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# Population-based outcomes of men with a single negative prostate biopsy: Importance of continued follow-up among older patients

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## Abstract

**Purpose:** To determine in Ontario-based men with a single negative transrectal ultrasound-guided prostate biopsy the long-term rates of prostate cancer-specific mortality, diagnosis, and treatment; number of repeat biopsies; and predictors of prostate cancer diagnosis and mortality.

**Materials and methods:** This was a population-based cohort study, using data from linked, validated health administrative databases, of all Ontario-based men with a negative first biopsy between January 1994 and October 2014. Patients were followed from time of first biopsy till death, administrative censoring, or end of study period. Cumulative incidence functions were used to calculate the study outcomes' cumulative incidences. Univariable and multivariable regression analyses using Fine and Gray's semiparametric proportional hazards model were used to assess predictors of prostate cancer diagnosis and mortality.

**Results:** The study cohort included 95,675 men with a median age of 63.0 years. Median follow-up was 8.1 years. The 20-year cumulative rates of prostate cancer-specific mortality and diagnosis were 1.8% and 23.7%, respectively. Men ages 70 to 79 and 80 to 84 at initial biopsy had 20-year prostate cancer-specific mortality cumulative rates of 3.2% and 6.4% respectively. The 20-year cumulative rate of receiving radical prostatectomy was 7.6%. Higher socioeconomic status and urban residence were associated with higher diagnosis risks yet lower prostate cancer-specific mortality risks.

**Conclusions:** This is the first population-based study assessing long-term cancer outcomes in North American men with a single negative transrectal ultrasound-guided prostate biopsy. Following a negative initial biopsy, 23.7% of men are still diagnosed with and 1.8% die of prostate cancer within 20 years. Cancer-specific mortality outcomes are significantly worse in older men, with prostate cancer mortality rates several times higher than the rest of the population. 

*Keywords:* Prostate cancer; Diagnosis; Mortality; Health services research; Administrative database; Sensitivity and specificity

## 1. Introduction

Prostate cancer (CaP) is the most commonly diagnosed visceral cancer in men, with lifetime diagnosis and

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mortality rates of 14% and 2.6%, respectively [1]. Transrectal ultrasound-guided prostate biopsy (TRUS-Bx) is currently the gold standard for diagnosing CaP. The performance characteristics of this procedure are far from ideal, with reported false-negative rates in the 20% to 30% range [2,3]. Consequently, men with negative TRUS-Bxs may still be subjected to repeat biopsies, get diagnosed with CaP, receive treatment for CaP, and potentially even die of CaP.

Men with a negative biopsy represent a unique cohort, and numerous ancillary testing (e.g., imaging modalities/biomarkers) are used to risk-stratify this cohort [4,5]. The long-term health outcomes of Ontario-based men with a single negative TRUS-Bx have yet to be defined at a population level. Data describing long-term diagnosis, treatment, and most significantly, mortality rates of such patients, particularly for men over age 70 as prostate-specific antigen (PSA) testing sharply declines [6] and guidelines recommend against CaP screening over this age [7], are thus needed. We thus set out to determine the cumulative incidences of these health outcomes in men with a single negative TRUS-Bx in Ontario, Canada between 1994 and 2014.

## 2. Material and methods

### 2.1. Study design, setting, and participants

Population-level data from health administrative databases housed at the Institute for Clinical and Evaluative Sciences was used to identify all Ontario-based men aged 40 years and older with a single negative TRUS-Bx between January 1, 1994 and October 1, 2014. Ontario employs a publicly funded health care system enabling these administrative databases to store medical records of all universal health coverage-eligible Ontario residents [8]. Patient-level information from these databases is linkable using unique, encoded identifiers.

Our cohort was identified using data from the Ontario Cancer Registry (OCR), which has an accuracy of greater than 93% in identifying incident CaP cases [9,10], The Ontario Health Insurance Plan database, which tracks claims paid to physicians, laboratories, and out-of-province providers [11], and the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), which contains in-patient hospitalization data [12]. Men with a single negative TRUS-Bx were identified as those who had Ontario Health Insurance Plan billing codes for both a prostate biopsy and a transrectal ultrasound, no biopsy-associated CaP diagnosis in the OCR, and no treatment for CaP. A look-back window from January 1991 till date of cohort entry (minimum of 3 years) was implemented to ascertain that included TRUS-Bxs were truly the first negative biopsies and that men had no previous CaP diagnosis. Men were followed from the date of negative TRUS-Bx until death, last health services contact in Ontario, or end of the study period (December 31, 2015). Men with missing data were excluded. Ethics approval was obtained from the participating institutions.

### 2.2. Study outcomes

Our primary outcome was CaP-specific mortality. Secondary outcomes were cumulative rates of: other-cause (i.e., non-CaP) mortality, CaP diagnosis, receiving radical prostatectomy, definitive radiotherapy, and androgen deprivation therapy (ADT injection or bilateral orchiectomy), as well as predictors of CaP diagnosis and CaP mortality.

### 2.3. Study variables and data sources

CaP was considered the cause of death if it was noted as the immediate cause of death on the patient's death certificate, obtained via the Office of the Registrar General. CaP diagnosis was defined as having either an OCR record of CaP or having received treatment for CaP, if no OCR record was present. This definition was used to ensure that any tumor registry-missed cases were captured as patients occasionally may be treated without a histological diagnosis.

Patient age, socioeconomic status (derived from the individual's residential postal code), area of residence (urban vs. rural), and comorbidity status, quantified using the Collapsed Ambulatory Diagnostic Groups score (derived from the Johns Hopkins Adjusted Clinical Groups System [13]), all at time of index biopsy, were evaluated as predictors of both CaP diagnosis and mortality. Variable database sources and codes used to identify procedures/variables are listed in Appendix Table 1. These definitions have been previously used in other similar studies [14,15].

### 2.4. Statistical methods

Continuous variables were described using medians and interquartile ranges (IQR), whereas categorical variables were characterized using proportions. Competing risks analyses were implemented to examine the risk of each study outcome where death from other causes was treated as the competing event. The cumulative probabilities for our study outcomes were estimated using cumulative incidence functions, which, in contrast to Kaplan Meier curves, account for the occurrence of competing events [16].

Univariable and multivariable regression analyses using Fine and Gray's semiparametric proportional hazards model were used to assess predictors of CaP diagnosis and mortality, with the subdistribution hazard ratio used to assess the strength of association between predictor and outcome. Statistical significance was set at a 2-sided $P$ value of 0.05. Statistical analyses were performed using R version 3.3.1.

## 3. Results

### 3.1. Patient population

Our cohort included 95,675 men with a single negative TRUS-Bx. The study flow chart documenting all steps used to derive our final cohort is illustrated in Appendix Figure 1. Median age at index biopsy was 63.0 years (IQR: 57.0–70.0), with 73.3% in the 50 to 69 years age category (Table 1). Median follow-up time was 8.1 years (IQR: 4.5–12.3).

### 3.2. Prostate cancer diagnosis

The total number of CaP diagnoses was 15,690 (16.4%). The CaP diagnosis cumulative rates at 5, 10, 15, and 20 years were 12.7% (95% confidence interval [CI]: 12.5–12.9%), 18.4% (18.1–18.6%), 21.7% (21.3–22.0%), and 23.7% (23.3–24.2%), respectively (Fig. 1). The 20-year CaP diagnosis cumulative incidences by age group are presented in Table 2 and Fig. 2.

31.5% of patients underwent at least 1 repeat biopsy. Among patients who had a subsequent histological diagnosis via repeat biopsy, 8,928 (71.3%) were diagnosed after a single repeat biopsy, 2,429 (19.4%) after a second repeat biopsy, and 1,158 (9.3%) after 3 or more repeat biopsies.

### 3.3. Mortality outcomes

There were a total of 16,153 (16.9%) deaths in our cohort, with CaP the cause of death in 629 patients (0.66% of total cohort). The CaP-specific mortality cumulative incidences at 5, 10, 15, and 20 years of follow-up were 0.16% (95% CI 0.14–0.19%), 0.57% (0.51–0.63%), 1.3% (1.2–1.4%), and 1.8% (1.6–2.0%), respectively. The 20-year other-cause mortality rate was 45.9% (45.0–46.8%, Fig. 3).

The 20-year cumulative incidences of CaP deaths by age group are listed in Table 2, with rates successively increasing from 0.2% in the 40 to 49 to 6.9% in the 80+ age group (Fig. 4, Appendix Table 2).

Table 1
Study cohort baseline characteristics ($n = 95,675$).

| | |
|---|---|
| Median age, years (interquartile range) | 63.0 (57.0–69.0) |
| Age categories | |
| 40–49 | 5131 (5.4%) |
| 50–59 | 28835 (30.1%) |
| 60–69 | 41310 (43.2%) |
| 70–79 | 18417 (19.2%) |
| 80+ | 1982 (2.1%) |
| Median Collapsed Ambulatory Diagnostic Groups Score (interquartile range)[a] | 16 (7–22) |
| Socioeconomic status quintile[b] | |
| 1 (lowest) | 13730 (14.4%) |
| 2 | 17064 (17.8%) |
| 3 | 18582 (19.4%) |
| 4 | 20817 (21.8%) |
| 5 (highest) | 25187 (26.3%) |
| Area of residence | |
| Urban | 88170 (92.2%) |
| Rural | 6932 (7.8%) |

[a] Collapsed Ambulatory Diagnostic Groups score ranges from 0 to 100, with higher scores indicating greater comorbidity.
[b] Socioeconomic status missing for 295 patients.

### 3.4. Predictors of prostate cancer diagnosis and mortality

Age at index biopsy, socioeconomic status, and area of residence (urban vs. rural) were all significant predictors of CaP diagnosis and CaP mortality, both on univariable and multivariable regression analyses (Table 3). On multivariable regression analysis, age at index biopsy, categorized into 5 distinct age groups, was significantly associated with increased risks of both CaP diagnosis and mortality. Compared to patients in the 40 to 49 years age group, those in the 70 to 79 and 80+ age groups had CaP diagnoses risks 1.96 (1.69–2.28) and 2.00 (1.60–2.49) fold higher. As for CaP-specific mortality, men in the 70–79 and 80+ age groups had mortality risks 14.48 (5.40–38.88) and 37.18 (13.56–101.92) folds higher compared to those in the 40–49 years age group, respectively (Table 3).

Increasing socioeconomic status was associated with a higher risk of CaP diagnosis ($P = 0.04$), yet a lower CaP-specific mortality risk ($P = 0.04$). Compared to patients living in a rural area, those living in an urban area had an 11% significantly higher risk of CaP diagnosis ($P = 0.02$), yet a 31% significantly lower risk of dying from CaP ($P < 0.001$, Table 3).

### 3.5. Treatment outcomes

Among the 15,690 patients diagnosed with CaP, the primary treatment modality was radical prostatectomy in 5,401 patients (34.4%), definitive radiotherapy only in 2,326 patients (14.8%), ADT only in 2,139 patients (13.6%), and radiotherapy plus ADT in 877 patients (5.6%), with the remaining 4,947 patients (31.5%) receiving none of the aforementioned therapies (possibly underwent watchful waiting/active surveillance) (Appendix Table 3).

The 20-year cumulative incidences of receiving radical prostatectomy, definitive radiotherapy, and ADT were 7.6% (95% CI: 7.4–7.8%), 6.1% (5.8–6.4%), and 7.2% (6.9–7.6%), respectively (Fig. 5). Following surgery, 19.0% (17.6–20.4%) and 13.9% (11.2–16.7%) received radiotherapy and ADT, respectively, within 20 years. The 20-year cumulative incidence of receiving ADT following definitive radiotherapy was 18.7% (15.3–22.0%).

### 3.6. Health outcomes in men ages 70 to 79 and 80 to 84

The 20-year cumulative incidences of CaP diagnosis and mortality in those ages 70 to 79 were 23.2% and 3.2%, respectively (Table 4). Of the 18,417 patients in this age

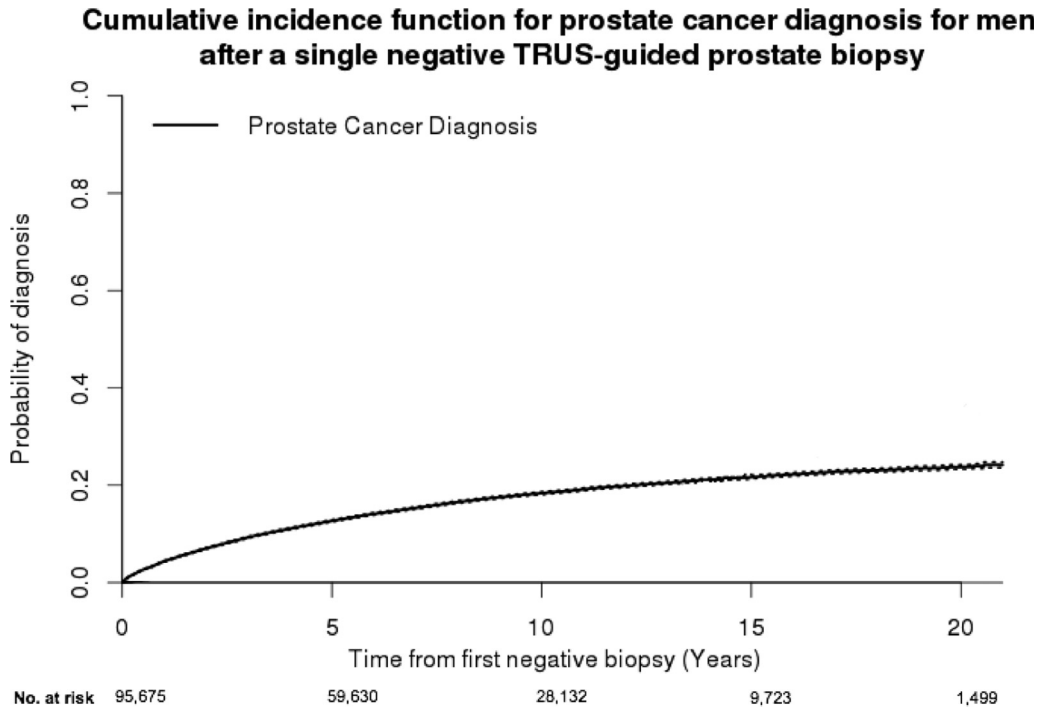



Fig. 1. Cumulative incidence functions for prostate cancer-specific and other-cause mortalities in men with a single negative TRUS-guided prostate biopsy.

group, 5,063 (27.5%) underwent at least 1 repeat biopsy. Of the 3,369 patients diagnosed with CaP, 273 (8.1%) underwent radical prostatectomy as the primary treatment modality, 871 (25.9%) underwent definitive radiotherapy, 999 (29.7%) received ADT, and 1,266 (37.6%) underwent watchful waiting/active surveillance.

The 20-year cumulative incidences of CaP diagnosis and mortality in those ages 80 to 84 were 21.1% and 6.4%, respectively (Table 4). Of the 1,594 men in this age group, 205 (12.9%) underwent at least 1 repeat biopsy. Of the 283 patients diagnosed with CaP, 25 (8.8%) underwent radical prostatectomy or definitive radiotherapy as the primary treatment modality, 134 (47.3%) received ADT, and 124 (43.8%) underwent watchful waiting/active surveillance.

## 4. Discussion

This is the first population-based study examining long-term health outcomes of North American men, specifically Ontario-based men, with a single negative TRUS-Bx. Our cohort of 95,675 men with a single negative TRUS-Bx is the largest series of such patients to date, and our median follow-up of 8.1 years is also the longest.

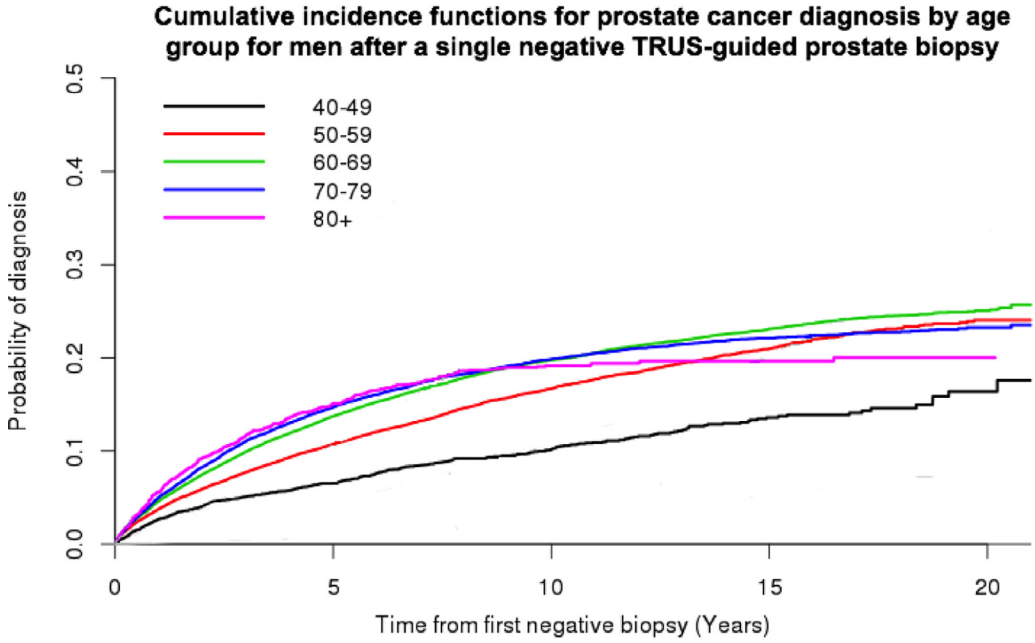
Despite already having had a negative TRUS-Bx, 1.8% eventually died of CaP within 20 years, which is only 31% lower than the current lifetime risk of 2.6% [1]. This strongly suggests that such men need to be diligently followed after a negative TRUS-Bx. As for CaP diagnosis, 23.7% of men were subsequently diagnosed, with 71.3% diagnosed on the first repeat biopsy.

The CaP-specific mortality rates in older men were considerably higher, as 3.2% of those ages 70 to 79 and 6.4% of those ages 80 to 84 died of CaP within 20 years. Physicians' natural tendency is to adopt a relatively less strict follow-up approach in older men following a negative biopsy and to forgo definitive treatment, as appropriate. This was reflected in our results whereby only 27.5% and 12.9% of men in the 70 to 79 and 80 to 84 age groups,

Table 2
Twenty-year prostate cancer diagnosis and mortality rates following a single negative TRUS-Bx by age group

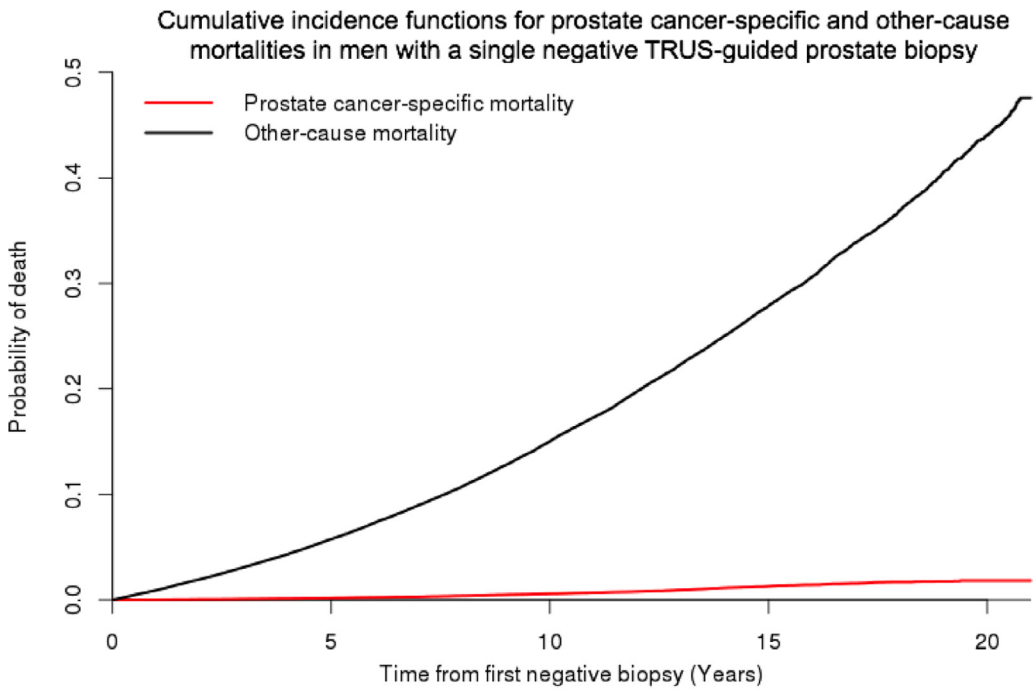
| Prostate cancer diagnosis rates | | | | | |
|---|---|---|---|---|---|
| Age group (years) | 40–49 | 50–59 | 60–69 | 70–79 | 80+ |
| Diagnosis rates (95% CI) | 16.4% (16.1–16.7) | 24.1% (23.8–24.4) | 24.0% (23.6–24.3) | 23.3% (23.0–23.6) | 20.0% (19.7–20.3) |
| **Prostate cancer mortality rates** | | | | | |
| Age group (years) | 40–49 | 50–59 | 60–69 | 70–79 | 80+ |
| Mortality rates (95% CI) | 0.2% (0.2–0.2) | 0.7% (0.7–0.7) | 1.7% (1.6–1.8) | 3.2% (3.1–3.3) | 6.9% (6.7–7.1) |

Abbreviation: CI = confidence interval.




| No. at risk | | | | | |
|---|---|---|---|---|---|
| 40-49 | 5,131 | 3,791 | 2,278 | 1,006 | 186 |
| 50-59 | 28,835 | 19,851 | 10,140 | 3,539 | 575 |
| 60-69 | 41,310 | 26,425 | 13,337 | 5,007 | 815 |
| 70-79 | 18,417 | 12,158 | 6,528 | 2,412 | 411 |
| 80+ | 1,982 | 1,422 | 930 | 428 | 81 |

Fig. 2. Cumulative incidence functions for prostate cancer diagnosis by age group for men after a single negative TRUS-guided prostate biopsy.




| No. at risk | | | | | |
|---|---|---|---|---|---|
| | 95,675 | 68,672 | 35,153 | 12,612 | 1,979 |

Fig. 3. Cumulative incidence functions for prostate cancer-specific mortality by age group for men after a single negative TRUS-guided prostate biopsy.

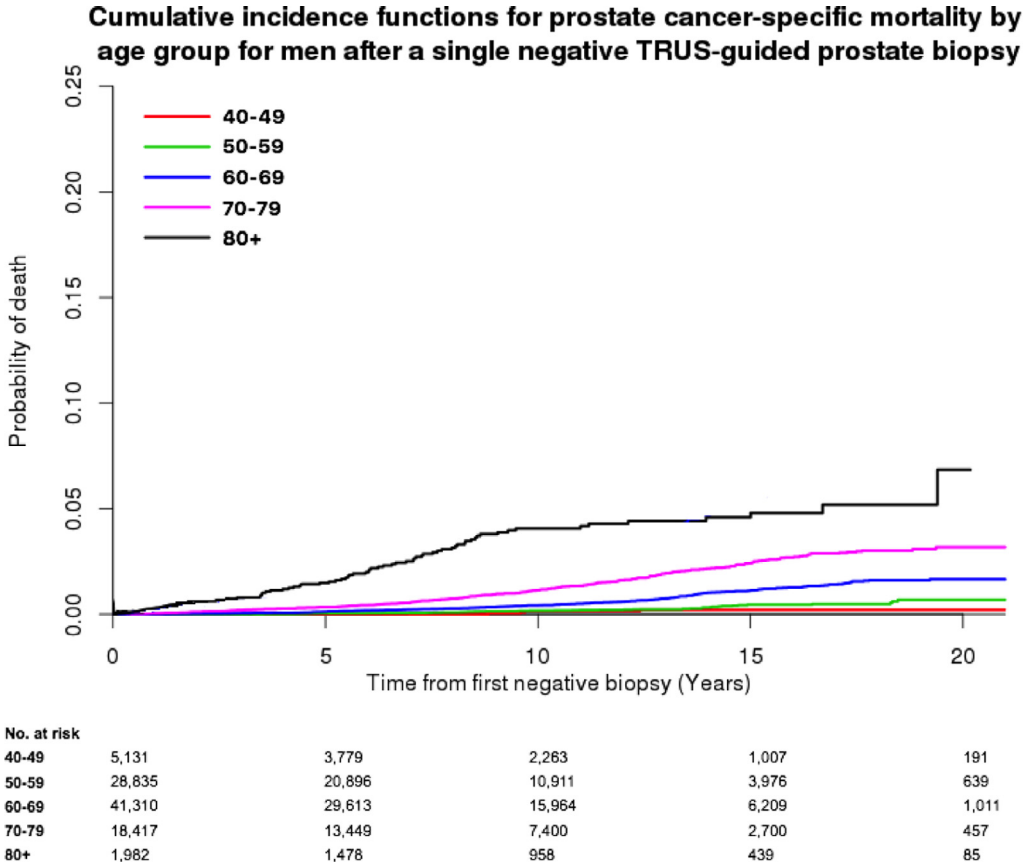



Fig. 4. Cumulative incidence function for prostate cancer diagnosis for men with a single negative TRUS-guided prostate biopsy.

respectively, underwent at least 1 repeat biopsy, compared to 31.5% overall in the study cohort. Likewise, among those diagnosed with CaP, only 34% and 8.8% of those ages 70 to 79 and 80 to 84 at initial biopsy underwent potentially curative therapy (i.e., radical prostatectomy or radiotherapy), respectively, compared to 54.8% overall in the study cohort. These results strongly suggest that adoption of more aggressive approaches, both with regards to looking for cancer following a negative biopsy as well as subsequently treating patients with curative intent, may be warranted in medically fit older patients. Although these patients may have shorter life expectancies [17] and radical prostatectomy and radiotherapy are not without complications [18,19], the fact remains that older men have more aggressive, potentially lethal forms of cancer [20] that may necessitate radical treatment and that the current management approaches are not sufficiently preventing CaP deaths in these men. Future studies that prospectively assess long-term survival benefits of radical therapy in such men are needed to reach definitive conclusions.

Patients of higher socioeconomic status and those living in an urban area had higher CaP diagnosis, yet significantly lower CaP-specific mortality risks. As such patients are known to follow-up more closely with their physicians [21–23], these results suggest that superior mortality outcomes in these subgroups may be related to increased follow-up. However, no conclusions can be drawn without analysis that directly evaluates the impact of frequency of physician follow-up on diagnosis, treatment, and mortality outcomes, while accounting for confounders that influence frequency of follow-up such as PSA levels, clinical stage, and family history.

Klemann et al. recently evaluated long-term cancer outcomes in 27,181 Danish men with a benign initial TRUS-Bx, with a median follow-up of 5.9 years [24]. Their reported 20-year CaP-specific mortality cumulative rate of 5.2% was almost 3-fold higher than our reported rate of 1.8%. Conversely, their 20-year CaP diagnosis cumulative rate of 11% was less than half of ours (24%). These results strongly suggest the presence of geographic variations in CaP screening, diagnosis, and/or management. As mentioned by Klemann et al., the uptake of PSA screening in Denmark has historically been slower compared to North American countries. Thus, it is likely that an elevated PSA level was a more frequent indication for a biopsy in our cohort compared to the Danish population, whose patients were comparatively more likely to have had a positive rectal exam or positive urinary signs/symptoms as an indication, leading to these patients having a significantly higher pretest risk of disease compared to our patients. This was clearly reflected in the percentages of first TRUS-Bxs that were positive, whereby 55% of all first biopsies in the Danish cohort were positive compared to 42% in

Table 3
Predictors of prostate cancer diagnosis and mortality (using Fine and Gray's semiparametric proportional hazards model)

| Variable | Univariable regression | | | Multivariable regression | | |
|---|---|---|---|---|---|---|
| | sHR | 95% CI | *P* value[a] | sHR | 95% CI | *P* value[a] |
| **Prostate cancer diagnosis** | | | | | | |
| Age (40–49 as reference) | | | <0.001 | | | <0.001 |
| 50–59 | 1.85 | 1.71–1.99 | <0.001 | 1.72 | 1.48–1.99 | <0.001 |
| 60–69 | 2.26 | 2.14–2.38 | <0.001 | 2.05 | 1.77–2.38 | <0.001 |
| 70–79 | 2.12 | 2.01–2.23 | <0.001 | 1.96 | 1.69–2.28 | <0.001 |
| 80+ | 2.08 | 1.95–2.21 | <0.001 | 2.00 | 1.60–2.39 | <0.001 |
| Socioeconomic status (lowest as reference) | | | 0.03 | | | 0.04 |
| 2 | 1.09 | 0.98–1.20 | 0.10 | 1.02 | 0.94–1.12 | 0.61 |
| 3 | 1.13 | 1.03–1.25 | 0.02 | 1.09 | 1.00–1.19 | 0.04 |
| 4 | 1.07 | 0.97–1.18 | 0.12 | 1.04 | 0.95–1.13 | 0.39 |
| 5 | 1.15 | 1.05–1.27 | 0.01 | 1.10 | 1.01–1.19 | 0.02 |
| Urban residence (vs. rural) | 1.07 | 1.01–1.13 | 0.03 | 1.11 | 1.01–1.22 | 0.02 |
| Collapsed Ambulatory Diagnostic Group score | 1.00 | 0.98–1.02 | 0.88 | 1.00 | 0.99–1.01 | 0.93 |
| **Prostate cancer-specific mortality** | | | | | | |
| Age (40–49 as reference) | | | | | | <0.001 |
| 50–59 | 2.18 | 0.79–6.04 | 0.13 | 2.10 | 0.76–5.82 | 0.15 |
| 60–69 | 6.36 | 2.37–17.08 | <0.001 | 6.28 | 2.34–16.88 | <0.001 |
| 70–79 | 14.67 | 5.46–39.38 | <0.001 | 14.48 | 5.41–39.01 | <0.001 |
| 80+ | 37.52 | 13.68–102.90 | <0.001 | 37.18 | 13.62–102.54 | <0.001 |
| Socioeconomic status (lowest as reference) | | | 0.02 | | | 0.04 |
| 2 | 0.85 | 0.66–1.10 | 0.22 | 0.85 | 0.66–1.10 | 0.22 |
| 3 | 0.69 | 0.53–0.99 | <0.001 | 0.73 | 0.56–0.95 | 0.02 |
| 4 | 0.77 | 0.60–0.99 | 0.04 | 0.86 | 0.67–1.10 | 0.23 |
| 5 | 0.70 | 0.55–0.89 | <0.001 | 0.80 | 0.62–1.02 | 0.07 |
| Urban residence (vs. rural) | 0.65 | 0.51–0.83 | <0.001 | 0.69 | 0.53–0.83 | <0.001 |
| Collapsed Ambulatory Diagnostic Group score | 1.01 | 1.01–1.02 | <0.001 | 1.00 | 0.99–1.01 | 0.89 |

Abbreviations: CI = confidence interval; sHR = subdistribution hazard ratio.
[a] Wald test.

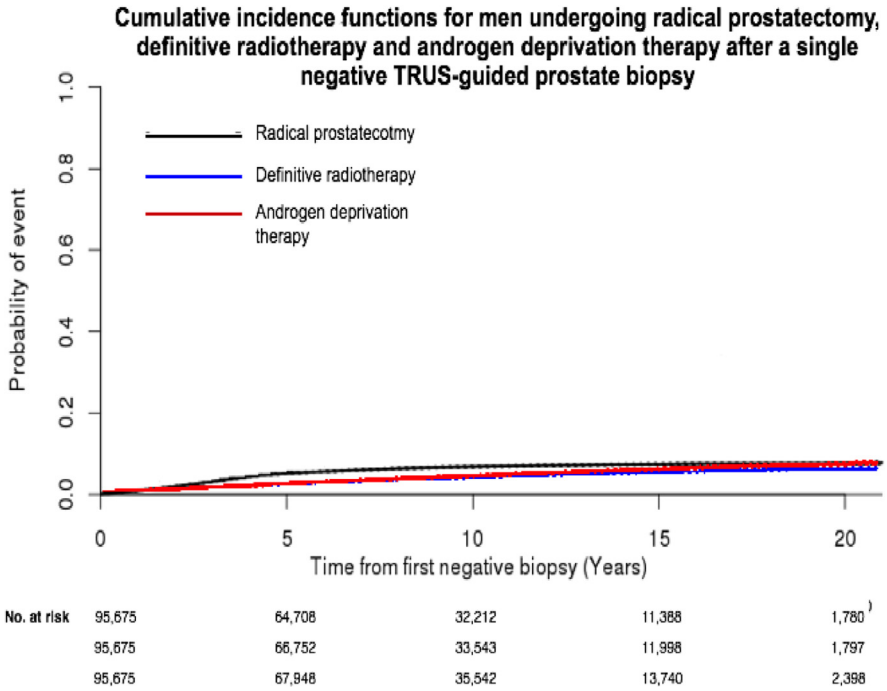



Fig. 5. Cumulative incidence functions for men undergoing radical prostatectomy, definitive radiotherapy and androgen deprivation therapy after a single negative TRUS-guided prostate biopsy.

Table 4
Cancer outcomes in men ages 70 to 79 and 80 to 84 at date of single negative transrectal ultrasound-guided prostate biopsy

| Number of years since initial biopsy | 5 | 10 | 15 | 20 |
|---|---|---|---|---|
| 70–79 y at index biopsy ($n$ = 18,417) | | | | |
| Number of patients who completed follow-up | 12,158 | 6,528 | 2,412 | 412 |
| Total number of CaP diagnoses | 2,542 | 3,180 | 3,337 | 3,369 |
| Cumulative incidences of CaP diagnosis (95% CI) | 14.7% (14.7–14.7) | 19.9% (19.8–20.0) | 22.1% (21.8–22.3) | 23.2% (22.7–23.7) |
| Total number of CaP deaths | 56 | 151 | 241 | 266 |
| Cumulative incidences of CaP death (95% CI) | 0.3% (0.3–0.4) | 1.1% (1.0–1.2) | 2.4% (2.2–2.6) | 3.2% (2.8–3.6) |
| 80–84 y at index biopsy ($n$ = 1,594) | | | | |
| Number of patients who completed follow-up | 711 | 450 | 214 | 40 |
| Total number of CaP diagnoses | 231 | 279 | 282 | 283 |
| Cumulative incidences of CaP diagnosis (95% CI) | 15.4% (15.3–15.5) | 19.3% (19.1–19.6) | 20.0% (19.6–20.5) | 21.1% (20.4–21.8) |
| Total number of CaP deaths | 22 | 51 | 54 | 57 |
| Cumulative incidences of CaP death (95% CI) | 1.3% (1.1–1.5) | 3.7% (3.4–4.0) | 4.3% (3.8–4.8) | 6.4% (5.6–7.2) |

our cohort [24]. It thus becomes obvious that the 2 cohorts are significantly different and this explains in large part the disparity in CaP mortality rates. Given the widespread use of PSA testing nowadays, which is likely to increase further given the recent changes in the U.S. Preventive Services Task Force recommendations regarding PSA screening [25], we believe that the results from our study cohort may be more reliably applicable to current patients with a negative TRUS-Bx.

Our study limitations include lack of prebiopsy PSA levels, clinical stage, family history, ethnicity, biopsy-derived Gleason score, number of sampled cores, and imaging information (e.g., multiparametric MRI). Given that our study inclusion period extended back to 1994, it is likely that a significant proportion of men in our cohort underwent a sextant biopsy as opposed to the currently used systematic 12-core biopsy protocol. Only 31.5% of men underwent a repeat biopsy, which is expected to have had a large influence on future diagnosis rates. The study cohort includes men from Ontario, Canada only, which limits its generalizability to other populations.

The number of men in the 80 to 84 years age group who completed 20 years of follow-up was relatively low ($n$ = 40). However, 10- and 15-year follow-up data for this age group were considerably larger (Table 4). These men likely had high-risk prebiopsy features that prompted a TRUS-Bx despite their older age. However, due to lack of PSA and rectal exam data, we were unable to quantify the prebiopsy characteristics of these patients. We must also note that we used data from health administrative databases, which by definition are not created for research purposes. Data from these sources are retrospective in nature and may be subjected to information biases/misclassification errors.

## 5. Conclusions

This is the first population-based study assessing long-term cancer outcomes in North American men with a single negative TRUS-Bx. Despite having a negative biopsy, 23.7% of such men are subsequently diagnosed with and 1.8% die of CaP within 20 years. Given the significantly higher CaP mortality rates in older men, more aggressive follow-up and treatment approaches may be warranted in medically fit older individuals with a history of a negative TRUS-Bx. Future studies that help discern which patients need continued follow-up following a negative TRUS-Bx, as well as the ideal frequency and modalities of follow-up, are needed to optimize care of men with a single negative TRUS-Bx.

## Conflicts of interest

Dr. Neil E. Fleshner has served as a consultant for Abbvie, Amgen, Astellas, Bayer, Ferring, Janssen, Sanofi, Hybridyne Imaging Technologies and has served on advisory boards for Abbvie, Amgen, Astellas, Bayer, Ferring, Janssen, and Sanofi.

The other coauthors have no relevant conflicts of interest to disclose.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.01.030.

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