PSA screening and prostate cancer mortality

Research

Recherche

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Abstract

Background: Physicians have speculated that prostate-specific antigen (PSA) screening may be responsible for the reduction in prostate cancer mortality observed in the late 1990s. In order to test this hypothesis, we assessed the relation between the change in prostate cancer incidence in the early 1990s, attributed largely to PSA screening, and the subsequent change in prostate cancer mortality.

Methods: We divided the adult male population of Quebec aged 50 years and more into 15 birth cohorts. For each birth cohort, we computed the change in prostate cancer incidence between 1989 and 1993 and the change in prostate cancer mortality between 1995 and 1999. We then assessed the correlation between the changes in prostate cancer incidence and the subsequent changes in prostate cancer mortality by weighted linear regression. We also split up the study population into 15 regional populations and repeated the analysis described above.

Results: We found that even though most birth cohorts showed an increase in prostate cancer incidence and a subsequent decrease in mortality, the sizes of these changes were not inversely correlated (Pearson's r = 0.33, 1-sided p = 0.89). Similarly, in the regional population study, we found that a greater increase in prostate cancer incidence did not indicate a greater decline in mortality (Pearson's r = 0.13, 1-sided p = 0.68).

Interpretation: These results suggest that for our study population PSA screening was not associated with, and therefore cannot explain, the decline in prostate cancer mortality.

From the 1970s to the early 1990s, age-standardized mortality rates for prostate cancer increased steadily in Canada, making prostate cancer the second most common cause of death from cancer in men. In 1995, however, the prostate cancer mortality rate started to decline.[1–7] It has been speculated that prostate-specific antigen (PSA) screening, introduced into North American medical practice by the end of the 1980s, may be responsible for this decline in mortality.[4,8–10] However, many physicians and scientists consider that even if PSA screening was effective in preventing or postponing death from prostate cancer, it is too early to observe such an effect.

The effectiveness of screening with the PSA test to reduce prostate cancer mortality has not yet been established by randomized controlled trials. Moreover, the 2 studies that have attempted to establish whether the recent decline in prostate cancer mortality seen at the population level could be attributed to PSA screening did not support this hypothesis.[11,12]

Our aim was to test whether the declining trend in the prostate cancer mortality rate seen between 1995 and 1999 in the Quebec population could be attributed to PSA screening. We hypothesized that the changes in prostate cancer incidence between 1989 and 1993 were to a large extent attributable to PSA screening and that, if PSA screening had reduced prostate cancer mortality, an inverse association should be observed between the changes in incidence and mortality. Therefore, we expected to find a negative correlation showing the greater the increase in incidence due to PSA screening, the greater the decrease in prostate cancer mortality.

Methods

Study population

We conducted 2 separate analyses to assess whether the changes in prostate cancer incidence between 1989 and 1993 were related to the changes in prostate cancer mortality that occurred between 1995 and 1999. The year 1993 was chosen as the cutoff point for incidence because it corresponds to the peak of the epidemic period of prostate cancer incidence caused by improved detection using PSA screening. The year 1999 was selected as the cutoff point for the assessment of the mortality rate, because the latest data are available for that year.

For the first analysis, the study population was composed of 15 birth cohorts. Each birth cohort included all adult male residents of Quebec born in 2 successive years. The men in these cohorts were aged between 50 and 79 years in 1993 and between 56 and 85 years in 1999.

For the second analysis, the study population consisted of 15 geographically defined populations of Quebec. There are 16 administrative regions in Quebec, but we grouped together the regions of Côte-Nord and Nord-du-Québec because each has a small population. In this case, we used data from the male population aged 50–79 years to compute the changes in prostate cancer incidence rates and from the male population aged 55–84 years to compute the changes in prostate cancer mortality rates.

Data sources

The provincial Institut de la Statistique du Québec provided information about all deaths from prostate cancer for the years 1986 through 1999. The initial disease or condition that ultimately led to death (the underlying cause) was considered to be the cause of death. Data about all newly diagnosed cases of prostate cancer were obtained from the Quebec provincial cancer registry for the years 1986 through 1996. Information about the adult male population of Quebec by age and calendar year was extracted from Statistics Canada census publications. Age-standardized rates of prostate cancer incidence and mortality were computed using the 1991 Canadian population as the reference population.

Variables

The 2 variables computed were the magnitude of change in the prostate cancer incidence rate during the period 1989–1993 (the incidence difference) and the magnitude of change in the prostate cancer mortality rate during the period 1995–1999 (the mortality difference).

The difference in the prostate cancer incidence rates of the birth cohorts between 1989 and 1993 results from changes in prostate cancer detection (mainly by PSA screening) and the effect of 4 years of aging of the cohorts. Because we aimed to capture the degree of exposure of each cohort to PSA screening, we needed to exclude the effect of aging from the measure of incidence difference. To do so, we computed the difference between the 1993 observed prostate cancer incidence rate and an expected 1993 prostate cancer incidence rate. The expected rate was the rate that would have appeared in a given birth cohort, in 1993, if aging had explained most of the increase in incidence between 1989 and 1993. Therefore, the difference between the observed and the expected 1993 incidence rates captures the increase in prostate cancer incidence of each birth cohort, between 1989 and 1993, above that which could be explained by aging.

In order to obtain the expected 1993 prostate cancer incidence rate for each birth cohort, we built a predictive model. Using a Poisson distribution, we carried out a regression analysis of the number of incident prostate cancer cases by age and calendar year, in a generalized linear model.[13] The data used to derive the predictive model were provided by all birth cohorts of men living in Quebec who were aged 50–79 years during 1986–1989. This period was not affected by changes in medical practice with regard to prostate cancer screening, and aging explained most of the increase in incidence in the cohorts from one calendar year to the next. Thereafter, the expected incidence rate of each birth cohort for 1993 was computed using the parameter estimates of the predictive model. The difference between the 1993 observed and expected prostate cancer incidence rates was divided by the 1993 expected rate in order to obtain a relative difference in incidence rate. Therefore, if the observed rate is twice the expected rate, the relative difference in incidence rate equals 1.0 or 100%.

Similarly, for each birth cohort, we computed a relative mortality rate difference. It was the difference between the 1999 observed and expected mortality rates, divided by the 1999 expected rate. The expected 1999 mortality rate was calculated using the same method as described for incidence. The observations used to derive this predictive model were provided by all birth cohorts of men living in Quebec who were aged 56–85 years during 1992–1995.

For the geographically defined study population, the measure of the incidence difference was more straightforward. It was the difference between the 1993 age-standardized prostate cancer incidence rate and the mean age-standardized prostate cancer incidence rate for the years 1986–1989. We divided this rate difference by the mean 1986–1989 rate to obtain a relative incidence rate difference. Similarly, for each Quebec region, we computed the relative difference between the age-standardized 1999 prostate cancer mortality rate and the mean age-standardized prostate cancer mortality rate for the years 1992–1995. Because the age-standardized prostate cancer incidence and mortality rates were very stable during the years 1986–1989 and 1992–1995 respectively, we used the 4-year mean rates instead of a 1-year rate for greater precision.

Analysis

In both study populations, we assessed the association between the relative incidence difference and the relative mortality difference by weighted linear regression. To test the hypothesis that there might be an inverse relation between the 2 variables, 1-sided p values were calculated for Pearson's product-moment correlation coefficient (r).

Results

Quebec experienced a 47% increase in its age-standardized prostate cancer incidence rate between 1989 and 1993, as it rose from 336 cases per 100 000 man-years to a peak of 493 cases per 100 000 man-years (Fig. 1). The age-standardized rate of prostate cancer mortality in Quebec decreased by 15% between 1995 and 1999, that is, from 124 deaths per 100 000 man-years to 105 deaths per 100 000 man-years (Fig. 1).

Fig. 2A shows that the 15 birth cohorts had increases of 22%–178% in prostate cancer incidence rates in 1993, compared with 1989. It also shows that 11 of the 15 birth cohorts experienced a decline in the prostate cancer mortality rate in 1999, compared with 1995. These declines ranged from –3% to –50%. The scatter plot of the relative incidence and mortality differences in the 15 birth cohorts is presented in Fig. 2B. Weighted linear regression analysis of these 2 variables resulted in a Pearson's product-moment correlation coefficient of 0.33 (1-sided p = 0.89, determination coefficient [r^2] = 10.9%). Therefore, even though most cohorts had a positive incidence difference and a negative mortality difference, the sizes of the differences are not negatively correlated. This means that, within the 15 birth cohorts, a greater increase in prostate cancer incidence is not associated with a greater decline in mortality. For example, the cohort born in 1942/43, which had a larger increase in incidence than the one born in 1914/15 (177% v. 31%), did not experience a larger decrease in mortality (–26% in both cohorts) (Fig. 2B).

Fig. 3A shows that the 15 Quebec regions experienced a 44%–155% elevation in the age-standardized prostate cancer incidence rate between 1989 and 1993. In addition, all but 2 regions had an age-standardized prostate cancer mortality rate in 1999 that was lower than their 1995 corresponding rate. The rates ranged from –12% to –57%. Although we anticipated that large centres would have a greater increase in incidence, because PSA screening was more likely to have been adopted earlier, the 2 largest urban areas, Montreal (region 6) and Quebec City (region 3), did not show a greater increase in incidence from 1989 to 1993 than the other Quebec regions. Fig. 3B shows the scatter plot of relative incidence and mortality differences in the 15 Quebec regions. Weighted linear regression analysis of these 2 variables resulted in a Pearson's product-moment correlation coefficient of 0.13 (1-sided p = 0.68, r^2 = 1.7%). Therefore, as in the birth cohorts, a greater increase in prostate cancer incidence within the 15 Quebec regions did not indicate a greater decline in mortality. For example, the Quebec City area showed a greater increase in incidence than the Montreal area (67% v. 44%) but experienced a smaller decline in mortality (–12% v. –16%).

Interpretation

The age-standardized incidence rate of prostate cancer in the male population of Quebec, aged 50 years and more, rose sharply from 1989 to 1993, whereas the age-standardized mortality rate slowly decreased from 1995 to 1999. This increase in incidence was presumably caused by the detection of preclinical cases following the introduction of PSA screening. By dividing the study population into 15 birth cohorts and into 15 regional populations, we aimed to assess whether the rise in incidence was correlated with the fall in mortality.

Our results do not show the anticipated inverse correlation between the differences in incidence rate and the differences in mortality rate. In fact, in both study populations, even if the rate differences were in the expected direction (increase in incidence and decrease in mortality), the sizes of the changes were not negatively correlated. In other words, we did not observe that a larger increase in incidence, due to PSA screening, was associated with a larger fall in mortality 6 years later.

These results need to be considered with caution. First, we relied on a single year for the increase in incidence (1993) and a single year for mortality reduction (1999). In fact, the change in incidence of any single year should be
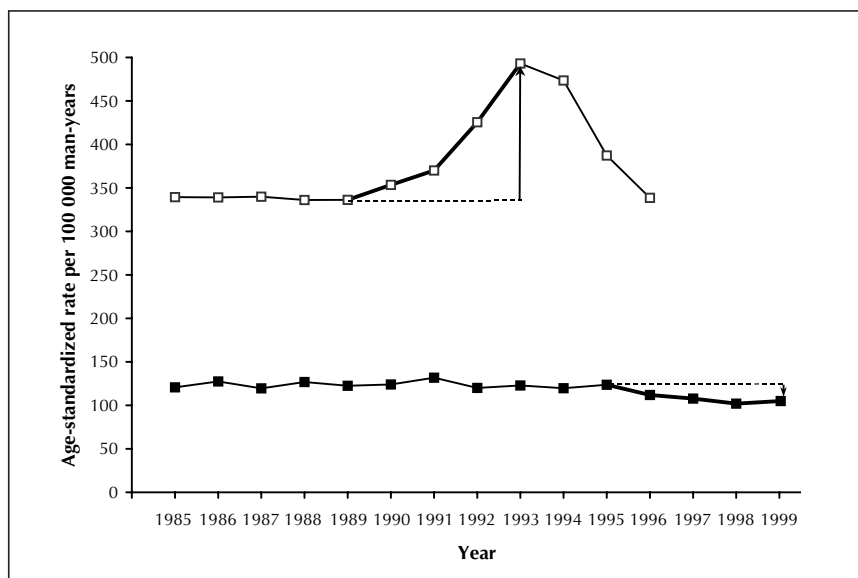

Fig. 1: Age-standardized incidence rates (white squares) and mortality rates (black squares) for prostate cancer among men in Quebec, aged 50–85 years.

reflected downstream over several years. Moreover, we did not measure directly the degree of exposure to PSA screening. There is, however, a clear consensus among health researchers that the changes in prostate cancer incidence rates in the early 1990s are good indicators of the extent to which PSA testing was used for screening purposes.[14,15] Second, because prostate cancer incidence and mortality rates are strong functions of age, the correlation performed with the birth cohorts might be distorted by age, even though we took aging into account while computing the rate differences. Nevertheless, the correlation test performed with the rate differences of the 15 regions is not limited by this, because in this case all the rates were age-standardized. Finally, it is probable that the completeness of the Quebec cancer registry with regard to this cancer decreased over the study period, because individuals with prostate cancer were being managed increasingly as outpatients and the Quebec cancer registry relies exclusively on hospital discharge sources. This underestimate of prostate cancer cases should affect all age groups and all regions equally.

Other researchers have studied the possible relation between PSA screening and the decline in the rate of prostate cancer mortality and have suggested that there is no link between the intensity of screening activities and the recent decrease in prostate cancer death rates. Etzioni and colleagues addressed the question of whether the PSA tests conducted in the late 1980s and early 1990s could provide a reason for the decline in prostate cancer mortality observed from 1992 through 1994 in the United States.[11] Using simulation models, they showed that if PSA screening reduced prostate cancer mortality by 20% over 10 years (as postulated in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[16]) and if the mean lead time (time by which diagnosis is advanced by screening) was close to 3 years, PSA screening could explain most or all of the decline in prostate cancer mortality since 1991 in the United States. However, using the hypothesis of a 5-year lead time, which better corresponds to

our current knowledge about the mean lead time associated with initial PSA screening[17] (the lead time for repeat screens is much longer), PSA screening could not explain the recent decline in prostate cancer mortality rate.[11]

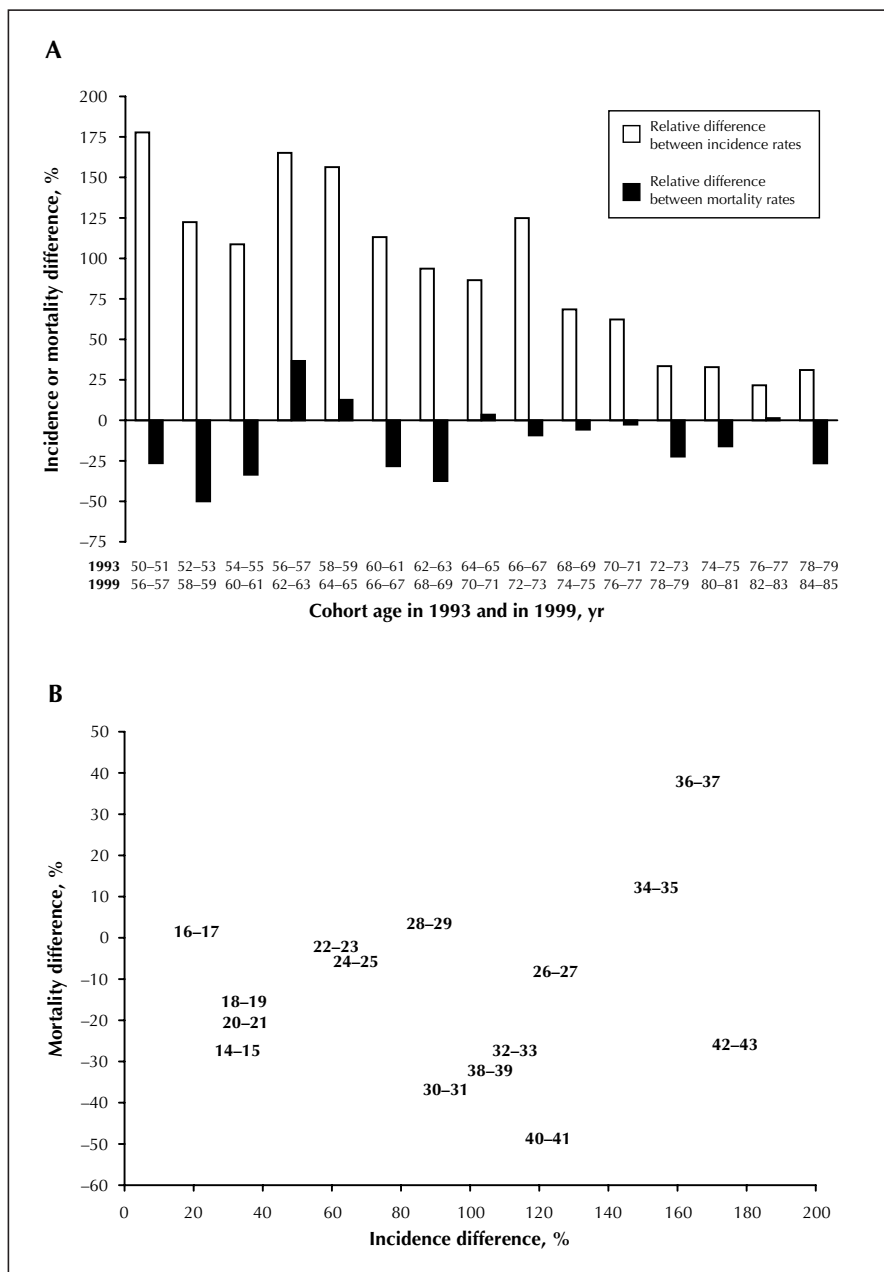In another study, Oliver and colleagues compared data

Fig. 2: (A) Relative differences between observed and expected prostate cancer 1993 incidence rates (incidence difference) (white bars) and relative differences between observed and expected prostate cancer 1999 mortality rates (mortality difference) (black bars) for each birth cohort (born from 1914/15 to 1942/43). **(B)** Scatter plot of the incidence differences and the mortality differences in the 15 birth cohorts. The numbers in the figure correspond to the last 2 digits of the years of birth of the men in each cohort (e.g., 22–23 refers to the cohort of men born in 1922/23 and therefore aged 70–71 years in 1993 and 76–77 years in 1999). Weighted Pearson's product-moment correlation coefficient = 0.33 (1-sided $p = 0.89$)

from the United States with those from England and Wales with regard to age-standardized prostate cancer incidence and mortality rates.[12] The authors noted that in spite of very divergent trends in incidence reflecting a different use of PSA testing, a similar reversal in secular mortality trends was observed in the United States, England and Wales between 1991 and 1997. They, thus, concluded that falling death rates in the United States did not, for the moment, support claims for the effectiveness of prostate cancer screening.

Randomized trials that address the issue of the efficacy of screening for prostate cancer are underway in Europe and in North America.[18] Only one group has published preliminary results, and these suggest that PSA screening markedly reduced prostate cancer mortality up to 5 years after screening.[19] However, in this report, most of the results did not come from the comparison of screened and unscreened groups as randomized, and they may reflect more bias than real efficacy.[20,21] Moreover, when the groups formed by randomization were compared, prostate cancer mortality rates were identical in the 2 groups.[21]

Therefore, in accordance with the observational studies described here, our results do not support the hypothesis that the present decline in prostate cancer mortality is attributable to PSA screening. If PSA screening is effective in preventing or postponing death from prostate cancer, its impact at a population level has yet to be felt. Moreover, there may be other explanations for the recent decline in prostate cancer mortality, consisting primarily of changes in disease management and in hormonal treatment of advanced disease.[22,23]
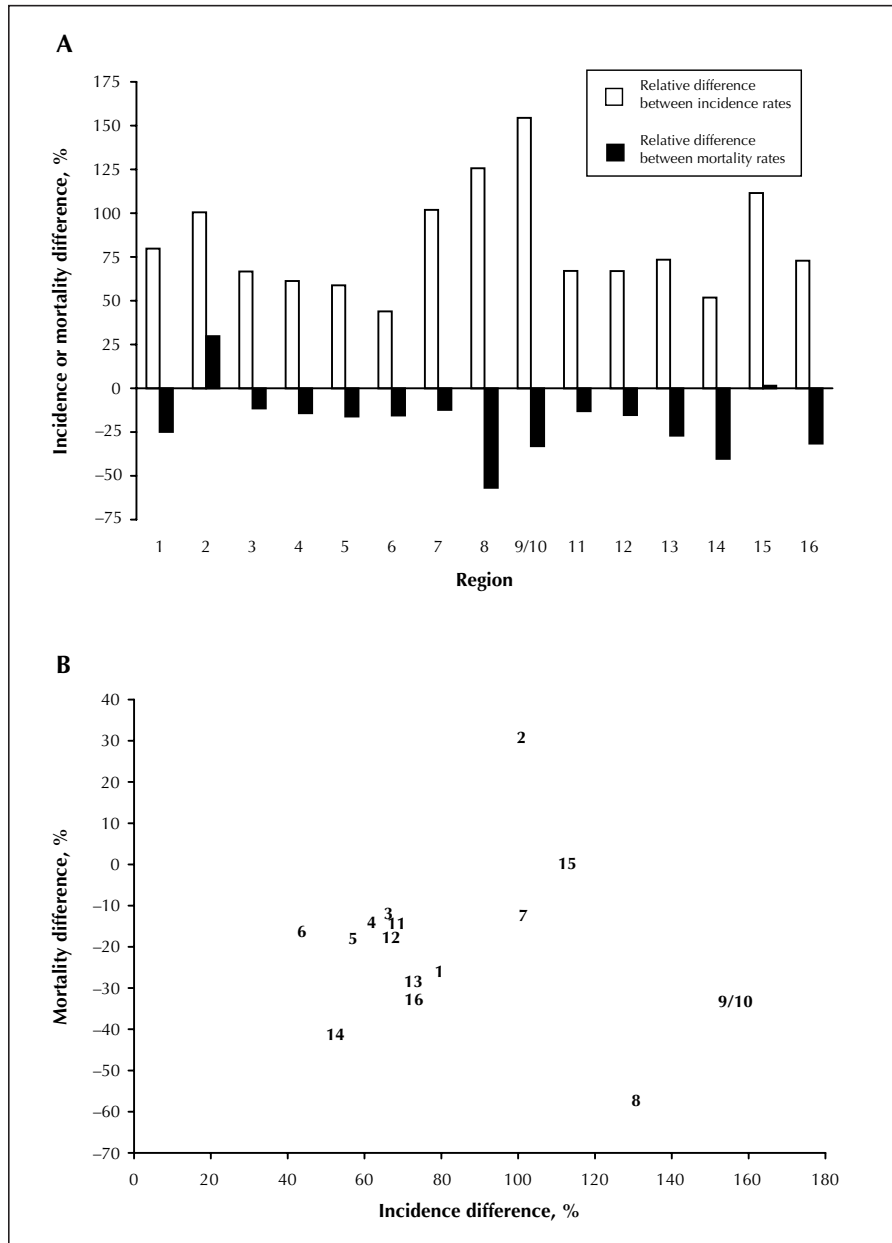
Fig. 3: (A) Relative differences between 1993 and mean 1986/89 age-standardized prostate cancer incidence rates (incidence difference) (white bars) and relative differences between 1999 and mean 1992/95 age-standardized prostate cancer mortality rates (mortality difference) (black bars) for each region. Codes for regions: 1 Bas St-Laurent; 2 Saguenay; 3: Quebec City; 4 Mauricie et Centre-du-Québec; 5 Estrie; 6 Montreal; 7 Outaouais; 8 Abitibi; 9/10 Côte-Nord and Nord-du-Québec; 11 Gaspésie; 12 Chaudière-Appalaches; 13 Laval; 14 Lanaudière; 15 Laurentides; 16 Montérégie. Weighted Pearson's product-moment correlation coefficient = 0.13 (1-sided *p* = 0.68). (B) Scatter plot of the incidence differences and the mortality differences in the 15 regions. The numbers in the figure correspond to the Quebec regions as outlined above.

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