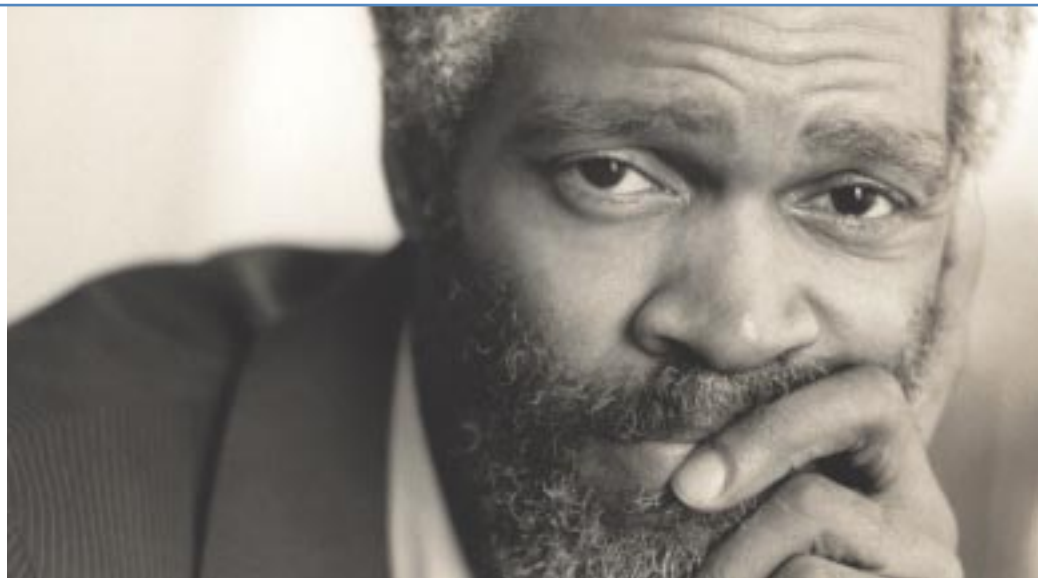
INSIGHT ON CANCER

news and information on prostate cancer

HIGHLIGHTS

- **Prostate cancer is the most common cancer in Ontario men**
- **Many more men are diagnosed with prostate cancer than die of it**
- **Incidence rates have been increasing steadily**
- **Mortality rates are falling**
- **Survival for prostate cancer has improved; almost 90% of men are still alive 5 years after being diagnosed**
- **Important risk factors are age, family history, and African descent**
- **There are currently few clear, modifiable risk factors, although increased physical activity probably lowers the risk of prostate cancer**
- **Treatments for prostate cancer, while effective and improving, can have important complications**
- **Innovative research is currently under way which will illuminate the harms and benefits of mass screening with PSA and other methods, the effectiveness of possible prevention agents, and various approaches to improving treatment and quality of life**



Insight on Cancer is a series of joint Cancer Care Ontario and Canadian Cancer Society (Ontario Division) publications designed to provide up-to-date information about cancer and cancer risk factors in the province.

insight on cancer
volume one
may 2003

Canadian Cancer Society / Société canadienne du cancer
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cancer care ontario | action cancer ontario
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Acknowledgements

The authors are grateful to L. Klotz (Professor of Surgery, University of Toronto and Chief, Division of Urology, Sunnybrook & Women's College Health Sciences Centre) and H. Lukka (Chair, Genitourinary Cancer Site Group, Cancer Care Ontario Practice Guidelines Initiative; Head, Radiation Oncology Programme, Hamilton Regional Cancer Centre, Cancer Care Ontario; and Director, Division of Radiation Oncology, McMaster University) for their assistance in writing clinical sections of this document.

The authors would also like to acknowledge several external reviewers of an earlier draft (A. Davis, V. Goel, R. Gray, R. Kyle, R. Sanderson, D. Sider, and members of the board of Man to Man) and Cancer Care Ontario and Canadian Cancer Society, Ontario Division, staff who assisted in various ways with the development of this document (T. Sullivan, D. Cowan, L. Chambers, E. Holowaty, D. Kline, V. Mai, and P. Payne).

The operations staff within the Surveillance Unit and the Registry Support Group (Information Technology) are to be thanked for their ongoing efforts in ensuring the generation of timely and high-quality cancer incidence data for Ontario.

Published and distributed by the Canadian Cancer Society, Ontario Division. The information was interpreted and analyzed by staff of Cancer Care Ontario's Division of Preventive Oncology:

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PROSTATE CANCER IN CONTEXT

What is prostate cancer?

The prostate is a walnut-sized gland located below the bladder and in front of the rectum. It surrounds the upper part of the urethra. The prostate makes and stores seminal fluid, which nourishes and carries sperm through the urethra and is released to form part of the semen.[1]

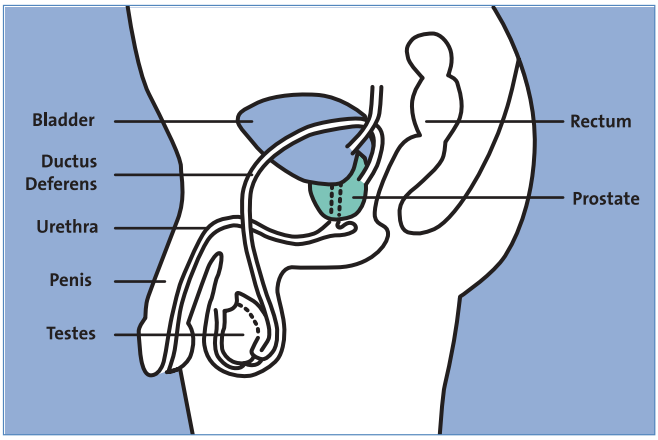
Most prostate cancers are adenocarcinomas. Prostate malignancies may begin as either of two precursor lesions, prostatic intraepithelial neoplasia or atypical adenomatous hyperplasia.[2] Prostate cancer is dependent on male hormones for growth and survival.

Prostate cancer may have no symptoms. Most men as they age experience symptoms like frequency of urination, dribbling, and waking at night to urinate. While these may indicate prostate cancer, they are more likely the result of benign prostatic enlargement. Prostate cancer which has spread to other parts of the body may present with bone pain.

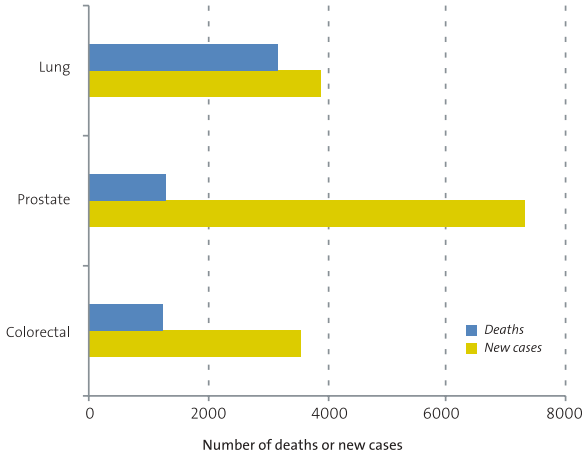
How common is prostate cancer?

Prostate cancer caused 1,335 deaths in Ontario men in the year 2000. This was more than the 1,300 for colorectal cancer but far fewer than the 3,238 deaths in men due to lung cancer.

Prostate cancer represents the highest number of any cancer diagnosed in Ontario men, with 7,444 cases per year compared with 3,962 for lung and 3,651 for colorectal cancer.

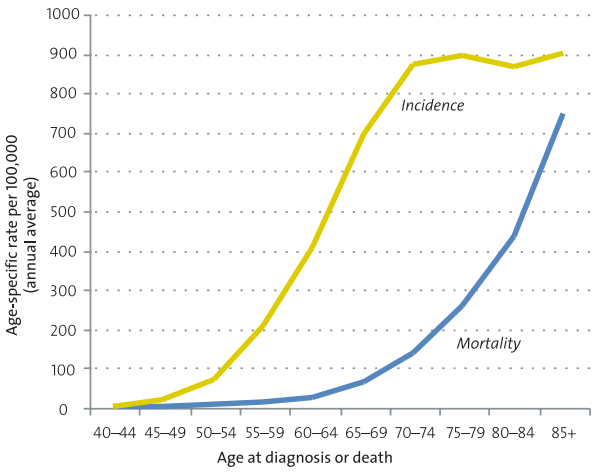


Annual numbers of deaths and new cases for the most common cancers in Ontario males, 2000



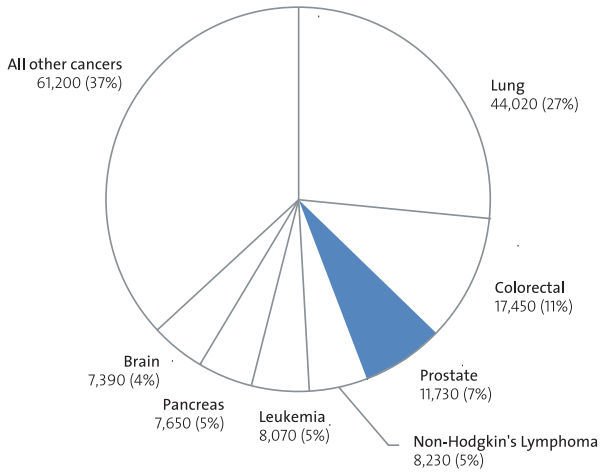
Source: Cancer Care Ontario (Ontario Cancer Registry, 2002[3])

Prostate cancer incidence and mortality rates in Ontario by age, 1996–2000



Source: Cancer Care Ontario (Ontario Cancer Registry, 2002[3])

Potential years of life lost (PYLL) due to cancer in Ontario males, 2000



Sources: Cancer Care Ontario (Ontario Cancer Registry, 2002[3])
Statistics Canada, 2002[4]

A disease of older men

Prostate cancer is rarely diagnosed before age 50. The age-specific incidence curve increases more rapidly for prostate cancer than for any other cancer. Incidence rises rapidly after age 50, from 68 per 100,000 men aged 50–54 to 866 per 100,000 in the 70–74 age group. The rate levels off at older ages during the 1996–2000 period. The median age at diagnosis was 70.

Mortality from prostate cancer is low before age 70 and then rises steeply, from 134 per 100,000 males aged 70–74 to 747 per 100,000 males aged 85 and older. Median age at death from prostate cancer is 78 for Ontario (1996–2000). About 60% of men diagnosed with prostate cancer die from some cause other than prostate cancer.

Prostate cancer ranks below lung and colorectal cancer for potential years of life lost (PYLL). This is despite the higher incidence of prostate cancer, and reflects the fact that it is a disease which results in more deaths of older men. Prostate cancer accounted for 7% of the potential years of life lost due to cancer in Ontario males in 2000, compared to 27% for lung cancer and 11% for colorectal cancer.

Incidence rises rapidly after age 50...median age at diagnosis was 70.

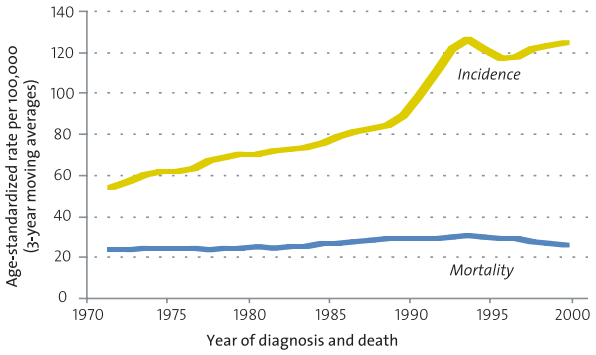
Incidence

The overall incidence of prostate cancer, adjusted for age, rose steadily in Ontario between 1971 and 1989, with an average increase of 2.3% per year. An abrupt increase between 1989 and 1992 was followed by a drop through 1995. This drop did not completely cancel out the previous increase, so the 1995 incidence was higher than it would have been had the 2.3% increase continued without interruption. After 1995 the gradual increase resumed. If this were to continue, estimated incidence for the year 2020 would be 144 per 100,000.

The reasons for the steady rise across the 1970s and 1980s are not clear; possible reasons include a real increase due to changes in risk factor prevalence or incidental findings in increasing numbers of men undergoing transurethral resection of the prostate (TURP) for benign disease.[5,6] This steady upward trend has been observed in other parts of the world; despite wide variation in international rates, most countries had rising rates throughout the 1970s and 1980s.[6,7]

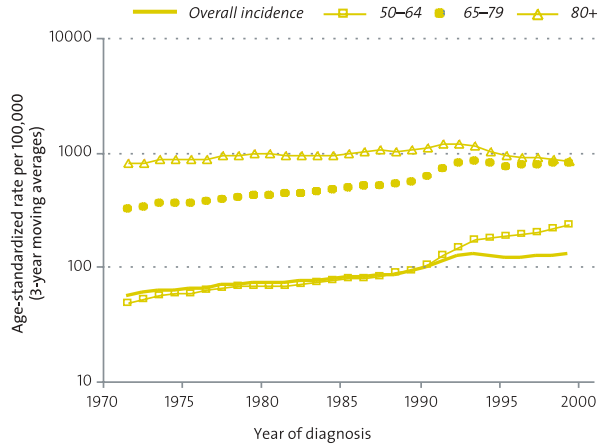
A sharp rise in rates, followed by a dip or levelling off, is a common pattern when a new screening test is introduced. This pattern for prostate cancer incidence likely represents additional cases found with the prostate-specific antigen (PSA) test. This test has been available in Canada since 1986, but its use did not become widespread until the early 1990s.[8] Its use in Ontario increased rapidly in the early 1990s; much of this increase appeared to be for screening.[9,10] Screening with PSA probably found cancers that otherwise would have been diagnosed later, or never in a man's lifetime.

Prostate cancer incidence and mortality rates in Ontario, 1971–2000



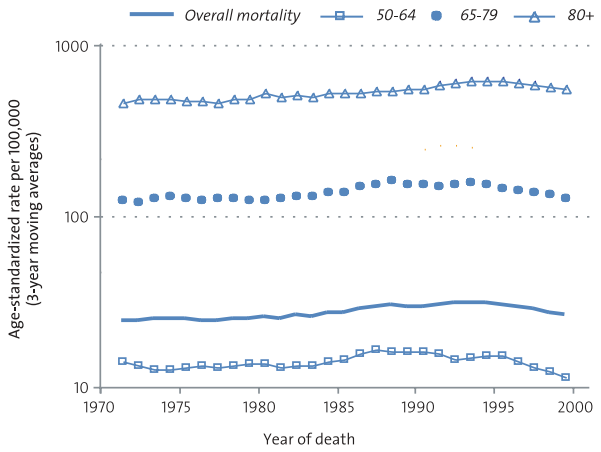
Source: Cancer Care Ontario (Ontario Cancer Registry, 2002[3])

Prostate cancer incidence rates
by age group, 1971–2000



Source: Cancer Care Ontario (Ontario Cancer Registry, 2002[3])

Prostate cancer mortality rates
by age group, 1971–2000



Source: Cancer Care Ontario (Ontario Cancer Registry, 2002[3])

Incidence trends differed according to age group. (Note that rates in the graph are shown on a log scale because of the much higher rates for older age groups.) For men in the age groups 50–64 and 65–79, the rate of increase rose from 3% per year through the 1970s and 1980s to about 17% per year between 1989 and 1992/3. After that, rates increased more slowly for men 50–64. The subsequent trends in men 65–79 paralleled those for all ages. Rates for men 80 and older rose from 1971 until 1992 and then fell. This drop may be partly because of lower incidental findings resulting from fewer TURPs during the late 1990s in this age group.

Mortality

Mortality rates for prostate cancer are much lower than incidence rates; many more men are diagnosed with prostate cancer than die from it. Overall mortality rose steadily (1.3% per year) from 1971 to 1994. It has since fallen back rapidly to the level of the early 1970s.

The gradual increase in mortality up to the early 1990s probably reflects increasing incidence over earlier decades. Recent declines in mortality may be the result of improvements in treatment (improved hormone therapy and greater use of radical prostatectomy) or changes in whether or not deaths are attributed to prostate cancer.[11, 12] Elsewhere in North America there has been a marked shift to lower stage of disease at diagnosis.[12]

Mortality has declined since the early 1990s in all age groups. The decline was steepest for men aged 50–64 (nearly 7% per year); their mortality is lower in 2000 than at any time over the preceding 29 years. For men aged 65–79, mortality has dropped to the same rate as during the 1970s, while for men 80 and over, mortality remains slightly higher than 1970s rates. (Note that rates are shown on a log scale because of the much higher rates for older age groups.)

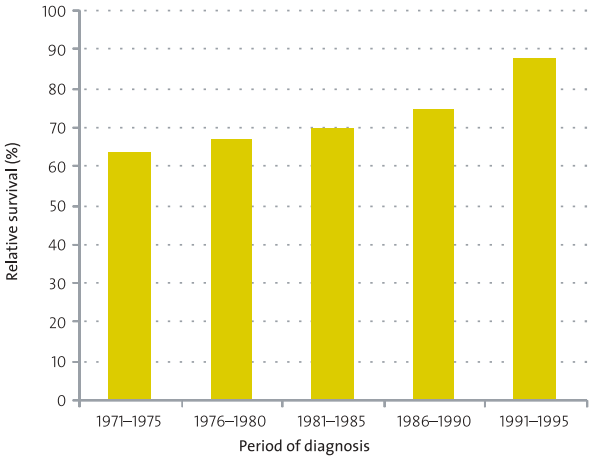
Improving

Relative survival for men with prostate cancer improved steadily from 64% at five years after diagnosis for men diagnosed in 1971–1975 to 75% for men diagnosed between 1986 and 1990. It then jumped to 88% for those diagnosed in 1991–1995, and is most likely even higher for men diagnosed more recently.

Five-year relative survival for prostate cancer is best for men in the age groups 50–64 and 65–79, at approximately 90%. It is lower, as for many cancers, in older men. The two younger age groups also showed a larger increase between the period 1986–1990 and the period 1991–1995 as compared with the steady improvement across earlier periods.

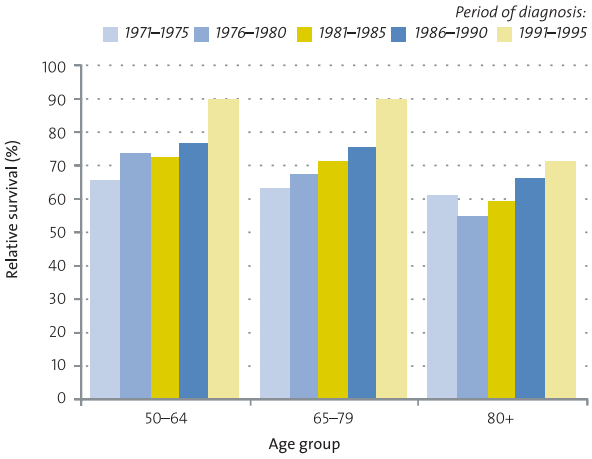
The gradual improvement in survival between 1971–1975 and 1986–1990 may be due to better treatment, and finding prostate cancers at an earlier stage. The larger gain in survival for men diagnosed in 1991–1995 may be partly caused by new screening methods. The PSA test was introduced in the late 1980s. PSA may have found some cancers so early that those men are living as long as they would have anyway, without their prostate cancer being detected. Survival would thus look artificially better: with PSA these cases are found early so that the men **appear** to be living longer after diagnosis, but their length of life is actually the same.

Prostate cancer 5-year relative survival by period of diagnosis, 1971–1995



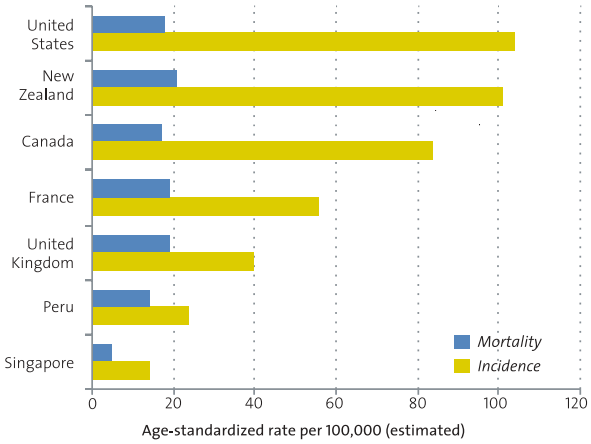
Source: Cancer Care Ontario (Ontario Cancer Registry, 2002[3])

Prostate cancer 5-year relative survival by age group, 1971–1995



Source: Cancer Care Ontario (Ontario Cancer Registry, 2002[3])

Prostate cancer mortality and incidence rates* for selected countries, 2000



*Standardized to the year 2000 estimated world population
Source: GLOBOCAN 2000[13]

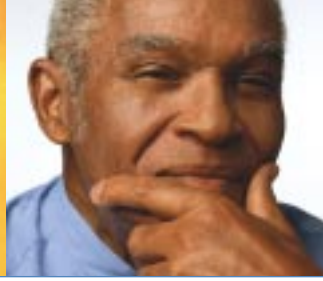
International differences

Worldwide, Canada's incidence rate for prostate cancer is among the highest. Recent estimates are also high for the US, New Zealand and Australia. European rates are lower. Prostate cancer mortality rates vary little among western developed countries. Both incidence and mortality rates are lower for less developed countries, and lowest in Asian countries.[7, 13]

Part of the international variation is probably because of differences in health care, and screening systems that find and report more cases in developed countries. These differences between well-developed and less-developed countries also reflect biologic differences. The highest reported rates are for US men of African ancestry, while Asian countries have low rates despite varying degrees of economic development.[6, 7, 14]

Ontario ranks fifth among the 10 provinces in terms of the estimated incidence rate for prostate cancer in 2000.[15]

Worldwide, Canada's incidence rate for prostate cancer is among the highest.



Regional differences

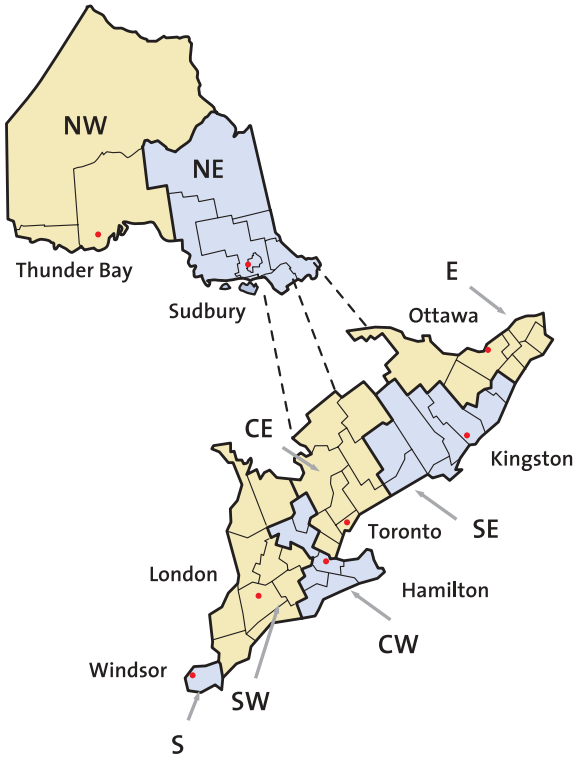
Within Ontario, mortality rates are significantly low in Central East, compared to the rate for all Ontario, and significantly high in Southeast and Southwest regions. Regional incidence rates are not included because of the relatively large number of recently diagnosed cases for which residence is not recorded in the Ontario Cancer Registry.

Reasons for the variation in mortality rates among Ontario's regions are not known. Possibilities include variation in: the biologic risk of the disease (for example, the low mortality in Central East may be due to its large population of immigrants from low-risk countries[16]), the prevalence of exposures that cause the disease, the extent of screening with the PSA test, or the quality of diagnosis and care.

Prostate cancer mortality rates by region, 1996–2000

Region	Age-standardized rate per 100,000
All Ontario	**27.0**
Northwest (NW)	29.4
Northeast (NE)	29.5
South (S)	29.8
Southwest (SW)	29.8*
Central West (CW)	28.6
Central East (CE)	24.1†
Southeast (SE)	29.7*
Eastern (E)	28.1

*Significantly greater than Ontario rate (p<0.05)
†Significantly lower than Ontario rate (p<0.05)



Sources: Cancer Care Ontario (Ontario Cancer Registry, 2002[3])
SAS, 1999–2001[17]

Risk factors

Population differences and the rise in prostate cancer incidence over time probably result from **a complex interplay of genetic and lifestyle factors related to hormones.**[7,18] Risk factors may differ between early stage tumours and more aggressive, symptomatic prostate cancers.[19–21]

- **Family history** of prostate cancer in a first degree relative is consistently associated with at least a doubling of risk.[22]
- **Ethnicity:** The incidence of prostate cancer is highest in men of African descent, and lowest in Asian men.[7]
- **Inactivity and obesity:** Physical inactivity and obesity appear to increase risk, possibly through their effects on hormones and growth factors.[23–26]
- **Diet:** No clear evidence has emerged on dietary factors which raise or reduce the risk of prostate cancer. Findings are mixed on whether dietary fat, meat and calcium increase risk.[19,20] There is some evidence that risk is reduced by tomatoes and tomato products, beans, legumes, nuts, carrots, green leafy and possibly cruciferous vegetables, and by specific micronutrients and plant chemicals from vegetables, such as soy isoflavones.[21,27]

Prevention

Although there is insufficient evidence on modifiable risk factors to develop specific public health strategies for prostate cancer at this time, 30 to 45 minutes of moderate to vigorous activity most days of the week is a general recommendation for reducing the risk of cancer.

Preventing prostate cancer with dietary supplements or drugs is a relatively new concept. Trials of some agents are in progress: micronutrients (vitamins C and E, beta-carotene, selenium, and zinc) and the drug finasteride (used to reduce testosterone production).[28,29]

30 to 45 minutes of moderate to vigorous activity most days of the week is a general recommendation for reducing the risk of cancer.

Early detection

Screening for prostate cancer in the general population is not currently recommended.

There are three potential screening tests for prostate cancer: PSA, digital rectal examination (DRE) and transrectal ultrasound (TRUS).

Several reviews of the current evidence for PSA testing have concluded that risks outweigh benefits, or that evidence is insufficient for recommending for or against it.

Reviewing body	Conclusion
US Preventive Services Task Force (2002)[30]	Insufficient evidence to recommend for or against routine screening
Ontario's Ministry of Health and Long-Term Care (with a report from the Institute for Clinical Evaluative Sciences) (2002)[31]	PSA should not be used for population-wide screening in asymptomatic males and is not paid for by the provincial health plan
Canadian Task Force on Preventive Health Care (1994)[32]	Exclude routine screening with PSA from the periodic health examination of asymptomatic men over 50 years of age*

*Currently under review

While the PSA test can detect early cancers, false-positive rates are high and there are significant risks associated with treating the disease once detected. Trials now under way in Europe and the US may provide evidence to support screening, perhaps in population subgroups.[33]

DRE can detect only small cancers in the posterior and lateral aspects of the prostate. TRUS does not specifically detect prostate malignancies.

Screening tests do have a role to play in men whose doctors suspect that they may have prostate cancer, and perhaps for high-risk men (of African ancestry, for instance, or with a family history of symptomatic prostate cancer in a close relative).

Diagnosis

If prostate cancer is suspected, the next step may be a PSA test or DRE. A needle biopsy, so that cells can be examined under a microscope, is needed for definitive diagnosis following a positive test result.

An elevated PSA does not mean that a man has cancer. Only about one out of every three men with an abnormal PSA will have prostate cancer.

Prognosis

Disease outcome depends on the grade and stage of the tumour. Grade describes how abnormal the cancer cells appear under the microscope compared with normal cells; the Gleason grading system is commonly used to describe the aggressiveness of the tumour.[1, 34] Once cancer is identified, the tumour is staged to determine its spread; this will help to guide treatment recommendations. A Stage I tumour cannot be felt during a rectal examination; Stage II can be felt during a rectal examination and is confined to the prostate; Stage III has spread outside the prostate to nearby tissues; Stage IV is fixed in position or invades adjacent structures, lymph nodes or more distant parts of the body.[35]

Treatment strategies

Prostate cancer treatments include surgery, radiation, observation (watchful waiting), hormone therapy and chemotherapy. The specific treatment depends on initial stage of disease, progression, individual characteristics such as age and overall health, and personal preference.

- **Surgery** is a good option for men with localized (Stage I and II) prostate cancer who are in good health, and have a life expectancy of at least 10 years. The surgical procedure is radical prostatectomy. Although this is major surgery, significant improvements in technique have made it relatively safe, with low mortality and complication rates.[36]

- **Radiation therapy** is a good choice for older men with localized prostate cancer who may be at higher risk of health problems from surgery. There are two methods of delivery: external radiation (a high energy X-ray beam) and internal radiation or brachytherapy (placing radioactive seeds into the prostate).[1, 37]

- **Watchful waiting** is generally advised in older men and/or if the cancer is small and growing so slowly that it is unlikely to cause any problems during one's lifetime.

  In this method, the physician watches the patient closely and looks for any symptoms or signs of the cancer spreading. Usually the PSA test, increase in Gleason score on rebiopsy, and physical examination are used to monitor the cancer's progression.

- **Hormone therapy** is used for patients with metastatic disease or recurrent disease after the failure of definitive local therapy, and increasingly, in conjunction with radiation and/or surgery. Removal of male hormones results in the death of most cancer cells. Hormone therapy can be by a periodic injection of luteinizing hormone-releasing hormone (LHRH) analogues, or by surgical removal of the testicles. The major advantage of the LHRH analogues is that their effects are reversible.

- If prostate cancer becomes resistant to hormone therapy, it may be treated with a combination of radiation to painful sites of metastasis and **chemotherapy**. Drugs currently used include mitoxantrone and docetaxel.

Treatment complications

Surgery and radiation treatment have three relatively common and important complications: erectile dysfunction, diminished urinary control and bowel problems.[36–38] (These may also occur as complications of the disease itself regardless of treatment.[39, 40]) Estimates of the proportions of men affected vary according to geographic location, time and type of treatment. Improved surgical techniques have reduced complication rates in recent years. In some men, problems improve with length of time after treatment. Although the effects of these conditions can be alleviated, their impact on quality of life can be substantial and depends on their severity, duration and importance to the individual.[36, 37] Men may experience discomfort, fear and confusion with the side effects of treatment. Supports exist for helping men and their families, including members of the health care team, local support groups, and counselling.

Prevention

- **Prevention trials** in Europe and North America are assessing the usefulness of nutritional supplements or chemoprevention. Reports are expected in the next few years from a French trial (SU.VI.MAX) of vitamin, selenium and zinc supplements, and from the Prostate Cancer Prevention Trial of the drug finasteride. The SELECT trial of selenium and vitamin E began in 2001 and is expected to continue for 12 years.

- **Prevention** studies in Ontario are investigating the effectiveness of vitamin E, selenium and lycopene in preventing prostate cancer in animals.

Genetic research

- Studies are under way to assess risk levels in men with identified genetic mutations (in BRCA2), to identify other genetic alterations which increase risk, and to identify genes associated with more serious prostate cancer.

Early detection

- **Screening trials** should tell us in the next few years whether routine screening by PSA or other means is useful, for which age groups and at what frequency, and whether benefits are concentrated in high-risk groups. Two large trials, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and the European Study of Screening for Prostate Cancer, are expected to begin yielding results between 2005 and 2008.

- New **blood tests which analyze protein patterns** may help screen for early stage prostate cancer, to help decide whether men with elevated PSA levels even require a biopsy.

Treatment

- Researchers in Ontario are comparing the benefits of different types of treatment (surgery, radiation, and careful monitoring) for localized disease in order to develop a **toolkit** to help doctors recommend treatment options tailored to different men's needs.

- A treatment approach for patients with good-risk prostate cancer is being tested in Ontario. This approach, termed **active surveillance with selective delayed intervention**, represents a middle ground between treating all patients aggressively and not treating (i.e., watchful waiting). In this method, the rate of rise of PSA over time is used to determine who needs treatment. It may be possible to spare many from the side effects of therapy, while those with aggressive disease can be given radical therapy.

- Improved drug therapy for both localized and advanced prostate cancers is being investigated, particularly **anti-angiogenesis** (to block development of blood vessels that nourish cancer cells), **gene therapies** (to normalize defective genes in cancerous cells), **immune therapies** (vaccines and stimulatory growth factors) and **hormone treatment** (before or after radiation treatment or surgery, and new anti-androgen therapies).

- Various molecules are being tested for their usefulness in **predicting prostate cancer progression.** For example, focal adhesion kinase (FAK), NF-kappa B and fat-related factors in prostate cells may act as markers for changes in the aggressiveness of disease.

Quality of life

- **Support groups for prostate cancer patients and their families** are being assessed for reducing the distress of both patients and their partners.

- Social scientists are using **innovative methods like drama** to investigate the impact of prostate cancer on men's lives. The recent "No Big Deal?" production, for example, disseminated the findings from a study of men with prostate cancer and their spouses.

- Studies are assessing the impact of **physical activity** on life with prostate cancer. An Ontario-based trial is examining the effects of an exercise program on quality of life and fitness. An Alberta study will follow men to see whether physical activity helps to improve survival.

GLOSSARY OF TERMS, DATA SOURCES AND METHODS

Adenocarcinoma
Cancer in cells that have glandular (secretory) properties.[41]

Age-standardized rate
The number of new cases of cancer or cancer deaths per 100,000 that would have occurred in the standard population (1991 Canadian population) if the actual age-specific rates observed in a given population had prevailed in the standard population.[15]

Age-specific rate
The number of new cases of cancer or cancer deaths during the year, expressed as a rate per 100,000 persons in a given age group.[15]

Average annual percent change in rate
A measure used to assess the rate of change over time of an incidence or mortality rate. It is calculated by fitting a linear model to the annual rates after applying a logarithmic transformation. The estimated slope is then transformed back to represent a percentage increase or decrease.[15] The method used allows for a series of straight line segments with different slopes to be fit to long-term trend data. It estimates both the specific years at which the slope (rate of change) changes significantly and the slope of each line segment.

Digital rectal exam (DRE)
Physical exam which involves inserting a gloved, lubricated finger into the rectum to feel the prostate for abnormalities.[42]

Erectile dysfunction
Persistent inability to attain and maintain an erection sufficient for intercourse.

Gleason grading system/score
The most common method of assessing the aggressiveness of prostate cancer. This system assigns a grade to each of the two largest areas of cancer in the tissue sample. The two grades are added together to produce a Gleason score. A tumour with a high score grows aggressively, while one with a low score grows slowly and may not be a threat to the patient in his lifetime.[1]

Median age at diagnosis/death
The age for which 50% of the diagnoses/deaths occur in younger men and 50% occur in older men.

Luteinizing hormone-releasing hormone (LHRH) analogues
Synthetic compounds, similar to natural LHRH, that interfere with male hormones to slow the growth of prostate cancer cells.

Ontario Cancer Registry (OCR)
The population-based database which includes information on all diagnoses of cancer reported in residents of Ontario since 1964.[43] It includes limited data about diagnosis (date, type of cancer), death (date, cause), treatment, and the individual (date of birth, sex, census division of residence at diagnosis/death) for all cancer patients. It does not include data on risk factors, stage, grade, or non-melanoma skin cancers.

Population data
Population counts used as denominators of rates. Statistics Canada, which conducts the National Population Census every five years, provides annual population estimates by five year age groups and census divisions.[44]

Potential years of life lost (PYLL)
A method for assessing cancer burden that helps to describe the extent to which life is cut short by cancer. The total number of years of life lost is calculated by multiplying the number of deaths in men with prostate cancer for each individual age by the life expectancy of survivors.[15]

Prostate-specific antigen (PSA) test
Measurement in blood of a substance produced by prostate cells. High PSA levels in the blood may be a sign of a prostate problem, either cancer or nonmalignant condition. In addition to prostate problems, some medical treatments can affect PSA levels.[41, 42]

Radical prostatectomy
The surgical removal of the prostate gland and the seminal vesicles.

Regions
Cancer planning regions that correspond to aggregations of census divisions, and are to some extent defined by the locations of specialized cancer treatment centres.

Regional variation
Rates are considered significantly different from Ontario if the 95% confidence interval excludes the overall provincial rate.

Five-year relative survival (%)
A measure of the reduction in life expectancy due to a diagnosis of prostate cancer. Relative survival is estimated from life tables as the ratio of the observed survival of prostate cancer cases five years after diagnosis to the expected survival of men in the general population who are the same age. The ratio is expressed as a percentage. Deaths from all causes occurring in Ontario through 2000 were used.

Staging
A method to describe the size and extent of spread of cancer.

Three-year moving average rate
Rate calculated using the sum of the new cases of cancer or cancer deaths for a three-year period and the population estimates for those same years. Three-year moving average rates are shown on all graphs describing trends in order to smooth out annual fluctuations.[43]

Transrectal ultrasound (TRUS)
Insertion of a probe into the rectum to direct sound waves to the prostate to image the prostate.[42]

Transurethral resection of the prostate (TURP)
The use of a special instrument inserted through the urethra in the penis to remove non-cancerous prostate tissue.

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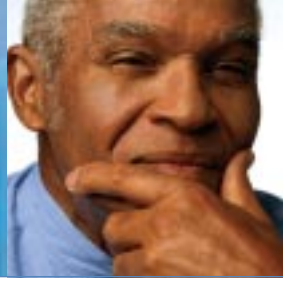

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