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Examining the relationship between COVID-19 vaccines and recall rates in breast screening

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Keywords: Breast cancer lymphedema; diagnostic screening programs; COVID-19 vaccine; recall rate
Parole chiave: Linfedema correlato al cancro al seno; programmi di screening diagnostico; vaccino anti COVID-19; tasso di richiamo

Abstract

Background. *It has been observed that women vaccinated against coronavirus disease 2019 (COVID-19) may show axillary lymphadenopathy at screening mammogram, which may become suspicious for malignancy, leading to an increased recall rate for further diagnostic evaluations and a higher number of false-positive results, as well as considerable emotional distress for the women involved.*

Study design. *The study aimed to assess the incidence of doubt/positive results in the 1st level mammogram among women who received a COVID-19 vaccine within 4 weeks before mammogram, compared to unvaccinated women. Further aims included the analysis of the distribution of doubt/positive 1st level screening mammogram results according to different women-related and diagnostic work-up-related characteristics, and the evaluation of the incidence of false-positive results observed at the 2nd level.*

Methods. *The cohort study was carried out by retrospectively reviewing electronic data records related to the breast screening program of the Local Health Authority of Bologna in 2021 concerning women between 45 and 74 years old. Excluded were the women outside the age range, with prior breast cancer history, or receiving COVID-19 vaccination more than 4 weeks before the mammogram.*

Results. *A total of 43,856 (mean age 56.6 ± 8.7) women met the study's inclusion criteria. Among all enrolled women, the recall rate was 5.5% (N=2,394). There were no statistically significant differences in doubt/positive results between vaccinated within 4 weeks before the mammogram and unvaccinated women (5.5% versus 5.4%, p=0.649). However, those who received the Pfizer vaccine showed a significantly higher rate of doubt/positive results.*

Conclusions. *Healthcare professionals' awareness of vaccine records and educating patients about rare adverse effects can help prevent unnecessary biopsies, interventions, and changes in patient management. Further research is needed to confirm our findings.*

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Introduction

In December 2020 the European Medicine Agency authorized the emergency use of the first three coronavirus disease 2019 (COVID-19) vaccines: 2 mRNA-vaccine, produced by Pfizer/BioNTech (Pfizer) and Moderna Biotech (Moderna) (1,2), and a viral vector vaccine made up of chimpanzee adenovirus produced by AstraZeneca (AstraZeneca) (3), mainly used in people over 65 years of age; in 2021, a fourth vaccine (viral vector) produced by Johnson & Johnson (Janssen) also received the authorization (4).

Since December 27, 2020, COVID-19 vaccination has been promoted in Italy, at first to a restricted target (community health workers, staff and guests of residential and nursing home, persons aged over 80) and gradually to the entire population aged ≥ 5 years (5). In particular, on December 2021, in Italy 46,305,897 people aged ≥ 12 years had received their second dose (6); in the Local Health Authority (LHA) of Bologna, approximately 90% of this population had been vaccinated, as well as in the Emilia-Romagna Region (7).

It has been observed that women vaccinated against COVID-19 may show axillary lymphadenopathy at screening mammogram, which may appear suspicious for malignancy, leading consequently to an increased recall rate (RR) for further diagnostic evaluations and to a higher number of false-positive results (FPR), as well as considerable emotional distress for the women (8-14). The literature still discusses the time required between vaccination and resolution of any local vaccine-induced reactions that could affect breast screening; researchers suggested performing screening mammogram 4-12 weeks after vaccination, depending on the study (10,11,15-19). The National Comprehensive Cancer Network (NCCN) and the Society of Breast Imaging (SBI) have suggested to perform screening mammogram before the first dose of COVID-19 vaccine or 4-6 weeks after the second dose (10,17); the European Society of Breast Imaging (EUSOBI), instead, has proposed ten recommendations to standardize the management of mammograms and reduce unnecessary additional costs and invasive procedures, including waiting at least 12 weeks after the last dose of COVID-19 vaccine before performing the mammogram (18). Keshavarz et al. published a review of 68 cases, of which 97% developed lymphadenopathy within 4 weeks of vaccination (12); the studies by Robinson et al. also identified a 28 day period post-vaccination, after which the incidence of adenopathies decreases (11,15); similarly, Park et al. concluded that a 4 week interval significantly reduced the finding of axillary lymphadenopathy (19) during mammogram.

On the other hand, literature data has consistently emphasized the significance of obtaining anamnestic information on vaccination status prior to performing mammogram (9,16). This recommendation was recently reiterated by the Italian Group for Mammographic Screening (GISMa) on September 3, 2021 (20).

The primary aim of this study is to assess the incidence of doubt/positive results at the 1st level mammogram that require further diagnostic investigations among women who had received at least one dose of COVID-19 vaccine within 4 weeks before performing the examination, compared to those who have not received the vaccine. Further aims of this study are to evaluate associations with possible risk factors, stratifying on the type of vaccine administered, and to assess the incidence of FPR observed at the 2nd level.

Methods

Women eligible for the study

The cohort study was conducted by retrospectively reviewing electronic data records related to the breast screening program of the LHA of Bologna on May 15, 2022. Data were obtained on women aged 45 to 74 years, who were recruited from January 1, 2021 to December 31, 2021; specifically, information included socio-demographic (age, nationality, district of residence) and clinical characteristics (date of the 1st level diagnostic mammogram, 1st level diagnostic conclusion, hospital of 1st level mammogram, date of the 1st level diagnostic procedures, 2nd level diagnostic conclusion, date of the 2nd level diagnostic conclusion, 2nd level diagnostic laterality, date of COVID-19 vaccination, laterality of vaccination, number of vaccine doses, type of COVID-19 vaccine). Based on the literature, only women who received vaccination within 4 weeks before the mammogram were selected for the vaccinated cohort. Women who were older than the screening age range (ie, 75 and older), had a prior history of breast cancer, or had COVID-19 vaccination longer than 4 weeks before the mammogram were excluded. A flowchart summarizing the methodology is shown in Figure 1.

The Ethics Committee of LHA of Bologna approved the protocol of the study (Prot.E.C.No. 460-2022-OSS-AUSL-BO) in 28/06/2022. Considering the nature of the present study, which was based on

reviewing medical records of discharged patients, no written consent was required from the patients according to the ethics committee Area Vasta Emilia Centro of Region Emilia-Romagna (CE-AVEC), which waived the need for consent.

Screening procedure

The breast screening program protocol of the LHA of Bologna has been previously described (21). Briefly, women between 45-49 years were invited annually to undergo the 1st level diagnostic mammogram, while women between 50-74 years were invited every two years. If the mammogram was considered doubt/positive by two radiologists, the woman was called to undergo the 2nd level diagnostic. The finding of isolated axillary lymphadenopathy during a screening mammogram requires a recall for further investigations (22), but this is not the only reason to move to the 2nd level. The RR is the frequency with which a radiologist interprets the finding of a screening mammogram examination as doubt/positive. Women were considered to have undergone a FPR if they received a doubt/positive result at 1st level test, but a negative result at the 2nd level test.

Statistical analysis

Univariate analysis was performed using χ^2 test for all categorical variables and Student *t*-test for independent samples to compare all continuous variables. Considering that the dependent variable is dichotomous, we adjusted for potential confounders using multivariate logistic regression model, therefore the results were expressed as Odds Ratio (OR) with 95% confidence interval (95% CI) and *p* values. A two-sided *p*-value less of 0.05 was considered as indicating a statistically significant difference. The following independent variables were studied: age group (45–49 = 1; 50–69 = 2; 70–74 = 3), nationality (Italian = 0; other = 1), district of residence (Pianura Ovest = 1; Città di Bologna = 2; Pianura Est = 3; Reno, Lavino e Samoggia = 4; Savena Idice = 5; Appennino Bolognese = 6), hospital of 1st level mammogram (hospital 1 = 0; hospital 2 = 1), vaccine (no = 0; yes, within 4 weeks before the mammogram = 1), dose of vaccine (first dose = 1; second dose = 2; third dose = 3), type of vaccine (AstraZeneca/Janssen = 1; Moderna = 2, Pfizer = 3). The statistical analysis was performed by using Stata Statistical Software (Version 16.1) (23). We confirm that all the analyses

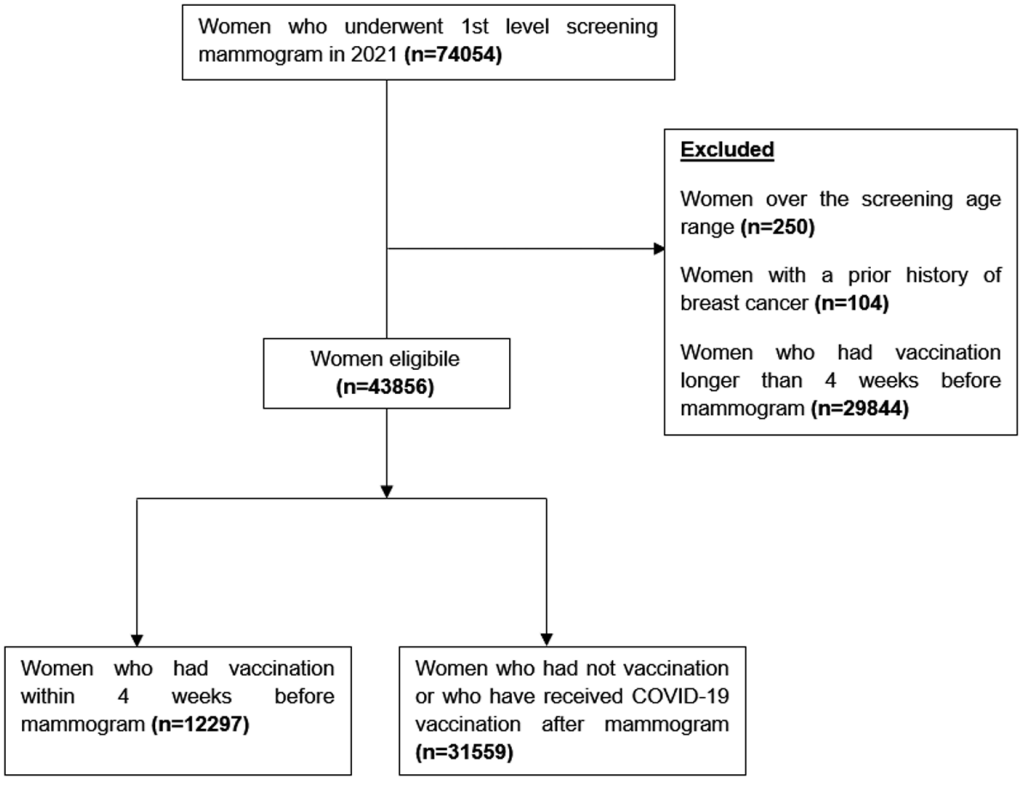

Figure 1. Flow-chart of the women eligible for the study

were conducted in accordance with relevant guidelines and regulations; authors had access to information that could identify individual participants during and after data collection.

Results

As shown in Figure 1, during the study period, a total of 74,054 women underwent 1st level screening mammogram; of these, 59.2% (N=43,856) met the inclusion criteria of the study with a mean age of 56.6 ± 8.7. The population characteristics are shown in Table 1. The women were mainly Italian (86.3%) and resided in the City of Bologna district (38.9%). The 1st level mammograms were read in two different settings, with 90.4% being read at hospital 2. Additionally, 12,297 women (28%) received a COVID-19 vaccine within 4 weeks before the mammogram, with 18.4% receiving either the AstraZeneca or Janssen vaccine, 17% receiving the Moderna vaccine, and 64.6% receiving the Pfizer vaccine. Of the women who

Table 1 - Distribution of doubt/positive I level screening mammogram results according to different women-related and diagnostic work-up-related characteristics.

Characteristics	Eligible women		P[a]
	Total N (%)	With doubt/positive result N (%)	
Total	43856	2394 (5.5)	
Age group (years)			
45-49	12715 (29.0)	1035 (8.1)	***χ2=258.99, 2 df p<0.001***
50-69	26209 (59.8)	1189 (4.5)	
70-74	4932 (11.2)	170 (3.4)	
Nationality			
Italian	37834 (86.3)	2027 (5.4)	***χ2=5.46, 1 df p=0.019***
Other	6022 (13.7)	367 (6.1)	
District of residence			
Pianura Ovest	4484 (10.2)	236 (5.3)	
Città di Bologna	17059 (38.9)	1125 (6.6)	
Pianura Est	9421 (21.5)	482 (5.1)	***χ^2=90.02, 5 df p<0.001***
Reno, Lavino e Samoggia	5993 (13.7)	221 (3.7)	
Savena Idice	4542 (10.4)	231 (5.1)	
Appennino Bolognese	2357 (5.4)	99 (4.2)	
Hospital of 1st level mammogram			***χ^2=580.10, 1 df p<0.001***
Hospital 1	4206 (9.6)	567 (13.5)	
Hospital 2	39650 (90.4)	1827 (4.6)	
Vaccine			
No	31559 (72.0)	1713 (5.4)	*χ^2=0.21, 1 df p=0.649*
Yes, within 4 weeks before the mammogram	12297 (28.0)	681 (5.5)	
Dose of vaccine (N=12297)			
First dose	5621 (45.7)	317 (5.6)	*χ^2=1.95, 2 df p=0.378*
Second dose	5147 (41.9)	291 (5.6)	
Third dose	1529 (12.4)	73 (4.8)	
Type of vaccine (N=12297)			
Astrazeneca/Janssen	2260 (18.4)	95 (4.2)	**χ^2=11.45, 2 df p=0.003**
Moderna	2094 (17.0)	109 (5.2)	
Pfizer	7943 (64.6)	477 (6.0)	

[a] Bold P-values are statistically significant.

Table 2 - Multivariate logistic regression analysis results examining doubt/positive results according to vaccination status and socio-sanitary variables (**A**); Multivariate logistic regression analysis results examining doubt/positive results according to vaccination status and socio-sanitary variables stratified by vaccine type (**B**).

(**A**)

Variable	OR	SE	95% CI	*P*[a]
Log likelihood=-8936.48, χ^2=705.16 (10df), p<0.00001, No. of obs =43856				
Age group (years)				
45-49	1.00[b]			
50-69	0.53	0.02	0.48 - 0.57	**<0.001**
70-74	0.41	0.04	0.35 – 0.49	**<0.001**
Nationality				
Italian	1.00[b]			
Other	0.97	0.06	0.86 – 1.09	0.584
District of residence				
Città di Bologna	1.00[b]			
Pianura Ovest	1.15	0.09	0.98 – 1.34	0.084
Pianura Est	1.09	0.07	0.96 – 1.22	0.183
Reno, Lavino e Samoggia	0.79	0.06	0.67 – 0.92	**0.003**
Savena Idice	1.09	0.09	0.93 – 1.27	0.292
Appennino Bolognese	0.88	0.10	0.71 – 1.09	0.231
Hospital				
Hospital 1	1.00[b]			
Hospital 2	0.31	0.02	0.27 – 0.35	**<0.001**
Vaccine				
No	1.00[b]			
Yes, within 4 weeks before the mammogram	1.07	0.05	0.98 – 1.18	0.142

[a]Bold P-values are statistically significant.
[b]Reference category.

(**B**)

Variable	OR	SE	95% CI	P[a]
Log likelihood=-8935.11, χ^2=707.90 (12df), p<0.00001, No. of obs =43856				
Type of vaccine				
No vaccine	1.00[b]			
Astrazeneca/Janssen	0.95	0.10	0.76 – 1.17	0.612
Moderna	1.00	0.10	0.82 – 1.22	0.982
Pfizer	1.12	0.06	1.01 – 1.24	**0.036**

[a]Bold P-values are statistically significant.
[b]Reference category.

underwent the 1st level screening within 4 weeks of vaccination, 681 (5.5%) had doubt/positive results. In December 2021, most of these women had received only their first dose of vaccine (45.7%). Among all enrolled women, the RR was 5.5% (N=2,394), with 2,199 results available at the 2nd level investigations. The univariate analysis (Table 1) did not reveal any statistically significant differences between the vaccinated within 4 weeks before the mammogram and unvaccinated women with regard to doubt/positive results (5.5% vs 5.4%, p=0.649). The frequency of doubt/positive results significantly varied by age, nationality, district of residence, hospital of 1st level mammogram and type of vaccine. Specifically, women with doubt/positive results were more likely to be younger (8.1%), of non-Italian nationality (6.1%), living in the City of Bologna district (6.6%), having had their diagnostic test read at hospital 1 (13.5%),

Table 3 - Descriptive summary of women characteristics by COVID-19 vaccination status.

Characteristics	Vaccine within 4 weeks before the mammogram N (%)	No Vaccine N (%)	P^a
Total	12297 (28.0)	31559 (72.0)	
Age group (years)			
45-49	3087 (24.3)	9628 (75.7)	χ^2=230.40, 2 df p<0.001
50-69	7455 (28.4)	18754 (71.6)	
70-74	1755 (35.6)	3177 (64.4)	
Nationality			
Italian	10892 (28.8)	26942 (71.2)	χ^2=76.69, 1 df p<0.001
Other	1405 (23.3)	4617 (76.7)	
District of residence			
Pianura Ovest	1215 (27.1)	3269 (72.9)	
Città di Bologna	4938 (28.9)	12121 (71.1)	
Pianura Est	2275 (24.1)	7146 (75.9)	χ^2=108.62, 5 df p<0.001
Reno, Lavino e Samoggia	1794 (29.9)	4199 (70.1)	
Savena Idice	1402 (30.9)	3140 (69.1)	
Appennino Bolognese	673 (28.5)	1684 (71.5)	

[a]Bold P-values are statistically significant.

and, among vaccinated women, having received the Pfizer vaccine (6.0%). Multivariate logistic models results underlined those of the univariate analysis, except for nationality that was no more significantly associated to doubt/positive result, and for the district of residence, where only Reno, Lavino e Samoggia district had significantly lower rates of doubt/positive results compared to City of Bologna (OR: 0.79; 95% CI: 0.67-0.92) (Table 2A). The administration of the vaccine did not appear to affect the doubt/positive result. However, when stratified by vaccine type, a significantly higher rate of doubt/positive results was observed in women who had received the Pfizer vaccine (OR: 1.12; 95% CI: 1.01-1.24) (Table 2B). About the characteristics of the women vaccinated within 4 weeks before the mammogram, they were mostly older, Italian and lived in the Savena Idice district (Table 3). At the 2nd level analyses, 1,444 women had negative results, resulting in a FPR rate of 65.7%; of these, 234 had received a vaccine dose in the same arm as the diagnostic investigation, but laterality was not associated with the FPR outcome (p=0.986) (data not shown).

Discussion and conclusions

In our study, we have observed a RR of 5.5% among women who had been vaccinated within 4 weeks before the mammogram, which is higher than what was found in the literature. For example, Robinson and Raj found an incidence of about 3% of lymphadenopathy in women who received the COVID-19 vaccine 28 days and 8 weeks before the instrumental investigation respectively (13,15), while lymphadenopathy is usually reported in mammograms ranging from 0.02% to 0.04% (9). Literature shows that a higher rate of lymphadenopathy has been observed with ultrasound for screening or diagnostic mammograms, such as Park et al, who found 49% of lymphadenopathy (19,24-26).

Regarding the type of vaccine, we observed a significantly higher percentage of doubt/positive results in those women who received the Pfizer vaccine (6.0%, p=0.003), compared to those who received the Moderna (5.2%) or AstraZeneca/Jannsen vaccine (4.2%), regardless of the dose number, as Robinson's study (15). Conversely, Garreffa et al showed that receiving a single dose of the vaccine was associated with lower rates of lymphadenopathy (22). The Centers for Disease Control and Prevention (CDC) reported a higher percentage of self-reported axillary lymphnode swelling in response to those who received a second dose of the Moderna COVID-19 vaccine, more frequently in younger individuals (up to 16%) (27); lower percentages were found after the Pfizer (from 5.8% to 7.5%) and Janssen vaccine (from 2.7% to 7%) (28,29). Regarding the AstraZeneca vaccine,

lymphadenopathy is known to be a rare adverse event, occurring in approximately one in 100 people (30).

Higher rates of lymphadenopathy have been observed in younger women, as reported by Garreffa and Park et al. (19,22). Additionally, the rate of adverse events reported from the COVID-19 vaccination is higher among women between 20 and 60 years old (31). However, interpreting mammograms in younger women (aged 45-59 years) is challenging compared to the older age groups, and therefore, more frequent tests are needed although the detection of breast cancer may be lower (32).

Current guidelines recommend a short-term follow-up examination within 4–12 weeks after the second vaccine dose (25). In 2021, in Italy, Schiaffino et al recommend that breast imaging should be performed either before or 12 weeks after the last dose of the vaccine to account for the possibility of COVID-19 post-vaccination unilateral axillary lymphadenopathy (18). On the other hand, GISMa considers the resumption of activities a priority in order to fully restart screening programs, at the same time implementing the necessary organizational measures to limit the spread of the virus and promote vaccination (20).

At the LHA of Bologna, due to staffing shortage issues, the screening call delay was about three months when the lockdown started in February 2020. To avoid increasing the delay and consequently increasing undiagnosed or late-stage diagnosed cancers, at the end of lockdown it was recommended that screening calls should be resumed at full capacity. Given the extended period of time for lymphadenopathy to solve, testing should not be delayed, especially for those women with a history of cancer.

In our study, the potential presence of lymphadenopathy post COVID-19 vaccine did not result in a higher rate of doubt/positive results, maybe because we had three readers for each mammogram, which helped to avoid unnecessary insights. The overall RR in 2021 (5.3%) is consistent with the GISMa indicator (<5.0%) (33) and our historic data, which ranged from 5.5% to 6.4% in the three years before the study.

The results of this study suggest that despite numerous studies demonstrating the possibility of subjecting women to unnecessary diagnostic imaging and invasive procedures after COVID-19 vaccination (8,10-13), proper awareness of radiologists about axillary lymphadenopathy as a potential effect of vaccination, the use of the third reader, and the double-blind reading of images may reduce the risk of FPR.

Study limitations and strengths

Most studies have focused on the ultrasound findings of individual cases of axillary lymphadenopathy and not on the incidence or factors associated with vaccination (24,34-36). Even when this was done, such as in the works by Park et al (19) or Wolfson et al (25), the sample size was small, especially for subjects who were not administered the Pfizer vaccine; furthermore, Park et al (19) only investigated the vaccinated population, without comparing it with those who did not receive the vaccine. Finally, published studies on this topic have mostly been conducted in the United States of America (9,25,26,37).

However, there are some potential limitations to consider. The overall RR of hospital 1 (RR 2021 12%) is higher than that of hospital 2 (RR 2021 4.7%); and the catchment area of hospital 1 mostly includes women from the City of Bologna district (93.2%). Moreover, we do not know the exact percentage of lymph node swellings that require a 2nd level investigation. Additionally, different types of vaccines were used in different age groups at different times; for example, AstraZeneca vaccine was used only for the over 60 from April 2021 (38). Therefore, comparisons with other studies may be difficult, due to differences in screening and vaccination protocols between countries.

Conclusions

Studies have shown the importance of knowledge of the incidence of lymphadenopathy. This is crucial since its detection subsequent to COVID-19 vaccination can have an impact on clinical decision-making. The awareness of healthcare professionals regarding updated vaccine records and educating patients about rare adverse effects of the COVID-19 vaccine can help prevent unnecessary biopsies, interventions, and changes in patient management. Therefore, as suggested by Garreffa et al, healthcare providers should routinely inquire about patients' vaccination history when evaluating breast conditions (22). Further research on the incidence of lymphadenopathy in women after receiving the third dose of the COVID-19 vaccine, along with any consequent changes in mammogram guidelines, needs to be explored.

Acknowledgements

The Ethics Committee of LHA of Bologna (Italy) approved the protocol of the study (Prot.E.C.No. 460-2022-OSS-AUSLBO) in 28/06/2022. Considering the nature of the present study, which

was based on reviewing medical records of discharged patients, no written consent was needed by the patients according to the ethics committee Area Vasta Emilia Centro della Regione Emilia-Romagna (CE-AVEC), which waived the need for consent.
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Riassunto

Analisi della relazione tra i vaccini anti COVID-19 ed i tassi di richiamo nello screening mammografico

Background. È stato osservato che le donne vaccinate con il vaccino anti COVID-19 (coronavirus disease 2019) possono presentare linfoadenopatia ascellare alla mammografia di screening. Questa condizione potrebbe apparire sospetta per malignità, portando ad un aumentato tasso di richiamo per ulteriori valutazioni diagnostiche e ad un numero più elevato di risultati falsi-positivi, oltre ad un notevole stress emotivo per le donne.

Disegno dello studio. Lo studio ha avuto l'obiettivo di valutare l'incidenza di risultati dubbi/positivi alla mammografia di I livello tra le donne che avevano ricevuto un vaccino anti COVID-19 entro le 4 settimane precedenti l'esame, rispetto alle donne non vaccinate. Ulteriori obiettivi includevano l'analisi della distribuzione dei risultati dubbi/positivi alla mammografia di screening di I livello in base a diverse caratteristiche relate alle donne ed al percorso diagnostico, e la valutazione dell'incidenza dei risultati falsi positivi osservati alla mammografia di II livello.

Metodi. Lo studio di coorte è stato condotto mediante una revisione retrospettiva dei dati elettronici relativi al programma di screening mammografico dell'Azienda Sanitaria Locale di Bologna nel 2021, riguardante donne di età compresa tra 45 e 74 anni. Sono state escluse le donne fuori fascia di età, con una storia pregressa di tumore al seno o che avevano eseguito la vaccinazione più di 4 settimane prima della mammografia.

Risultati. Un totale di 43.856 donne (età media 56,6 ± 8,7 anni) ha soddisfatto i criteri di inclusione. Tra tutte le partecipanti, il tasso di richiamo è stato del 5,5% (N=2394). Non sono state riscontrate differenze statisticamente significative riguardo alla frequenza di risultati dubbi/positivi tra le donne vaccinate entro 4 settimane prima della mammografia e le donne non vaccinate (5,5% versus 5,4%, p=0,649). Tuttavia, le donne che avevano ricevuto il vaccino Pfizer hanno mostrato un tasso significativamente più alto di risultati dubbi/positivi.

Conclusioni. La consapevolezza da parte degli operatori sanitari delle informazioni sulle vaccinazioni ed un'adeguata educazione delle pazienti sugli effetti avversi rari possono aiutare a prevenire biopsie non necessarie, interventi inutili e modifiche nella gestione clinica delle pazienti. Sono necessarie ulteriori ricerche.

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