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ORIGINAL ARTICLE

Imaging-based prostate cancer screening among *BRCA* mutation carriers—results from the first round of screening

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Background: Male-carriers of *BRCA1/2* gene mutations have an increased risk of prostate cancer (PCa) with a more aggressive phenotype. Current screening-guidelines suggest the use of prostate-specific antigen (PSA) only among *BRCA2* carriers. Female carriers have extensive guidelines that include imaging. Our objective was to test the prevalence of PCa among *BRCA* carriers and examine screening strategies, using PSA and multiparametric magnetic resonance imaging (mpMRI).

Patients and methods: We recruited men aged 40—70 years with *BRCA1/2* germline mutations and no prior history of prostate biopsy. All men underwent an initial round of screening which included PSA, and prostate mpMRI. PSA was considered elevated using an age-stratified threshold of $\geq$1 ng/ml for 40—50 years of age, $\geq$2 ng/ml for 50—60 years of age, and 2.5 ng/ml for 60—70 years of age. Men with elevated PSA and/or suspicious lesion on mpMRI were offered a prostate biopsy. PSA levels, MRI findings, PCa incidence, and tumor characteristics were evaluated. Decision curve analysis was used to compare screening strategies.

Results: We recruited 188 men (108 BRCA1, 80 BRCA2), mean age 54 years (9.8). One hundred and ten (57%) had either elevated age-stratified PSA (75; 40%), a suspicious MRI lesion (67; 36%), or both (32; 17%). Of these, 92 (85%) agreed to perform a prostate biopsy. Sixteen (8.5%) were diagnosed with PCa; 44% of the tumors were classified as intermediate- or high-risk disease. mpMRI-based screening missed only one of the cancers (6%), while age-stratified PSA would have missed five (31%). Decision curve analysis showed that mpMRI screening, regardless of PSA, had the highest net benefit for PCa diagnosis, especially among men younger than 55 years of age. We found no difference in the risk of PCa between BRCA1 and BRCA2 (8.3% versus 8.7%, $P = 0.91$). Ninety percent had a Jewish founder mutation, thus the results cannot be generalized to all ethnic groups.

Conclusions: PCa is prevalent among *BRCA* carriers. Age may affect screening strategy for PCa in this population. Young carriers could benefit from initial MRI screening. *BRCA* carriers aged older than 55 years should use PSA and be referred to mpMRI if elevated.

Trial registration: ClinicalTrial.gov ID: NCT02053805.

Key words: BRCA, magnetic resonance imaging, prostate cancer, PSA, screening

INTRODUCTION

A higher incidence of prostate cancer (PCa) has been consistently described in *BRCA2* carriers and is debatable in *BRCA1* carriers.[1–3] The study be Nyberg et al.[3] reported an increased risk of PCa in both *BRCA1* and *BRCA2* mutation carriers, the relative risk being higher in *BRCA2* than *BRCA1*. In addition to an increased risk, *BRCA* mutations may confer a more aggressive phenotype of PCa. Germline *BRCA1* and *BRCA2* mutations are associated with higher grade and higher stage disease, nodal involvement, and metastases at time of presentation compared with non-*BRCA*-associated PCa.[2–5] Furthermore, *BRCA1* and *BRCA2* are significantly associated with an increased risk of recurrence, progression to metastatic disease, and PCa-specific death.[2–6]

The IMPACT study is the first prospective study to evaluate screening in *BRCA* carriers for PCa.[7] After 3 years of screening, compared with non-carriers, *BRCA2* mutation carriers were associated with a higher incidence of PCa,

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younger age of diagnosis, and clinically significant tumors. Based on these findings, the authors recommend a systematic prostate-specific antigen (PSA) screening for men with a *BRCA2* mutation.[7,8]

In female *BRCA* carriers, magnetic resonance imaging (MRI) is routinely used as part of the breast cancer screening protocol.[9,10] The role of MRI screening among males has not been explored. European Association of Urology (EAU) guidelines recommend the use of prostate MRI before biopsy, but specifically state it should not be used for screening.[11] We now report the results of a prospective screening study for PCa among a genetically high-risk population of male *BRCA* carriers using PSA and MRI.

PATIENTS AND METHODS

The study design and methods were previously reported.[12] The protocol was approved by the Rabin Medical Center Ethics Committee in Israel. Written informed consent was obtained for all participants.

Study population

We recruited men aged 40—70 years with *BRCA1* and *BRCA2* germline mutation between the years 2014 and 2018. Men were excluded if they had a previous history of PCa and/or prostate biopsy.

First round screening protocol

Upon enrolment, all patients underwent PSA and multiparametric (mp) MRI. Patients with an abnormal finding on any of these tests were offered a prostate biopsy.

PSA thresholds

Since this was a screening trial for a high-risk, genetically predisposed population, we used strict age-stratified PSA criteria. PSA was considered elevated when: PSA $\geq$ 1 ng/ml for ages 40—50 years,[11] $\geq$2 ng/ml for ages 50—60 years,[13] and $\geq$2.5 ng/ml for ages 60—70 years.[14,15]

Multiparametric MRI

mpMRI was carried out with a Philips Ingenia 3.0 Tesla MRI scanner, Eindhoven, Netherlands using an external coil. The imaging protocol included T2-weighted images obtained in three orthogonal planes, axial diffusion-weighted images obtained with multiple b values (0, 100, 1000, and 1500 s/mm^2), and axial dynamic contrast-enhanced images. Areas suggestive of PCa were graded by two dedicated uroradiologists (ST, OB) according to the Prostate Imaging-Reporting and Data System, version 2 (PI-RADS v2); suspected lesions with PI-RADS score $\geq$3 were considered abnormal.[16]

Prostate biopsy

Prostate biopsy was offered only if any screening test was abnormal (i.e. elevated age-stratified PSA or MRI PI-RADS 3 or above). Per institutional review board (IRB) request, we did not perform biopsies to those with normal PSA and imaging.

All consenting subjects had a 12 core systematic prostate biopsy (BK-flex500, BK Medical, Quickborn, Germany). Subjects with a suspicious MRI lesion (PI-RADS $\geq$3) underwent additional targeted biopsy during the same session (Navigo, UC-Care, Yokneam, Israel). A dedicated uropathologist reviewed all pathology specimens (YM).

Statistical analysis

Primary outcome and sample size calculation. The primary outcome of this study was to estimate the prevalence of PCa among male *BRCA* carriers in Israel. To estimate the prevalence of PCa in Israel we utilized the Clalit Health Services databases. Clalit is the largest health insurer in Israel and covers more than half of the Israeli population. We found that the prevalence of PCa among Israeli males aged between 40 and 70 years is 0.65%. Initial results from the IMPACT study suggest that among male *BRCA* carriers, the prevalence of PCa was 2.8%. To determine that the rate of PCa among *BRCA* carriers is at least 2.8%, we required a study with 190 carriers.[7] This analysis used a power of 80% and a two-tailed α of 0.05.

Evaluation of possible screening strategies. As the criteria we used for biopsy included the lowest PSA threshold or any imaging finding, we were able to compare stricter criteria. These were chosen based on clinical utility. We modeled the possible outcomes of these screening strategies based on the actual results of our cohort. We restricted this analysis to those who carried out a biopsy.

PSA only screening	Strategy 1:	PSA>3
	Strategy 2:	Elevated Age-stratified PSA
MRI only screening:	Strategy 3:	PI-RADS≥3
PSA triage before MRI screening:	Strategy 4:	PSA>3 AND PI-RADS≥3
	Strategy 5:	Elevated age-stratified PSA AND PI-RADS≥3

We calculated the number of biopsies avoided in each screening strategy by subtracting the number of biopsies that would have been carried out from the total number of biopsies actually carried out in our cohort. The numbers of cancers diagnosed and/or missed for each strategy were calculated. Finally, we carried out decision curve analysis to compare the net benefit of each screening strategy. The net benefit is a number that reflects the probability of detecting PCa at the cost of additional biopsies carried out.

All statistical analyses were carried out with SPSS version 21 IBM, Armonk, NY and decision curve analysis was carried out with Stata version 14.2, College Station, TX.

RESULTS

We recruited 188 men with a mean age of 54 years (9.8). Of these, 108 subjects had a *BRCA1* mutation and 80 had a *BRCA2* mutation (Table 1). Most patients (187, 99.5%) had a

Table 1. Baseline characteristics of the study cohort

Variable	Total ($N = 188$)	*BRCA1* ($n = 108$)	*BRCA2* ($n = 80$)	*P* value*
Mean age in years (± SD)	54 (± 9.8)	55.4 (± 9.5)	52.1 (± 9.9)	0.02**
Type of mutation *N* (%)				
185delAG		84 (44)		
5382inSC		17 (9)		
Tyr987X		4 (2)		
6174delIT			69 (36)	
8765delAG			4 (2)	
Other		3 (2)	7 (4)	
Patients with familial history of cancer *N* (%)				
Any cancer	187 (99.5)	107 (99.5)	80 (100)	0.53
Prostate	45 (24)	23 (21.5)	22 (27.5)	0.43
Ovary	74 (40)	42 (39.3)	32 (40.0)	0.91
Breast	151 (80)	90 (84.1)	61 (76.3)	0.22
Pancreas	41 (22)	19 (17.8)	22 (27.5)	0.15
Colon	46 (25)	30 (28)	16 (20)	0.27
Melanoma	23 (12)	13 (12.1)	10 (12.5)	0.94
Patients with personal history of cancer *N* (%)				
Any cancer	24 (12.8)	11 (10)	13 (16)	0.21
Melanoma	8 (4.3)	4 (3.7)	4 (5)	0.66
Non-melanoma skin caner	8 (4.3)	4 (3.7)	4 (5)	0.66
Breast	3 (1.6)	1 (0.9)	2 (2.5)	0.39
Non-*BRCA* related	5 (2.7)	2 (1.8)	3 (3.7)	0.42

SD, standard deviation.
* *P* value for the comparison between *BRCA1* and *BRCA2* mutation carriers. *P* value calculated by chi-square test.
** *P* value calculated by Student's *t*-test.

familial history of cancer and 24% had a familial history of PCa. Ninety percent of subjects had one of the three Ashkenazi Jewish founder mutations (*BRCA1*: *185delAG* $n = 84$; *5382inSC* $n = 17$ patients; *BRCA2*: *6174delT* $n = 69$).

For initial screening we carried out PSA on 187 subjects and MRI on 177 subjects in our cohort (Figure 1). Sixty-nine subjects (37%) had both normal MRI and normal age-adjusted PSA. All other subjects (110; 57%) had either elevated age-stratified PSA (75; 40%), a suspicious MRI lesion (67; 36%), or both (32; 17%). Of these, 92 (85%) agreed to perform a prostate biopsy (Figure 1).

Median PSA was 1 (interquartile range 0.6—1.8) and median prostate volume was 30 (interquartile range 22—44); both increased with age (Table 2). Forty percent of our cohort had an elevated age-stratified PSA. This was equal across age groups. We detected a suspicious MRI lesion in 67 (36%) subjects (PI-RADS 3, 18%; PI-RADS 4, 14%; PI-RADS 5, 3%). Subjects between 40 and 50 years of age had significantly less findings on prostate MRI ($P = 0.005$) (Table 3).

We detected a total of 16 PCa (8.5%), out of which 7 cases (44%) were Gleason grade group 2 (GG2) and above (Table 4). Eleven of 16 cancers (69%) and 4 of the 7 GG2 and above cancers (57%) were detected only by MRI-targeted biopsies (Table 5). Three cancers had intraductal carcinoma (Table 5). Among subjects between 40 and 50 years of age, we detected three cases of PCa (3.7%); all were GG1. All these cases had PSA levels <1, and were sent to biopsy based only on MRI findings. Among subjects aged more than 50 years, we detected 13 (12.1%) cases of PCa, (six cases of GG1; five of GG2; one of GG3; and one of GG5). There were no differences between the 50—60 years and 60—70 years age groups in PCa prevalence or in the percentage of GG2 and above cancers (Table 4).

We found no difference between PCa detection rates of *BRCA1* carriers (8.3%) and *BRCA2* carriers (8.8%; $P = 0.91$). However, 23% of the *BRCA1* cancers were GG2 or above, compared with 71% of *BRCA2* cancers ($P = 0.049$) (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2020.06.025). Data stratified by *BRCA* type and age is presented in Supplementary Tables S1—S3, available at https://doi.org/10.1016/j.annonc.2020.06.025.

Among the 92 men who underwent a prostate biopsy, we tested five possible screening strategies using different PSA thresholds with or without prostate MRI (Table 6). All strategies that included MRI as a screening tool were more effective than PSA alone in detecting PCa. The best strategy that detected 15 out 16 cancers (94%) was the use of MRI only without PSA as a screening tool. However, this comes at a cost of performing many unnecessary biopsies {positive predictive value (PPV) = 23.8% [95% confidence interval (CI) 20.2—27.9]}. The second-best strategy that detected 10 out of 16 cases (63%) was based on elevated age-stratified PSA followed by MRI. Although this strategy missed six cases, five of them were GG1.

We used decision curve analysis to compare the net benefit of each approach (Figure 2A). When the probability for PCa is low, the highest net benefit is imaging regardless of PSA; MRI for every patient and fusion biopsy in case there is a lesion. When the probability of PCa increases and reaches approximately 20%, the highest net benefit stems from triaging imaging using PSA first. PSA without imaging shows a linear line and has the same low net benefit.

To identify a clinical parameter that may be useful to optimize the screening protocol for *BRCA* carriers, we stratified our cohort based on age. Figure 2B shows that for *BRCA* subjects less than 55 years of age, MRI regardless of PSA has the highest net benefit. Conversely, for subjects

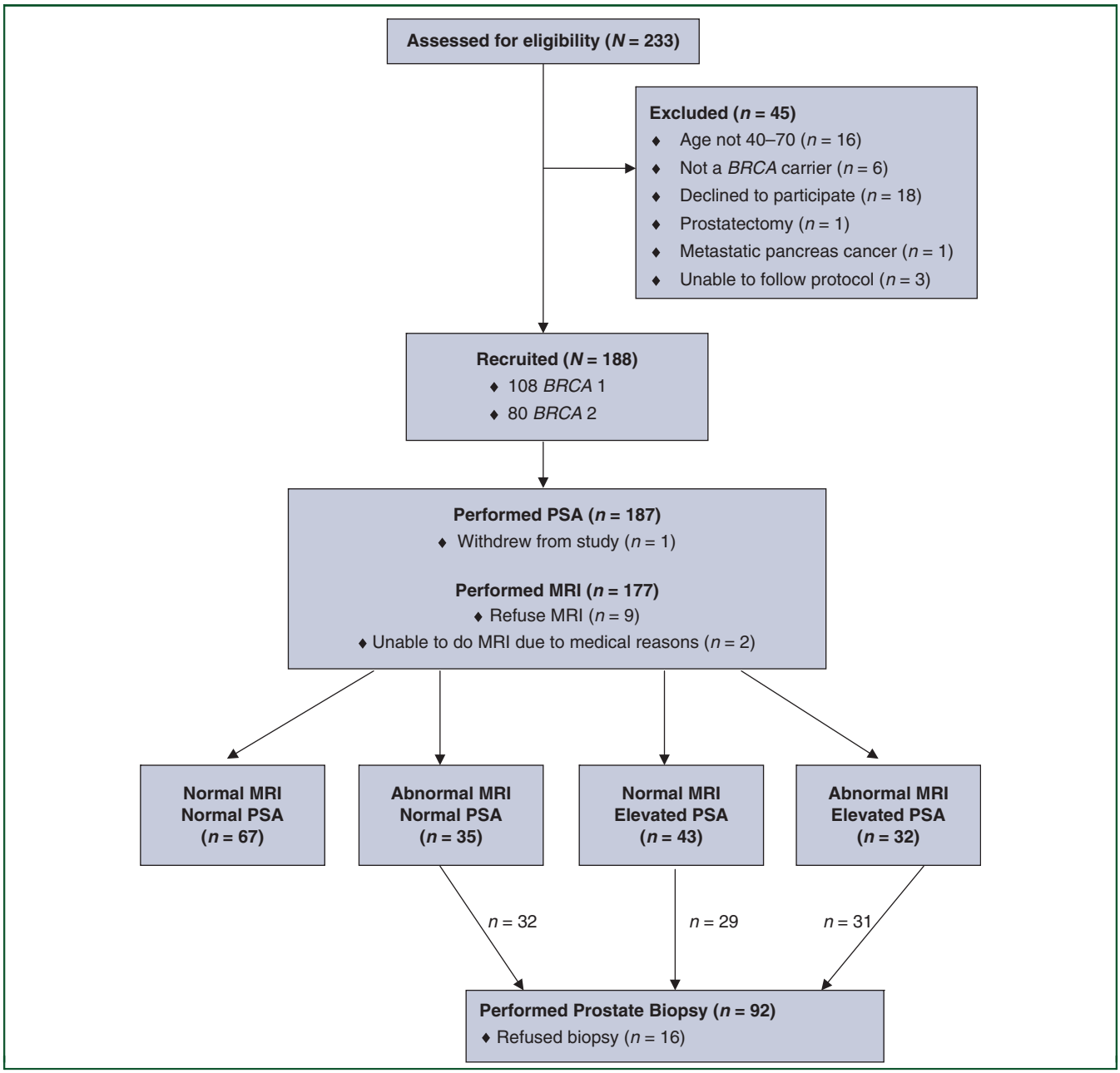

Figure 1. CONSORT diagram.
Study enrollment and flow—first round of screening. MRI, magnetic resonance imaging; PSA, prostate-specific antigen.

aged more than 55 years old, PSA screening added value, and age-stratified PSA followed by MRI had the highest net benefit for diagnosis of PCa (Figure 2C). Of note, for young carriers (less than 55 years old), the net benefit for the PSA only strategies was zero, meaning MRI was vital for diagnosis at this age group.

Table 2. Summary of initial PSA results from the first round of prostate cancer screening stratified by age

	40–50 *n* = 81	50–60 *n* = 41	60–70 *n* = 66	*P* value*	Total *N* = 188
PSA, ng/ml (median, IQR)	0.7 (0.5–1)	1 (0.6–1.7)	2 (1–4.1)	<0.001	1 (0.6–1.8)
PSA density, ng/ml^2 (median, IQR)	0.03 (0.01–0.05)	0.03 (0.02–0.05)	0.04 (0.02–0.07)	0.019	0.03 (0.02–0.05)
Prostate volume, ml (median, IQR)	23 (19–29)	33 (25–42)	45 (33–69)	<0.001	30 (22–44)
Patients with age-specific elevated PSA[a] (no. pts., %)	31 (38)	13 (31)	31 (47)	0.27	75 (40)

IQR, interquartile range; no. pts., number of patients; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density.
[a] PSA value was considered elevated if ≥1 ng/ml for ages 40–50 years, ≥2 ng/ml for ages 50–60 years, and ≥2.5 ng/ml for ages 60–70 years.
* *P* value for comparison between age groups calculated by Kruskal–Wallis test.

Table 3. Summary of mpMRI findings from the first round of prostate cancer screening stratified by age

	Age group (years)	40–50 *n = 81*	50–60 *n = 41*	60–70 *n = 66*	Total *N = 188*
mpMRI findings[a] (no. pts., %)*	No MRI	5 (6)	1 (2)	5 (8)	11 (6)
	Normal MRI	56 (69)	18 (44)	36 (55)	110 (59)
	PI-RADS 3	11 (14)	10 (24)	13 (20)	34 (18)
	PI-RADS 4	9 (11)	9 (22)	9 (14)	27 (14)
	PI-RADS 5	0	3 (7)	3 (5)	6 (3)

no. pts., number of patients; mpMRI, multiparametric magnetic resonance imaging; PI-RADS, Prostate Imaging-Reporting and Data System.

[a] Highest score given among all lesions found on mpMRI.

* *P* value for comparison between age groups = 0.008 (chi-square test).

DISCUSSION

This is the first trial to use prostate-MRI as a screening tool for a high-risk population. In this first round of screening, PCa prevalence among *BRCA* carriers was 8.5%. We found that the most effective screening strategy was MRI, regardless of PSA values. This was most prominent among males younger than 55 years of age. The prevalence of PCa was similar between *BRCA1* (8.3%) and *BRCA2* (8.75%) carriers.

The IMPACT study was the first prospective study evaluating the role of PCa screening in an international cohort of men with *BRCA1/2* mutations.[7,8] They used PSA > 3 as a cut-off for prostate biopsy. Patients underwent systematic biopsy. The mean age at enrollment was 54 years, similar to our cohort. In the first round of screening, they reported a diagnostic rate of 2.3% (*BRCA1*) and 3.3% (*BRCA2*).[7] Implementing this strategy in our study (i.e. PSA > 3 and systematic biopsy, our Strategy 1), we would have detected a similar rate (five cancers, 2.7%). The IMPACT based their screening on PSA alone. Recent studies have shown a benefit for using MRI before performing prostate biopsy. Data from the PRECISION trial,[17] MRI-FIRST, and 4M support the use of MRI before prostate biopsy, but not as a screening tool.[18,19]

To the best of our knowledge, only one previous study evaluated MRI as a screening tool for PCa in the general population. Nam et al.[20] carried out a pilot study among unselected men. They recruited 47 men and detected 18 cancers (38.3%). They found that MRI was a stronger predictor of PCa compared with PSA.

Table 4. Summary of biopsy findings from the first round of prostate cancer screening stratified by age

	Age group (years)	40–50 *n = 81*	50–60 *n = 41*	60–70 *n = 66*	Total *N = 188*
Prostate biopsy results (no. pts., %)*	PCa GG1	3 (3.7)	2 (4.9)	4 (6)	9 (4.8)
	PCa GG2		2 (4.9)	3 (4.5)	5 (2.7)
	PCa GG3			1 (1.5)	1 (0.5)
	PCa GG4				
	PCa GG5		1 (2.4)		1 (0.5)
TOTAL		3 (3.7)	5 (12)	8 (12)	16 (8.5)

GG, Gleason grade group; no. pts., number of patients; PCa, prostate cancer.

* *P* value for comparison between age groups = 0.22 (chi-square test).

Current guidelines specifically object to the use of MRI as a screening tool for PCa.[11] In contrast, all guidelines recommend breast MRI as a screening tool for *BRCA* female carriers.[9,10] This, despite several studies that found the PPV of breast MRI is only between 10% and 42%,[21–23] leading to many needless biopsies. In our study, MRI was the most effective screening strategy for PCa. This came at a cost of performing many unnecessary prostate biopsies [PPV = 23.8% (95% CI 20.2–27.9)]. Given the ratio of PCa incidence to PCa-related mortality, performing unnecessary biopsies in the general population may be unacceptable. However, data suggest that PCa among *BRCA* carriers has the worst prognosis and may be a more deadly disease,[2–6] underscoring the need to diagnose these cancers at an early, curable stage.

We used stringent criteria for prostate biopsies. We offered a biopsy to subjects with either abnormal MRI or elevated age-stratified PSA. PSA cut-offs were selected based on previous studies showing that PSA higher than 1 ng/ml before the age of 50 years was associated with PCa mortality.[11] This may have led to a higher rate of GG1 cancers diagnosed (9/16 cases, 56%). GG1 PCas may be indolent in the general population; however, there is a debate regarding the clinical significance of these cancers among BRCA carriers. Taylor et al.[24,25] have shown that *BRCA2* carriers develop PCa with high mutational load at early stages, higher tumor instability, and are more likely to harbor intraductal carcinoma, even in GG1 cancers. A recent study by Carter et al.[26] explored the rate of upgrading during active surveillance for carriers of *BRCA1/2*. In their study, the hazard ratio for grade progression among *BRCA*2 carriers compared with non-carriers was 2.74 (95% CI = 1.26–5.96, *P* = 0.01). Combined, these data suggest that early detection of any grade PCa among carriers may be vital.

In the recent publication from the IMPACT study, the detection rate of PCa among *BRCA1* carriers (2.6%) was lower than among *BRCA2* carriers (2.8%), and even comparable with non-carriers (1.8%).[8] In our study, the PCa detection rate of *BRCA1* carriers was similar to that of *BRCA2* carriers (8.3% versus 8.8%). However, PCa among *BRCA1* was mostly of lower grade (GG1). These differences may be accounted for by the unique mutational landscape of our cohort. Most of the *BRCA1* carriers in our study (78%) have the *185delAG* Jewish founder mutation. Data regarding possible clinical differences between mutation types are limited. Others have found a possible link between cancer risk and mutation type in BRCA.[27–29] Our data might suggest that *185delAG* mutation may be associated with a higher risk of lower grade PCa.

Our study design allowed us to test the clinical utility of different screening strategies. Traditionally, screening strategies are compared using sensitivity and specificity or area under the curve. However, these measures are statistical abstractions and are not directly translated to inform clinical decision-making. We chose to compare the different screening strategies using decision curve analysis and net benefit. PCa screening involves a trade-off between diagnosing patients with cancer versus unnecessary biopsy for

Table 5. Summary of PSA, MRI, and biopsy findings of the PCa cases diagnosed

Case	Age (years)	*BRCA* type	Mutation	PSA	PI-RADS	GG group	Intraductal carcinoma — cribiform pattern	Identified by systematic/fusion	GG in fusion biopsy	GG in systemic biopsy
1	40.7	2	6174delIT	0.9	4	1	no	Fusion only	1	BPH
2	43.0	1	5382inSC	0.5	3	1	no	Fusion only	1	BPH
3	49.6	1	185delAG	0.2	4	1	no	Fusion only	1	BPH
4	53.0	2	6174delIT	1.2	4	2	no	Fusion only	2	BPH
5	54.5	1	185delAG	7.9	5	2	no	Fusion only	2	BPH
6	57.2	1	185delAG	4.1	3	1	no	Fusion only	1	BPH
7	59.5	1	185delAG	5.1	5	1	no	Fusion and systematic	1	1
8	59.5	2	8765delAG	6.0	5	5	yes	Fusion and systematic	5	5
9	60.7	2	6174delIT	3.0	4	2	no	Fusion only	2	BPH
10	63.9	2	6174delIT	8.4	3	1	no	Fusion only	1	BPH
11	66.1	1	185delAG	4.5	3	1	no	Fusion only	1	BPH
12	67.0	1	185delAG	6.1	—	1	no	Systemic only[a]	—	1
13	67.3	2	8765delAG	6.2	4	2	no	Fusion and systematic	2	1
14	68.0	1	185delAG	1.5	3	1	no	Fusion only	1	BPH
15	70.0	2	6174delIT	10.6	5	2	yes	Fusion only	2	BPH
16	70.1	1	185delAG	5.0	4	3	yes	Fusion and systematic	3	3

BPH, benign prostatic hyperplasia; GG, Gleason grade group; PCa, prostate cancer; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, protein specific antigen.
[a] Patient unable to perform mpMRI due to medical reasons.

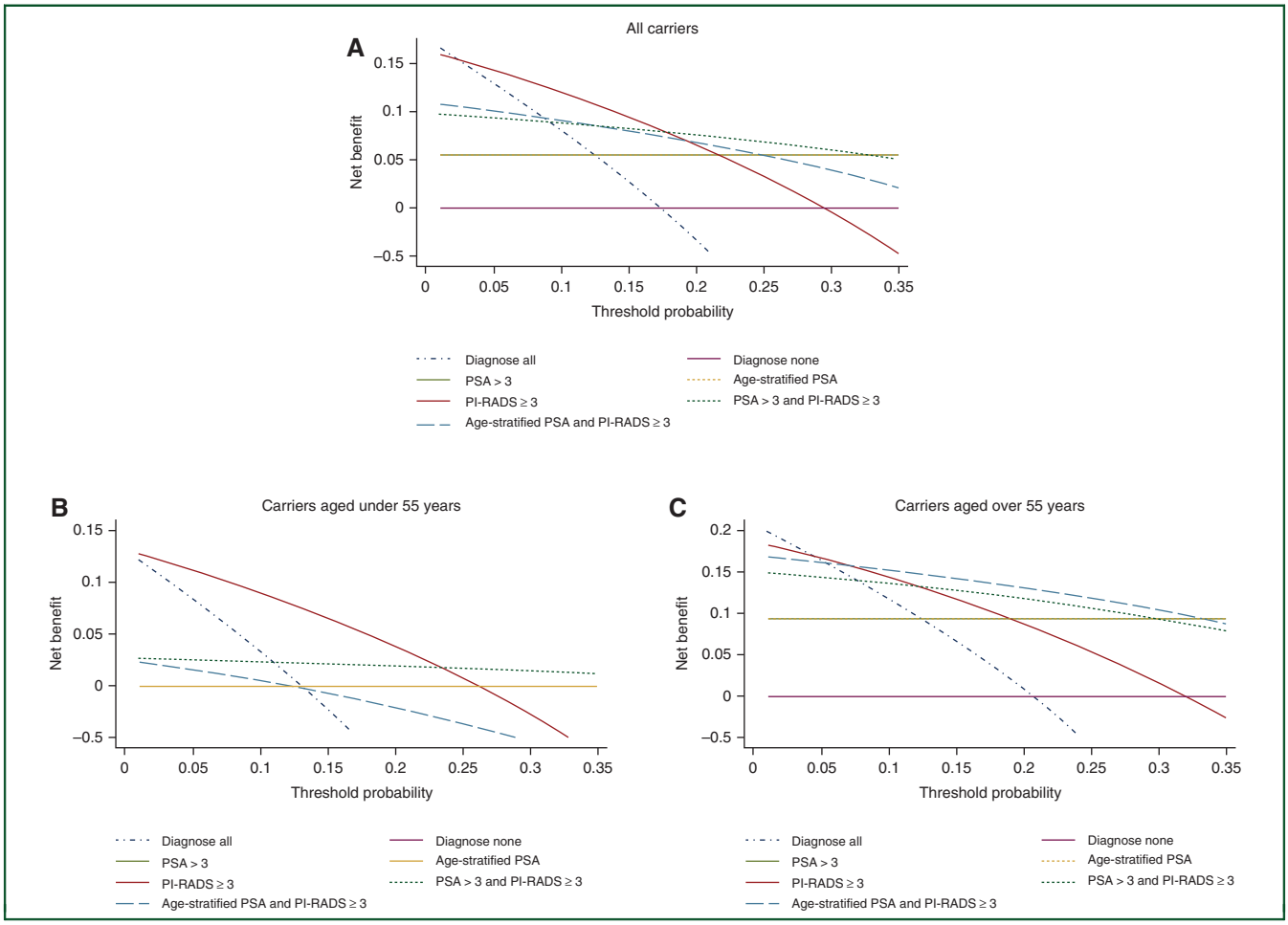

Figure 2. Decision curve analysis comparing five possible screening strategies.
(A) Decision curve analysis for prediction of prostate cancer diagnosis, comparing PSA only screening (PSA > 3 and age-stratified cut-offs), MRI only screening, and PSA triage before MRI screening (PSA > 3 and age-stratified cut-offs). X-axis (threshold probability) is the probability of prostate cancer diagnosis. Y-axis is the net clinical benefit for the different clinical strategies. The lines for both PSA only strategies are identical. Analysis carried out on data from 92 subjects with biopsy. (B) Decision curve analysis for prediction of prostate cancer diagnosis in subjects younger than 55 years, comparing PSA only screening (PSA > 3 and age-stratified cut-offs), MRI only screening, and PSA triage before MRI screening (PSA > 3 and age-stratified cut-offs). X-axis (threshold probability) is the probability of prostate cancer diagnosis. Y-axis is the net clinical benefit for the different clinical strategies. The lines for 'diagnose none' and the two PSA only strategies are identical. Analysis carried out on data from 92 subjects with biopsy. (C) Decision curve analysis for prediction of prostate cancer diagnosis in subjects older than 55 years comparing PSA only screening (PSA > 3 and age-stratified cut-offs), MRI only screening, and PSA triage before MRI screening (PSA > 3 and age-stratified cut-offs). X-axis (threshold probability) is the probability of prostate cancer diagnosis. Y-axis is the net clinical benefit for the different clinical strategies. The lines for both PSA only strategies are identical. Analysis carried out on data from 92 subjects with biopsy. PI-RADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen.

Table 6. Impact summary of the five strategies used to detect prostate cancer in *BRCA* carriers

	Biopsies avoided[a] *n*, (% from a total of 92 carried out)	Any cancer detected *n*, (% from total of 16 cancers)	Any cancer missed *n*, (% from total of 16 cancers)	Negative predictive value %, (95% CI)	Positive predictive value %, (95% CI)
Strategy 1	67 (73)	5 (31)	11 (69)	83.6 (78.1—87.9)	20 (9.9—36.2)
Strategy 2	32 (35)	5 (31)	11 (69)	84.4 (71.1—92.2)	18.3 (13.4—24.5)
Strategy 3	29 (32)	15 (94)	1 (6)	96.6 (80.4—99.5)	23.8 (20.2—27.9)
Strategy 4	74 (80)	9 (56)	7 (44)	90.6 (84.5—94.4)	50 (32.1—67.9)
Strategy 5	61 (66)	10 (63)	6 (27)	90 (82.5—94.5)	31.3 (21.3—43.3)

Strategies:

PSA only screening
- Strategy 1: PSA>3
- Strategy 2: Elevated Age-stratified PSA

MRI only screening:
- Strategy 3: PI-RADS≥3

PSA triage before MRI screening:
- Strategy 4: PSA>3 AND PI-RADS≥3
- Strategy 5: Elevated age-stratified PSA AND PI-RADS≥3

CI, confidence interval; MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen.
[a] Biopsies avoided was calculated as the total number of biopsies done in the cohort minus the number of biopsies that would have been done if the specific strategy was used.

those who are healthy. This is even more pronounced in our high-risk population, where the stakes are higher. The net benefit is an increasingly reported decision analytic measure that puts benefits and harms on the same scale.[30] This is achieved by specifying an exchange rate, a clinical judgment of the relative value of benefits (i.e. detecting cancer), and harms (i.e. unnecessary biopsy).

Using this analysis we found that the screening strategy with the highest net benefit for threshold probability lower than 20% was MRI. However, in higher threshold probabilities, the highest net benefit was triaging with PSA before MRI. To enable clinical decision-making, we stratified our cohort by age. Among patients younger than 55 years, PSA values in our cohort were low, and not useful for prediction, thus MRI had the highest net benefit. However, in older carriers, PSA triaging before MRI had better clinical utility.

Our study has several limitations. First, this is a single-arm study, without a non-carrier group. As prostate biopsies may be harmful, applying our stringent biopsy protocol among non-carriers seemed unethical. For a similar reason, we did not biopsy carriers with both normal PSA and MRI. Thus, we cannot rule out PCa in these subjects.

Generalizability of our findings may be hampered, as a vast majority of our carriers had a Jewish founder mutation. Thus, our results may be limited to this population. However, when comparing similar strategies, our detection rate is comparable with the multinational IMPACT study. Finally, the ultimate outcome of screening is overall mortality, and not cancer detection. This is the first report of our screening study, and we are continuing to monitor these subjects.

CONCLUSIONS

We found a high rate of PCa in the first round of screening of *BRCA*-carriers. We employed a contemporary screening-strategy with both imaging and biomarkers. We found that among carriers younger than 55Y, mpMRI had the best clinical utility and that in older carriers; PSA should be used first to triage before mpMRI.

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DISCLOSURE

The authors have declared no conflict of interests.

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