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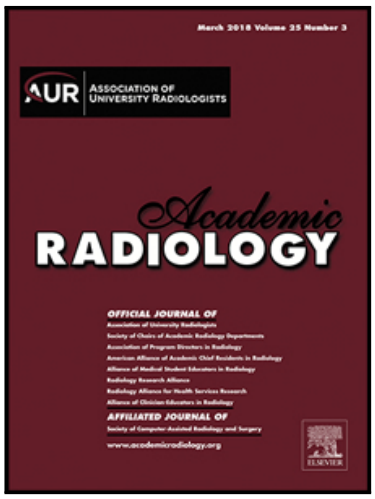

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PII: S1076-6332(23)00124-1
DOI: https://doi.org/10.1016/j.acra.2023.03.012
Reference: XACRA 6088

To appear in: *Academic Radiology*

Received date: 15 February 2023
Revised date: 8 March 2023
Accepted date: 10 March 2023

Please cite this article as: Rooshi Parikh BS , Kimberly N Feigin MD , Varadan Sevilimedu MBBS, DrPH , Jorge Huayanay MD , Katja Pinker MD, PhD , Joao V Horvat MD , Comparison of Axillary Lymph Nodes on Breast MRI Before and After COVID-19 Booster Vaccination, *Academic Radiology* (2023), doi: https://doi.org/10.1016/j.acra.2023.03.012

Comparison of Axillary Lymph Nodes on Breast MRI Before and After COVID-19 Booster Vaccination

Rooshi Parikh BS[1,2], Kimberly N Feigin MD[1], Varadan Sevilimedu MBBS DrPH[3], Jorge Huayanay MD[1], Katja Pinker MD PhD[1], Joao V Horvat MD[1]

1- Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

2- The City University of New York (CUNY) School of Medicine, New York, NY 10031, USA

3- Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY 10017, USA

Corresponding author: Joao V Horvat

Address: 300 E 66th St.

New York, NY 10044

USA

Telephone: (646) 888-5200

Email: machadoj@mskcc.org

ABSTRACT

Rationale and Objectives: Vaccine-related lymphadenopathy is a frequent finding following initial COVID-19 vaccination, but the frequency after COVID-19 booster vaccination is still unknown. In this study we compare axillary lymph node morphology on breast MRI before and after COVID-19 booster vaccination.

Material and Methods: This retrospective, single-center, IRB-approved study included patients who underwent breast MRI between October 2021 and December 2021 after the COVID-19 booster vaccination. The axillary lymph node with the greatest cortical thickness ipsilateral to the side of vaccination was measured on MRI after booster vaccination and before initial COVID-19 vaccination. Comparisons were made between patients with and without increase in cortical

thickness of ≥ 0.2 cm. Continuous covariates were compared using Wilcoxon rank-sum test and categorical covariates were compared using Fisher's exact test. Multiple comparison adjustment was made using the Benjamini–Hochberg procedure.

Results: 128 patients were included. 24/128 (19%) displayed an increase in lymph node cortical thickness of ≥ 0.2 cm. Patients who received the booster more recently were more likely to present cortical thickening, with a median of 9 days (IQR 5, 20) vs. 36 days (IQR 18, 59) ($p < 0.001$). Age ($p = 0.5$) and type of vaccine ($p = 0.7$) were not associated with thickening. No ipsilateral breast cancer or malignant lymphadenopathy were diagnosed on follow-up.

Conclusion: Axillary lymphadenopathy on breast MRI following COVID-19 booster vaccination is a frequent finding, especially in the first 3 weeks after vaccination. Additional evaluation or follow-up may be omitted in patients with low concern for malignancy.

KEYWORDS

Vaccines; Pandemic; Lymphadenopathy; Magnetic resonance imaging; Breast neoplasms

ABBREVIATIONS

- FDA – Food and Drug Administration
- IQR - Interquartile Range
- WHO – World Health Organization

INTRODUCTION

The first cases of SARS-CoV-2 virus emerged in December of 2019. Rapid spread of the virus led the World Health Organization (WHO) to declare it a pandemic in March of 2020(1). The COVID-19 pandemic sparked a worldwide effort to reduce the rate of transmission. Countries went into lockdown while numerous efforts began to develop effective vaccines against the virus(2, 3).

The United States Food and Drug Administration (FDA) first granted emergency use authorization for the Pfizer-BioNTech vaccine (BNT162b2) followed by the Moderna vaccine (mRNA-1273) in December of 2020(4, 5). As the pandemic progressed, the emergence of new COVID-19 variants and the potential waning of antibodies pushed for the rollout of additional doses and booster vaccinations(6-9). In September of 2021, the first booster dose became available for the Pfizer-BioNTech vaccine, and approval of the Moderna booster vaccine followed in October of 2021. In March of 2022, a second Pfizer-BioNTech booster dose became available for adults over the age of 50 and immunocompromised individuals above the age of 12;

a second Moderna booster next became available for immunocompromised individuals above the age of 18(10-12).

Lymphadenopathy can be associated with benign conditions, such as infections, mastitis, and abscesses. Malignant infiltration of the axillary lymph nodes is most commonly seen in breast cancer but can also be seen in several other cancer types(13, 14). Lymphadenopathy can also represent lymphoma(15). Ipsilateral axillary lymphadenopathy following COVID-19 vaccination, shown in patients using both physical examination and imaging modalities(16-20), poses a diagnostic concern for physicians evaluating patients for new, current, or recurring breast cancer(21, 22).

As more studies reveal the frequency of lymphadenopathy following initial COVID-19 vaccination, much about this association remains unknown. There is a lack of information available in the literature regarding the frequency and appropriate management of lymphadenopathy in patients after the COVID-19 booster vaccination. In this study, we compared axillary lymph node morphology based on change in cortical thickness on breast MRI before and after COVID-19 booster vaccination and report the outcomes of patients with vaccine-related lymphadenopathy.

MATERIAL AND METHODS

Population

We conducted a retrospective single-center study approved by the Institutional Review Board and compliant with the Health Insurance Portability Act and Accountability Act. Patients who underwent breast MRI at our tertiary care cancer center following COVID-19 booster vaccination between October 2021 and December 2021 were identified. The Institutional Review Board waived the necessity to obtain patient-informed consent. The exclusion criteria were as follows: (1) missing information regarding COVID-19 booster vaccination (date, site of vaccination administration, vaccine type), (2) history of treated ipsilateral breast cancer, (3) current breast cancer, (4) no prior MRI before initial COVID-19 vaccination within 5 years for comparison, (5) no visible axillary lymph nodes on either current or prior MRI. The final study sample was 128 patients. A flowchart of patient inclusion is demonstrated in Fig. 1.

MRI protocol

Breast MRIs were performed on a 1.5T or 3.0T equipment with a dedicated breast coil with 8 or 16 channels. The protocol included axial T1 non-fat sat, T2 fat sat, T2 non-fat sat and dynamic contrast-enhanced sequences with 3 or more contrast-enhanced phases depending on the protocol utilized at the period. Post-contrast sequences were obtained after the intravenous injection of gadobutrol at 0.1 mL/kg followed by a 20 mL saline flush.

Imaging analysis

The axillary lymph nodes ipsilateral to the side of COVID-19 booster vaccination were evaluated on current and prior breast MRIs. In patients that had more than 1 prior breast MRI, the most recent MRI prior to first COVID-19 vaccination was utilized. The lymph node with greatest cortical thickness on the breast MRI after COVID-19 booster vaccination was identified on contrast-enhanced sequence. Measurements of cortical thickness and short and long axes were obtained from the lymph node by a breast radiologist with 10 years of experience in breast imaging. The same lymph node was then identified on prior MRI and measured in the same fashion.

Statistical analysis

The results were expressed in medians, ranges and proportions. Interquartile ranges (IQR) were provided. The measurements of cortical thickness and long and short axes of lymph nodes before and after COVID-19 vaccination were compared. Subjects were separated in groups according to increase in cortical thickness of < 0.2 cm or ≥ 0.2 cm. Patient age, type of vaccine, and days between booster vaccination and breast MRI were compared between patients with and without cortical thickening. Continuous covariates were compared using the Wilcoxon rank-sum test and categorical covariates were compared using Fisher's exact test. Multiple comparison adjustment was made using the Benjamini–Hochberg (false discovery rate) procedure. The adjusted type I error rate was set to 0.05 (α). For sample size calculation, we initially assumed that the prevalence of lymphadenopathy in this subpopulation would be 5% and powered our study to detect this estimate with a one-sided precision of 5% and obtained a total sample size requirement of 107.

RESULTS

Study sample

All 128 patients who underwent a breast MRI after receiving a COVID-19 booster vaccination were female (100%). 119/128 (93%) patients had a screening breast MRI while 9/128 (7%) had a diagnostic breast MRI, all to follow-up a probably benign finding. The median age of these patients was 56 years (IQR 47, 64). The Moderna booster vaccine was administered in 38/128 (30%) patients. The Pfizer-BioNTec booster vaccine was administered in 90/128 (70%) patients. The median number of days between the MRI and administration of the booster vaccine was 31 (IQR 15, 57). On MRI prior to initial COVID-19 vaccination, the median value for lymph node cortical thickness was 0.3 cm (IQR 0.2, 0.4), the median long axis was 1.2 cm (IQR 0.9, 1.6), and the median short axis was 0.6 cm (IQR 0.5, 0.8). On MRI after booster vaccination, the

median value for lymph node cortical thickness was 0.3 cm (IQR 0.2, 0.5), the median long axis was 1.3 cm (IQR 1.0, 1.7), and the median short axis was 0.7 cm (IQR 0.5, 0.9). Patient information is summarized in Table 1.

Change in morphology of axillary lymph nodes

There were 24/128 (19%) patients who had an increase in lymph node cortical thickness of ≥ 0.2 cm from MRI prior to the initial COVID-19 vaccination. The number of days between MRI and administration of the booster vaccine was significantly associated with an increase in cortical thickness of ≥ 0.2 cm ($p < 0.001$). The median number of days between MRI and booster vaccine in patients with an increase in cortical thickness of ≥ 0.2 cm was 9 days (IQR 5, 20) as compared to 36 days (IQR 18, 59) in patients with an increase in cortical thickness of < 0.2 cm. Thickening of ≥ 0.2 cm occurred from 3 to 113 days after the booster. Statistically significant increases in both long and short axes were observed in patients with an increase in cortical thickness of ≥ 0.2 cm ($p < 0.001$ for both). Median increases in long and short axes were 0.4 cm (IQR 0.1, 0.4) and 0.2 cm (IQR 0.2, 0.3) for patients with an increase in cortical thickness of ≥ 0.2 cm compared to 0.1 cm (IQR 0, 0.2) and 0 cm (IQR 0, 0.1) for patients with an increase in cortical thickness of < 0.2 cm. Increases in cortical thickness of ≥ 0.2 cm were not statistically significantly associated with age ($p = 0.5$) or type of booster vaccine ($p = 0.7$). A summary of the results is demonstrated in Table 2.

Follow-up

All patients with cortical thickening of ≥ 0.2 cm had imaging follow-up except for 1/24 (4%). A following breast MRI or axillary ultrasound at different time points was available for 18/24 (75%) patients while only a mammogram 5–12 months after the post-vaccination breast MRI was available for 5/24 (21%). No ipsilateral breast cancer or axillary malignancy was detected as of December 31st, 2022. One patient presented contralateral breast cancer on follow-up with negative lymph nodes on sentinel lymph node biopsy. A case example of axillary lymphadenopathy following COVID-19 booster vaccination that resolved on follow-up is demonstrated in Fig 2.

DISCUSSION

The frequency of increase in lymph node cortical thickness on breast MRI following COVID-19 booster vaccination was 19%. An increase in long and short axes was also observed in patients with cortical thickening. The number of days following booster vaccination was associated with cortical thickening; patients who received the booster vaccination more recently were more likely to have lymph nodes with increased cortical thickness.

The detection of lymphadenopathy on imaging is a challenging task for the radiologist. Several features have been described to be associated with lymphadenopathy on breast MRI, including lack of a fatty hilum, decreased long/short axis ratio, irregular contours, heterogeneity, and asymmetry when compared to the contralateral axilla(23). Cortical thickness is the morphological feature most commonly used to detect malignant lymphadenopathy, with previous publications demonstrating moderate accuracy in patients with breast cancer when utilizing a cutoff of 0.3 cm(24, 25). In spite of that, the identification of an abnormal lymph node can be subjective. The detection of lymphadenopathy may be facilitated when a prior MRI is available for comparison. A change in morphology, including an increase in cortical thickness is indicative of lymphadenopathy. Although there is not a specific cutoff for increase in cortical thickness to classify a lymph node as abnormal, for the purpose of our study we chose a cutoff of ≥ 0.2 cm of increase in thickness.

The frequency of ipsilateral axillary lymphadenopathy after initial COVID-19 vaccination has been frequently reported, but with highly variable rates. Initial reports found the presence of clinically evident lymphadenopathy in 0.3% of patients following Pfizer-BioNTec COVID-19 vaccination and up to 16% of patients following Moderna COVID-19 vaccination on physical examination(26, 27). In a previous publication, lymphadenopathy on breast MRI following initial COVID-19 vaccination was demonstrated to occur in 29% of patients(28). Other studies demonstrated even higher frequencies. Wolfson et al.(29) found lymphadenopathy in 44% of patients using a combination of mammography and breast ultrasound and Antwi et al.(30) found lymphadenopathy in 37% of patients who underwent PET/CT following COVID-19 vaccination. Our study showed a lower but still considerable frequency of lymphadenopathy in patients after the booster vaccination. Therefore, information regarding recent COVID-19 booster vaccination is necessary for adequate imaging interpretation and management of patients with lymphadenopathy.

The presence of lymphadenopathy was more likely when less time had passed since the most recent COVID-19 booster vaccination, in agreement with previous findings on initial COVID-19 vaccination(28, 31, 32). Our study found that the number of days following booster vaccination was statistically significant in the case of a cortical thickness increase of ≥ 0.2 cm, with a median of 9 days (IQR 5, 20) after the vaccine dose. Most patients presented lymphadenopathy in the first 3 weeks after the vaccine dose.

In the beginning of the COVID-19 vaccination program, many authors recommended imaging follow-up for patients with lymphadenopathy in order to avoid misdiagnosis of metastatic adenopathy or lymphoma(33-37). As more information was gathered in the literature, the perceived need for imaging follow-up diminished. Given the high frequency of lymphadenopathy following COVID-19 vaccination, further evaluation or follow-up may not be necessary in patients without a suspicious finding within the breast(13). Follow-up, fine needle aspiration or core needle biopsy may be considered in cases with persistent lymphadenopathy several weeks after the vaccination(22). A similar strategy should be considered for patients

following the COVID-19 booster vaccination, as the frequency of lymphadenopathy can be considered high, especially during the first 3 weeks after the booster.

Previous publications have demonstrated features that can be used to differentiate vaccine-related from malignant lymphadenopathy (38, 39). Unfortunately, these features may overlap. In patients with abnormal lymph nodes and known ipsilateral breast malignancy, lymphadenopathy should not be assumed to represent vaccine-related changes.

Although axillary lymphadenopathy is known to occur after COVID-19 vaccination, delaying breast exams is currently not encouraged (29, 35). Delaying breast imaging studies may decrease breast cancer screening compliance with a potential negative impact on morbidity and mortality.

There were several limitations to this study. First, this was a retrospective study with patients undergoing breast MRI at different time points after the COVID-19 booster vaccination. Second, not all patients had follow-up and, for those who did, follow-up times were inconsistent. Third, all MRI measurements were made by only a single radiologist.

CONCLUSIONS

In conclusion, ipsilateral axillary lymphadenopathy on breast MRI following COVID-19 booster vaccination is a frequent finding, observed in 19% of patients. Vaccine-related axillary lymphadenopathy is associated with shorter time between the COVID-19 booster and MRI, often detected in the first 3 weeks after the vaccine dose. Given the high frequency of lymphadenopathy following COVID-19 booster vaccination, additional evaluation or follow-up may be omitted in patients with low concern for malignancy.

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Tables

Table 1 - Patient characteristics

Characteristics of patients	**n**	**%**
Total number of participants (100% women)	128	100
Patient median age = 56 years (IQR, 47–64)		
Median days since booster = 31 days (IQR, 15–57)		
Indication for breast MRI		
Screening	119	93
Diagnostic	9	7
Personal history of breast cancer		

Yes	45	35
No	83	65
Family history of breast cancer	38	30
Yes	103	80
No	25	20
Type of booster vaccination		
Pfizer BioNTech	90	70
Moderna	38	30
Arm side of vaccine		
Right	34	27
Left	94	73

Abbreviations: IQR = interquartile range

Table 2 – Comparisons between patients with and without cortical thickening utilizing a cutoff of ≥ 0.2 cm.

	Cortical Thickness Increase ≥ 0.2 cm			
	< 0.2 cm (n=104)	**≥ 0.2 cm (n=24)**	**p value**	**q-value**
Age (median, IQR)	56 (47, 64)	53 (46, 61)	0.5	0.6
Pfizer BioNTech	74 (71%)	16 (67%)	0.7	0.7
Moderna	30 (29%)	8 (33%)		
Days from booster (median, IQR)	36 (18, 59)	9 (5, 20)	**<0.001**	**<0.001**

Increase in long axis (cm, median, IQR)	0.1 (0, 0.2)	0.4 (0.1, 0.4)	**<0.001**	**<0.001**
Increase in short axis (cm, median, IQR)	0 (0, 0.1)	0.2 (0.2, 0.3)	**<0.001**	**<0.001**

Abbreviations: IQR = interquartile range

Figures

Figure 1 – Flowchart demonstrating patient inclusion.

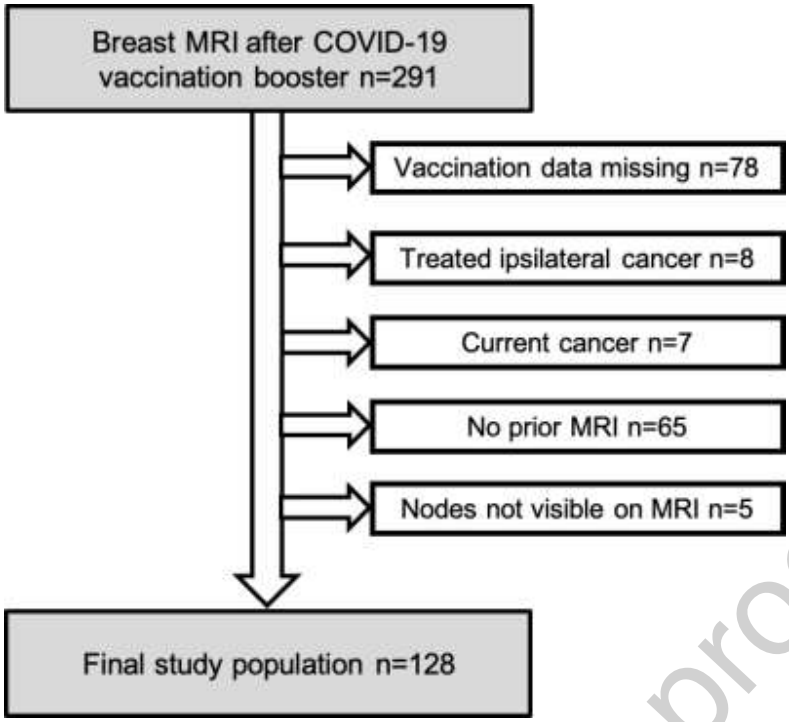
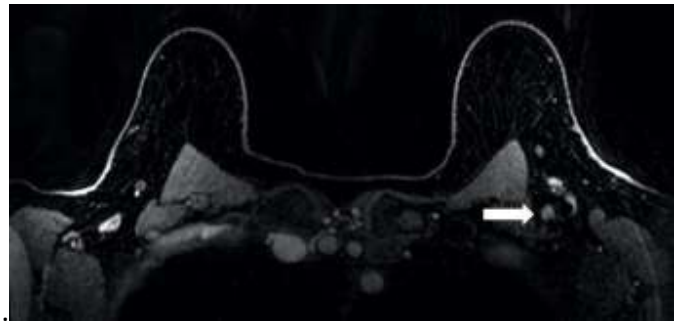
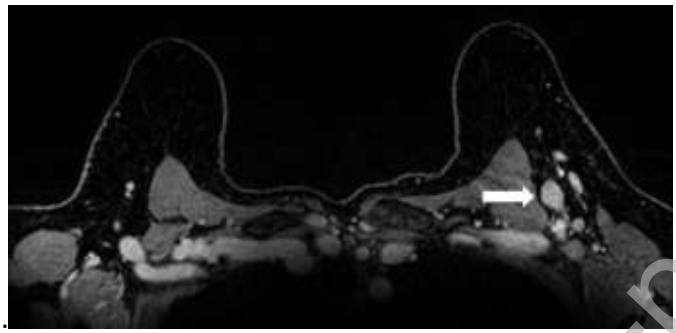


Figure 2 – 57-year-old woman with normal-appearing left axillary lymph node on Breast MRI before initial COVID-19 vaccination (a, arrow). Breast MRI performed 3 days after the booster vaccination in the left arm demonstrates an enlarged lymph node lacking a fatty hilum (b). Breast MRI performed 1 year after the booster demonstrates that the lymph node has returned to its normal morphology.

a. 

b. 

c. 

Disclosures

Disclosures: Kimberly N Feigin is a clinical advisor for Covera Health, Inc. and consultant for FujiFilm. Katja Pinker is a consultant for Genentech, Inc., Merantix Healthcare, and AURA Health Technologies GmbH.

Acknowledgements

The authors thank Garon Scott, BA for providing assistance in editing this manuscript

Funding information: Memorial Sloan Kettering has received funding by the NIH/NCI Cancer Center Support Grant P30 CA008748