# The natural history of prostate cancer

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**KEY MESSAGES**

- The long lead time for PCa development and progression makes it difficult to establish the true natural history.
- Challenges remain in the early detection of lethal cancers while sparing men with indolent disease the side effects associated with radical treatment.
- There have been improved efforts to establish widespread screening for PCa, with the number needed to treat now similar to breast cancer screening.
- Although there is strong evidence for chemoprevention of PCa with 5-alpha reductase inhibitors, uptake has not been widespread due to side effects.
- Modern imaging techniques, including PSMA-PET CT, are changing what we know about the natural history of advanced and recurrent PCa.

## HISTORICAL PERSPECTIVES

Prostate cancer was first described in 1853, by J. Adams at the London Hospital. In his report, the surgeon in question described the affliction as "a very rare disease"[1]. In the 21st century, prostate cancer represents the most commonly diagnosed cancer in men in the United States[2] apart from skin cancer, and the second most common cancer in men worldwide[3]. Reported prostate cancer incidence has increased dramatically across a relatively short period in history, bearing in mind that robust epidemiological information on cancer is a relatively new phenomenon and that J. Adams had no way of confirming his thesis that this was in fact a rare disease. From the 1930s onwards, autopsy studies began confirming the high rates of incidental prostate cancer in males[4–6]. Prostate cancer risk rises significantly with age, being rare before the age of 45 and exceedingly common after the age of 70[7]. During J. Adams time at the London Hospital (Figure 1) in the mid 19th century, life expectancy at birth in the U.K. was 42 years of age[5–7]. Thus the incidence of prostate cancer and indeed deaths from prostate cancer have risen alongside an approximate doubling of life expectancy during the intervening time period. Recording of cancer prevalence statistics is a relatively recent phenomenon, meaning that J. Adams did not have way to truly deduce the apparent rare nature of the disease during his time.

There is increasing evidence that lifestyle factors including eating a 'Western diet' are linked to a higher risk of prostate cancer[5–7]. Lastly, a significant portion of the increase in prostate cancer incidence in the last few decades can no doubt be attributed to the

introduction and uptake of widespread PSA testing globally. The correlation between community PSA testing and prostate cancer incidence is evident from the steady increase in cases in the US throughout the years following the introduction of PSA testing, with a decrease in incidence then coinciding with the recommendation against PSA screening in 2012[8]. However PSA testing is not the sole factor in the increase in incidence of prostate cancer. In Canada, a steady increase in prostate cancer can be seen in the decades prior to the introduction of PSA testing, with a sharp increase in the years after (Fig. 1)[9].

Our ability to diagnose and treat prostate cancer has improved exponentially in the past few decades, as has our understanding that many prostate cancers are not life threatening. We now know that low grade prostate cancer has been overtreated in past, and that we are still some way off being able to detect lethal prostate cancers at an early stage while sparing men with indolent cancers the significant side effect burden associated with treatment for prostate cancer.

## PROBLEMS WITH DESCRIBING THE TRUE NATURAL HISTORY OF PROSTATE CANCER

In the early 20th century, Hugo Hampton Young advocated for screening for prostate cancer in order to find the disease at an early stage with the intention of cure by radical surgery[10]. Early detection is now possible with PSA screening, albeit at the cost of over-detection of low grade tumors. Prostate cancer is a highly heterogenous disease, and the natural history varies according to tumor grade and likely according to inherent tumor biology beyond Gleason grade. Prostatic intraepithelial neoplasia is found in 20% men in the 4th decade of life and 44% men in the 5th decade of life in autopsy studies[11]. It is still unknown how many of these men would have progressed to experience symptomatic high grade prostate tumours.

Several longitudinal follow up studies have sought to answer this question. Albertsen et al[12] followed a cohort of men resident in Connecticut diagnosed with clinically localized prostate cancer between 1st Jan 1971 and 31st Dec 1984 for a median period of 24 years; prostate cancer mortality was found to be 33 per 1000 person years and men with low grade disease had a low risk of dying from the disease (6 deaths per 1000 person years). A Swedish cohort study[13] followed men with prostate cancer for three decades and found that the overall rate of death from prostate cancer was 17%, and that the risk of death from untreated low grade disease was 12.3%. The rate of progression of disease was reported as 20 events per 1000 person-years (95% CI, 14.7-27.2) and the rate of prostate cancer deaths was 17.9 deaths per 1000 person-years (95% CI, 13.0-24.6). 64% of men in this study remained untreated for prostate cancer throughout the entire study period. Long-term follow up of one of the largest active surveillance cohorts from University of Toronto reported a 1.5% rate of death from prostate cancer, which is comparable to the expected mortality rate for favorable risk patients treated with radical therapy[14]. In this cohort, there were 4 baseline variables which predicted overall survival: age ≥ 70 years (hazard ratio [HR], 2.87; 95% CI, 1.88 to 4.38; $p < 0.001$), transrectal ultrasonography volume (HR, 0.983; 95% CI, 0.973 to 0.993; $p = .001$), Gleason score ≥ 6 (HR, 1.70; 95% CI, 1.14 to 2.55; $p = 0.010$), and PSA values (log scale; HR, 1.52; 95% CI, 1.00 to 2.31; $p = 0.048$).

Another issue in accurately describing the natural history of prostate cancer occurs with reclassification of disease descriptors, as illustrated by the Will Rogers phenomenon[15]. Albertsen et al[16] suspected that the decrease in incidence of low grade prostate cancer could not be fully explained by the introduction of PSA testing, but that the reclassification of Gleason grade during this same period may have contributed. They re-examined histology slides from men diagnosed with prostate cancer during the years 1990-1992 with a contemporary pathologist blinded to the original Gleason grade. Contemporary Gleason scores were significantly higher, resulting in a Gleason score–standardized contemporary prostate cancer mortality rate which appeared to be 28% lower than standardized historical rates, even though the overall outcome was unchanged (mean score increased from 5.95 to 6.8; 95% CI = 0.79 to 0.91; p <0.001).

By the time the results of many longitudinal studies in prostate cancer are reported, treatment paradigms have completely evolved. The Albertsen study was performed in the pre-PSA era, and used acid-phosphatase to follow disease progression. The Swedish study from Popiolek et al was performed in the era of single line treatment only with androgen deprivation therapy (ADT) for metastatic prostate cancer. The landscape of intervention and therapeutics for prostate cancer is unrecognisable from that of 30 years ago.

## NATURAL HISTORY IN THE ERA OF PSA TESTING

Prostate specific antigen (PSA) was first isolated in 1979[17]. In 1986 the FDA approved its use for the monitoring of disease in men diagnosed with prostate cancer, and followed this in 1994 with approval for its use in conjunction with a digital rectal exam to aid in the diagnosis of prostate cancer. It was hoped that PSA could be used for screening to identifying men with prostate cancer at an early stage of disease. Several screening trials have been conducted with mixed results. The ERSPC study was a study of 162,243 men investigating prostate cancer screening with PSA against a control group who were not screened[18]. Screening increased detection of prostate cancer from 4.8% to 8.2% and reduced prostate cancer death by 20% (95% CI, 0.65 to 0.98; p=0.04). However the absolute difference in deaths was only 0.71 per 1000 men. The number needed to be invited to screening to prevent one prostate cancer death was 1410, however this decreased to 570 with longer follow up[19]. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial followed men diagnosed with prostate cancer at 10 centers in the USA, and did not find a significant difference in the rate death from prostate cancer between the screening and control group, with incidence of death per 10,000 person years of 2 in the screening group vs 1.7 in the control group (rate ratio, 1.13; 95% CI, 0.75 to 1.70)[20]. The lack of difference persisted at follow up to 17 years, and in addition a significant increase in low grade (Gleason ≤6) disease was found in the screening group compared to the control arm (RR=1.17, 95% CI: 1.11–1.23; p <0.001)[21]. A major criticism of this trial is the high levels of contamination in the control arm, with over half the men in the control undergoing PSA testing by the 6$^{th}$ year of the study. The Göteborg study was a population based prostate cancer screening trial of 20,000 men in Sweden, which reported an absolute cumulative risk reduction of death from prostate cancer at 14 years of 0·40% (95% CI 0·17–0·64), from 0·90% in the control group to 0·50% in the screening group, translating to a rate ratio for death from prostate cancer of 0·56 (95% CI 0·39–0·82;

p=0·002) in the screening group compared with the control arm[22]. 293 men needed to be invited to screening to prevent one death, which is comparable to breast cancer screening programmes. The Göteborg-2 study examined an MRI-guided biopsy pathway for men at risk of prostate cancer in a screening study[23]. Omission of systematic biopsy in favour of MRI guided biopsy only resulted in a 75% lower rate of diagnosis of clinically insignificant cancers with repeat rounds of screening (RR, 0.46; 95% CI, 0.33 to 0.64; P<0.001).

Although PSA is a highly sensitive test for the detection of prostate cancer, it has low specificity[24]. Several variations have been coupled to PSA testing to improve accuracy, including PSA velocity and PSA density[25]. However a normal PSA cannot definitively rule out prostate cancer. In the Prostate Cancer Prevention Trial (PCPT), 15% men with "normal" PSA (<4ng/ml) had prostate cancer diagnosed on sextant biopsy, although only 15% of these patients had Gleason ≥7[26].

In a large Swedish study, having a PSA below the median (0.68 µg/L) at age 45-49 resulted in a 0.09% 15-year risk of prostate cancer[27]. Similar results were seen in a US case-control study, with the majority of prostate cancers occurring in men who had PSA above the median in mid-life[28]. The authors advocate for longer screening intervals for such men, with heightened screening tactics for men with PSA above the median. 15 year outcomes from the PROTECT trial revealed that mortality from localized prostate was low (~3%) regardless of whether patients undertook active surveillance, surgery or radiation treatment[29].

## NATURAL HISTORY FOLLOWING TREATMENT

After radical treatment, men are no doubt keen to know the chances of their cancer returning. Grossfeld et al[30] determined pre-treatment predictors of disease recurrence in 547 men who underwent radical prostatectomy at the University of California, San Francisco (UCSF). They found PSA (47% vs 19% 5 year disease-free survival [DFS] for PSA cut-off 10ng/ml, p<0.05), Gleason score (45% 5-year DFS for score ≤7 vs 0% for score ≥8), ethnicity (OR for disease recurrence in men of black race 1.571 (95% CI 1.010–2.444; p=0.045) and percentage of biopsies cores positive for prostate cancer (OR 1.006; 95% CI 1.001–1.011; p=0.03) were predictive of disease recurrence post radical prostatectomy. The UCSF Cancer of the Prostate Risk Assessment (CAPRA) score was developed from a cohort of 1439 men who underwent radical prostatectomy. PSA, Gleason score, age, tumour (T) stage and % biopsy cores positive for cancer are weighted to give a score from 0-10, with approximately double the risk of recurrence for each increase in score by 2 points[31].

Unlike radiation or focal treatment, radical prostatectomy allows for accurate pathological analysis of the whole prostate gland, which can then inform disease prognosis. Eggener et al[32] developed a model to predict cancer specific mortality after radical prostatectomy at 4 academic centers in the USA. Overall prostate cancer specific mortality was 7% at 15 years, with primary Gleason pattern ≥4 (p<0.001) and seminal vesicle invasion (p<0.001) being highly predictive of mortality after radical prostatectomy. More recently, the group from UCSF produced the CAPRA-S score to include the additional accuracy provided by pathologic data after radical prostatectomy in predicting recurrence[33]. Variables found to be statistically significant in this predictive model include pre-operative PSA, pathological Gleason grade, surgical margin status, extra-prostatic extension, seminal vesicle invasion, and

lymph node status. Recurrence-free survival in this cohort was 78%, ranging from 85% for a CAPRA score of 0-1 (95% CI 73-92%) to 8% for a score of 7-10 (95% CI 0-28%), with each 2-point increase in score associated with a 2.4-fold increase in risk of recurrence.

## NATURAL HISTORY OF BIOCHEMICAL RECURRENCE

PSA is a highly reliable marker for monitoring disease recurrence after prostatectomy. Failure to reach an undetectable PSA level after prostatectomy is associated with poorer outcomes. A from Johns Hopkins study of 160 men who failed to achieve an undetectable PSA post prostatectomy, and who did not receive adjuvant treatment until there was documentation of metastasis, reported metastasis-free survival rates of 68%, 49% and 22% at 3, 5, and 10 years respectively, with a median time until occurrence of metastases of 5 years[34]. The authors reported pathological Gleason grade, seminal vesicle invasion, lymph node positivity and the slope of PSA rise as predictive of metastases, with PSA slope 3–12 months after undergoing prostatectomy was found to be the most powerful predictor of metastasis-free survival, followed by initial Gleason score and clinical stage (HR = 2.9, 2.6, and 2.0, respectively).

The natural history of biochemical recurrence is highly variable. The group at Johns Hopkins followed nearly 2000 men post prostatectomy and reported 85% metastasis-free survival for the entire cohort (95% CI, 76%-88%) at 15 years post-surgery[35]. 315 (15%) patients developed BCR, 34% of whom developed documented metastases during the study period, with median time to metastases of 8 years. In this study, time to BCR ($p<0.001$), PSA doubling time ($p<0.001$), and Gleason score ($p<0.001$) were predictive of the development of metastases. A retrospective cohort study of 379 who underwent radical prostatectomy at Johns Hopkins reported the 5-, 10-, and 15-year cause-specific survival from the respective time of biochemical recurrence as 93% (95% CI, 90%-96%), 73% (95% CI, 66%-79%), and 55% (95% CI, 41%-67%) respectively[36]. Median survival had not been reached after 16 years of follow up in this cohort. There is a lack of randomized controlled data for treatment options for men with BCR after prostatectomy. Several studies have attempted to report prognostic variables or propose treatment algorithms to inform which men need treatment for BCR[3738]. There appears to be an approximately equal risk of death from prostate cancer and competing causes in men with BCR[37].

## NATURAL HISTORY OF METASTATIC DISEASE

The concept of using castration to control the growth of prostate cancer dates back to the surgeon John Hunter in the late 18th century[39]. Huggins & Hodges were the first to report on the clinical benefit of castration in patients with prostate cancer[40], with Charles Huggins being eventually awarded the Nobel Prize in Medicine in 1966 for his use of systemic castration to treat prostate cancer. However, even in Huggins' early studies, he noted that in many cases complete tumor regression did not occur. Two problems with castration for prostate cancer became evident relatively quickly- development of castration resistant disease, and an increase in cardiovascular problems in castrate men[41].

Time to development of metastatic castrate-resistant prostate cancer (mCRPC) has been found to predictive of survival[42,43]. In the last two decades, multiple novel hormonal therapies have been developed to overcome mechanisms of castrate resistance in prostate

cancer. Treatment intensification is now also the standard of care for de novo metastatic hormone-sensitive prostate cancer (mHSPC). The emergence of combination systemic therapy targeting multiple hormone and signalling pathways is changing the natural history of metastatic prostate cancer, which is reflected in the increase in median overall survival in de novo metastatic prostate cancer[44].

## IATROGENIC PERTURBATION OF THE NATURAL HISTORY OF PROSTATE CANCER

There have been many efforts by the scientific community over the last several decades to influence the natural history of the development and progression of prostate cancer. The long latency period of prostate cancer makes it an ideal target for chemoprevention[45]. The androgen-dependent signalling in prostate carcinogenesis allows for potential modification of cancer risk with agents such as finasteride[46]; a drug that inhibits 5-alpha-reductase (the preferred androgen of prostate tissue). The results of the PCPT trial were promising, with a relative risk reduction of 24.8% for the development of prostate cancer in men taking finasteride (95% CI, 18.6 to 30.6 percent; $p<0.001$)[47]. Clinically significant (Gleason ≥7) cancers were, however, more common in the finasteride group, and there has been poor adoption of this drug into clinical practice for prostate cancer prevention. Long term follow up studies after 18 years demonstrated no difference in cancer-specific or overall survival between the two groups, with an unadjusted hazard ratio for death in the finasteride group of 1.02 (95% CI, 0.97 to 1.08; $p=0.46$)[48]. Similar results were reported in the REDUCE study, an placebo controlled multi-centre RCT, wherein dutasteride reduced the relative risk of prostate cancer by 22.8% (95% CI, 15.2 to 29.8; $p<0.001$)[49]. In years 3 and 4 of the study, more Gleason ≥8 cancers were seen in the dutasteride arm. The authors suggest this may be in part explained by the removal of patients from the study with any diagnosis of cancer on the scheduled biopsy in year 2, which may have resulted in non-random removal of patients who may have been harbouring higher grade cancer on repeat biopsy. The reduction in prostate volume with dutasteride therapy may also have a role to play[50].

The REDEEM study was a multicentre RCT undertaken at 65 centers across North America, which examined the use of dutasteride in men on active surveillance for low risk localized prostate cancer[51]. Use of dutasteride resulted in pathological or therapeutic disease progression at 3 years of 38%, compared to 48% in the control group (HR 0·62; 95% CI 0·43–0·89; $p=0·009$). There were no prostate cancer deaths or incidences of metastases, reiterating the safety of active surveillance for low Gleason 6 disease.

There have been several investigations of chemoprevention outside of the androgen axis. The SELECT trial compared using selenium and vitamin E supplementation either in combination or alone, compared to placebo[52]. Selenium (HR1.04; 99% CI, 0.87-1.24) or vitamin E (HR1.13; 99% CI, 0.95-1.35) alone or combination (HR 1.05; 99% CI, 0.88-1.25) did not alter any cancer related endpoints, and this trial was stopped early interim analysis at median follow up of 5.46 years. The MAST trial was recently presented at the American Society of Clinical Oncology (ASCO) annual meeting. Despite promising preclinical and population-based data, metformin use did not alter progression-free survival in men on active surveillance for low risk prostate cancer compared to placebo ($p=0.63$)[53].

## NATURAL HISTORY IN THE ERA OF MODERN IMAGING

The use of magnetic resonance imaging (MRI) in the diagnosis and staging of prostate cancer has changed prostate cancer landscape dramatically. A UK study of 553 patients on active surveillance who had at least 2 MRI scans found that patients who had no evidence of radiological progression of disease had a very low likelihood of clinical progression (defined as histological progression or initiation of treatment), and clinical progression was almost always detected in patients with radiological progression[54]. A study following 115 small lesions (median size 11mm) across serial MRI found that 76% either stayed stable or decreased in size. 24% lesions increased in size and only 16% increased in PIRADS score[55]. Small index lesions (≤7mm) appear to usually represent benign or low-grade disease, and are usually stable in size across multiple MRI scans[56]. The MRI Prostate Imaging Reporting and Data System (PI-RADS) score can be combined with PSA density the predict the risk of finding clinically significant prostate cancer on biopsy[57], allowing men with indeterminate lesions and low or very low PSA density to be counselled about their low risk of prostate cancer.

The natural history of high-grade lesions on MRI (PIRADS ≥4) is predictably less indolent. A study from Turkey followed 190 patients with initial PIRADS ≥4 lesions on MRI which were negative for malignancy on biopsy. 72 patients underwent repeat MRI for persistently elevated PSA, and PIRADS 4 and 5 lesions were subsequently downgraded in 53 patients (73.6%)[58,59]. Persistent PIRADS score of 4 or 5 is associated with a higher risk of missed cancer, and most authors advocate for repeat biopsy in this scenario[59,60].

Prostate specific membrane antigen (PSMA) positron emission tomography (PET) has changed the landscape of prostate cancer diagnosis and staging in the last decade. Its use in the pre-treatment allows for more accurate staging than conventional imaging[61]. PSMA also out-performs MRI in detection of recurrent disease at low PSA levels in men with biochemical recurrence[62]. PSMA activity in the primary tumor pre-treatment, has been found to be highly predictive of clinically significant prostate cancer[63] and there is emerging evidence that PSMA uptake in the primary tumor can help predict outcomes post radical prostatectomy. One study from Germany reported that lower SUVmean and SUVmax as quantitative parameters from 68Ga-PSMA-11 PET were associated with longer biochemical recurrence-free survival in patients post prostatectomy (log-rank, $p = 0.035$, $p = 0.037$) respectively[64].

## FUTURE PERSPECTIVES: NATURAL HISTORY IN THE ERA OF PERSONALISED MEDICINE

In the modern era, urologists aim to provide treatment strategies tailored to each individual, rather than a 'one size fits all' model. Men diagnosed with prostate want to know their odds of survival with and without treatment, and what effects treatment may have on their quality of life.

In the UK, the 'Predict Prostate' multivariate model for localized prostate cancer has been developed to compare prostate cancer specific mortality against all-cause mortality and

estimate the impact of treatment for prostate cancer on survival[65]. This is a freely available online tool (available at https://prostate.predict.cam/tool) which men can use to input their individual data to produce visual estimates of overall survival, cancer-specific survival, and treatment effects on functional outcomes. The development of patient resources such as this, written in plain language, allows for enhanced shared decision making between healthcare providers and men with prostate cancer.

Several biomarkers and genetic panels have been developed and are being developed to attempt to predict the risk of prostate cancer in an individual[66]. However, we are still a long way from successfully identifying men with potentially lethal cancer at an early stage while sparing men with indolent cancers from the effects of over treatment.

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## FIGURES AND TABLES

**Figure 1.** 'The London Hospital' by Hanslip Fletcher (1874–1955).

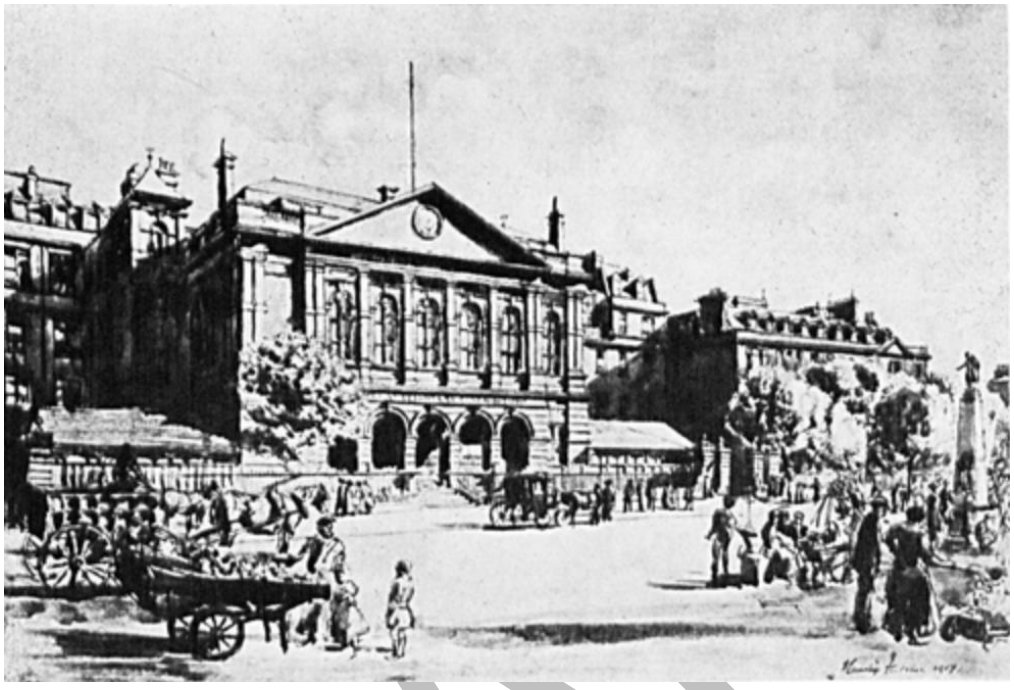

**Figure 2.** Prostate cancer incidence and mortality in Canada from 1969–2009. Reproduced with permission from Dickinson et al (2016).