Age-related Changes of the Prostate on Magnetic Resonance Imaging: Quantitative and Qualitative Evaluation in a Screening Cohort of BRCA Mutation Carriers

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ABSTRACT **Background:** Age-related changes in multiparametric magnetic resonance imaging (mpMRI) of the prostate have been reported in the general population but not in screening cohorts.

Objectives: To evaluate age-related changes on prostatic mpMRI in a screening cohort of BRCA1/2 mutation carriers.

Methods: Asymptomatic BRCA1/2 mutation carriers underwent mpMRI as part of a screening program. All included patients were followed for 3 years with no evidence of prostate cancer. mpMRIs were retrospectively evaluated by two abdominal radiologists for peripheral zone (PZ) patterns on T2 (homogenous hyperintensity, wedge-shaped hypointensities, patchy hypointensities, or diffuse hypointensity), and transition zone (TZ) pattern on T2 (homogenous, heterogeneous, nodular). Apparent diffusion coefficient (ADC) values of PZ and TZ were measured. Statistical analysis was performed using a predefined age cutoff of 50 years old.

Results: Overall, 92 patients were included: 38 in the younger age group (40–49 years) and 54 in the older age group (50–69 years). PZ homogenous hyperintensity and wedge-shaped hypointensities were more common in the older patients, whereas diffuse hypointensity was more common in younger patients ($P < 0.001$ for both readers) with substantial inter-reader agreement between the readers (kappa=0.643). ADC values were lower in young patients in the PZ ($P < 0.001$) and TZ ($P = 0.003$).

Conclusions: Age-related differences in mpMRI are validated in BRCA mutation carriers. As some features overlap with prostatic carcinoma, awareness is crucial, specifically to diffuse T2 hypointensities of the PZ and lower ADC values in the PZ and TZ, which are more common in younger patients.

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KEY WORDS: age, BRCA, diffusion weighted imaging, magnetic resonance imaging, prostate

Multiparametric magnetic resonance imaging (mpMRI) is accepted as the leading non-invasive imaging modality for detection of prostate cancer (PCa) and is integrated into main guidelines in the workup of clinically suspected PCa. mpMRI is currently not recommended as a screening tool for PCa in the general population; however, recent studies have shown that mpMRI alone [1,2] and mpMRI combined with prostate specific antigen (PSA) [3] are superior to PSA alone for the detection of clinically significant cancer. Risk factors for PCa other than age, such as genetic mutations, family history of PCa, and African descent [4], suggest that some populations may benefit from tailored mpMRI screening programs. Our group recently published data from a cohort of BRCA1/2 mutation carriers prospectively screened for malignancies. We identified prostate cancer in 8.5% of the patients [5]. mpMRI in such screening cohorts poses a unique radiological challenge as participants may be younger than the frequently encountered patient with clinically suspected cancer.

Literature regarding age-related changes in mpMRI of the prostate is scarce, including reports that apparent diffusion coefficient (ADC) values of the peripheral zone (PZ), increases with age in healthy volunteers [6,7]. Bura et al. [8] reported on patients with clinically suspected PCa in which the PZ in young patients demonstrated lower T2 signal intensity, lower ADC values, and diffuse enhancement.

Such age-related differences are important when interpreting mpMRIs of patients with clinically suspected cancer as well as screening cohorts because some of these features, for example low ADC values, may potentially mimic or obscure cancer. As paradigms for screening prostate cancer continue to evolve and prostate MRI is being studied as a screening tool [9], awareness of potential age-related pitfalls is important. Literature regarding age-related differences is scarce, and we found no reports on such differences in a screening cohort in the absence of clinical suspicion of cancer.

We evaluated age-dependent changes on prostatic mpMRI in a screening cohort of BRCA1/2 mutation carriers, both qualitative and quantitative.

PATIENTS AND METHODS

POPULATION AND SCREENING PROTOCOL

Our single center, retrospective analysis included asymptomatic patients who participated in a larger prospective screening study for BRCA1/2 mutation carriers at our tertiary medical center, following institutional review board approval and patient consent. The prospective study included an mpMRI scan, which was reported according to Prostate Imaging-Reporting and Data System (PI-RADS). All participants were offered a systematic prostate biopsy following mpMRI as well as targeted biopsies for any suspicious lesion (≥ PI-RADS 3). A dedicated uropathologist reviewed all pathology specimens.

The retrospective analysis included consecutive patients scanned from 1 February 2014 to 31 July 2016, at which date we initiated dedicated retrospective cohort image interpretation. Patients were included if they were 18 years of age or older with no history of malignancy and no urinary symptoms, had data available through electronical medical records including baseline PSA levels up to 1 month prior to MRI scan, and were tracked for a minimum of 3 years of follow up including clinical data and PSA levels with no evidence of PCa.

Exclusion criteria were previous prostatic surgical interventions, diagnosis of prostate carcinoma or prostatic intraepithelial neoplasia (PIN) on initial biopsy or during follow up, refusal for biopsy in the presence of suspicious lesions at baseline, missing follow-up data, clinically suspected PCa during follow up defined as urinary symptoms, unstable PSA levels (increase above 3 ng/ml or doubling PSA level within 2 years), or abnormal digital examination not evaluated with repeat biopsy.

MRI SCAN PROTOCOL

mpMRI was performed using a 3-Tesla device (Ingenia 3.0 T MR System, Philips, the Netherlands). Scans included high resolution T2 weighted images (T2WI) in the axial, sagittal, and coronal planes; diffusion weighted images (DWI) (b-values of 0, 100, 1000, 1500, ± 2000) with corresponding ADC maps; and T1 dynamic contrast enhancement (DCE) with 10 phases following Dotarem IV administration. Endorectal coil was not used. This scan protocol correlates with the generally accepted protocol used worldwide.

MRI INTERPRETATION

mpMRI studies were separately reviewed by two fellowship trained radiologists with 15 (OB, reader 1 [R1]) and 3 (ST, reader 2 [R2]) years of experience reading prostate mpMRIs. Readers were blinded to PSA levels and whether the patient had undergone a biopsy or not.

Prostates were evaluated for quantitative and qualitative variables. Prior to reading the studies separately, the readers reviewed 8 random studies together, to reach a consensus on a categorization system for qualitative variables and measurement methods of quantitative variables.

Quantitative measurements requiring separate dedicated software (Phillips Intellispace Portal [PIP]) were performed by a radiology resident (MDS), reader 3 [R3]).

QUANTITATIVE VARIABLES

Whole prostate length measurements were performed in T2WI: craniocaudal (CC) and anteroposterior (AP) in a sagittal view at the level of the urethra, and transverse axis (TR) in an axial view at the level of the mid-gland. Volumes were calculated using the ellipsoid volume formula width × height × length × pi/6.

Direct volume measurements were performed using PIP software including PZ and central gland (CG), which included the transitional and central zones. Entire prostate volume was calculated by summing the PZ and CG volumes.

ADC values of the TZ, right PZ, and left PZ were measured by R3 using the PIP software on a single slice at the level of the midgland using a geographical region of interest (ROI) tool, mean as well as standard deviation values were documented, PZ average was calculated from values of right and left PZ.

QUALITATIVE VARIABLES

Peripheral zone signal intensity texture was classified as homogenous hyperintensity, wedge shaped or linear hypointensities, patchy hypointensities, diffuse hypointensity [Figure 1].

Transitional zone signal intensity was classified as homogenous, heterogenous nodular, or nodular if the nodules consisted of < 5%, 5–50%, and > 50% of the tissue, respectively, by eye bowling assessment.

The border between the TZ and PZ (known as the surgical capsule) was categorized as ill-defined or well-defined.

The pseudo-capsule of the prostate was classified as fully delineated or partially delineated.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). A cutoff point of 50 years was selected to define the young and old age groups. This cutoff was arbitrary, relying in part on a previous study by Zhang et al. [6], which found differences in ADC values in three different age groups with cutoffs at 30 and 50 years. Additional sensitivity analysis was performed using cutoffs of 54 years (the median age in our cohort). The chi-square test was used to compare cat-

Figure 1. Peripheral zone signal intensity texture on T2 weighted images

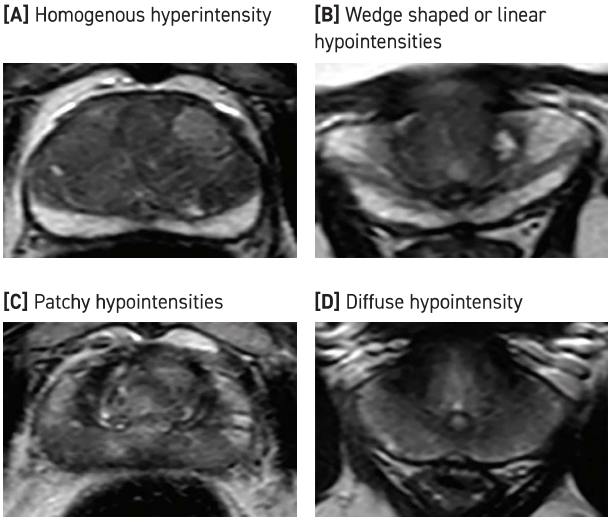


Table 1. Quantitative variables by age group, using a 50-year cutoff

	Younger age group, n=38, median (IQR)	Older age group, n=54, median (IQR)	*P*-value
Age	44.3 (42.1–46.1)	61.6 (57–64.9)	< 0.001
PSA levels*	0.7 (0.4–1.1)	1.3 (1–2.4)	< 0.001
PZ volume**	10.9 (8.3–13.9)	13 (9.9–18.7)	0.025
TZ volume**	9.3 (7.2–12.1)	15.2 (10.1–24.5)	< 0.001
Overall volume**	18.9 (16.5–25.2)	31.5 (22.1–45.1)	< 0.001
PSA Density***	0.04 (0.02–0.05)	0.05 (0.04–0.06)	0.014
ADC PZ¥	1.23 (1.04–1.35)	1.36 (1.23–1.59)	< 0.001
ADC TZ¥	1.06 (0.9–1.15)	1.15 (1.04–1.25)	0.003

ADC = apparent diffusion coefficient, IQR = interquartile range, PSA = prostate specific antigen, PZ = peripheral zone, TZ = transition zone

*PSA units ng/ml

**Measurements in dedicated software

***PSA density - PSA/overall volume

¥ADC units $\times 10^{-3}$ mm^2/sec

egorical variables and ANOVA to compare continuous variables. Since there was no normal distribution for continuous data, Spearman correlation was used to correlate between variables and the Mann Whitney U-test, an A-parametric test that ranks each value according to its location within the entire population was used to compare differences between the groups. Two-sided *P*-value < 0.05 was considered statistically significant. Spearman correlation was considered negligible, low, moderate, high, and very high positive correlation when the coefficient was 0.0–0.3, 0.3–0.5, 0.5–0.7, 0.7–0.9, and 0.9–1.0, respectively [10]. The level of agreement between readers was evaluated with Cohen's Kappa coefficient. Agreement was defined poor, fair, moderate, substantial, and almost perfect for k values of < 0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.00, respectively [11].

RESULTS

PATIENT COHORT, HISTOPATHOLOGICAL FINDINGS, AND FOLLOW-UP

Between March 2014 and July 2016, 99 patients underwent mpMRI as part of the BRCA carrier screening program [Figure 2]. One patient who had previous transurethral resection of the prostate (TURP) was excluded. Fifty-four patients had a 12-core systematic sextant biopsy, 7 had additional targeted biopsies for suspicious lesions on MRI. Four patients were diagnosed with prostatic adenocarcinoma of Gleason 6 and above and one patient was found to have high grade PIN. All five were excluded from the study. The remaining 49 biopsies were negative for malignancy. During follow-up, PSA levels were unstable in two patients, both underwent biopsies, and one was positive for PCa, and therefore excluded from the study. One patient died from pancreatic cancer without known prostatic cancer and the remaining 42 patients were followed for ≥ 3 years (mean 49.8 months, median 51 months) with no clinical evidence of pancreatic cancer.

A total of 92 patients were included in the study, with an average age of 53.8 years (median 53.7, 40–70 ± 9.3). When employing a dichotomous cutoff point of 50 years to define the young and old age groups, there were 38 young (41.3%) and 54 old (58.7%) patients [Table 1, Table 2].

QUANTITATIVE VARIABLES

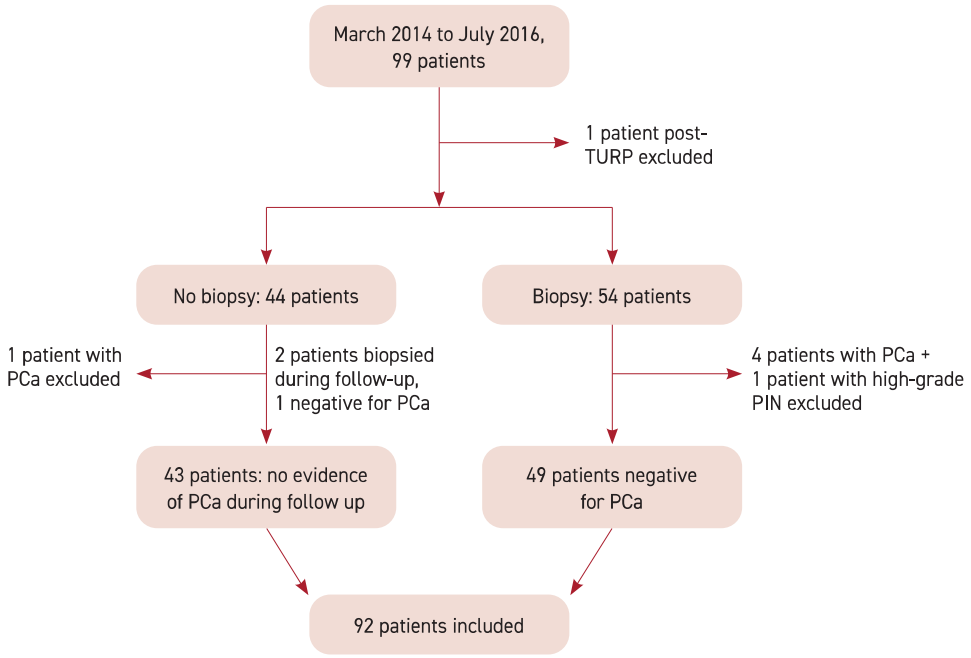
Quantitative characteristics of the two groups are shown in Table 1. The older age group had higher PSA levels ($P < 0.001$) and slightly higher PSA density ($P = 0.014$) than the younger age group. Whole prostate volume and lengths as well as TZ volume were all greater in the older age group ($P < 0.001$ for R1, R2, and PIP). PZ volume was slightly higher in the older age group when measured directly on PIP (16.1 cc vs. 11.7 cc, respectively, $P = 0.025$). Volumetric data are shown in Table 1 [Length measurements are detailed in Supplemental Table A, available in the online version only].

ADC values were higher in the older age group in the PZ ($P < 0.001$) and TZ ($P = 0.003$), with an average of 1.41 and 1.15 in the older versus 1.24 and 1.03 in the younger group, respectively (all values are presented without the unit suffix $\times 10^{-3}$ mm^2/s to simply).

Positive correlation was found between age and PSA levels (r=0.683), PSA density (r=0.376), overall volume (r=0.576, 0.626, 0.7 for PIP, R1, and R2, respectively), TZ volume

Figure 2. Study flow diagram

PCa = prostate cancer, PIN = prostatic intraepithelial neoplasia, TURP = transurethral resection of the prostate



(r=0.576), and overall prostatic lengths in all dimensions. [Correlation of quantitative variables with age is shown in Supplemental Table B, available in the online version only].

QUALITATIVE VARIABLES

Qualitative characteristics of the two groups are shown in Table 2. The signal pattern on T2WI was significantly different between the age groups for both readers ($P < 0.001$). Diffuse hypointensity appeared almost exclusively in the younger age group, accounting for 51.4%/42.1% of the younger patients, compared to 1.9%/7.4% in the older age group by both readers (percentage for R1/R2, respectively). Homogenous hyperintensity and wedge shaped or linear hypointensities were more common in the older age group (21.1%/20.4% and 13.5%/27.8% respectively) compared to the younger age group (8.1%/7.9% and 0%/0%, respectively) by both readers. Patchy hypointensities accounted for 63.5%/44.4% of the older age group and 40.5%/50.0% of the younger age group. When comparing diffuse hypointensity to all other patterns the difference remained statistically significant ($P < 0.001$). Agreement between readers was substantial with a kappa of 0.643 (< 0.001) when evaluating the four different patterns and a kappa of 0.749 when evaluating diffuse hypointensity versus all other patterns.

In an attempt to validate data that was published by Bura et al. [8] after our data collection was completed, the peripheral zone pattern on T2 was also graded with an ordinal score whereby 1=homogenous hyperintensity, 2=wedge shaped or linear hypointensities, 3=patchy hypointensities, 4=diffuse hypointensity, compared to Bura's 1-4 scale (1=Almost entirely high signal intensity (SI), 2=Scattered linear/wedge-shaped area/s of intermediate SI, 3=Moderate geographical and wedge areas of intermediate SI, 4=Very heterogeneous SI with loss of zonal border or diffuse low SI). The mean score for the younger age group was 3.26 ± 0.857 and that of the older age group was 2.46 ± 2.46, $P < 0.001$.

TZ texture showed a significant difference by reader 2 defined as homogenous, heterogenous nodular, and nodular in 7.9%, 86.8% and 5.3% in the younger age group and 1.9%, 79.6% and 18.5% in the older age group ($P < 0.001$). However, no statistically significant difference between the age groups was found for reader 2, defined as homogenous, heterogenous nodular, and nodular in 7.9%, 86.8%, and 5.3% in the younger age group and 1.9%, 79.6%, and 18.5% in the older age group ($P = 0.081$). Agreement between the readers was poor (k=0.161).

The surgical capsule was more frequently conspicuous and well defined in the older age group (66%/50%) compared to the younger age group (31.6%/10.5%), $P = 0.001$ and $P < 0.001$ for readers 1 and 2 respectively. Agreement between the readers was fair (k=0.261).

The pseudo-capsule was fully delineated in most cases both

Table 2. Qualitative variables by age group, using a 50-year age cutoff

		Younger age group, n=38	Older age group, n=54	*P*-value*	Agreement-kappa
Peripheral zone pattern, n (%)					
R1	Homogenous hyperintensity	3 (8.1%)	11 (21.1%)	**< 0.001**	0.64
	Wedge shaped/linear hypointensities	0 (0%)	7 (13.5%)		
	Patchy hypointensities	15 (40.5%)	33 (63.5%)		
	Diffuse hypointensity	19 (51.4%)	1 (1.9%)		
R2	Homogenous hyperintensity	3 (7.9%)	11 (20.4%)	**< 0.001**	
	Wedge shaped/linear hypointensities	0 (0%)	15 (27.8%)		
	Patchy hypointensities	19 (50.0%)	24 (44.4%)		
	Diffuse hypointensity	16 (42.1%)	4 (7.4%)		
*R1***	*Diffuse hypointensity*	*19 (51.4%)*	*1 (1.9%)*	**< 0.001**	*0.70*
	All other patterns	*18 (48.6%)*	*51 (98.1%)*		
*R2***	*Diffuse hypointensity*	*16 (42.1%)*	*4 (7.4%)*	**< 0.001**	
	All other patterns	*22 (57.9%)*	*50 (92.6%)*		
Conspicuity of TZ/PZ border (surgical capsule), n (%)					
R1	Well defined	12 (31.6%)	35 (66%)	**0.001**	0.26
	Ill defined	26 (68.4%)	18 (34%)		
R2	Well defined	4 (10.5%)	27 (50%)	**< 0.001**	
	Ill defined	34 (89.5%)	27 (50%)		
Pseudo-capsule (capsule), n (%)					
R1	Fully delineated	35 (92.1%)	46 (86.8%)	0.424	0.21
	Partially delineated	3 (7.9%)	7 (13.2%)		
R2	Fully delineated	35 (92.1%)	47 (87%)	0.442	
	Partially delineated	3 (7.9%)	7 (13%)		

R1 = Reader 1, R2 = Reader 2

PZ = peripheral zone, TZ = transition zone

*Bold signifies significance

**Italics shows a different way to categorize peripheral zone patterns, diffuse hypointensity versus all other patterns

in the older (86.8%/87%) and the younger (92.1%/92.1%) age groups, with no difference between the groups. Agreement between the readers was fair (k=0.214).

Sensitivity analysis was performed using different age cutoff values of 54 (the median age in this cohort) [Supplemental Table C, available in the online version only]. Differences between older and younger age groups remained statistically significant for all quantitative and qualitative variables which were different between the age groups in the primary 50 years cutoff analysis.

DISCUSSION

In our study, age-related changes in prostate mpMRI included not only the well-established increase in size, but also imaging features such as signal pattern on T2WI in the PZ and ADC values in the PZ and TZ. The peripheral zone frequently demonstrated diffuse T2 hypointensity in younger patients, in contrast to homogeneous hyperintensity and wedge-shaped or linear hypointensities, which appeared almost exclusively in older patients. PZ patchy hypointensities on T2WI were com-

mon in both young and old patients. The ADC values of the PZ and TZ were lower in prostates of younger patients. The surgical capsule delineating the border between the TZ and PZ was more conspicuous in older age. Although some of these findings were previously reported in cohorts of patients with clinically suspected cancer and in healthy volunteers, we found no report of age-related differences in screening cohorts of patients with risk factors for prostate cancer such as BRCA mutation carriers.

Bura et al. [8] examined the peripheral zones of patients referred for suspected PCa and found that the PZ of younger patients exhibit lower T2-weighted imaging signal intensity, lower ADC values, and diffuse enhancement. Those authors used a graded ordinal scoring system of variables including T2 signal, while ours was a nominal scoring system for T2 signal pattern. Nonetheless, there are similarities between these systems and on converting our system to an ordinal score parallel to the Bura score. Our results supported and validated theirs, as the mean T2 Bura score was lower for the younger age group compared to the older one (2.39 vs. 3.29, $P < 0.001$).

In our cohort, ADC values were significantly lower in young patients, both in PZ and TZ, like reports by Tamada and colleagues [7] and Shi and co-authors [12], who found lower ADC values in the PZ as well as the TZ in groups of healthy volunteers. These changes may reflect age-related alterations in sex hormones resulting in increased volume of fluid combined with decreased fraction of epithelium in the prostatic glands [13]. Zhang et al. [6] reported similar findings in the PZ between different age groups of healthy volunteers; however, they found no significant change in TZ ADC values. Bura et al. [8], who focused on the peripheral zone, also found positive correlation between ADC values and age.

We believe that our results serve as validation of Bura's findings dealing with peripheral zone parenchyma, thus highlighting the need for dedicated attention to background parenchyma. Low ADC values and low T2 signal may mimic or obscure cancer, thus reducing specificity or sensitivity, respectively. Reduced sensitivity [14] and specificity [15] of MRI for detection of PCa in patients younger than 50 years has been previously reported and it is plausible that morphological and diffusion characteristics contribute to these findings. We also support the suggestion that Bura and colleagues made, that background parenchyma, which is currently not incorporated into PIRADS, should be considered for routine evaluation in a similar approach to the Breast Imaging-Reporting and Data System (BI-RADS), which recommends assigning a breast composition category [16].

To the best of our knowledge, this report is the first to recognize mpMRI characteristics of the prostate in a screening cohort for patients at risk for developing PCa. Our cohort consisted of BRCA1/2 male mutation carriers, who are prone to malignancies, the most common being prostatic [17], thus raising the question whether MRI features in these patients may represent pre-malignant processes. However, the consistency of most findings with those reported in healthy volunteers suggests that they are not related to the risk factor itself, rather it is the normal appearance of the prostate in younger age. Further supporting this assumption is the fact that more than half of the patients underwent biopsies, which were negative for malignancy.

Screening strategies for prostate cancer remain controversial both in the healthy population and in patients at increased risk for developing cancer. While MRI as a primary screening tool is not currently recommended, and such a model is probably not economically feasible, studies in unselected populations have shown that it is superior to PSA in the detection of prostate cancer [1,2] and additional screening studies are underway [9]. As research continues to evolve, specific populations may be considered for tailored screening programs, which include mpMRI, with participants of variable ages and awareness of age-related differences that may influence mpMRI accuracy is important.

This study has several limitations. It was a retrospective, single center research and the cohort was relatively small. ADC values were measured in a single slice and may not reflect the entire prostate. The mpMRI scans were performed between 2014 and 2016; however, the scan parameters that were used meet the standard that was later defined in PI-RADS v2.1. Last, we did not compare background features to those of cancerous lesions, as the aim was to assess the normal parenchyma.

CONCLUSIONS

BRCA mutation carriers, who are at increased risk of PCa, demonstrated age-related changes in MRI features including T2WI pattern and ADC values comparable to previously reported changes in the general population. The recently suggested Bura-score for T2 pattern is supported by our data. Further research is needed to evaluate whether PI-RADS is as accurate in younger patients as it is in the older population and whether quantitative parameters should be normalized to the patient's age.

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Capsule

Coopting virus-neutralizing antibodies

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) stimulated interest in repurposing neutralizing antibodies against related viruses such as SARS-CoV-1, which caused a smaller outbreak in 2002–2004. **Zhao** et al. engineered mutations in a SARS-CoV-1–neutralizing monoclonal antibody isolated from a convalescent donor to enable this antibody to neutralize SARS-CoV-2. A candidate-engineered antibody blocked SARS-CoV-2 infection of cells in vitro and prophylactically protected hamsters from viral challenge. These results highlight the potential of this approach for refocusing an existing antibody to neutralize a related virus.

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Eitan Israeli

Capsule

Post-acute sequelae of COVID-19 at 2 years

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to post-acute sequelae in multiple organ systems, but evidence is mostly limited to the first year post-infection. **Bowe** et al. built a cohort of 138,818 individuals with SARS-CoV-2 infection and 5,985,227 noninfected control group from the U.S. Department of Veterans Affairs and followed them for 2 years to estimate the risks of death and 80 pre-specified post-acute sequelae of COVID-19 (PASC) according to care setting during the acute phase of infection. The increased risk of death was not significant beyond 6 months after infection among non-hospitalized patients but remained significantly elevated through the 2 years in hospitalized individuals. Within the 80 pre-specified sequelae, 69% and 35% of them became not significant at 2 years after infection among non-hospitalized and hospitalized individuals, respectively. Cumulatively at 2 years, PASC contributed 80.4 (95% confidence interval [95%CI] 71.6–89.6) and 642.8 (95%CI 596.9–689.3) disability-adjusted life years (DALYs) per 1000 persons among non-hospitalized and hospitalized individuals; 25.3% (18.9–31.0%) and 21.3% (18.2–24.5%) of the cumulative 2-year DALYs in non-hospitalized and hospitalized were from the second year. While risks of many sequelae declined 2 years after infection, the substantial cumulative burden of health loss due to PASC calls for attention to the care needs of people with long-term health effects due to SARS-CoV-2 infection.

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