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Screening men at increased risk for prostate cancer diagnosis: Model estimates of benefits and harms

Roman Gulati[1], **Heather H Cheng**[1], **Paul H Lange**[2], **Peter S Nelson**[1], and **Ruth Etzioni**[1]

[1]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

[2]Division of Medical Oncology, University of Washington, Seattle, WA

Abstract

Background—Guidelines for prostate-specific antigen (PSA) screening in subgroups with increased risk of prostate cancer (PCa) diagnosis due to race or genotype are underdeveloped. Our goal was to investigate types of increased PCa risk and implications for targeted screening.

Methods—Computer simulation of subgroups with average and hypothetical increased risk(s) of onset of latent disease, progression, and/or cancer-specific death. For each subgroup, we predicted lifetime probabilities of overdiagnosis and life saved under more and less intensive PSA screening strategies. An application estimated risks of onset among *BRCA1*/*2* mutation carriers in the IMPACT study using maximum likelihood.

Results—Our simulations implied PSA screening can save more lives among subgroups with increased risk than with average risk, but more intensive screening did not always improve harm-benefit tradeoffs. IMPACT data were consistent with increased risks of onset among *BRCA1* and *BRCA2* mutation carriers (HR=1.05, 95% CI 0.63–1.59 and HR=1.81, 95% CI 1.14–2.78, respectively). Our analysis suggests screening *BRCA2* mutation carriers earlier and more frequently than the average-risk population, but a lower PSA threshold for biopsy is unlikely to improve outcomes.

Conclusions—Effective screening in men with increased PCa risk depends on the manner in which the risk is increased. More intensive screening is not always optimal.

Impact—Guidelines for screening men at increased PCa risk should consider the mechanism inducing the increased risk. While the benefit of screening may be greater in men with increased risks, more intensive screening is not always appropriate.

Keywords

Family history; germline mutations; prostatic neoplasms; prostate-specific antigen; targeted screening

Correspondence: Roman Gulati, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, M2-B230, Seattle WA 98109-1024. Tel: +1.206.667.7795. Fax: +1.206.667.7264. rgulati@fredhutch.org.

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Introduction

Among men in economically developed countries, prostate cancer (PCa) is the most frequently diagnosed tumor and the third most common cause of cancer death (1). Prostate-specific antigen (PSA) screening can advance the point of diagnosis and, when coupled with early treatment, can likely reduce the risk of cancer-specific death (2). However, PSA screening can also detect cancer that would never have presented clinically (3). Current guidelines either recommend against routine PSA-based screening (4, 5) or advocate shared and informed decision-making (6–8) in men with average risk.

Certain subgroups have increased risk for PCa diagnosis. African American men historically had PCa incidence that is 1.6 times that in Caucasian peers. Family history of PCa has also long been recognized as a risk factor (9). Recently, the Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls (IMPACT) study found higher PCa incidence among *BRCA1/2* carriers relative to non-carriers (10).

Higher observed incidence may be due to greater risk of disease onset or more aggressive cancer. Though still controversial, many believe that men of African descent are more likely to be diagnosed with advanced PCa and to die of the disease (11). Studies have indicated that *BRCA1/2* carriers may have higher risk of metastasis and worse cancer-specific survival than non-carriers (12, 13).

A common reaction to identifying a subgroup with increased risk is to consider screening that subgroup more intensively than average-risk individuals. A recent editorial stated that since male germline *BRCA2* mutation carriers have higher risks of early-onset, aggressive disease and higher PCa mortality, “screening intervals should be shorter and the PSA thresholds lower for them than for men in the general population” (14). However, connections between the ways that risk may be increased and appropriate screening approaches have not been systematically studied. Different types of increased risk, including higher frequency of onset of latent disease, more rapid progression to an advanced state, and shorter survival (e.g., due to poor response to standard therapies), may have different implications for targeted screening.

In this article, we investigate targeted screening in men with increased risk of PCa diagnosis. We adapt an established model of PCa natural history, detection, and survival to implement possible mechanisms of increased risk and use the resulting models to examine harm-benefit tradeoffs of different strategies. We demonstrate general lessons by considering screening decisions for men with germline *BRCA* mutations.

Materials and Methods

Modeling average and increased risks

To investigate targeted screening in subgroups with average and increased PCa risks, we used the Fred Hutchinson Cancer Research Center (FHCRC) model (15, 16). The model projects PSA growth before and after onset of latent disease using data from the placebo arm

of the Prostate Cancer Prevention Trial (17). The risk of onset increases with age, and risks of progression to metastasis and to diagnosis increase with PSA levels. These risks were estimated so the model simulates PCa incidence under US screening patterns that matches incidence in the Surveillance, Epidemiology, and End Results (SEER) program.

To implement US screening patterns, we used a reconstruction (18) that combined data from the National Health Interview Survey and the SEER-Medicare database. Following common practice in the US, we assumed men with PSA >4.0 ng/mL were referred to biopsy. Receipt of biopsy was based on frequencies in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial (19), which involved patient-physician decision-making and reflects real-world practice. Finally, we assumed biopsy sensitivity to detect latent cancer increased with calendar year to reflect dissemination of extended-core biopsy schemes (15).

In the absence of treatment, cancer-specific survival was derived from SEER untreated cases diagnosed in 1983–1986, just before PSA screening began. Early detection improves survival by detecting would-be metastatic cases while they are still localized and re-assigns survival accordingly. This “stage-shift” effect of screening is consistent with the mortality reduction in the European Randomized Study of Screening for Prostate Cancer (16) and is not contradicted by PLCO results (20). Frequencies of initial treatment were derived from SEER cases diagnosed in 2010 by age and tumor stage and grade. Efficacy of radical prostatectomy was based on the Scandinavian trial of prostatectomy vs watchful waiting (hazard ratio [HR] 0.56) (21), and we assumed similar efficacy for contemporary radiation therapy (22, 23). Non-cancer survival was based on US life tables (24), and overall survival was the earlier of cancer-specific and non-cancer survival.

The model allowed us to project disease prevalence, incidence, and PCa mortality in the average-risk population. Under a specified screening strategy, we estimated the lifetime probability of overdiagnosis as the frequency of screen-detected cancers that would not present clinically before non-cancer death and the lifetime probability of life saved as the difference between model-projected frequencies of PCa death with and without screening (16).

To represent hypothetical increased risks, we applied a multiplicative factor (HR=2.0) to risks of latent onset, progression to a symptomatic or metastatic state, and/or PCa death following diagnosis. For each type of increased risk, we simulated outcomes for 10 million men under all combinations of starting age (40, 45, or 50 yr), ending age (64 or 69 yr), frequency (annual or biennial), and PSA threshold for biopsy (1.0 or 3.0 ng/mL). We calculated lifetime probabilities of overdiagnosis and life saved, and we compared approaches using the additional number needed to diagnose to prevent one PCa death (NND), calculated as the ratio of these probabilities. We defined preferred strategies as those with NND≤5 as an example of a policy target; in specific settings other criteria could be used.

Men with germline *BRCA* mutations

To investigate how risk might be increased for men with germline *BRCA* mutations, we estimated the risk of latent onset corresponding to *BRCA* status using published results from

the first screening round of the IMPACT study (10). IMPACT investigators recruited undiagnosed men aged 40–69 yr from families with known or suspected *BRCA1* or *BRCA2* mutations in 2005–2013 and assigned carrier status based on genetic testing. Participants were offered annual (biennial in the Netherlands) PSA screening with referral to biopsy for PSA >3.0 ng/mL.

We simulated *BRCA1* and *BRCA2* cohorts in the IMPACT study and identified increased risks of onset relative to the general population that best matched study results. Before entering the study, we assumed participants were screened according to patterns in the US before 1995 (18) with biopsy frequency and sensitivity as for average-risk men. After recruitment, we assumed 80% of men with PSA >3.0 ng/mL received a biopsy to match study results (10) and a biopsy had 90% sensitivity to detect cancer for consistency with the number of cores in the study protocol. We simulated each cohort 10,000 times over a range of values for the HR for onset; estimation was based on maximizing a Poisson likelihood for observed and projected cancers diagnosed, and 95% confidence intervals (CIs) were derived using the profile likelihood method (25).

Results

Figure 1 illustrates model-projected Kaplan-Meier curves for the specified endpoints among men at average and increased (doubled) risks of latent onset, diagnosis, and cancer-specific death. The risk of diagnosis is among men with onset in their lifetimes, and the risk of cancer death is among men who present clinically. All endpoints are in the absence of screening, treatment, or competing death.

Figure 2 illustrates projected lifetime probabilities of overdiagnosis and life saved by screening for men with average and all combinations of increased risks. Dashed lines show NND=5; strategies above this line have fewer than 5 overdiagnoses per life saved.

In the average-risk population (upper left panel), biennial screening to age 64 yr with biopsy referral when PSA >3.0 ng/mL had the smallest NNDs (range across starting ages 4.1–4.4), changing to annual screening raised NNDs closer to 5, and screening to age 69 yr pushed NNDs above 5. All strategies with biopsy referral for PSA >1.0 ng/mL implied substantially higher NNDs (range 7.8–9.9) due to more overdiagnosis with few additional lives saved.

In men with increased risk of onset, the NNDs of all strategies had similar rank order as in average-risk men, but probabilities of overdiagnosis and life saved were both higher. In men with increased risk of progression, the probability of overdiagnosis was lower and the probability of life saved was higher compared to average-risk men under the same strategies. In men with increased risk of cancer death, the probability of overdiagnosis was similar and the probability of life saved was higher compared to average-risk men. These results match expectations.

In men with increased risks of onset and progression, a greater number of screening strategies yielded NND≤5 compared to average-risk men. Thus, if our goal was to achieve NND≤5 while maximizing benefit, we could consider more intensive strategies in men at higher risk. For example, annual screening to age 69 yr with PSA threshold 3.0 ng/mL could

be considered in men with increased risks of onset and progression but not in average-risk men or in men with only increased risk of onset. This example shows that preferred strategies may differ across subgroups with different mechanisms of increased risk. In no subgroup did lowering the PSA threshold from 3.0 to 1.0 ng/mL improve outcomes, indicating that, under our model assumptions, these strategies would not be preferred.

Last, we examine men with germline *BRCA1/2* mutations. Our assumptions about screening before the IMPACT study implied 35% of simulated participants received at least one PSA test, similar to the reported 37% of participants (10). Comparing observed and projected cancers diagnosed during a single round of screening, we estimated non-significantly increased risk of onset in *BRCA1* carriers (HR=1.05, 95% CI 0.63–1.59) and significantly increased risk of onset in *BRCA2* carriers (HR=1.81, 95% CI 1.14–2.78). Consequently, our general results about screening men at increased risk of onset may apply to *BRCA2* mutation carriers. In particular, a wider range of screening ages may be acceptable, but lowering the PSA threshold for biopsy referral is likely to increase overdiagnosis with few additional lives saved.

Discussion

Risk stratification promises to reduce the costs and harms of screening by focusing resources on the subgroups most likely to benefit. However, realizing its potential requires that we understand the mechanisms by which the subgroups have increased risk. Is the increased risk due to earlier and more frequent disease onset, greater likelihood of progression to symptoms or metastasis, shorter survival, or some combination of these?

This article investigates ways in which the risk of PCa diagnosis might be increased and links the mechanism of increased risk to targeted screening strategies. Although it may seem intuitive that higher risk strata should be screened more intensively than those with average risk, we note that in certain cases, more intensive screening may achieve greater benefit only at the expense of much greater harm. A key conclusion of our investigation is that the way in which risk is increased should factor into the decision about whether and how to recommend screening.

We also offer the following specific conclusions. (1) Individuals with increased risk of onset are both more likely to be overdiagnosed and more likely to benefit from early detection, and thus appropriate screening ages and intervals depend on the tradeoffs deemed acceptable. (2) Individuals with increased risk of progression are less likely to be overdiagnosed, and a shorter interval between screens may be recommended. (3) Individuals with increased risk of cancer death are more likely to benefit from early detection, and a shorter interval between screens may also be recommended provided the survival benefit is greater with earlier detection (as assumed in this study). However, in general, we find that a lower PSA threshold for biopsy disproportionately increases overdiagnoses relative to additional lives saved. Therefore we do not recommend this unless the increased chance of overdiagnosis is considered to be acceptable given the additional lives saved.

It might seem surprising that men with increased risk of onset can be more likely to be overdiagnosed. This association is a direct consequence of representing this increased risk using a hazard ratio: a hazard ratio greater than 1 implies not only onset at an earlier age, on average, but also a higher cumulative prevalence of latent disease at every age, relative to the general population. In other words, under this mechanism of increased risk, the high-risk subgroup always has a larger pool of latent disease, and consequently greater absolute magnitudes of screening harms and benefits. However, the higher chance of overdiagnosis due to increased risk of onset may be partially or completely offset by increased risk of progression, so the net effect on the chance of overdiagnosis depends on the relative magnitudes of these increased risks.

This work was motivated by research linking the frequency of PCa, and particularly metastatic PCa, with germline mutations in *BRCA2* and other DNA repair genes (26, 27). As genetic screening appears set to expand in these patients, counseling unaffected family members may become increasingly common. Within our model, we estimated that *BRCA2* germline mutation carriers in the IMPACT study have 81% higher risk of onset than the general population. If *BRCA2* is only associated with increased risk of onset, we would recommend a wider range of screening ages than in the average-risk population. However, there is accumulating evidence that men with germline *BRCA1/2* mutations also exhibit varying degrees of more aggressive tumor features and worse baseline survival than average-risk men (12). A recent study estimated HR=2.36 for the risk of metastasis after treatment and HR=2.17 for cause-specific survival after treatment among all (*BRCA1* and *BRCA2*) mutation carriers combined (13). These results suggest that *BRCA2* carriers may resemble the highest-risk subgroup in Figure 2 and motivates considering an expanded range of screening ages and more frequent screen tests in these men. However, based on our analysis, lowering the PSA threshold for biopsy (e.g., using a PSA threshold of 1.0 ng/mL over a more accepted threshold like 3.0 ng/mL) would not be well-advised.

The problem of tailoring screening to subgroups with differing genetic risk has been recognized previously. In breast cancer, Kurian et al. considered women with *BRCA1* and *BRCA2* mutations and developed a tool to project disease incidence and mortality under different prevention and screening strategies (28, 29). Heijnsdijk et al. examined natural history in these women and evaluated mammography screening with and without magnetic resonance imaging (30). In PCa, Yen et al. considered risk stratification using single-nucleotide polymorphisms and presented suggestions for more intensive screening in men with higher risk to reduce mortality by a similar magnitude to that achievable in the average-risk population (31). Pashayan et al. projected implications of screening based on polygenic risk rather than age in breast and PCa (32). These studies also reflect the importance of understanding mechanisms and magnitudes of increased risk before developing targeted screening strategies.

In practice, developing an appropriate screening strategy in a particular subgroup requires prospectively collected serial screening and incidence data and a model that can estimate average and increased risks of disease onset and sojourn times (33). For PCa and other cancers, natural history has already been studied for the average-risk population and certain increased-risk subgroups (34). Once preferred screening strategies are determined in

particular high-risk subgroups, further research is needed to investigate programs to identify the high-risk strata (e.g., genetic screening).

Like all modeling applications, ours is subject to limitations. The FHCRC model is a simplification of PSA growth and cancer progression designed to approximate the general male population. Because different components of the model were estimated using different data sources, its absolute projections may be less reliable than relative comparisons. Furthermore, although it closely approximates US PCa incidence trends with and without PSA screening by age, stage, and grade, the model abstracts a set of complex biological processes and interventions, and it may not generalize to particular subgroups. For example, increased risks may not be simple multiples of average risks. Our main data source for germline *BRCA* mutation carriers, the IMPACT study, is also limited. Importantly, carriers in this study may not be representative of the general carrier population. Further, it involves only one round of screening and no metastatic cases. Thus, we cannot use this study to determine precisely which mechanism of increased risk (onset or progression) explains the observed incidence in that study. Consequently, we also consider other studies that bear on the mechanism of increased risk among *BRCA1/2* mutation carriers.

In conclusion, different mechanisms and magnitudes of increased PCa risks produce different levels of harms and benefits for a given screening approach. Consequently, screening guidelines for men with increased risk should take evidence about these factors into account. In general, while an efficacious screening test can produce greater benefit in subgroups with increased risk than in the average-risk population, more intensive screening does not always improve harm-benefit tradeoffs.

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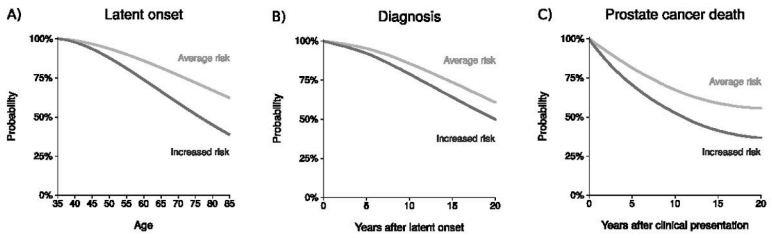

Figure 1.

Average risks of prostate cancer A) latent onset, B) diagnosis, and C) death in the absence of screening, treatment, or competing mortality estimated by the FHCRC model, and hypothetical increased risks reflecting hazard ratios of 2.0.

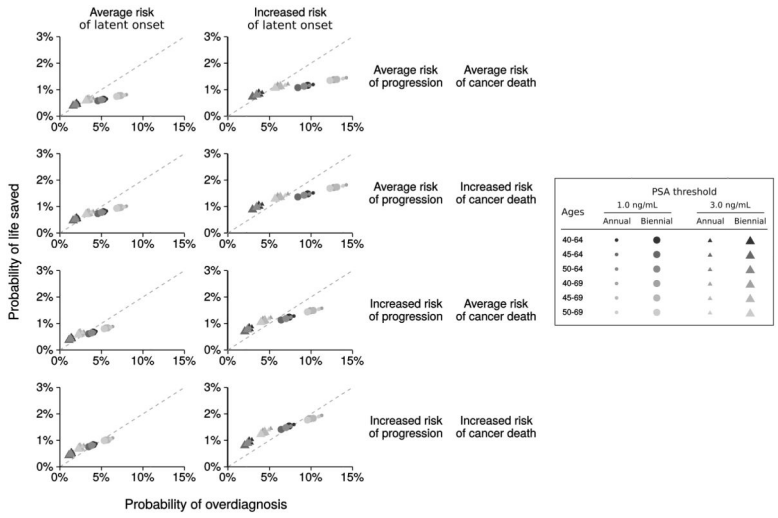

Figure 2.

Lifetime probability of overdiagnosis and life saved by screening for men with average and increased risk(s) of onset of latent prostate cancer, progression to a symptomatic or metastatic state, and/or cancer death predicted by the FHCRC model.