



Side effects of COVID-19 vaccinations in patients treated for breast cancer

Brooke C. Juhel¹ · Cheryl L. Brunelle² · Madison C. Bernstein¹ · Louisa H. Smith^{3,4} · Amanda W. Jung¹ · Hazim S. Ababneh¹ · Elizabeth K. Hausman¹ · Loryn K. Bucci¹ · Tess Bernstein¹ · George E. Naoum^{1,5} · Alphonse G. Taghian¹

Received: 21 December 2022 / Accepted: 17 March 2023
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2023

Abstract

Lymph node swelling is a side effect of the mRNA COVID-19 vaccines, a distressing side effect for women treated for breast cancer. The purpose of this study is to present side effects reported by a cohort of patients treated for breast cancer. A survey link was sent to 4945 women who received breast cancer treatment and were prospectively screened for breast cancer-related lymphedema. In total, 621 patients who received an mRNA vaccine and responded to the survey were included in analysis. We assessed the frequency and predictors of side effects. The most frequent side effects reported were injection site soreness, fatigue, generalized muscle soreness, headache, and chills, with median duration ≤ 48 h. Lymph node swelling occurred most often in the axilla ipsilateral to the vaccine. The median duration was 1 week or less after all doses. These data will inform patient education regarding future vaccine doses, including reassurances about which side effects to expect, particularly lymph node swelling which may impact mammograms after vaccination. Type and duration of side effects were similar to that reported by the general population in Phase 3 testing trials of the mRNA vaccines. *Clinical Trial Registration* NCT04872738 posted May 4, 2021.

Keywords COVID-19 · Vaccines · Breast cancer · Lymphedema · Lymphoedema

Abbreviations

LN	Lymph node
BC	Breast cancer
BCRL	Breast cancer-related lymphedema
BMI	Body mass index
MGH	Massachusetts General Hospital
GMS	Generalized muscle soreness
J&J	Johnson & Johnson
D1, D2, D3	Dose 1, Dose 2, Dose 3

Background

Since the introduction of the COVID-19 vaccines, some patients have voiced concerns regarding vaccination, especially vaccine-associated side effects. Side effects, specifically lymph node (LN) swelling associated with the mRNA vaccines, are of particular concern for patients with a history of breast cancer (BC), as lymphadenopathy is also a sign of BC recurrence [1–3]. Research focused specifically on COVID-19 vaccination in women treated for BC is limited but warranted to assuage their unique concerns [4]. Both the Moderna and Pfizer vaccines elicit a strong immune response [5, 6]. In the lymph nodes, white blood cells recognize the antigen from the vaccine and create antibodies to fight the virus. It is this cellular activity that can lead to inflammation and swelling of the lymph nodes, specifically the lymph nodes closest to the injection site [7, 8]. Since vaccines are typically given in the deltoid muscle [3], the lymph nodes that would be most impacted are the axillary and supraclavicular lymph nodes which are also the lymph nodes most closely associated with BC. When an injection

✉ Alphonse G. Taghian
ataghian@mgh.harvard.edu

¹ Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

² Department of Physical and Occupational Therapy, Massachusetts General Hospital, Boston, MA, USA

³ Department of Health Sciences, Bouvé College of Health Sciences, Northeastern University, Boston, MA, USA

⁴ Roux Institute, Northeastern University, Portland, ME, USA

⁵ Present Address: Department of Radiation Oncology, Northwestern University Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

is given, this swelling is a sign that the immune system is acting as it should.

For patients with BC and breast cancer-related lymphedema (BCRL), a dysfunction of the lymphatic system, LN swelling can be a concerning side effect. BCRL is a devastating sequelae of BC treatment that affects over 20% of treated women and is caused by fluid buildup after damage (surgery or radiation) to the lymph nodes [10]. BCRL is highly feared in this population [9]. Risk factors for BCRL include axillary lymph node dissection, regional lymph node radiation, and high body mass index (BMI) at time of breast cancer diagnosis [10–16]. Although sentinel lymph node biopsy significantly reduces the risk of BCRL compared to axillary lymph node dissection, the risk is not negligible [10, 14, 16–18]. Patients with BCRL may experience a range of symptoms, including heaviness, pain, tightness, changes in skin quality, and decreased range of motion, and they are at a higher risk for infection in the affected area(s) [19–22]. The morbidity resulting from BCRL is significant and negatively impacts almost all aspects of patients' lives, contributing to anxiety and depression [23–26].

The Lymphedema Research Program at Massachusetts General Hospital (MGH) prospectively screens patients with BC for BCRL and has screened >6,500 women since 2005 [27] (ClinicalTrials.gov identifier: NCT01521741; institutional review board identifiers: 2008P000540 and 2005P001038). Upon the advent of the COVID-19 vaccines, the program received many calls of concern from patients at MGH and across the country. Patients were concerned about the newly announced side effect of the COVID-19 vaccine and worried that LN swelling may incite or worsen BCRL. We initiated the LymphVAX study to better understand vaccine side effects experienced by patients treated for BC and to provide patient education, increase knowledge, and empower patient self-advocacy. In addition to LN swelling, other side effects of COVID-19 vaccines that may also be experienced secondary to BC treatment include fatigue, generalized muscle soreness (GMS), nausea, and vomiting [28–30]. Due to the inherent activity of mRNA vaccines and the immune system, as well as the role of the lymph nodes in BC and in BCRL, this study analyzed the side effect profile in patients treated for BC and who received up to three doses of the COVID-19 vaccinations [Moderna, Pfizer]. A separate analysis is presented on results from participants who received the Johnson & Johnson (J&J) vaccine as lymph node swelling is not a listed side effect of this non-mRNA vaccine and only a small proportion of the population received this vaccine (n = 49).

Older participants and participants who had received more intense cancer treatment (i.e., radiation, chemotherapy) were hypothesized to experience fewer side effects than younger participants and those with less intense treatment. The former group was anticipated to experience a lower

immune response to a vaccine than the latter group due to the natural weakening of the immune system as adults age, and certain cancer treatments which may weaken the immune system temporarily [31–35]. Additionally, more participants were expected to experience side effects with their second dose than after their first dose, as the immune system should recognize the vaccine and initiate a more intense immune response to subsequent doses.

This study aims to assess side effect profiles for patients treated for BC across vaccine doses and whether age and BMI, BC surgery type, axillary surgery, chemotherapy, or radiation therapy influenced side effects experienced after the COVID-19 mRNA vaccinations (Moderna and Pfizer).

Methods

Beginning in April 2021, a survey link was sent to 4,945 women over the age of 18 who had been treated for BC and prospectively screened for BCRL with perometry (Mitaka USA, Inc. Wheat Ridge, CO, USA) by the MGH Lymphedema Research Program. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MGH, a secure, web-based software platform designed to support data capture for research studies. BC treatment data were collected through medical record review, and additional survey links and phone calls were made as reminders and to obtain booster dose information. The MGH Institutional Review Board approved this study in April 2021 (2021P000528), and data were collected prospectively through June 2022. Recall bias is a potential concern for this study; therefore, data collection ended roughly a year after survey distribution.

Participants were asked about each dose of the vaccine they received. This included the first two doses for the Moderna (mRNA-1273) and Pfizer (BNT162b2) vaccinations along with a third booster dose, if received, or one dose of J&J (Ad26.COV2.S) along with a booster dose, if received. First, participants were asked about vaccine type, education received regarding the vaccine, where on the body the vaccine was received and reasons behind that decision. Second, participants were asked which side effects they experienced and duration of side effects after vaccination. Solicited side effects included: injection site symptoms (soreness, swelling, or redness), symptoms in the arm on the side of injection (swelling, numbness, or heaviness), and generalized symptoms [muscle soreness, feeling tired (fatigue), headache, joint pain, chills, nausea, vomiting, fever, Bell's palsy], other, or none of the above. Lastly, participants were asked specifically about LN swelling after each dose of the vaccine. LN swelling was defined as "discomfort or noticeable swelling when looking or touching" and questions specified

whether this occurred in the axilla (underarm/armpit) or in the supraclavicular region (lower neck/above the collarbone) and laterality of the swelling. While it was not feasible for this study to have a professional examine participants' lymph nodes, the definitions likely standardized any bias that would be a result of the patient-reported outcome. Survey questions were compiled based on clinician expertise from a certified lymphedema therapist and a breast radiation oncologist. The side effects list was derived from side effects published by Moderna and Pfizer. A patient advocate was consulted for ease of completion of the survey, and ensuring questions were appropriately worded. All survey questions are presented in the supplementary information (Additional File 1).

Statistical Methods

Side effect frequencies and median duration for each mRNA dose were analyzed. To investigate predictors of side effects, multivariable logistic regression models across all doses were fit separately for each side effect, with random effects for participants to account for clustered responses. We investigated age, BMI (< 25, 25–30, ≥ 30 kg/m²), surgery type (lumpectomy, mastectomy, mastectomy with reconstruction), axillary surgery (none, sentinel lymph node biopsy, axillary lymph node dissection), radiation (yes/no), and chemotherapy (none, neoadjuvant, adjuvant only). Analysis was conducted across all three doses to determine any differences in side effect profiles. Coefficients with $p < 0.05$ were considered significant predictors of that side effect. Because lymph node swelling is not a listed side effect of the J&J vaccine, and because far fewer patients received that vaccine, we analyzed side effects among those receiving the J&J vaccine separately.

General Population

Data from the LymphVAX study were compared to two randomized, placebo-controlled, phase 3 trials conducted in adults who were healthy or with stable chronic medical conditions for the Pfizer and Moderna vaccines [5, 6]. The Pfizer study enrolled participants over the age of 16 to receive two doses of the BNT162b2 vaccine ($n = 21,720$) or a placebo ($n = 21,728$) 21 days apart at 152 sites worldwide, with 8183 participants reporting on reactogenicity up to 7 days after each injection. The Moderna study enrolled participants over the age of 18 to receive two doses of the mRNA-1273 vaccine ($n = 15,210$) or a placebo ($n = 15,210$) 28 days apart at 99 centers across the USA, monitoring reactogenicity for 7 days after each injection.

The solicited side effects listed in the general population studies were also solicited in the LymphVAX study, with the addition of swelling, heaviness, and arm numbness in the LymphVAX study as these are symptoms which have

been found to be predictive of BCRL [21, 22]. The Pfizer study of the general population did not include LN swelling as a solicited event; however, it was reported as an adverse unsolicited event in 64 participants compared with 6 participants in the placebo group [6]. In contrast, the Moderna study of the general population included lymphadenopathy (LN swelling) as a solicited event, similar to the LymphVAX study. Therefore, LN swelling in patients in the LymphVAX study is compared to the Moderna group in the general population to maximize similarities between study designs.

In addition, an international, randomized, placebo-controlled, phase 3 trial tested the efficacy and safety of the J&J vaccine in the general population over the age of 18. The cohort included 3,356 participants who received the Ad26.COV2.S vaccine and reported on reactogenicity for 7 days after the injection [36].

Results

We received 714 survey responses regarding patients' primary vaccination series (two doses of Pfizer or Moderna and one dose of J&J). We excluded 44 incomplete surveys or surveys from patients who received the first vaccine prior to BC treatment, resulting in data from 670 patients for analysis. For booster dose surveys (either a third dose of Moderna or Pfizer or a second dose of any vaccine after receiving J&J), 503 responses were received from patients who had completed the initial vaccination survey (75%). An additional 24 patients indicated over the phone that they had not yet received a booster dose when the survey was distributed.

Patient Population

In total, 621 patients who received an mRNA vaccine (259 Moderna, 362 Pfizer) and responded to the survey were included in the analysis, and 469 of those participants completed booster dose surveys. In total, 49 participants received the J&J vaccine and 34 of these participants completed booster surveys (23 received a Moderna booster, 8 received a Pfizer booster, 3 received a J&J booster). The primary analysis was restricted to the sample with mRNA primary doses, and we report results for the J&J recipients separately as previously discussed (Fig. 1).

Demographic and breast cancer-related characteristics for the 621 patients receiving an mRNA primary vaccine series are presented in Table 1. The median age was 53.0 years with a median BMI of 26.0 kg/m². 43.9% of participants underwent mastectomy, 28.3% underwent axillary lymph node dissection, 57.3% had BMI > 25 at time of BC diagnosis, and 30.3% of participants underwent regional lymph node radiation. The median follow-up time between breast surgery and date of first vaccine dose was 69.0 months.

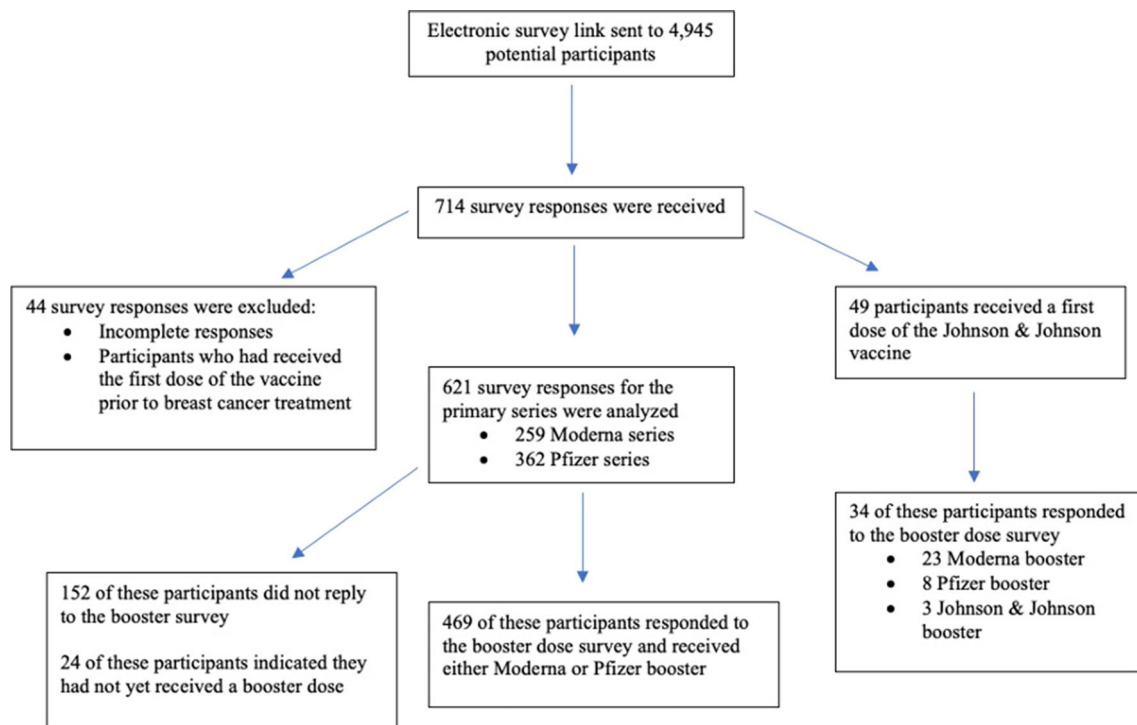


Fig. 1 Study Population

Table 1 Demographics and treatment-related characteristics

Factor	Total Cohort (n = 621) Number (%)
Age*	53.0 (26.2, 83.6)
BMI*	26.0 (15.8, 50.4)
BMI > 25	356 (57.3%)
Missing Data	2
Surgery	
Mastectomy with Reconstruction	222 (35.7%)
Mastectomy without Reconstruction	51 (8.2%)
Lumpectomy	348 (56.0%)
Nodal surgery	
Axillary Lymph Node Dissection	176 (28.3%)
Sentinel Lymph Node Biopsy	393 (63.3%)
No Nodal Surgery	52 (8.4%)
Regional Lymph Node Radiation	188 (30.3%)
Neoadjuvant ± adjuvant chemotherapy	109 (17.6%)
Adjuvant chemotherapy, only	196 (31.6%)
Time between breast surgery & first dose*	69.0 months (0.13, 361.5)

*median (range)

Most Frequently Reported Side Effects

The most frequently reported local side effects were injection site soreness, injection site swelling, injection site redness, LN swelling, and arm heaviness (Figure 2A). The most frequently reported systemic side effects were fatigue, GMS, headache, chills, and joint pain (Figure 2B). Aside from injection site soreness, all systemic side effects were more commonly reported than the other local side effects. After the first, second, and booster doses, 14.3%, 12.1%, and 15.4% of patients reported experiencing no side effects at all.

Multivariable model results: Systemic side effects

In the multivariable model, fatigue, GMS, headache, chills, and joint pain were reported by a significantly lower percentage of older participants (set linearly with odds ratios at 10-year increments) than younger participants ($p < 0.001$). These side effects were also all reported significantly more after dose 2 compared with dose 1 ($p < 0.001$). Headache ($p = 0.046$), chills ($p < 0.001$), and joint pain ($p = 0.014$) were reported significantly more after dose 3 compared with dose 1. Complete results from the multivariable models are presented in the supplementary information (Additional File 2).

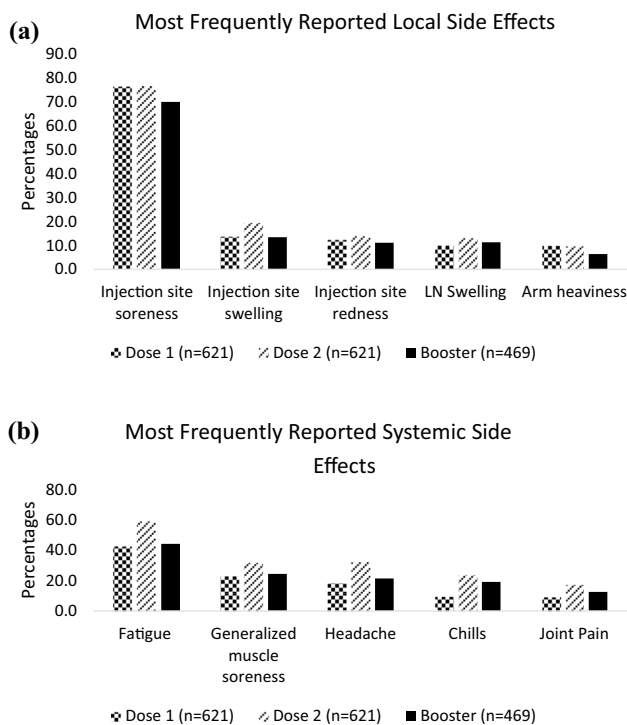


Fig 2 Most Frequently Reported Local (a) and Systemic (b) Side Effects among Participants receiving mRNA Vaccines as a Primary Series (n = 621 Dose 1, n = 621 Dose 2, n = 469 Booster)

Multivariable model results: Local side effects

Injection site soreness was reported significantly less in older participants ($p < 0.001$) and after dose 3 compared with dose 1 ($p = 0.004$). Injection site swelling was reported significantly more after dose 2 compared with dose 1 ($p < 0.001$). Arm heaviness was reported significantly less after dose 3 compared with dose 1 ($p < 0.033$).

Lymph Node Swelling

After the first, second, and booster doses, 9.8% (61/621), 12.9% (80/621), and 11.3% (53/469) of participants reported LN swelling, respectively. Of note, 54.1% (33/61), 62.5% (50/80), and 71.7% (38/53) of participants who reported LN swelling reported it in the axilla ipsilateral to the vaccine after each dose. LN swelling was also reported in the axilla contralateral to the vaccine [45.9% (28/61) D1, 45.0% (36/80) D2, 24.5% (13/53) D3], supraclavicular region ipsilateral to [29.5% (18/61) D1, 26.3% (21/80) D2, 32.1% (17/53) D3], and contralateral to the vaccine [18.0% (11/61) D1, 20.0% (16/80) D2, 9.4% (5/53) D3] (Figure 3). Next, LN swelling was analyzed in relation to side of vaccine and side of BC and whether the swelling occurred on the affected side. 10.8% (67/621) of participants for the first 2 doses and 13.6% (64/469) of participants who received the booster

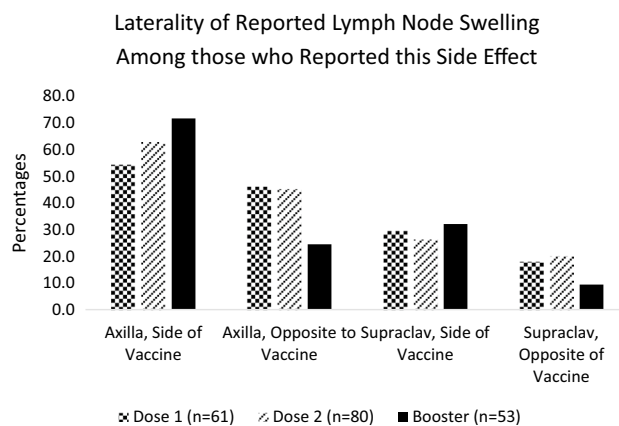


Fig.3 Laterality of Lymph Node Swelling among those who Reported this Side Effect (n = 61 Dose 1, n = 80 Dose 2, n = 53 Booster)

were excluded from this analysis due to bilateral cancer or receiving a vaccine in the leg. For dose 1, dose 2, and dose 3, respectively, 78% (432/554), 78.5% (435/554), and 81.7% (331/405) of participants received the vaccine contralateral to side of BC treatment. LN swelling was reported on the side opposite to the vaccine on the side of BC treatment by 6.9%, 9.7%, and 3.6% of these participants, respectively. Conversely, 22.0% (122/554), 21.5% (119/554), and 18.3% (74/405) received the vaccine on the side of BC treatment. 11.5%, 14.3%, and 13.5% of these participants had LN swelling on the side of the vaccine and side of BC treatment (Figure 4). The median duration of LN swelling either in the supraclavicular region or the axilla was 1 week or less after all 3 doses. A higher percentage of participants reported longer duration of axillary LN swelling than supraclavicular swelling, although few participants experienced swelling after 1 week.

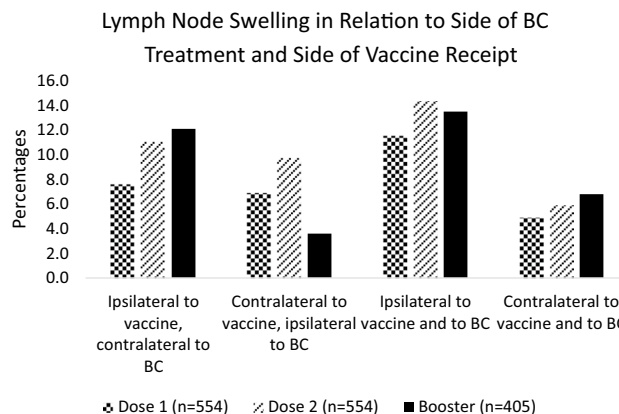


Fig.4 Lymph Node Swelling in Relation to Side of BC Treatment and Side of Vaccine Receipt (n = 554 Dose 1, n = 554 Dose 2, n = 405 Booster)

Side Effect Duration and Progression

The median duration of side effects for all three doses was 48 h or less, with the duration ranging from 24 h or less (41.0% D1, 38.7% D2, 44.1% D3) to more than 4 weeks (2.6% D1, 5.2% D2, 2.5% D3). Of the participants who reported side effects for multiple doses, 32.1% had side effects that lasted the same duration in each dose. 39.2% had side effects for a longer duration in at least one subsequent dose compared to an earlier dose, and 28.7% experienced their longest side effects after the first dose.

General Population

Compared with the general population, fatigue, GMS (new or worsening muscle pain/myalgia), and chills were reported by a similar but slightly higher percentage of the LymphVAX cohort after dose 1 (fatigue: 42.7% vs. 38.1%; GMS 23.0% vs. 21.7%; chills 9.5% vs. 8.8%) [5–8]. Additional comparisons are presented in Table 2. A very similar percentage of patients in the LymphVAX study reported LN swelling (9.8% and 12.9% after dose 1 and 2) to that in the general population (10.2% and 14.0% after dose 1 and 2), although due to study methodology, the data were not suitable for statistical analysis.

Johnson & Johnson (J&J) Cohort

Of the 49 patients who received the J&J vaccine, 69.4% (34/49) received a booster and responded to that survey. 67.6% (23/34) received Moderna, 23.5% (8/34) received Pfizer, and 8.8% (3/34) received a second dose of J&J. 73.5% reported experiencing any side effect for dose 1, and 70.6% reported experiencing any side effect for dose 2. The five most frequently reported side effects included injection site soreness (63.3% D1, 55.9% D2), fatigue (42.9% D1, 29.4% D2), headache (30.6% D1, 23.5% D2), chills (20.4% D1, 14.7% D2), and GMS (18.4% D1, 14.7% D2). For dose 2, 14.7% of participants experienced a fever. The median duration of side effects for both doses 1 and 2 was 48 h or less, with many participants reporting side effects lasting 24 h or less (44.4% D1, 50% D2). Although LN swelling is not a listed side effect of the J&J vaccine, 8.2% (4/49) of

participants in this study reported LN swelling on the side of vaccine (three in the axilla and one in the supraclavicular lymph nodes). Side effects reported by those participants who received the J&J vaccine are presented in Table 3. Injection site soreness and fatigue were more common in women treated for BC who received the J&J vaccine in the LymphVAX study than the general population (63.3% vs. 48.6% injection site soreness; 42.9% vs. 38.2% fatigue); headache and GMS were less common in women who received J&J in the LymphVAX study (30.6% vs. 38.9% headache; 18.4% vs. 33.2% GMS). Due to study methodology, the data were not suitable for statistical analysis.

Discussion

When a vaccine is given in the deltoid muscle, LN swelling in the axillary and supraclavicular lymph nodes is a sign that the immune system is responding to the vaccine as it should

Table 3 Johnson & Johnson Cohort – Reported Side Effects

Side effect reported	Dose 1 (n=49) (%)	Booster (n=34) (%)
Injection site soreness	63.3	55.9
Fatigue	42.9	29.4
Headache	30.6	23.5
Chills	20.4	14.7
Generalized muscle soreness	18.4	14.7
Joint pain	16.3	11.8
Fever	14.3	14.7
Injection site swelling	10.2	5.9
Nausea	8.2	11.8
Injection site redness	8.2	2.9
Lymph node swelling	8.2	2.9
Arm heaviness	4.1	5.9
Arm swelling	2.0	2.9
Other	2.0	0
Vomiting	0	2.9
Arm numbness	0	0
Bell's Palsy	0	0

Table 2 Most frequently reported side effects: Comparison of women treated for BC with GP

	Injection site soreness	Fatigue	Generalized muscle soreness (GMS)	Headache	Chills
Dose 1	76.0% BC 82.4% GP	42.7% BC 38.1% GP	23.0% BC 21.7% GP	18.4% BC 33.1% GP	9.5% BC 8.8% GP
Dose 2	76.2% BC 85.0% GP	59.3% BC 63.2% GP	31.9% BC 52.5% GP	32.4% BC 55.9% GP	23.7% BC 40.8% GP

*BC = women treated for breast cancer (n=621 Dose 1, n=621 Dose 2)

*GP = general population reported by NEJM (n=19256 Dose 1, n=17702 Dose 2)

[37]. However, LN swelling can also raise concerns of cancer progression or recurrence, or that the swelling may incite or worsen lymphedema [1, 3, 38]. The CANVAX study was conducted in multiple cancer centers at MGH and found that patients with a history of or active cancer, including BC, had a lower immune response to the COVID-19 vaccines; however, most still had antigen concentrations and neutralization titers predicted to be protective against illness [39]. In addition, participants in the CANVAX study who reported more systemic symptoms after receiving the vaccines were more likely to have a higher immune response. While it is promising that the COVID-19 vaccine was found to be effective in patients with cancer, side effects such as LN swelling remain a serious concern for this population. The results of the LymphVAX study are therefore imperative to inform patient education regarding side effect profiles for women treated for BC.

Based on the results of this study, the vast majority of women treated for BC may expect to experience at least one side effect after any dose of the mRNA COVID-19 vaccines, most commonly injection site soreness, fatigue, GMS, headache, and chills. Side effects commonly last 24 h or less, with a median of 48 h or less; however, for some participants, the duration of side effects increased in a subsequent dose. Aside from injection site soreness, systemic side effects were much more common than local side effects, including LN swelling and arm swelling, which is promising for women at risk of BCRL.

Older participants reported significantly less fatigue, GMS, headache, chills, joint pain, and injection site soreness, consistent with the hypothesis that participants with weaker immune systems would experience fewer side effects [31–34]. Reports of fatigue, GMS, headache, chills, joint pain, and injection site swelling all significantly increased for the second dose of the vaccine compared to the first dose. This is consistent with the hypothesis that after repeated vaccine doses, the immune system already has the antigens ready to fight the virus; thus, the side effects may worsen as the immune response has increased [40].

General Population

We felt it important to comment on whether the side effect profile looks different in patients who have been treated for BC than in the general population. This information may assist patients in making informed decisions about the COVID-19 vaccine.

It should be noted that although numbers between the two studies are very close, due to study methodology, statistical analysis was not possible. The value that stands out most is that the percentage of patients reporting fatigue after the vaccination was higher in the LymphVAX cohort. Given these participants had endured cancer treatment in the past,

it is possible that some could still be experiencing cancer-related fatigue, a known long-term side effect of treatment that can result in functional deficits [29]. This, in combination with the COVID-19 vaccine, may result in higher numbers of participants previously treated for BC reporting fatigue after vaccination. Otherwise, injection site soreness (pain) and headache after dose 1, and all most frequently reported LymphVAX side effects after dose 2 occurred more in the general population than in women treated for BC.

Perhaps the most distressing side effect of COVID-19 vaccination reported by patients who have been treated for BC is LN swelling, which is particularly prominent after COVID-19 vaccinations compared with others as these elicit higher immune responses [4–6]. As previously discussed, this mimics signs of BC recurrence or progression; therefore, this side effect has received great attention from patients treated for BC who have found it difficult to find information or advice to help guide their decisions around COVID-19 vaccination. The Society of Breast Imaging no longer suggests delaying screening mammograms; however, previous recommendation was to receive the first dose of the vaccine after screening mammogram or to delay screening until 4–6 weeks after second dose of the vaccine. Guidelines continue to be updated as information regarding further doses of the COVID-19 vaccines becomes available [41]. Additionally, MGH guidelines suggest that patients with BC receive the vaccine in the arm opposite to BC (i.e., without node removal), or in the case of bilateral cancer, in the thigh if possible, or alternatively in the arm where fewer lymph nodes were removed if thigh administration is not possible [42–46]. Further research is required to determine the long-term impact of LN swelling as a result of the vaccine and to draw conclusions regarding the impact of the COVID-19 vaccine on risk of BCRL after BC treatment. Although lymph node swelling is not a listed side effect of the J&J vaccine, side effects are still a concern to the study population. Women treated for BC should receive education about expected side effects, particularly LN swelling, in order to make informed decisions regarding their health.

Lymph Node Swelling and Patient Education

The proportion of patients in this study who reported LN swelling was qualitatively similar to those who reported LN swelling in the Phase 3 Moderna trial. Furthermore, it is reassuring that LN swelling was found to be more common ipsilateral to the vaccine, regardless of side of BC. Although less common, some patients reported swelling contralateral to the vaccine, and for the majority of these patients, the swelling did occur on the side of BC. It is important that patients are aware that LN swelling may occur contralateral to the site of vaccination. As doses progressed, fewer

patients received the vaccine on the side of BC, which is expected due to more prominent patient education prior to booster doses that the vaccine should be administered on the contralateral side to BC [42–46].

As a precautionary measure, women treated for BC were historically told to avoid injections in the arm at risk of BCRL. However, ipsilateral injections were not associated with increased arm volume in a prospective study of 632 patients who were prospectively screened for BCRL with 3041 arm volume measurements [47]. However, this study did not analyze data from vaccines that specifically target the immune system and carry a known side effect of LN swelling. Therefore, the conclusions from this study cannot be applied to patients treated for BC receiving the COVID-19 vaccine. The thigh or the arm opposite to BC (i.e., without nodal removal) is recommended in the interim as the safest option as more research is required to make informed decisions. As previously stated, for women with bilateral cancer, the thigh is a recommended alternative vaccination site to the deltoid for COVID-19 vaccination [48, 49]. Further research is warranted and will be conducted with the results of the LymphVAX study, to determine the relationship between LN swelling from the vaccine and BCRL risk.

Limitations

It is difficult to determine the exact response rate for this study as the survey link was sent at a time when many patients had not yet received the vaccine and institutional barriers limited survey dissemination; therefore, recall bias may have played a role. Questions regarding LN swelling relied on self-report as it was not feasible to include imaging or clinical examination within the scope of this study. The surveys do not include questions regarding the severity of the side effects reported; therefore, conclusions about severity of side effects cannot be drawn. Methodological limitations prevent statistical comparisons with studies of the general population.

Future Directions

Patients are prospectively screened for BCRL as standard of care at MGH [27]. As patients receive further COVID-19 vaccinations, additional analysis will be conducted to analyze the effect of mRNA COVID-19 vaccinations on BCRL risk, comparing reported side effects with immunogenicity data, and investigating patterns in side effects among patients infected with COVID-19 prior to vaccination. These data, collected specifically for patients with BC, provide an evidence base to enhance guidelines for more structured and universal education regarding future booster doses of the

vaccine. This will allow patients to have a better understanding of COVID-19 vaccine side effect profiles after BC treatment, empowering women treated for BC to make informed decisions prior to future doses.

Conclusions

In summary, patients treated for BC experience injection site soreness, fatigue, GMS, headache, and chills most commonly after COVID-19 vaccination. These symptoms resolve in less than 1 week in most cases. The percentage of patients experiencing each symptom is similar to that in the general population (including LN swelling), although statistical conclusions cannot be made. These side effect profiles for a cohort of women treated for BC can be used to provide evidence-based patient education regarding future COVID-19 vaccine administration. Finally, the effect of the COVID-19 vaccines on BCRL risk is currently unknown and more research is required. In the interim, we would recommend vaccination away from the side of LN removal, either in the thigh or the contralateral arm. We believe that more patients would take advantage of having the vaccination in the thigh if it were available; however, this is proving difficult for patients as many locations where vaccines are administered do not offer the thigh as an option. It would be beneficial for patients treated for BC if national organizations would make this option more widely available. The goal of this study was to address concerns surrounding side effects, and the informed education that can be produced based on these results will hopefully ease the fears of women treated for BC and empower them to make informed decisions regarding future vaccine doses.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10238-023-01050-z>.

Acknowledgements This work has been presented as a poster (Side Effects of the mRNA Covid-19 Vaccines in Women Treated for Breast Cancer; San Antonio Breast Cancer Symposium; December 6–10, 2022) and in part during a symposium (Covid-19 and Breast Cancer-Related Lymphedema: Patient Experiences and the LymphVAX Study; Presented by Cheryl Brunelle; Lymphatic Education & Research Network; March 9, 2022).

Authors' contributions AGT, CLB, GEN, MCB, LKB, and BCJ designed the concept of the study and manuscript. LHS and BCJ performed data analysis for the paper. AWJ, HSA, EKH, MCB, LKB, TB, and BCJ conducted the study. TB and BCJ performed literature review. All authors edited and approved the manuscript.

Funding The project was supported by award no. R01CA139118 (A. G. Taghian) and award no. P50CA08393 (A.G. Taghian) from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. This

program was supported by the Adele McKinnon Research Fund for Breast Cancer-Related Lymphedema, the Heinz Family Foundation, and the Olayan-Xefos Family Fund for Breast Cancer Research.

Availability of data and materials Data are not available to share. Please reach out to the corresponding author with questions.

Declarations

Conflict of interest Alphonse G. Taghian has been loaned equipment from ImpediMed for use in an investigator-initiated clinical trial. Alphonse G. Taghian is on the Scientific Advisory Board of Puretech Health (not paid) and is a previous consultant for VisionRT. Both involvements are unrelated to this study. Cheryl L. Brunelle is on the Scientific Advisory Board of Puretech Health. The remaining authors have no conflict of interest.

Ethics approval and consent to participate The Massachusetts General Hospital Institutional Review Board approved protocols 2021P000528 (COVID-19 vaccine survey) and 2021P003414 (secondary use protocol to analyze the vaccine survey in conjunction with breast cancer-related demographic and treatment factors). Consent was obtained electronically from participants prior to beginning the survey. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication Not applicable.

References

- Chung HL, Whitman GJ, Leung JWT, Sun J, Middleton LP, Le-Petross HT. Ultrasound features to differentiate COVID-19 vaccine-induced benign adenopathy from breast cancer related malignant adenopathy. *Acad Radiol*. 2022;29(7):1004–12. <https://doi.org/10.1016/j.acra.2022.02.015>.
- Recurrent Breast Cancer. *Mayo Clin*. 2022; Available from: <https://www.mayoclinic.org/diseases-conditions/recurrent-breast-cancer/symptoms-causes/syc-20377135>
- Lehman CD, Lamb LR, D'Alessandro HA. Mitigating the impact of coronavirus disease (COVID-19) vaccinations on patients undergoing breast imaging examinations: a pragmatic approach. *Am J Roentgenol*. 2021;217(3):584–586.
- Tu W, Gierada DS, Joe BN. Covid-19 vaccination-related lymphadenopathy: What to be aware of. *Radiol Imaging Cancer*. 2021;3(3).
- Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403–16.
- Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603–15.
- Centers for Disease Control and Prevention. Website. Pfizer-BioNTech COVID-19 Vaccine Reactions & Adverse Events. Last reviewed 06/21/2022. Available from: <https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/reactogenicity.html>
- Center for Disease Control and Prevention. Website. The Moderna COVID-19 vaccine's local reactions, systemic reactions, adverse events, and serious adverse events. Available from: <https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/reactogenicity.html>
- Foldi E, Foldi M. Foldi's textbook of lymphology. In: Foldi M, editor. *Foldi's textbook of lymphology*. Munich, Germany: Elsevier; 2006. p. 417–27.
- DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2013;14(6):500–15.
- Tsai RJ, Dennis LK, Lynch CF, Snetelaar LG, Zamba GKD, Scott-conner C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. *Ann Surg Oncol*. 2009;16(7):1959–72.
- Bevilacqua JLB, Kattan MW, Changhong Y, et al. Nomograms for predicting the risk of arm lymphedema after axillary dissection in breast cancer. *Ann Surg Oncol*. 2012;19(8):2580–9.
- Warren LEG, Miller CL, Horick N, et al. The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: a prospective cohort study. *Int J Radiat Oncol Biol Phys*. 2014 1;88(3):565–71.
- McLaughlin SA, Wright MJ, Morris KT, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. *J Clin Oncol*. 2008;26(32):5213–9.
- Jammallo LS, Miller CL, Singer M, et al. Impact of body mass index and weight fluctuation on lymphedema risk in patients treated for breast cancer. *Breast Cancer Res Treat*. 2013;142(1):59–67.
- Naoum GE, Roberts S, Brunelle CL, et al. Quantifying the impact of axillary surgery and nodal irradiation on breast cancer-related lymphedema and local tumor control: long-term results from a prospective screening trial. *J Clin Oncol*. 2020;38(29):3430–8.
- Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. *J Natl Cancer Inst*. 2006;98(9):599–609.
- Wilke LG, McCall LM, Posther KE, et al. Surgical complications associated with sentinel lymph node biopsy: results from a prospective international cooperative group trial. *Ann Surg Oncol*. 2006;13(4):491–500.
- Fu MR. Breast cancer-related lymphedema: symptoms, diagnosis, risk reduction, and management. *World J Clin Oncol*. 2014;5(3):241–7.
- Asdourian MS, Skolny MN, Brunelle C, Seward CE, Salama L, Taghian AG. Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. *Lancet Oncol*. 2016;17(9):e392–405.
- Brunelle CL, Roberts SA, Horick NK, Gillespie TC, Jacobs JM, Daniell KM, Naoum GE, Taghian AG. Integrating symptoms into the diagnostic criteria for breast cancer-related lymphedema: applying results from a prospective surveillance program. *Phys Therapy*. 2020;100(12):2186–97. <https://doi.org/10.1093/ptj/pzaa162>.
- Armer JM, Radina ME, Porock D, Culbertson SD. Predicting breast cancer-related lymphedema using self-reported symptoms. *Nurs Res*. 2003;52(6):370–9.
- Jammallo LS, Miller CL, Horick NK, et al. Factors associated with fear of lymphedema after treatment for breast cancer. *Oncol Nurs Forum*. 2014;41(5):473–83.
- McLaughlin SA, Staley AC, Vicini F, et al. Considerations for clinicians in the diagnosis, prevention, and treatment of breast cancer-related lymphedema: recommendations from a multidisciplinary expert Asbrs panel: part 1: definitions, assessments, education, and future directions. *Ann Surg Oncol*. 2017;24(10):2818–26.
- Eaton LH, Narkthong N, Hulett JM. Psychosocial issues associated with breast cancer-related lymphedema: a literature review. *Curr Breast Cancer Rep*. 2020;12(4):216–24.
- Zhang L, Zhang H, Zhong Q et al. Predictors of quality of life in patients with breast cancer-related lymphedema: effect of age, lymphedema severity, and anxiety. *Lymphat Res Biol*. 2021

27. Brunelle C, Skolny M, Ferguson C, Swaroop M, O'Toole J, Taghian AG. Establishing and sustaining a prospective screening program for breast cancer-related lymphedema at the Massachusetts General Hospital: Lessons Learned. *J Pers Med*. 2015;5(2):153–64.
28. Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. *Eur Rev Med Pharmacol Sci*. 2021;25(3):1663–79.
29. Wechsler S, Kneiss J, Adams B, Wood Magee LJ. Persistent cancer-related fatigue after breast cancer treatment predicts postural sway and postexertional changes in sit-to-stand strategy. *Rehabil Oncol*. 2022;40(4):162–71.
30. Centers for Disease Control and Prevention. Website. Side Effects of Cancer Treatments. Last reviewed 06/09/2022. Available from: <https://www.cdc.gov/cancer/survivors/patients/side-effects-of-treatment.htm>
31. Montecino-rodriguez E, Berent-maoz B, Dorshkind K, Montecino-rodriguez E, Berent-maoz B, Dorshkind K. Causes, consequences, and reversal of immune system aging. *J Clin Invest*. 2013;123(3):958–65.
32. McElhaney JE, Dutz JP. Better influenza vaccines for older people: What will it take? *J Infect Dis*. 2008;198(5):632–4.
33. Reichert TA, Simonsen L, Sharma A, Pardo SA, Fedson DS, Miller MA. Influenza and the winter increase in mortality in the United States, 1959–1999. *Am J Epidemiol*. 2004;160(5):492–502.
34. Fleming DM, Elliot AJ. The impact of influenza on the health and health care utilisation of elderly people. *Vaccine*. 2005;23(1):S1–9.
35. Wyant T, Alteri R, Kalidas M, Ogoro C, Lubejko B, Eidsmoe K. Why people with cancer are more likely to get infections. *American Cancer Society*. 2021. pp. 1–41.
36. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med*. 2021;384(23):2187–201.
37. Hiller N, Goldberg SN, Cohen-Cymerknoh M, Vainstein V, Simanovsky N. Lymphadenopathy associated with the COVID-19 vaccine. *Cureus*. 2021. <https://doi.org/10.7759/cureus.13524>.
38. Cynthia V-G, Vaca-Cartagena BF, Becerril-Gaitan A. Attitudes and factors associated with COVID-19 vaccine hesitancy among patients with breast cancer. *JAMA Oncol*. 2021;7:1242.
39. Naranbhai V, Pernat CA, Gavralidis A, et al. Immunogenicity and reactogenicity of SARS-CoV-2 vaccines in patients with cancer: the CANVAX Cohort study. *J Clin Oncol*. 2022;40(1):12–23.
40. Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Da Silva FT. The how's and what's of vaccine reactogenicity. *npj Vaccines*. 2019. <https://doi.org/10.1038/s41541-019-0132-6>.
41. Grimm L, Srinii A, Dontchos B, et al. Revised SBI Recommendations for the Management of Axillary Adenopathy in Patients with Recent COVID-19 Vaccination Society of Breast Imaging Patient Care and Delivery Committee. 2022;(February):2020–3. Available from: <https://www.sbi-online.org/Portals/0/PositionStatements/2021/SBI-recommendations-for->
42. Mortimer PS, Gordon K, Macallan D, et al. Consensus document on COVID-19 vaccination for patients with lymphoedema. UK: British Lymphology Society; 2021.
43. NLN Highlight on COVID-19 Vaccination Injection Site. National Lymphedema Network.
44. Caron C. Do I have to get the COVID vaccine in my arm? *New York Times*. 2021.
45. Wells J. Lymph node swelling and the COVID-19 vaccine. *Mass General Giving*. 2021.
46. Receiving the COVID-19 Vaccine After Cancer Surgery Requiring Lymph Node Removal Under the Arm. *Mass General Cancer Center*. 2021. Available from: <https://www.massgeneral.org/cancer-center/news/covid-19-vaccine-after-cancer-surgery-requiring-lymph-node-removal#:~:text=Lymph node swelling is a, to lymphedema after cancer treatment.>
47. Ferguson CM, Swaroop MN, Horick N, et al. Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer. *J Clin Oncol*. 2016;34(7):691–8.
48. Moderna COVID-19 Vaccine: Standing Orders for Administering Vaccine. 2022;10–3. Available from: <https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/downloads/standing-orders.pdf>
49. Pfizer-BioNTech COVID-19 Vaccine: Standing Orders for Administering Vaccine. 2022;3–5. Available from: <https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/downloads/standing-orders.pdf>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).

Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.

These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.

We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.

While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval, sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.

These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.

To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.

Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.

If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com