

Screening guidelines for people at increased risk for prostate cancerJustin Lorentz¹, Julia Woollcombe¹, Douglas Andrew Loblaw¹, Stanley Liu¹, Danny Vesprini¹¹Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada; Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.**Cite as:** Lorentz J, Woollcombe J, Loblaw DA, et al. Screening guidelines for people at increased risk for prostate cancer. *Can Urol Assoc J* 2024 June 10; Epub ahead of print. <http://dx.doi.org/10.5489/cuaj.8710>

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ABSTRACT

Individuals at increased risk for prostate cancer (PCa) are inconsistently defined in national and international guidelines. The National Comprehensive Cancer Network (NCCN) defines people at increased risk for PCa to include those with a concerning family history, Black/African American individuals, and those who have germline mutations in known PCa-related genes.

Recommendations for screening are also inconsistently defined in national and international guidelines. The NCCN and American Urological Association state individuals at

increased risk for PCa be screened with prostate-specific antigen and digital rectal exam starting at age 40. Defining increased risk groups and defining lifetime risk is an ongoing academic process that can be facilitated through patient registries of these cohorts at academic centers.

KEY MESSAGES

- Germline pathogenic variants/likely pathogenic variants can inform PCa screening and management.
- Family history of PCa can be quantified into lifetime risk using models and family history data. Lifetime risks for prostate cancer in people with a brother with PCa can range from 30.3–62.6%.
- Black individuals with prostates have up to a 29% lifetime risk for PCa and an increased risk for developing high-risk PCa.
- The definition of who is at increased risk for PCa needs to be defined so it is clear who should access enhanced detection.
- Individuals at increased risk should be offered annual PSA and DRE annually starting at age 40.

INTRODUCTION

In Canada, prostate cancer is the leading cause of cancer in males and the fifth leading cause of cancer-related death¹. The current lifetime risk for a prostate cancer diagnosis in Canada is 12-13% however this risk may be higher (Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, Statistics Canada and the Public Health Agency of Canada. Canadian Cancer Statistics 2021. Toronto, ON: Canadian Cancer Society; 2021). Lifetime risk for a cancer diagnosis is calculated by comparing the incidence of cancer to a population. In 2014 the Canadian Preventive Task Force recommended against prostate cancer screening, as a result less people have been screened for, and diagnosed with, prostate cancer². The frequency of prostate specific antigen (PSA) screening in a population impacts the lifetime risk of being diagnosed with prostate cancer, with less screening associated with lowered lifetime risk³.

Aside from aging there are three risk factors for prostate cancer: inheriting a germline pathogenic variant or likely pathogenic variant (PV/LPV) in a cancer-related gene, a strong family history of prostate cancer, and West African/Caribbean (WA/C) ancestry. Screening and management approaches of people who have one or more of these risk factors remain inconsistent, and the cause of Increased Risk of prostate cancer in people with a family history and/or of WA/C ancestry remains largely elusive.

Who is at increased risk for prostate cancer?

Many cancer sites use the term increased risk and high risk synonymously. However, in prostate cancer, high-risk disease has its own definition (Table 2) relating to prostate cancer aggressiveness so to use “high risk” in the context of lifetime risk can be confusing and is best to be avoided. The CUA, the AUA, and NCCN have each defined Increased Risk for prostate cancer in their screening recommendations differently. The NCCN has the most comprehensive definition stating individuals at Increased Risk for prostate cancer being those with a family history, being Black or of West African/Caribbean ancestry, and/or having a known inherited (germline) predisposition to prostate cancer. Most cancers are sporadic in etiology and are caused by an accumulation of genetic mutations due to aging and environmental factors. Cancer can also be hereditary, where there is a known, typically Mendelian inherited genetic predisposition that can be identified through germline genetic testing. In contrast, familial cancers are caused by genetic factor(s) that are also inherited but cannot be identified through genetic testing as they are largely unknown.

Family history

Up to 57% of prostate cancer is familial in etiology⁴. Familial risk refers to shared genetic, environmental, and lifestyle factors that work together in ways that are too complex to understand at this time. With the mechanisms of risk unknown, association studies based on family history of prostate cancer are used to help quantify familial risk in unaffected individuals.

For example, the CanRisk-Prostate model generates lifetime risk percentages for prostate cancer in individuals based on family history of cancer, germline genetic status, and polygenic risk score analysis⁵. This model is based off a multitude of studies that have generated empirical data from large family registries. An example of such a study is one based out of Sweden that captured 98% of prostate cancers in the country and used family history to provide lifetime risks of low-risk prostate cancer and high-risk prostate cancer (Table 2) in unaffected individuals based on their family history alone (Table 3)⁶.

Although such assessment of risk of developing prostate cancer may be of benefit for the individual patient, it does not yet inform inclusion into an increased risk screening program such as is the case with breast cancer screening. In Ontario the definition of being at high risk (increased risk) for breast cancer is defined as 25% lifetime risk based on modelling⁷. As such, whether using models as outlined above or more empirical data, it is reasonable to suggest that a threshold risk of 25% or higher, based on family history, should be factored into whether to include prostate cancer screening in a patient's care, especially in families where there is an increased prevalence of high-risk prostate cancer. Any individual with a prostate who has a sibling with prostate cancer, or a sibling and a father with prostate cancer is expected to have a higher than 25% lifetime risk for prostate cancer themselves⁶. It is important to note however that there is a dearth in data relating to lifetime risk of prostate cancer based on family history of prostate cancer in second- (uncles and grandfathers) and third-degree relatives (cousins and great grandparents). As a result there is room for clinical opinion in defining whether a family history is strong enough to consider someone at Increased Risk.

Polygenic risk score (PRS) or genetic risk score

PRS is a method of identifying genetic risk associated with a medical outcome. PRS uses genome-wide association studies to identify multiple genetic variants over-represented in the genomes of a cohort with a medical outcome compared to an unaffected cohort. The score generated by a PRS shows an individual's risk for the medical outcome based on the number of variants associated with the outcome that provides a score. It is important to note that many conditions are multifactorial in nature, and genetics alone is not fully predictive as environmental factors play a role in medical outcomes as well. In the case of prostate cancer, there are multi-ancestry validated PRS designed to determine an individual's prostate cancer risk⁴², however clinical utility of PRS, especially in the context of PSA and family history remains unclear.

Black/West African ancestry

Prostate cancer incidence and progression is highly variable across people of different geographical ancestral origins. In the USA, non-Hispanic Black individuals have an increased risk of developing prostate cancer with an increased associated morbidity and mortality when compared to non-Hispanic White individuals⁸. In comparison to non-Hispanic White individuals, the Centers for Disease Control (CDC) shows prostate cancer incidence is approximately 75% higher in non-Hispanic Black patients and 45% lower in non-Hispanic Asian

and Pacific Islanders (U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; <https://www.cdc.gov/cancer/dataviz>, released in November 2022). An English study from 2008-2010 showed the lifetime risk of a Black person to be diagnosed with prostate cancer was 29% and the lifetime risk of dying from their disease was 9%, whereas the lifetime risk for a White person to be diagnosed prostate cancer was 13% and the lifetime risk of dying from it was 4%⁹. These significant differences, though incredibly important for health care providers and policy makers, need to take into context the racial disparities in access to and utilization of health care, particularly for Black men in the USA. As a result, it is unclear what component of the differences seen are genetic/inherited versus due to the result of systemic bias and other confounders¹⁰. Despite this uncertainty, it is important to note that Black individuals may have a greater than 25% lifetime risk for prostate cancer regardless of family history.

Hereditary cancer

Hereditary cancer conditions are caused by inherited pathogenic variants or likely pathogenic variants (PV/LPV) in cancer-protecting genes. The main genes associated with increased risk for prostate cancer include *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13*, *MSH2*, *MSH6*, and *PALB2* (Table 4) which are primarily involved in sensing and repairing DNA damage. Germline PV/LPVs have been documented in 11.8% of patients with metastatic prostate cancer (mPC) and 4.6% of patients with localized disease¹¹. There is increasing awareness that PV/LPVs in certain genes are not only of important for estimating risk of developing the disease but can also be used to help personalize treatment.

Patients with mPC who have inherited PV/LPVs (germline) or acquired PV/LPVs (somatic) in *ATM*, *BRCA1*, and *BRCA2* are eligible for poly(adenosine diphosphate-ribose) polymerase inhibitors (PARPi) treatment which has been shown to increase progression-free and overall survival (OS) of their disease¹². In mPC patients with germline PV/LPVs in mismatch repair genes such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*, programmed cell death inhibitors (PCDi) like pembrolizumab have been shown to decrease PSA levels by 50% in greater than half of treated men but not affect OS¹³. Additionally, knowledge of these genetic changes can be of value in the management of low-risk prostate cancer with active surveillance (AS), where patients are closely monitored through regular PSA testing, MRI imaging, and prostate biopsy, with treatment is being considered if there is progression in cancer grade¹⁴. Germline *ATM*, *BRCA1*, and *BRCA2* PV/LPVs have been shown to have increased risk of Grade Group reclassification in an AS cohort, with the strongest association being with *BRCA2* carriers¹⁵. Based on this evidence, *BRCA2* carrier status should be factored into a patients candidacy for AS, and may warrant a modified AS protocol or upfront treatment at time of diagnosis.

What are current screening guidelines for people at increased risk for prostate cancer?

The use of PSA screening for prostate cancer, while currently the standard screening practice recommended by many urological organizations, is also not without controversy, which stems in part from the high rate of false positive screening tests²³ but also from the conflicting data regarding prostate mortality in cohorts receiving PSA screening. Two examples of conflicting data being in the ERSPC and Göteborg studies showing decreased mortality^{24, 25} and the American PLCO trial showing no difference in mortality²⁶ when comparing the screened and unscreened groups. The findings of the PLCO study had longstanding implications for policy development in North America despite the near complete contamination of PSA screening in the control arm of this study and no efficacy analysis^{27 28}. The major organizations providing guidelines for prostate cancer screening may share some commonalities but are largely inconsistent (Table 5). The NCCN and two North American Urological Associations recommend individuals with prostates who are at Increased Risk for prostate cancer undergo decision making for PSA screening between ages 40-45.

As we become better at identifying people at Increased Risk for prostate cancer, we have an opportunity to provide a standardized approach to screening in these individuals. Currently in Canada, prostate screening is largely based on patient-clinician conversations with varying opinions based on inconsistent and sometimes conflicting data which largely applies to the general population and not to increased risk populations.

Increased Risk for prostate cancer can be defined as having a germline PV/LPV in a prostate cancer-related gene, having a family history of prostate cancer in closely-related family members, or being of Black ancestry. These criteria can be simplified as having a >25% lifetime risk for prostate cancer. The NCCN and the American Urological Association state all individuals at Increased Risk of Prostate Cancer should have annual PSA screening and digital rectal exam (DRE) starting at age 40.

Enhanced screening beyond annual DRE and PSA testing is needed for those at Increased Risk of high-risk prostate cancer. The use of MRI for prostate cancer screening is of interest due to its high sensitivity for intermediate-risk and high-risk prostate cancer (Table 1; NCCN 2020; ^{32 33}). The effectiveness of MRI as a screening tool has been found to be greater than PSA in both studies of the general population³⁴ and in an Increased Risk population such as people with *BRCA1* and *BRCA2* pathogenic variants³⁵ with more studies pending (NCT01990521). A comprehensive review and meta-analysis of 12 randomized clinical trials and prospective cohort studies comparing MRI-based to PSA-only screening of 80,114 men showed the MRI-based pathway had increased odds of castrate sensitive prostate cancer, decreased odds of biopsies, and decreased odds of insignificant cancers identified without significant differences in identified of castrate sensitive prostate cancer⁴³. Due to the accumulating evidence of use of MRI in the prostate detection process, NCCN recommends the following MRI-based pathway⁴¹:

- 1) PSA >3ng/mL or suspicious DRE in “high risk” individuals
- 2) PSA >4ng/mL or suspicious DRE in general population.

Integration of MRI screening of patients at Increased Risk is equally a matter of debate and investigation, though would appear clinically justifiable in those groups with a poorer prognosis than seen in the general population, such as those with a *BRCA2* PV/LPV³⁶.

How can screening increased risk populations for prostate cancer impact outcomes?

Among the individuals at Increased Risk for prostate cancer, are people at increased risk for high-risk prostate cancer. Identifying prostate cancer early through PSA decreases prostate cancer mortality^{24,25} and MRI-based pathways decrease odds of biopsies without significant differences in identified castrate sensitive prostate cancer⁴³. Clear prostate cancer detection strategies for people at Increased Risk for prostate cancer such as provided by the NCCN is expected to decrease mortality in this cohort.

Individuals with a significant family history of high-risk prostate cancer and/or are of West African/Caribbean Ancestry are at increased risk not only for prostate cancer, but for high-risk prostate cancer^{6,8}.

Individuals with PV/LPVs in known genes associated with prostate cancer are at Increased Risk for prostate cancer and some are at increased risk for high-risk prostate cancer. Of the known genes associated with prostate cancer, the *BRCA2* gene has the most consistent literature associating carriers with higher mortality rates for prostate cancer. A retrospective analysis between 1998-2010 showed a 12-year prostate cancer survival rate of 61.8% in *BRCA2* carriers compared to 94.3% in participants without *BRCA2* P/LPVs³⁶. The IMPACT study published their 3-year prospective PSA-only screening protocol identifying *BRCA2* carriers had higher rates of prostate cancer, as well as more clinically significant prostate cancer compared to *BRCA1* and *BRCA2* non-carriers⁴⁴. It remains to be determined whether people with PV/LPVs in *ATM*, *BRCA1*, *HOXB13*, *MSH2*, and *MSH6* are at increased risk for high-risk prostate cancer.

Who should be offered genetic testing for prostate cancer?

The Canadian Urological Association developed a genetic testing guidelines for germline and tumour genetic testing³⁷. The two main criteria from the CUA are 1) being diagnosed with mPC and 2) being diagnosed with localized prostate cancer and being of Ashkenazi Jewish ancestry and/or having a personal or family history related cancers (such as breast, ovarian, colorectal, endometrial, pancreatic cancer). The CUA highlights criteria for genetic testing of affected patients however once a germline PV/LPV is identified then potentially unaffected parents, siblings, children, and extended family are eligible for genetic testing of the identified variant. If the variant is identified in family member then they can be screened more carefully for the cancer risk associated. Each province may have more specific criteria for germline genetic testing (Figure 1) or for tissue genetic testing. To facilitate germline genetic testing, patients can be referred to a local genetics clinic or some centres work directly with genetics clinics to facilitate genetic testing themselves through a model called physician-initiated genetic testing or mainstreaming³⁷. Universal germline genetic testing is a process in which all patients with a specific cancer regardless of age are offered germline genetic testing. Currently there are studies

outlining how this process can be successfully implemented in rural and urban settings in the context of breast cancer^{45, 46}.

How can we continue to research people at increased risk for prostate cancer?

Registries act as a foundation for facilitating research in a target population. Regarding high-risk prostate cancer, there is the international IRONMAN registry (NCT03151629); in the USA there is the Prostate Cancer Genetic Risk, Experience, and Support Study (PROGRESS) registry and the PROMISE study (NCT05129605, NCT04995198); and in Canada the MORE Registry³⁸. These registries catalogue and collect comprehensive clinical, pathological and genomic information, which can be supplemented with biobanks to work to fill in gaps in our knowledge on target groups such as Black individuals with prostates and people with germline PV/LPVs that elevate risk for prostate cancer. Medical research mistrust within the Black community due to unethical research studies such as Tuskegee as well as healthcare discrimination has made recruiting Black men to registries challenging, resulting in a lack of knowledge within the community³⁹. Emphasis on building these registries cannot be emphasized enough to answer questions like why we see increased risk for high-risk prostate cancer, and the intersectionality between being Black and having a germline PV/LPV. Although individually rare, registries can facilitate research on large groups of people with germline PV/LPVs to validate prostate cancer prevention strategies such as ejaculation frequency⁴⁰, develop ways to predict prostate cancer aggressiveness with use of polygenic risk scores, and developed enhanced prostate cancer screening for people at increased risk for high-risk prostate cancer.

CONCLUSIONS

Individuals at Increased Risk for developing prostate cancer include those with a family history, Black individuals, and those who have germline PV/LPVs in known prostate cancer-related genes. Despite knowing these populations are at Increased Risk for prostate cancer, there is little consensus for screening of these individuals. Each physician in Canada adopts their own model of care for prostate cancer screening in individuals at Increased Risk for prostate cancer. The NCCN guidelines stating all individuals at Increased Risk for prostate cancer be screened with PSA and DRE starting at age 40 are the most comprehensive. We also encourage academic centers to establish registries of these cohorts to allow collaborative opportunities to contribute to the body of research on causes of cancer risk in individuals with a family history and/or who are Black and/or who have PV/LPVs in prostate cancer-related genes.

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DRAFT

FIGURES AND TABLES

Figure 1. Cancer Care Ontario genetic testing criteria for prostate cancer.

Hereditary cancer testing eligibility criteria: Version 3 provides specific criteria for genetic testing for hereditary prostate cancer, which includes:	
✓	1. Personal history of metastatic prostate cancer.
✓	2. Documented personal history of high-risk prostate cancer. a. High-risk prostate cancer can be confirmed with evidence of one or more of the following features: T3 (or higher) staging, grade group 4 or 5 (Gleason score 8–10), lymph node involvement, PSA \geq 20.
✓	3. Personal history of metastatic prostate cancer.
✓	4. Personal history of prostate cancer with \geq 1 close relatives with prostate cancer. a. One relative must have evidence of high-risk or metastatic disease.
✓	5. Personal history of prostate cancer with \geq 2 close relatives with prostate, pancreas, ovarian and/or breast cancer regardless of age or stage.

PSA: prostate-specific antigen.

	Canadian Urological Association (2017)²⁹	American Urological Association (2013)³¹	NCCN (2024)⁴¹
Definition of increased risk	Men with a first or second-degree relative with prostate cancer. Men with germline mutations	Men with a strong family history or of African American race.	Men who are of: Black/African American ancestry Have a germline mutation that increases risk for prostate cancer Have a concerning family or personal history

NCCN: National Comprehensive Cancer Network.

Low-risk prostate cancer	Gleason score 6/grade group 1 and PSA <10
Intermediate-risk prostate cancer	Gleason score 7/grade group 2–3 and/or PSA 10–20
High-risk prostate cancer	Gleason score 8–10/grade group 4–5 and/or PSA >20

PSA: prostate-specific antigen.

Family history	Average prostate cancer risk by age 65 (%)		Average prostate cancer risk by age 75 (%)	
	Any PCa	High-risk PCa	Any PCa	High-risk PCa
General population	4.8	1.4	12.9	5.2
1 brother any PCa	14.9	3.0	30.3	8.9
1 brother high-risk PCa	16.1	3.4	31.7	9.3
Father any PCa + 1 brother any PCa	29.8	5.6	47.8	13.8
Father died of PCa + brother any PCa	29.8	6.6	45.0	12.7
2 brothers any PCa	34.4	12.0	55.1	13.4
Father any PCa + 2 brothers any PCa	43.9	11.4	63.6	20.5

PCa: prostate cancer.

Table 4. Prostate cancer risk, aggressiveness, and management based on germline mutation				
Gene	Prostate risk (meta-analysis)	Aggressiveness	Inform care	Other associated cancers
<i>ATM</i>	OR 4.4 ¹⁶	Uncertain	Yes (AS, PARPi)	Breast cancer (male), pancreatic cancer, ovarian cancer
<i>BRCA1</i>	OR 1.35 ¹⁷	Maybe	Yes (AS, PARPi)	Breast cancer (male), pancreatic cancer, ovarian cancer
<i>BRCA2</i>	OR 2.64 ¹⁷	Yes	Yes (AS, surgery, PARPi)	Breast cancer (male), pancreatic cancer, ovarian cancer
<i>CHEK2 1100delC</i>	OR 3.29 ¹⁸	No	No	Breast cancer (male), thyroid cancer, colon cancer
<i>I157T</i>	OR 1.8 ¹⁸	No	No	Breast cancer, thyroid cancer, colon cancer
<i>HOXB13 p.Gly84Glu</i>	OR 3.25 ¹⁹	Uncertain	No	No evidence
Lynch syndrome*	OR 2.13 ²⁰	Uncertain	Yes (PCDi)	Colon cancer, uterine cancer, ovarian cancer, pancreatic cancer, gastric cancer, genitourinary cancers

<i>MSH2</i>	SIR 3.62 (retrospective study) ²¹	Uncertain	Yes (PCDi)	Colon cancer, uterine cancer, ovarian cancer, pancreatic cancer, gastric cancer, genitourinary cancers
<i>PALB2</i>	OR 1.38 ²²	Uncertain	No	Breast cancer (male), ovarian, pancreatic

*Lynch syndrome in this study included individuals with germline PV/LPVs in the genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*. AS: active surveillance; OR: odds ratio; PARPi: PARP-inhibitor; PCDi: programmed cell death inhibitor; SIR: standardized incidence ratio.

	Canadian Preventive Task Force (2014)²	Canadian Urological Association (2017)²⁹	US Preventive Services Task Force (2018)³⁰	American Urological Association (2013)³¹	NCCN (2024)⁴¹
Screening for general population	Against PSA screening for all ages.	Through shared decision-making with a healthcare provider: Men ≥ 50 can make the decision to undergo PSA screening.	Through shared decision-making with a healthcare provider: Men ages 55–69 can make the decision to undergo PSA screening.	Through shared decision-making with a healthcare provider: Men ages 55–69 can make the decision to undergo PSA screening.	Through shared decision-making with a healthcare provider: Men ages 45–75 at average risk can make the decision to undergo PSA screening.

			Against PSA screening in populations >70		
Screening for increased risk population	N/A	Men ages ≥ 45 can make the decision to undergo PSA screening.	N/A	Men ages ≥ 40 can make the decision to undergo PSA screening in a non-routine fashion.	Men ages 40–75 can make the decision to undergo PSA screening.

NCCN: National Comprehensive Cancer Network; PSA: prostate-specific antigen.

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