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PERSPECTIVES IN ONCOLOGY

Male Oncology Research and Education program for men at high risk for prostate cancer

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ABSTRACT

Three groups of men are at high risk of developing prostate cancer: men with a strong family history of prostate cancer, men of West African or Caribbean ancestry, and men with a germline pathogenic variant in a prostate cancer–associated gene. Despite the fact that those men constitute a significant portion of the male population in North America, few recommendations for prostate cancer screening specific to them have been developed.

For men at general population risk for prostate cancer, screening based on prostate-specific antigen (PSA) has remained controversial despite the abundance of literature on the topic. As a result, recommendations made by major screening authorities are inconsistent (ranging from no PSA screening to baseline PSA screening at age 45), allowing physicians to pick and choose how to screen their patients.

The Male Oncology Research and Education (MORE) program is an observational research program that serves as an academic platform for multiple research foci. For its participants, serum and DNA are biobanked, medical information is collected, and contact for relevant research-related opportunities is maintained. This research program is paired with a specialized clinic called the MORE clinic, where men at high risk are regularly screened for prostate cancer in a standard approach that includes physical examination and serum PSA measurement. In this article, we describe the goals, participant accrual to date, and projects specific to this unique program.

Key Words Prostate cancer, research programs, high-risk disease, biobanks, screening, PSA, cancer genetics

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INTRODUCTION

At a lifetime risk of 15%, prostate cancer (PCa) is one of the most commonly diagnosed cancers in men[1]. Fortunately, most men are diagnosed with relatively indolent, localized, and low-grade disease, which has a 98.9% 5-year survival rate for clinically detected cancers[1]. Although the excellent prognosis in screen-detected PCa is likely not solely a result of screening based on prostate-specific antigen (PSA), early detection, compared with waiting for symptomatic presentation at a more advanced stage, increases the chances of receiving potentially less-toxic curative treatment.

Although early detection results in high cancer-specific survival rates, treatment of localized PCa can result in significant complications affecting sexual, urinary, and bowel function—all known to negatively affect health-related quality of life[2]. Not surprisingly, "overtreatment" for an often-indolent disease has resulted in controversy about the use of PSA screening for PCa. That controversy raises a question: Should PSA screening be offered in the general population or on a personalized basis?

At its 13-year follow-up, the European Randomized Study of Screening for Prostate Cancer identified a 21% relative reduction in PCa mortality in men randomized to PSA screening[3]. However, the results of that study must be weighed against the fact that, for every PCa death prevented, 781 men had to be screened, and 27 PCas had to be detected (and presumably treated).

In contrast to the findings of the European Randomized Study of Screening for Prostate Cancer, the U.S. Prostate, Lung, Colorectal, and Ovarian cancer screening trial did not identify a statistically significant effect of PSA-based screening on lowering PCa mortality[4]. That conclusion has been challenged, partly because of concerns about contamination, given the fact that approximately 40% of participants had undergone PSA testing before randomization and that more than 80% of the men in the control arm received PSA testing outside of the study[5,6].

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For many years, the U.S. Preventive Services Task Force[7] and the Canadian Task Force on Preventive Health Care[8] have recommended against PSA screening for men in the general population, stating that the benefits of screening do not outweigh the harms. As a result there has been considerable controversy[9–12]. In 2017, the U.S. Preventive Services Task Force presented a grade C draft recommendation statement suggesting clinician-based discussion of the harms and benefits of PSA screening in men 55–69 years of age[13]. Other cancer organizations take a less conservative approach to PSA screening. For example, the U.S. National Comprehensive Cancer Network recommends that all men have a baseline PSA test at 45 and tailored PSA screening based on PSA level with the use of clinical judgment[14]. The American Urological Association recommends shared decision-making for PSA screening in men 55–69 years of age at average risk of PCa[15]. Men at higher risk of PCa should, on an individual basis, discuss annual PSA screening with their doctor as early as age 40[15].

A clear definition about what qualifies an individual—or population—as being at "high risk" of developing PCa is lacking. Aside from men with consistently elevated PSA or an abnormal digital rectal examination, these three groups of men are known to have an elevated risk for PCa:

- *Family History* A family history of PCa is one of the most powerful predictive factors for the disease. Men with fathers diagnosed with PCa have a relative risk of 2.2 for developing the disease; men with brothers diagnosed have a relative risk of 3.4 (Table I).
- *West African or Caribbean (WA/C) Ancestry* Data from the U.S. Surveillance, Epidemiology, and End Results program identify nearly twice the rate of PCa and more than double the rate of death from PCa in men of African ancestry compared with other men in the United States[1]. More specifically, men of WA/C ancestry connected to the transatlantic slave trade have the highest incidence of PCa in the world[17].
- *Known Genetic Predisposition* Many genes increase the risk for PCa if they contain germline pathogenic variants, with the most well-known being *BRCA1* and *BRCA2*. Men with pathogenic variants in *BRCA1* and *BRCA2* ("*BRCA* carriers") have an elevated risk of developing PCa[18]. Moreover, outcomes are worse—with higher rates of nodal involvement, early progression to metastatic disease, and decreased overall survival—in men with *BRCA2* pathogenic variants than in the general population[19–21]. Multiple studies have also shown that PCa develops at a younger age and a more advanced stage in men with a *BRCA2* pathogenic variant than in those from the general population[22–26]. The prognosis of men with *BRCA1*-associated PCa is less clear; some data suggest an association with a more aggressive course than is seen in the general population[27], but other data show little difference[28].

Given the controversy in PCa screening recommendations for the general population, screening recommendations for men at higher risk of PCa remain unclear. For example, the U.S. Preventive Services Task Force strongly encourages that additional research be done before PSA screening is recommended for men at high risk for PCa[7]. The dearth of research has left men at high risk of PCa vulnerable to inconsistent or no PCa screening. The Sunnybrook Male Oncology Research and Education (MORE) program seeks to address that void in this field of study by collecting data about men at high risk of PCa who undergo PCa screening in the Sunnybrook MORE clinic.

TABLE I Relative risk (RR) of prostate cancer (PCa), given a family history of PCa diagnosis[16]

Risk group	RR
Brother diagnosed at any age	3.4
Father diagnosed at any age	2.2
Affected 1st-degree relatives	
One diagnosed at any age	2.6
Diagnosed at <65 years	3.3
Diagnosed at >65 years	2.4
Two or more diagnosed at any age	5.1
Affected 2nd-degree relatives	
One diagnosed at any age	1.7

MORE PROGRAM

The MORE Clinic

The goal of the MORE clinic is to optimize clinical care for men at high risk of PCa, while also providing a research platform to investigate relevant research topics both independently and with collaborating partners. The MORE clinic began in 2012 with the accrual of male *BRCA* carriers identified through the Sunnybrook Cancer Genetics program. It has been reported in the literature that male *BRCA* carriers are as likely as female carriers to be advocates for research studies[29], and that trend has been corroborated by our experience as brothers, uncles, and cousins of participants who, as *BRCA* carriers, were referred for screening.

At the establishment of the MORE clinic, referrals for men at high risk for PCa—including men with a strong family history of PCa and men of WA/C ancestry—were accepted. Today, men with a *BRCA1* and *BRCA2* pathogenic variant are referred to the MORE clinic from the Sunnybrook Cancer Genetics and High Risk program and from 6 genetics clinics in the Greater Toronto Area and surrounding cities. The clinics were made aware of the MORE clinic through outreach efforts (presentations, information packages, and so on). Men with a family history of PCa and men of WA/C ancestry are referred to the MORE clinic by oncologists in the Sunnybrook Odette Cancer Centre and as a result of additional outreach efforts and word of mouth. The volume of referrals is continually increasing, and clinics have doubled from monthly to twice monthly to accommodate that increase.

Specialized clinics that follow male *BRCA* carriers are not unique[25,30–32]; however, clinics that follow all men at high risk of PCa, including men with a family history and men of WA/C ancestry have not yet been described in the literature. In the MORE clinic, unaffected patients are seen annually for follow-up, which involves serum PSA screening

and digital rectal exam, starting at 40 years of age. All men have a detailed 3-generation family history drawn up by a genetic counsellor, and all non-*BRCA* carriers undergo a risk assessment for genetic testing of *BRCA1* and *BRCA2*. In Ontario, there are 13 criteria for *BRCA1* and *BRCA2* testing, many of which are reserved for women or do not address the current landscape of multiple-gene testing in cancer genetics. When appropriate, male *BRCA* carriers receive clinical breast examinations and a discussion of mammography under a research criterion. The MORE clinic currently has 270 participants, almost 197 of whom are followed annually (Table II).

These are the eligibility criteria for inclusion in the MORE program:

- WA/C ancestry
- Family history of prostate cancer
- Germline pathogenic PCa-related gene variant (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13*, and *NBN*, among others)
- First- or second-degree relative with a PCa-related pathogenic gene variant who declined genetic testing

The MORE Program

The MORE program is an observational research initiative that collects clinical and biologic data from consenting participants. The goal of the MORE program is to act as the academic foundation for addressing research questions relating to the underserved and understudied populations of men at high risk for PCa. Most men involved in the MORE clinic participate in the MORE program, providing a unique opportunity for the research participants to be seen annually while they are visiting for clinical screening. It is during those visits that participants often consent to participating in ongoing and new academic studies at the MORE program or through a network of collaborators.

The MORE program maintains a biobank of blood samples collected from consenting participants (Table II). Per a standard operating procedure, DNA and serum are extracted from blood samples and are stored on-site under a research ethics board–approved protocol. In addition to blood samples, all men in the MORE program consent to provide urine samples and access to tissue samples (for example, prostate biopsies). Plans are in place to eventually expand the biobank to include other biologic samples, such as prostate epithelial cells harvested from urine samples obtained after a digital rectal examination.

ACADEMIC INITIATIVES

Can PCa Risk and Aggressiveness Be Predicted in High-Risk Populations?

There is evidence to support the use of serum biomarkers such as human kallikrein 2, early PCA antigen, urokinase-type plasminogen activator and urokinase-type plasminogen activator receptor, transforming growth factor β1, and interleukin 6 and interleukin 6 receptor to predict aggressive high-grade disease[33]. In addition to serum markers, tumour genetic biomarkers that have been cited as potential predictors of aggressive high-grade disease include *BRCA1* and *BRCA2*, *PTEN*, *KLK6*, cellular *Myc*, *NKX3-1*, and copy-number variation[33–35]. Commercially available single nucleotide polymorphism panels have not had widespread uptake in multiple jurisdictions (including Canada) given they have not been proved to be more effective than current clinical staging at predicting aggressive disease or affecting long-term outcomes[36]. Our serum and tissue biobank provides a foundation to identify novel (or to validate existing) diagnostic, predictive, and prognostic biomarkers of aggressive disease.

What Is the Underlying Cause of PCa in High-Risk Populations?

As many as 5%–10% of PCA cases are thought to be hereditary, but until recently, no "PCA gene" has emerged. Instead, PCA susceptibility genes have lived in the shadow of the high-risk breast and ovarian cancer susceptibility genes *BRCA1* and *BRCA2*[18,37]. A growing body of literature is demonstrating that pathogenic germline variants in other non-homologous DNA repair genes such as *PALB2*, *CHEK2*, and *ATM* are associated with aggressive PCA[38]. Evidence has also associated the mismatch repair genes responsible for Lynch syndrome (*MSH2*, *MSH6*, *MLH1*, *PMS2*, and *EPCAM*) with PCa-related risk, but again, as part of a syndrome of cancer risks[39–41]. In contrast to those syndromic cancer conditions, the germline variant G84E in *HOXB13* is thought to confer a risk solely for PCa, increasing that risk by as much as a factor of 4.5[42,43].

The MORE program aims to further evaluate families with a strong history of PCa for germline susceptibility loci such as those described here. Men in the MORE program who have a personal and family history of PCa would be offered a PCa gene-susceptibility panel. The goal would be to evaluate the utility of current PCa panels for identifying pathogenic germline variants and for establishing

TABLE II Summary of patients enrolled in the Male Oncology Research and Education (MORE) program

Participant characteristic	Participation type				
	Overall (*n*)	Blood and serum biobanked		Followed annually in MORE Clinic	
		(*n*)	(%)	(*n*)	(%)
BRCA carrier	152	126	83	118	78
Family history	105	72	69	78	74
WA/C ancestry	36	21	58	27	75
TOTAL	270	231	86	197	73

WA/C = West African or Caribbean.

preliminary guidelines for offering screening using those panels to men.

Should Screening Be Different for Men at High Risk Than for the General Population?

Prostate magnetic resonance imaging (MRI) is quickly coming into regular use for PCa diagnosis and treatment. Currently, multiparametric 3 T MRI is being used for guided biopsies in many active-surveillance populations around the world, including ours[44]. In Sunnybrook's active-surveillance population, MRI has been evaluated for predicting reclassification into a higher risk category, with positive and negative predictive values of 83% and 81% respectively[45]. Furthermore, a recent study from our group showed that, compared with systematic transrectal ultrasound–guided biopsy, MRI-fusion biopsy was 6.3 times more likely to identify an upgrade to Gleason 7 or greater disease[46]. The use of MRI-fusion biopsy as a first-line tool in diagnosis has been investigated by multiple groups and was recently systematically reviewed[47]; however, its clinical benefit in the general population is still a matter of debate. Yet, as advances in MRI lead to improved detection of significant PCa, the question arises of its utility as a screening tool in men at high risk for PCa.

One group followed in the MORE program that might benefit from earlier detection, given their poor prognosis, are male *BRCA* carriers. We are therefore currently investigating the use of multiparametric 3 T MRI imaging in male *BRCA* carriers 50 years of age and older, independent of PSA (see NCT01990521 at http://ClinicalTrials.gov). The results of that study might provide evidence about the utility of MRI as a screening tool in this at-risk population, as is similarly performed as the standard of care for female *BRCA* carriers.

Can Diet or Exercise, or Both, Lower the Risk of PCa in High-Risk Populations?

The correlation of diet and exercise with PCa risk and prognosis has long been researched and debated, and it remains largely inconclusive today. Inconsistent findings in diet and exercise studies have led to generalized conclusions supporting a heart-healthy diet[48] and an active lifestyle[49]. Despite ambiguity about the effects of diet and exercise in PCa prevention in the general population, information about such effects in men at high risk for PCa—particularly *BRCA* carriers—is notably lacking. Understanding the biology of *BRCA*-related cancer allows researchers to investigate how lifestyle factors might influence cancer risk. Take, for example, a study led by Kotsopoulos[50], demonstrating upregulation of *BRCA1* gene expression in women with germline *BRCA1* pathogenic variants after oral supplementation with 3,3′-diindolylmethane. The MORE program has a research arm evaluating the effects of diet and lifestyle on men at high risk for PCa, with the aim of establishing definitive forms of lifestyle-related PCa prevention.

What Are the Psychosocial Needs of Men at High Risk for PCa?

In North America, media coverage of *BRCA* genes as a women's issue has been solidified by famous women publicly discussing their *BRCA* genetic status[51]. That phenomenon has opened up the question of whether the *BRCA* genes are "gendered," and if so, what is it like being a man with a mutation in a gendered gene? Qualitative literature exploring experiences specific to men who are *BRCA* carriers, such as having a mammogram or living with an increased risk of developing PCa, is lacking. Instead, the literature is focused on men's experiences with genetic counselling and testing, or cancer risk perception[52,53]. The MORE program uses qualitative analysis to understand the long-term effects on men of their known *BRCA* status, with the goal of increasing an understanding on the part of health care providers about patient conceptualizations of self in the context of inherited biomarkers.

SUMMARY

The MORE program is an academic program and specialized clinic initiated by a genetic counsellor (JL) and an oncologist (DV) specializing in genitourinary cancers. It monitors and screens men at high risk for PCa. The goal of the MORE program is to create a foundation for research about men at high risk for PCa and to optimize clinical care for such men. The program has 270 men enrolled, and it continues to enrol 6–8 new patients each month.

The MORE program collaborates with local researchers to identify new biomarkers and pathogenic germline variants and to deliver PCa screening and general and psychosocial aspects of health care to these groups of men at increased risk for PCa. We invite collaborations, and we aim to grow our program into a leading national database for men at high risk for PCa. Please contact the corresponding authors for more information, or visit our Web site at http://www.sunnybrook.ca/MOREclinic.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: DV has received fees as an advisory board member for AbbVie and Astellas. The remaining authors have no conflicts to disclose.

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REFERENCES

1. Howlader N, Noone AM, Krapcho M, *et al. SEER Cancer Statistics Review, 1975–2011.* Bethesda, MD: United States, National Cancer Institute; 2013. [Available online at: http://seer.cancer.gov/csr/1975_2011; cited 18 July 2017]
2. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Intern Med* 2008;148:435–48. [Erratum in: *Ann Intern Med* 2008;148:888]
3. Schröder FH, Hugosson J, Roobol MJ, *et al.* Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet* 2014;384:2027–35.
4. Andriole GL, Crawford ED, Grubb RL 3rd, *et al.* Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst* 2012;104:125–32.
5. Schröder FH, Roobol MJ. ERSPC and PLCO prostate cancer screening studies: what are the differences? *Eur Urol* 2010;58:46–52.

6. Shoag JE, Mittal S, Hu JC. Reevaluating PSA testing rates in the PLCO trial. *N Engl J Med* 2016;374:1795–6.
7. Moyer VA on behalf of the U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012;157:120–34.
8. Bell N, Connor Gorber S, Shane A, *et al.* on behalf of the Canadian Task Force on Preventive Health Care. Recommendations on screening for prostate cancer with the prostate-specific antigen test. *CMAJ* 2014;186:1225–34.
9. McNaughton-Collins MF, Barry MJ. One man at a time—resolving the PSA controversy. *N Engl J Med* 2011;365:1951–3.
10. Brett AS, Ablin RJ. Prostate-cancer screening—what the U.S. Preventive Services Task Force left out. *N Engl J Med* 2011;365:1949–51.
11. Krahn M. Prostate cancer screening: going beyond the clinical evidence. *CMAJ* 2014;186:1201–2.
12. Catalona WJ, D'Amico AV, Fitzgibbons WF, *et al.* What the U.S. Preventive Services Task Force missed in its prostate cancer screening recommendation. *Ann Intern Med* 2012;157:137–8.
13. U.S. Preventive Services Task Force (USPSTF). Draft recommendation statement. Prostate cancer: screening [Web page]. Rockville, MD: USPSTF; 2017. [Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/prostate-cancer-screening1; cited 18 July 2017]
14. Carroll PR, Parsons JK, Andriole G, *et al.* NCCN guidelines insights: prostate cancer early detection, version 2.2016. *J Natl Compr Canc Netw* 2016;14:509–19.
15. Carter HB, Albertsen PC, Barry MJ, *et al.* Early detection of prostate cancer: AUA guideline. *J Urol* 2013;190:419–26.
16. Zeegers MP, Jellema A, Ostrer H. Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. *Cancer* 2003;97:1894–903.
17. Odedina FT, Akinremi TO, Chinegwundoh F, *et al.* Prostate cancer disparities in black men of African descent: a comparative literature review of prostate cancer burden among black men in the United States, Caribbean, United Kingdom, and West Africa. *Infect Agent Cancer* 2009;4(suppl 1):S2.
18. Leongamornlert D, Mahmud N, Tymrakiewicz M, *et al.* Germline *BRCA1* mutations increase prostate cancer risk. *Br J Cancer* 2012;106:1697–701.
19. Castro E, Goh C, Olmos D, *et al.* Germline *BRCA* mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* 2013;31:1748–57.
20. Castro E, Goh C, Leongamornlert D, *et al.* Effect of *BRCA* mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. *Eur Urol* 2015;68:186–93.
21. Akbari MR, Wallis CJ, Toi A, *et al.* The impact of a *BRCA2* mutation on mortality from screen-detected prostate cancer. *Br J Cancer* 2014;111:1238–40.
22. Agalliu I, Karlins E, Kwon EM, *et al.* Rare germline mutations in the *BRCA2* gene are associated with early-onset prostate cancer. *Br J Cancer* 2007;97:826–31.
23. Narod SA, Neuhausen S, Vichodez G, *et al.* Rapid progression of prostate cancer in men with a *BRCA2* mutation. *Br J Cancer* 2008;99:371–4.
24. Edwards SM, Evans DG, Hope Q, *et al.* on behalf of the UK Genetic Prostate Cancer Study Collaborators and BAUS Section of Oncology. Prostate cancer in *BRCA2* germline mutation carriers is associated with poorer prognosis. *Br J Cancer* 2010;103:918–24.
25. Thorne H, Willems AJ, Niedermayr E, *et al.* on behalf of the Kathleen Cunningham Consortium for Research in Familial Breast Cancer Consortium. Decreased prostate cancer-specific survival of men with *BRCA2* mutations from multiple breast cancer families. *Cancer Prev Res (Phila)* 2011;4:1002–10.
26. Kote-Jarai Z, Leongamornlert D, Saunders E, *et al.* *BRCA2* is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. *Br J Cancer* 2011;105:1230–4.
27. Pritchard CC, Mateo J, Walsh MF, *et al.* Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375:443–53.
28. Thompson D, Easton DF on behalf of the Breast Cancer Linkage Consortium. Cancer incidence in *BRCA1* mutation carriers. *J Natl Cancer Inst* 2002;94:1358–65.
29. Pal T, Vadaparampil S, Kim J, *et al.* Interest of individuals from *BRCA* families to participate in research studies focused on male *BRCA* carriers. *Fam Cancer* 2013;12:615–19.
30. Horsburgh S, Matthew A, Bristow R, Trachtenberg J. Male *BRCA1* and *BRCA2* mutation carriers: a pilot study investigating medical characteristics of patients participating in a prostate cancer prevention clinic. *Prostate* 2005;65:124–9.
31. Mitra AV, Bancroft EK, Eeles RA on behalf of the IMPACT steering committee and collaborators. A review of targeted screening for prostate cancer: introducing the IMPACT study. *BJU Int* 2007;99:1350–5. [Erratum in: *BJU Int* 2007;100:718–19]
32. Walker R, Louis A, Berlin A, Horsburgh S, Bristow RG, Trachtenberg J. Prostate cancer screening characteristics in men with *BRCA1/2* mutations attending a high-risk prevention clinic. *Can Urol Assoc J* 2014;8:E783–8.
33. Vesprini D, Liu S, Nam R. Predicting high risk disease using serum and DNA biomarkers. *Curr Opin Urol* 2013;23:252–60.
34. Donovan MJ, Cordon-Cardo C. Predicting high-risk disease using tissue biomarkers. *Curr Opin Urol* 2013;23:245–51.
35. Briollais L, Ozcelik H, Xu J, *et al.* Germline mutations in the kallikrein 6 region and predisposition for aggressive prostate cancer. *J Natl Cancer Inst* 2017;109:djw258.
36. Little J, Wilson B, Carter R, *et al.* Multigene panels in prostate cancer risk assessment: a systematic review. *Genet Med* 2016;18:535–44.
37. Tryggvadóttir L, Vidarsdóttir L, Thorgeirsson T, *et al.* Prostate cancer progression and survival in *BRCA2* mutation carriers. *J Natl Cancer Inst* 2007;99:929–35.
38. Murphy DG, Risbridger GP, Bristow RG, Sandhu S. The evolving narrative of DNA repair gene defects: distinguishing indolent from lethal prostate cancer. *Eur Urol* 2017;71:748–9.
39. Raymond VM, Mukherjee B, Wang F, *et al.* Elevated risk of prostate cancer among men with Lynch syndrome. *J Clin Oncol* 2013;31:1713–18.
40. Haraldsdottir S, Hampel H, Wei L, *et al.* Prostate cancer incidence in males with Lynch syndrome. *Genet Med* 2014;16:553–7.
41. Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2014;23:437–49.
42. Beebe-Dimmer JL, Hathcock M, Yee C, *et al.* The *HOXB13* G84E mutation is associated with an increased risk for prostate cancer and other malignancies. *Cancer Epidemiol Biomarkers Prev* 2015;24:1366–72.
43. Akbari MR, Trachtenberg J, Lee J, *et al.* Association between germline *HOXB13* G84E mutation and risk of prostate cancer. *J Natl Cancer Inst* 2012;104:1260–2.
44. Musunuru HB, Yamamoto T, Klotz L, *et al.* Active surveillance for intermediate risk prostate cancer: survival outcomes in the Sunnybrook experience. *J Urol* 2016;196:1651–8.
45. Margel D, Yap SA, Lawrentschuk N, *et al.* Impact of multiparametric endorectal coil prostate magnetic resonance imaging on disease reclassification among active surveillance candidates: a prospective cohort study. *J Urol* 2012;187:1247–52.
46. Da Rosa MR, Milot L, Sugar L, *et al.* A prospective comparison of MRI–US fused targeted biopsy versus systematic

ultrasound-guided biopsy for detecting clinically significant prostate cancer in patients on active surveillance. *J Magn Reson Imaging* 2015;41:220–5.
47. Haider MA, Yao X, Loblaw A, Finelli A. Multiparametric magnetic resonance imaging in the diagnosis of prostate cancer: a systematic review. *Clin Oncol (R Coll Radiol)* 2016;28:550–67.
48. Lin PH, Aronson W, Freedland SJ. Nutrition, dietary interventions and prostate cancer: the latest evidence. *BMC Med* 2015;13:3.
49. Mohamad H, McNeill G, Haseen F, N'Dow J, Craig LC, Heys SD. The effect of dietary and exercise interventions on body weight in prostate cancer patients: a systematic review. *Nutr Cancer* 2015;67:43–60.
50. Kotsopoulos J, Zhang S, Akbari M, *et al. BRCA1* mRNA levels following a 4–6-week intervention with oral 3,3′-diindolylmethane. *Br J Cancer* 2014;111:1269–74.
51. Lebo PB, Quehenberger F, Kamolz LP, Lumenta DB. The Angelina effect revisited: exploring a media-related impact on public awareness. *Cancer* 2015;121:3959–64.
52. Hesse-Biber S, An C. Within-gender differences in medical decision making among male carriers of the *BRCA* genetic mutation for hereditary breast cancer. *Am J Mens Health* 2017;11:1444–59.
53. Strømsvik N, Råheim M, Gjengedal E. Cancer worry among Norwegian male *BRCA1/2* mutation carriers. *Fam Cancer* 2011;10:597–603.