 1988, prostate cancer occurred mainly among older men. The increase in incidence prior to PSA testing can be ascribed to increased trans-urethral resection of the prostate (TURP) from about 1970 for benign hypertrophy (BPH), and higher number of pathology specimens examined, giving a greater chance of discovery of "cancers"[23,24]. The 1980s saw increased trans-rectal or perineal biopsies of suspicious areas using ultrasound guidance[25] with increases from 6 to 12 or more core biopsy specimens[23] to detect cancer as introduction of radical prostatectomy and newer radiation therapy gave hope for curative treatment[26]. Diagnostic patterns changed, with modification of Gleason grading[27,28], leading to higher diagnosis rates. Use of TURP declined, especially after introduction of alpha antagonists and 5-alpha-reductase inhibitors in 1993[23,26], which changed management of many men with BPH from surgical to medical therapy. Fewer TURPs likely reduced diagnoses of

"incidental" prostate cancer among older men because of less frequent microscopic examination. It has been argued that PSA testing revealed the prevalent and slow growing cancers, and thereafter incidence dropped because the reservoir had been depleted[17]. This speculation may be partly true, as when first available, PSA was often used by urologists to clarify urinary symptoms[3,29]. Thereafter, the drop in use of TURP likely accounts for reducing incidence in men over 70, while increasing use of PSA screening with recent emphasis on men as young as 40 years[30,31] causes continuing apparent increases in incidence among younger men.

The secular changes in prostate cancer mortality should be interpreted in the context of the slow rise noted from 1959[24]. Rates for the years 1969-1977 were 25 per 100,000, began rising slowly before the introduction of PSA testing, but then fell, declining below 1969 levels around year 2000. Advocates assert[17,31] that the decline in prostate cancer mortality observed since PSA testing began is evidence that screening is beneficial – but do not address the increase in mortality observed before screening was introduced and measure only from the peak. The fall began before PSA testing was widely used for screening, and the positive trials of PSA testing show that measurable effect cannot be expected until at least ten years after screening[30]. The most positive interpretation of the trials demonstrated an absolute risk reduction of 3 per 1000 in the screened group after 14 years. These men were aged 50 to 69 when screened, implying that mortality benefit might accrue among men aged 65 to 85 from 2005 onwards[30,32]. However, reductions in mortality were observed in men aged >55 beginning in the 1990s (see appendix). Since the uptake of PSA testing among Canadian men aged over 50 years was less than 50% by 2001[4], to reduce overall prostate cancer mortality by 30% the effect of screening and subsequent treatment would need to be much larger than observed in the trials.

Since there is no reason to believe there is any change in cancer biology, alternate explanations must be sought for the secular changes in prostate cancer incidence and mortality. Compared with "watchful waiting", prostatectomy reduced mortality by 6.1% in a trial of patients diagnosed before the PSA screening era[33] but these men mostly had palpable disease, more advanced than generally found after screening. Since the era of

screening, in the PIVOT trial, prostatectomy had minimal effect overall and 13% in a high-risk subgroup[34]. Thus while radical prostatectomy may reduce mortality by a small extent for men with clinically evident prostate cancer, it had no effect on mortality among those with cancer detected by screening (most of whom are not destined to die from prostate cancer[35]). It is possible that GnRH antagonists (another newer treatment) decrease deaths among those with advanced prostate cancer but not overall mortality, especially for men with early disease who may die earlier of cardiovascular disease instead[36-38]. Since less than 5% of men now diagnosed with early stage prostate cancer die from it[17,35], only small changes in the underlying cause of death among men with prostate cancer could substantially affect estimates of prostate cancer mortality. There may also be an attribution artefact: as more and more men were diagnosed with prostate cancer in the pre-PSA era, death from other causes may have been attributed to prostate cancer. At present, among men with a history of prostate cancer who have low PSA at the time of death, prostate cancer is likely to be categorised as an "other significant condition" -- instead of the cause, as might have occurred previously[36]. Thus reduced prostate cancer mortality in recent years may be due to reversal of the upward trend noted before PSA became available, to advances in medical and surgical treatment, or to secular changes in the cause of death attributed to men with known prostate cancer.

Overdiagnosis is "discovery of clinically irrelevant cancer that would not cause death"[39,40]. The effect of PSA screening on overdiagnosis is influenced by PSA threshold used, interval for screening, the age of men screened, the number of biopsies done, and how they are read. The incidence of prostate cancer in 1969 gives a conservative estimate of clinically important cancer. Overdiagnosis doubled the apparent incidence of prostate cancer between 1969 and 1990, then after PSA testing overdiagnosis rose to nearly three-fold higher in 1993 than in 1969. By 2007 total overdiagnosis increased apparent incidence by approximately 140% compared with 1969 – so 60% of incident cases diagnosed in 2007 were overdiagnosed. This represents over 15,000 men across Canada per year, many of who will consequently be overtreated – meaning that they will be given treatment that leads to harms but will not improve prognosis. "Watchful waiting" or "Active surveillance" decrease the physical harms of overtreatment[17] but these men still

carry the diagnosis of prostate cancer with all its psychological harm. It appears likely that most overdiagnosis today is driven by PSA screening.

Limitations

This is a descriptive national study using ecological data. First, these data depend upon the quality of cancer registry data, which in turn depends on the completeness and diagnostic quality of pathology for the incidence data, and upon the quality of death certification for the mortality data. Second, at the individual level, we are unable to link PSA testing and diagnosis with treatment and mortality. Finally, our estimates of overdiagnosis assume no changes in biology or true incidence of prostate cancer.

Comparison with other work

In the United States, secular changes in prostate cancer incidence share a common trajectory with Canada, Australia and New Zealand: but started and peaked higher, presumably because PSA testing was used more and earlier. Secular changes in mortality have been similar. By contrast, prostate cancer incidence in western European rose later, with peaks after 2005, yet the mortality began to drop in the early 1990s[41,42]. This is probably due to similar temporal trends in treatment patterns, but later uptake of PSA screening in these countries. These findings suggest that reduction in mortality has little relationship to screening.

Conclusions

If PSA testing leads to reductions in deaths from prostate cancer, one would expect the greatest reductions among men over 65, since screening trials demonstrate benefits for men screened at ages 50 to 69, after 10 to 15 years of follow-up. This process should have developed slowly over about 5 years, as the PSA test became more widely used, so major effects on mortality should not have been observed until about 2005. Instead, secular changes in mortality began in 1990 and are larger than could be expected from screening only about half the male population. Therefore it seems likely that the recently

observed reductions in prostate cancer mortality in Canada are mostly driven by factors other than the benefits of PSA screening.

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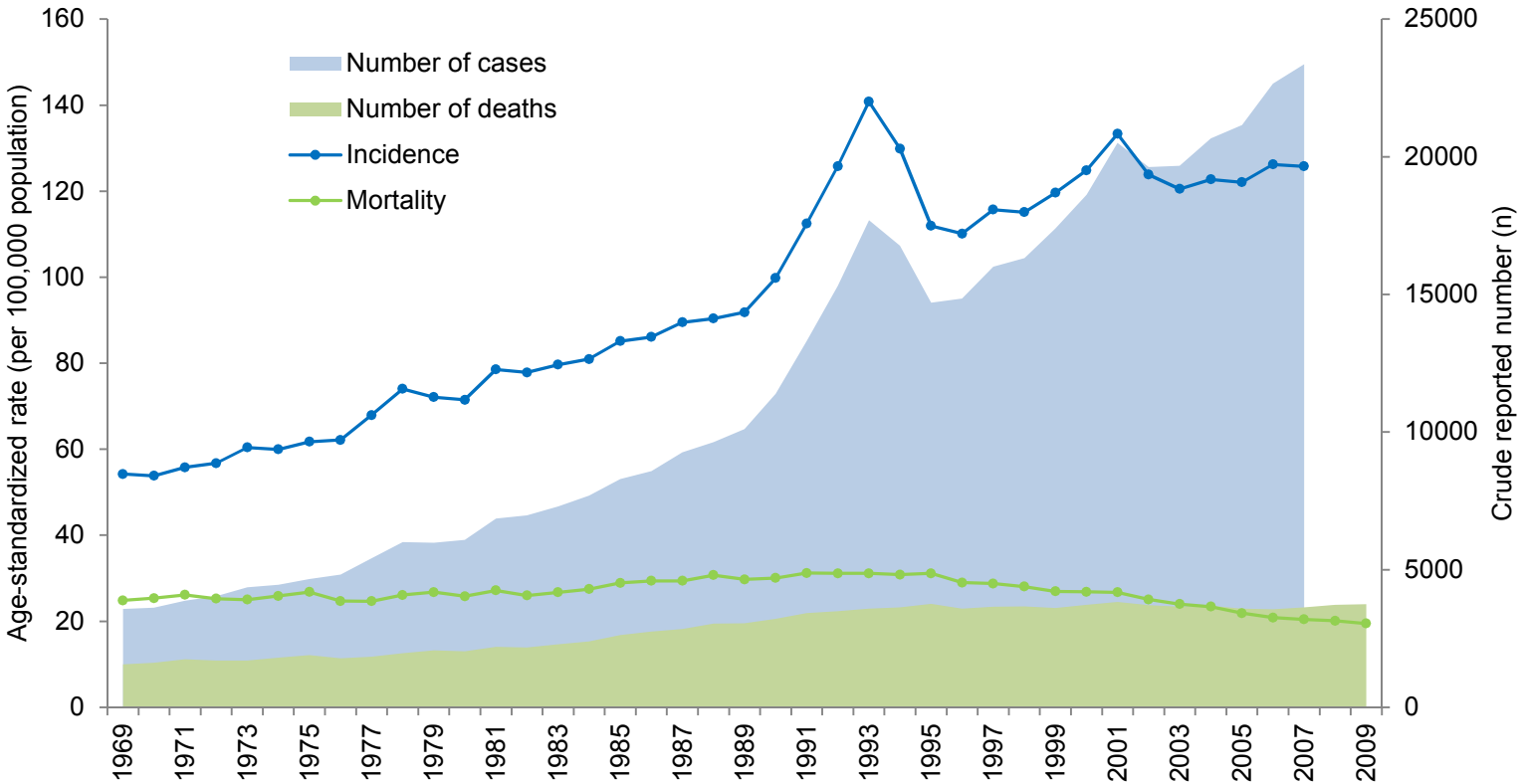

Figure 1. Age standardized incidence and mortality rates, and number of prostate cancer cases and deaths, 1969-2007/2009, Canada.

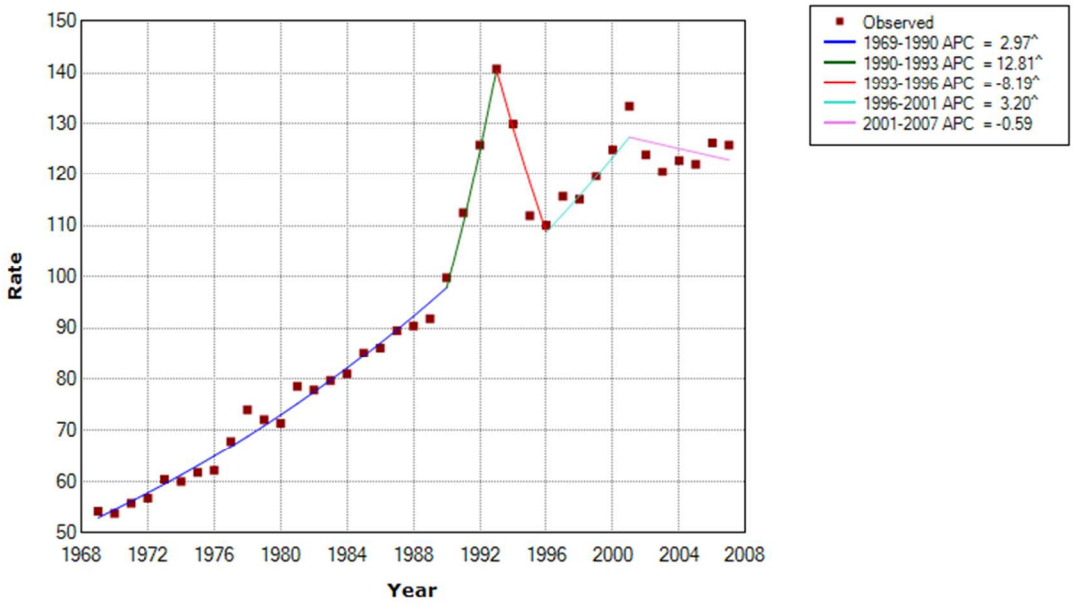

Figure 2. Age-standardized incidence rate (per 100,000) and annual percent change (APC) of prostate cancer incidence, 1969-2007, Canada.

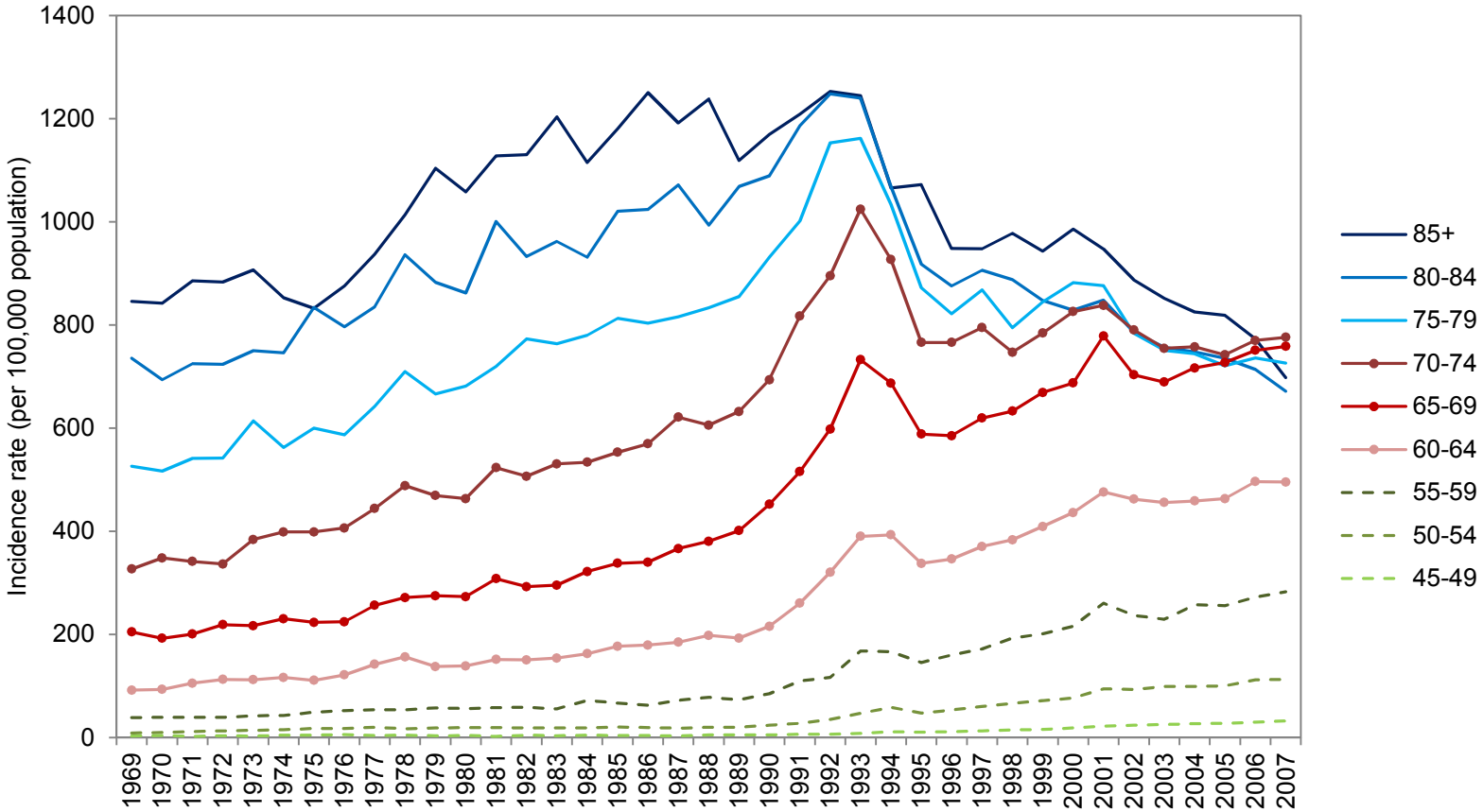

Figure 3. Incidence rates of prostate cancer by age group, 1969-2007, Canada.

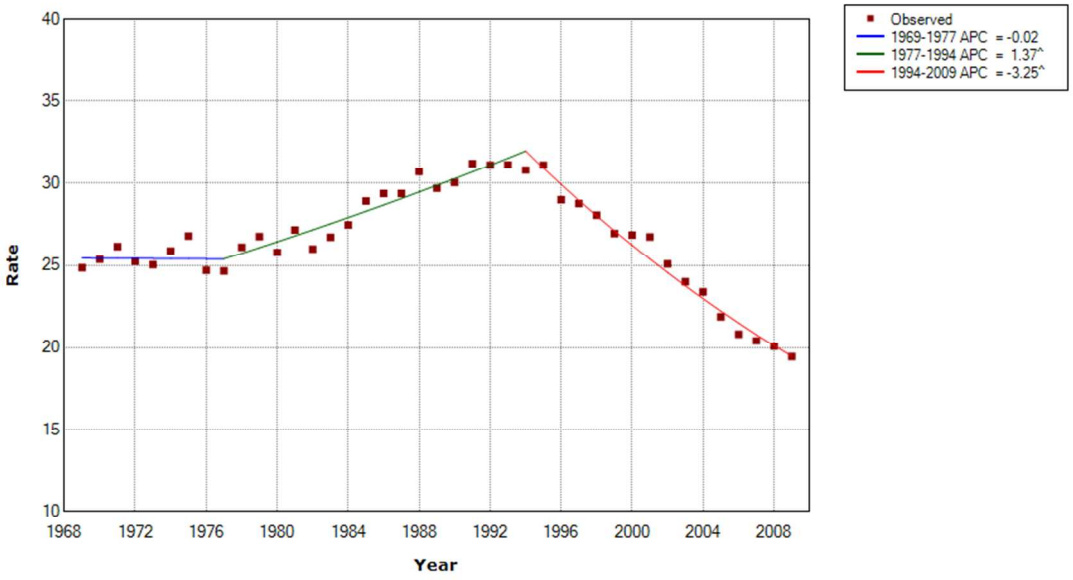

Figure 4. Age-standardized mortality rate (per 100,000) and annual percent change (APC) of prostate cancer mortality, 1969-2009, Canada

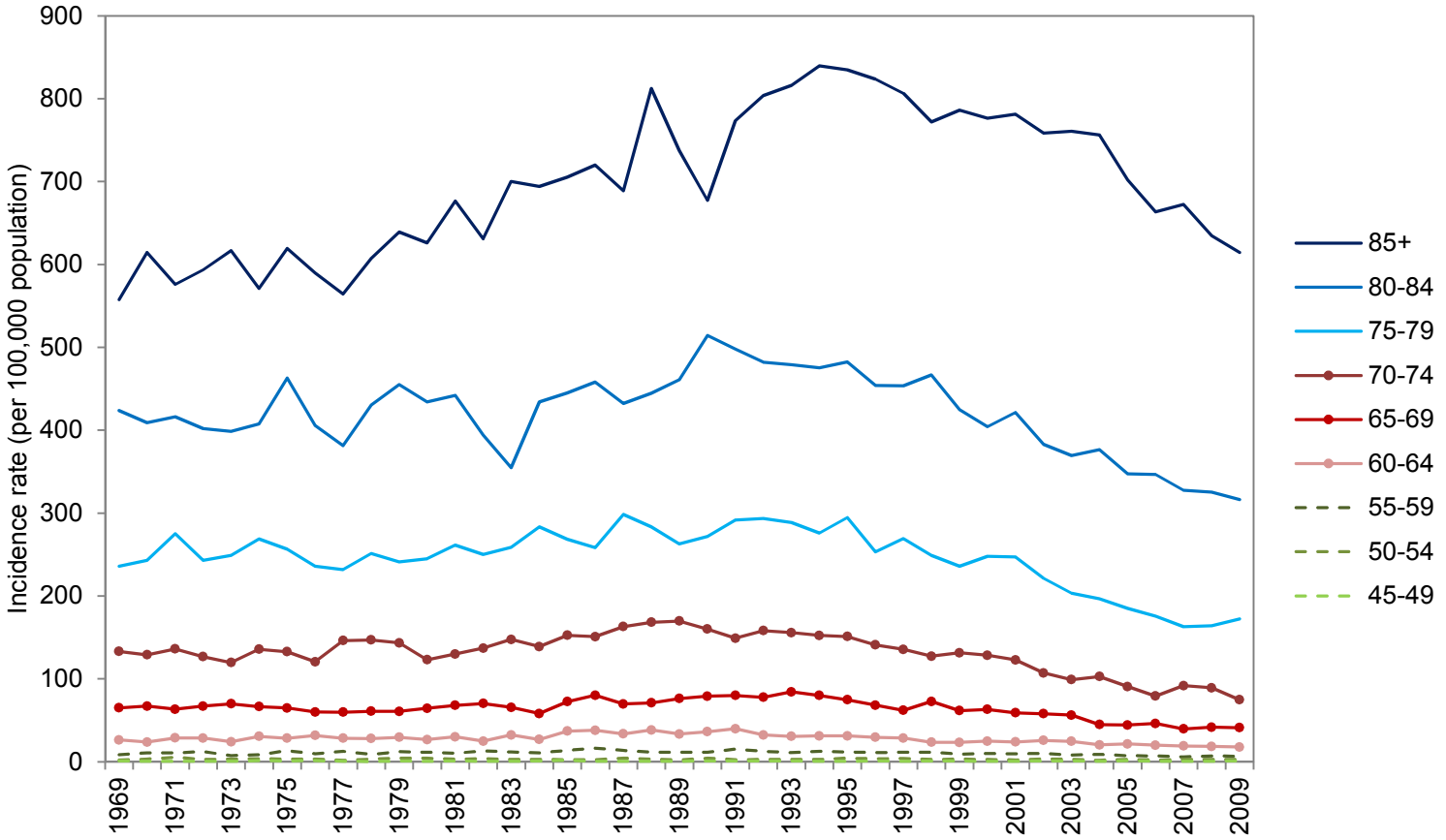

Figure 5. Mortality rates of prostate cancer by age group, 1969-2009, Canada.

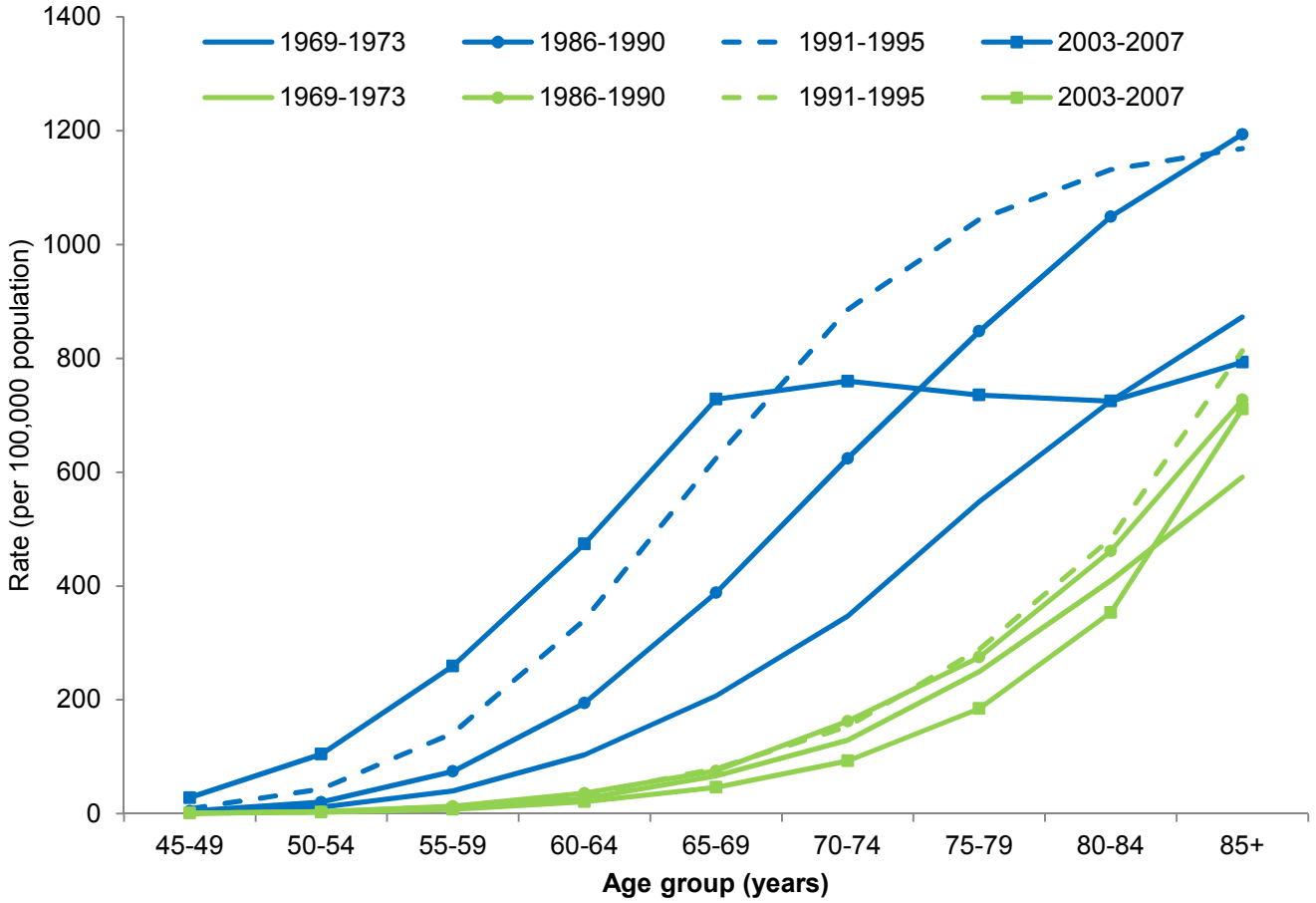

Figure 6. Comparison of incidence and mortality rates between the pre- and post-PSA eras. The pre-PSA period refers to 1969-1973; immediate pre-implementation period refers to 1986-1990; the implementation period refers to 1991-1995; and the post-PSA period refers to 2003-2007. Blue lines represent incidence and green lines represent mortality.

Supplementary File - Appendix

Prostate cancer epidemiology in the PSA era

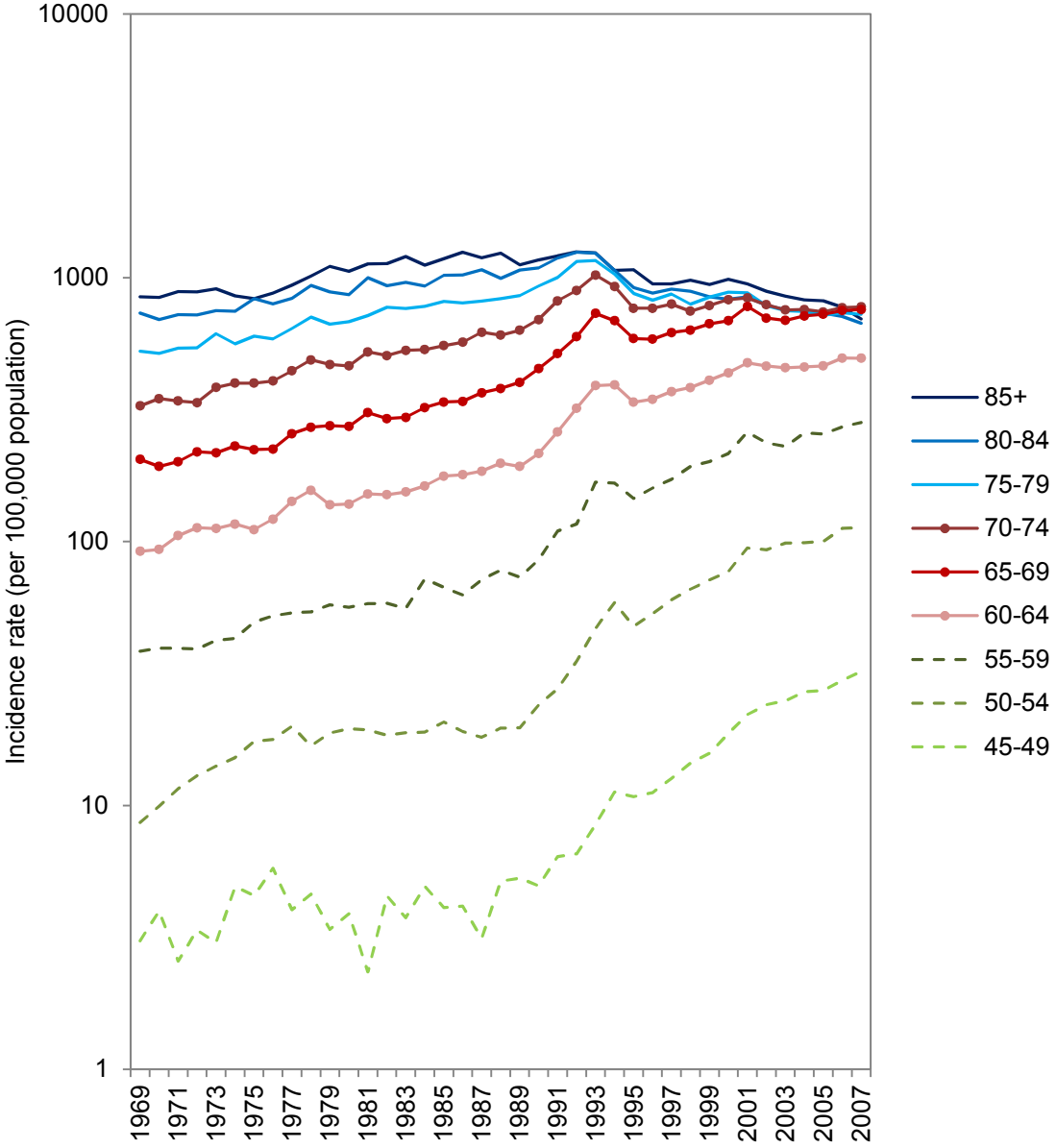

Figure 3b (Appendix). Incidence rates of prostate cancer by age group, 1969-2007, Canada. Logarithmic Y axis.

Supplementary File - Appendix

Prostate cancer epidemiology in the PSA era

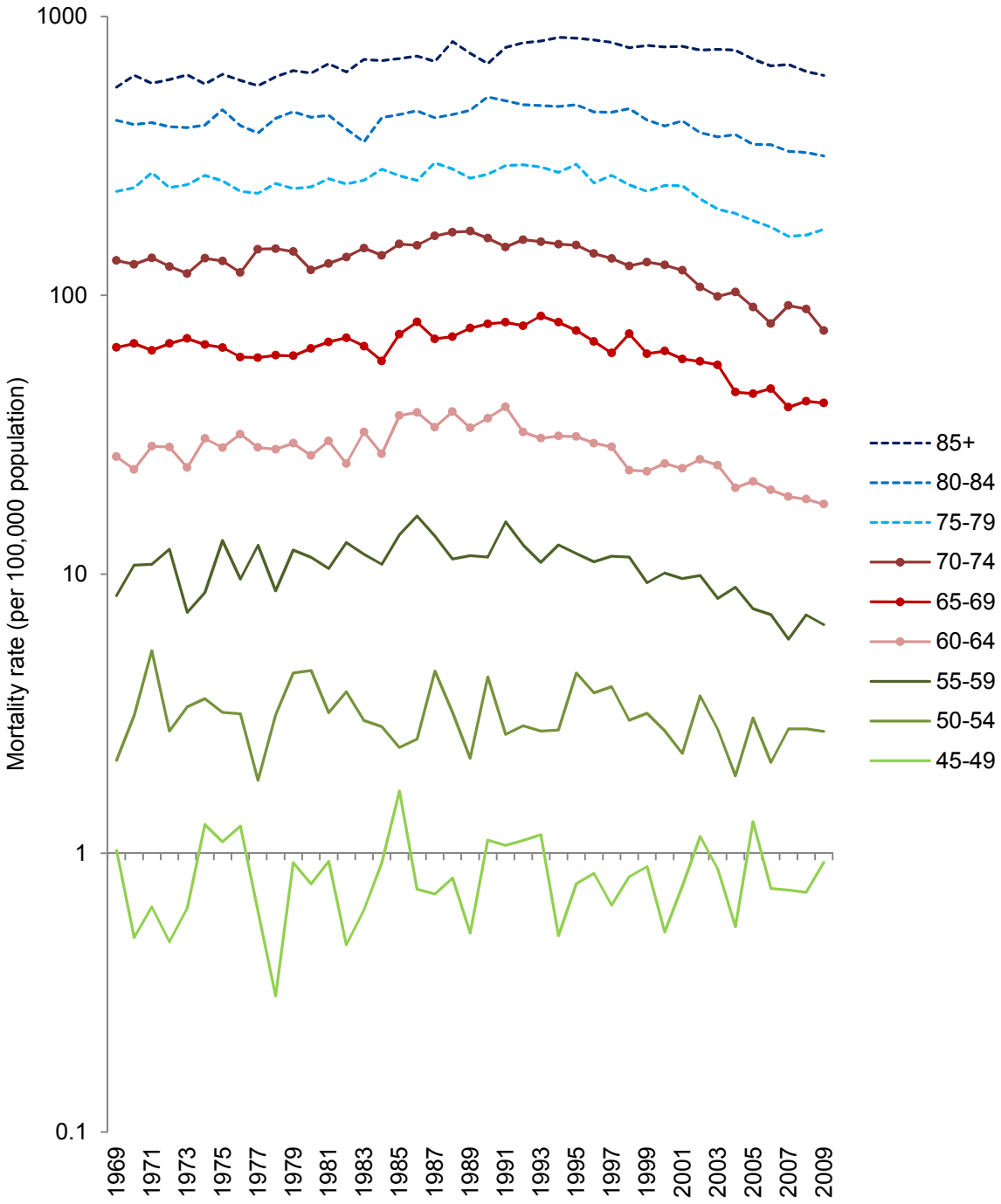

Figure 5b (Appendix). Mortality rates of prostate cancer by age group, 1969-2009, Canada. Logarithmic Y axis.