

Post-market In-depth Clinical Evaluation for the Safety of Breast Implants and its Relatedness with Squamous Cell Carcinoma within Saudi Healthcare Providers

Study Category:

- Post-market evaluation study (دراسة تقييم سريري)
- Risk analysis report (تقرير تحليل مخاطر)

BACKGROUND

In 2023, World Health Organization (WHO) reported that breast cancer incidence reaches 2.3 million cases yearly; thus, it is the first or second cause of cancer death for women in 95% of countries [1]. According to the American Cancer Society, 43,700 American women will die from breast cancer by 2023 [2].

One type of breast related cancer that has emerged recently is called breast implant-associated squamous cell carcinoma (BIA-SCC) [3]. Although BIA-SCC is rare, it is characterized by rapid progression and an aggressive nature that can reach lymph nodes, tissues, and other sites [4]. BIA-SCC is not breast cancer that arises from the breast tissue; however, it occurs as an epithelial tumor that arises in the capsule surrounding the breast implant [4]. According to some authors, “SCC of the breast develops from as extensive and prominent squamous metaplasia in infiltrating duct carcinoma; however, other authors suggest that it is caused by benign conditions including abscesses, fibroadenomas, or cysts or in association with implants” [5]. Referred to the safety communications issued by US FDA, in 2022, there have been accumulations of SCC incidents in women who have breast implants. Breast implants appear to be one of the etiological factors to increase SCC incidents; however, SCC is rare cancer with unknown risk factors, etiological factors, and occurrence rate [6]. Consequently, by 2023, the SCC of the capsule around the breast implants become one of the highlighted safety signals in several Medical device regulators.

From a biomedical field point of view, the breast implant is a medical device implanted surgically. The implant is typically made up of a gel-like material enclosed within a flexible sac that conforms to the shape of the female breast. Breast implants are divided into two categories based on the case condition: breast augmentation case, in which they increase the size of the breast, and breast reconstruction case, in which they are used to reconstruct the breast tissue following trauma, mastectomy, or to construct birth defects [7]. Moreover, implants are categorized by their surfaces: textured and smooth surface implants [7]. Not only that, but also implants are classified into two filled material types, Silicone implant is filled with silicone gel, while saline implant is filled with saltwater [7].

Collecting the evidence in a form of systematic review will assist in finding whether there is an association between breast implant and SCC or not. Therefore, this study is initiated for patient undergone breast implants surgery (any type, brand, and material) to assess whether there are safety concerns of SCC or not.

Purpose

The purpose of this study is to assess whether potential risks of squamous cell carcinoma (SCC) is associated with breast implant surgery as indicated by FDA safety communication. In light of that, we aim to evaluate the safety of breast implants and its relatedness with squamous cell carcinoma within Saudi Healthcare Providers.

Scope

This study is specific for evaluating the safety of breast implant of all brands and materials, as revealed by data collected from Saudi users. The deliverables are specific for this particular technique, and will be delivered in form of systematic review of the published literatures; in addition to, a survey-based recommendation, which are derived using appropriate statistical approaches in the data collection and validated through discussion with the expert in the field.

Objectives

- I. To systematically demonstrate of whether SCC is associated with breast implant.

RISKS AND COMPLICATION

The debate concerning of the association between SCC and breast implant has continued across regulatory authorities and specialized societies for the last few years. In fact, the amount of data has accumulated and the multimedia highlighted the device in question, which then turned it into a public matter. Consequently, the regulatory authorities and societies started to elevate awareness regarding the safety issues associated to breast implant [8, 6, 9].

The reason behind this concerned that the lack of clearly identifiable clinical data that would allow one to make an informed decision about this issue. In addition, the sample size of

an individual study/ report conducted earlier is not enough to provide sufficient statistical power to detect the primary causes of SCC and to evaluate the safety of breast implants.

Similarly, the last review published in 2018, which compare the results of several case reports about the association between SCC and breast implants [10].

To summarize, carrying out an updated systematic review will allow several types of data to be collected, and this will lend a greater statistical power to the findings of individual studies. In this systematic review, the focus to assess whether using breast implants is associated with SCC in women who have undergone breast implant surgery.

EVALUATION OUTCOMES

This section aims to evaluate the safety of breast implants in light of a clinical paper and experience review. The first aspect aimed to review the currently published papers in the topic to assess whether breast implant is associated with risks of squamous cell carcinoma (SCC) in the capsule. While the second part explored the opinions of other regulatory authorities, international specialized societies, and the third part was the opinions of the local experts to evaluate the safety and quality of current breast implant status within Saudi healthcare providers.

Clinical paper review

1.1.1 Search criteria

This review is carried out in the form of systematic review that was conducted via PubMed electronic databases. Through such an electronic database, the device in question can be explored and identified the related concerns regarding its usage in breast implant surgery globally. Aside from the mentioned electronic database, cross-referencing data will be considered.

The titles and abstracts of the obtained articles were screened according to inclusion and exclusion criteria to find suitable articles on the topic. The restricted search study period for 2015 to 2023 yielded 84 articles. During the title and abstract screening, articles were excluded because of the irrelevance of the inclusion criteria, or not being able to access the full text. Moreover, after screening the articles in full text, an additional 17 articles were withdrawn.

According to the findings, only 7 articles met predefined inclusion criteria along with titles and context. The detailed search strategy is outlined in Table 1 and Figure 1 in reference to PRISMA guidelines [11].

TABLE 1: PLANNING PHASE TEMPLATE

TABLE 2: PLANNING PHASE TEMPLATE	
a. Provide the research topic.	<i>Evaluating the safety of breast implants.</i>
b. Specify the search questions.	<i>Does squamous cell carcinoma (SCC) pose a safety concern for breast implant surgeries?</i>
c. Develop appropriate keywords.	<i>"breast implant*" AND (SCC OR "squamous cell carcinoma" OR complication* OR "side effect*")</i>
d. Identify the relative databases.	<i>PubMed</i>
e. Primary Inclusion criteria: <i>Database parameters (Database options selection)</i>	<ul style="list-style-type: none"> • Period: 2015-2023 • Language: English • Study type: <ul style="list-style-type: none"> <input checked="" type="checkbox"/> All clinical studies Or, other specific type <ul style="list-style-type: none"> <input type="checkbox"/> RCTs <input type="checkbox"/> Systematic reviews <input type="checkbox"/> Meta-analyses <input type="checkbox"/> Cohort studies <input type="checkbox"/> Case control studies
f. Secondary Inclusion criteria: <i>Other major parameters Abstracts screening</i>	<ul style="list-style-type: none"> • Population (P): <ol style="list-style-type: none"> 1. Female 2. Male 3. Child (exclude) • Intervention (I): <ol style="list-style-type: none"> 1. Breast implant 2. Other (exclude) • Comparison (C): <ol style="list-style-type: none"> 1. None • Outcome (O): <ol style="list-style-type: none"> 1. <i>squamous cell carcinoma (SCC) around the implant capsule</i> 2. Other (exclude)
g. Quality assessment measures <i>(Full-text screening)</i>	<ul style="list-style-type: none"> • This assessment will be based JBI Critical Appraisal tools for Case Reports.

Identification of studies via databases

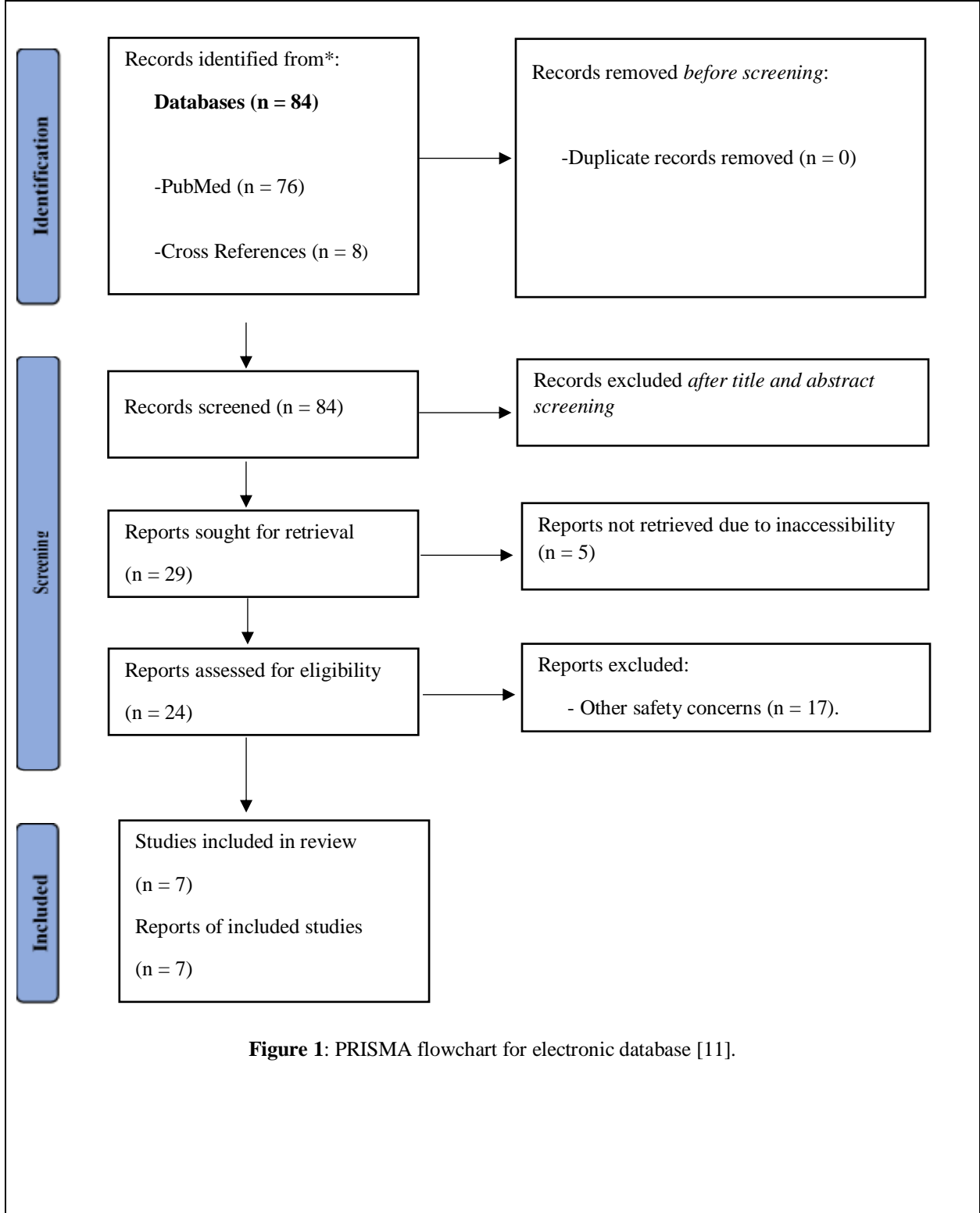


Figure 1: PRISMA flowchart for electronic database [11].

1.1.2 Clinical paper review for the safety of breast implant

Among the 7 included studies, there were 2 case series and 5 case reports, reporting 9 SCC complaints in the capsule. The majority of cases occurred in female and 1 in male during the follow-up period, ranging from 6 months to 8 years. The average age for the patients were 58 across the different studies.

The SCC reported along with 4 textured and 1 smooth implants, while 4 implants were not specified. Since SCC is rare, the diagnosis of SCC usually occurs after 10 to 42 years of the initial implant, with a mean of 26 years.

The 9 cases have numerous background history prior to SCC occurrence: 1 patient undergone breast implant surgery due to suffering from Poland's syndrome. Moreover, 1 case underwent mastectomy along with chemotherapy treatment, while 1 undergone breast reconstruction surgery. Last 6 patients performed breast augmentation surgery, and 4 of them went for a revision after couple of years.

The outcomes associated with the occurrence of SCC were categorized into three categories: 3 cases had no recurrence of disease, 1 patient died due to disease, and 3 complaints led to progress of disease with multiple metastasis.

TABLE 3: CLINICAL PAPER REVIEW FOR THE SAFETY AND PERFORMANCE OF MD TEMPLATE

Ref	Study Design/year	No. of cases*	Gender-Age at Diagnosis	History	Type/texture of Implant	Time Until SCC Diagnosis	Type of SCC	Management	Follow-up duration	Outcome
12	A case report / 2023	1	Male - 52years	Poland's syndrome	Textured	18 years	implant capsule	-surgical excision of the tumor -followed by removal of the implant -complete capsulectomy	1 year	occurrence of multiple metastases, including the skin of the chest, axillary lymph nodes and pleura.
14	A case report	1	Female 46 years	-in 1995 breast	silicone	19 years	implant capsule	-bilateral prosthesis	1 year	occurrence of metastasis

	t / 2018			augmentation. - The implantation was surgically revised in 2002 and 2006	implant	1995-2014		explantation -bilateral capsulectomy -radiation.		to the liver, lungs and retroperitoneum. She expired of her disease in July 2017.
88	A case report / 2018	1	Female -65 years	Subglandular bilateral breast augmentation in 1979. In 2010 patient underwent explantation of the silicone implant, capsulectomy, and revision augmentation with a saline implant.	foam covered silicone implant (Hyer Schulte).	31 years	implant capsule	after 1 month of the surgery patient undergone left radical mastectomy with medial chest wall resection and postoperative radiation therapy.	8 years	The patient remained alive and disease free
89	A case report / 2015	1	Female 58 years	- in 1980 primary bilateral augmentation mammoplasty - in 2000 bilateral mastopexy and right-sided subtotal capsulectomy	-saline implants - Smooth silicone implant	35 years	implant capsule extensive squamous metaplasia	-right total mastectomy -complete capsulectomy with concurrent left explant and simple mastectomy.	NA	NA
90	A case report / 2021	1	Female 45 years	- In 2008 invasive ductal carcinoma status post-	silicone prostheses	10 years	squamous cell carcinoma around	left chest wall mass resection, prosthesis removal	2 years	The patient is currently in a stable condition

				mastectomy and reconstruction. - 3 years post-chemotherapy.			breast implant	and adjuvant radiation and chemotherapy and monotherapy.		with no significant progress
91	A case series / 2017	2	Female 56 years	- in 1984 undergone bilateral for cosmesis - in 1994 Both implants were replaced	- silicone breast implants - textured saline implants.	28 years	implant capsule	surgical excision of the axillary metastasis followed by radiation and additional chemotherapy.	1 year	subcutaneous soft tissue metastases occurred in the left upper arm, axilla and upper chest wall.
			Female 81 years	- wide local excision of a reportedly benign breast mass, followed by reconstruction with a silicone breast implant in the 1970s	- silicone implant	42 years	implant capsule	left mastectomy.	6 months	died of disease.
92	A case series / 2022	2	Female 60 years	-Bilateral augmentation - her left implant Rupture.	- Textured Saline implant	26 years	implant capsule	-bilateral breast implant removal - capsulectomy.	9 months	The patient has no evidence of disease.
			Female 57 years	- Bilateral augmentation	- Textured Saline implant	25 years		- capsulectomy - excision of wound edges.	NA.	patient did not return for follow-up care.

Clinical experience review

1.1.3 International regulatory organizations opinions regarding the breast implant

The debate concerning the safety of the association of SCC and breast implant has continued across regulatory authorities and specialized societies in the year of 2022. The reason behind this is that there is a lack of clearly identifiable clinical data that would allow one to make an informed decision this association due to the rare nature of the disease. Therefore, the international regulatory authorities and societies started to elevate the awareness in regards to complaints of breast implants that might lead to SCC.

In 2023, the US FDA reported from published literature 19 SCC complaints occurred in the capsule around breast implants, not in the breast tissue. Among the 19 patients (breasts), the majority of cases occurred in female, 1 in male, and 1 without information. The average age of those patients at the time of diagnosis was 61. The SCC reported with 4 textured and 4 smooth implants, while 11 implants were not specified. According to the FDA, SCC around breast implants may be rare since it took an average of 25 years after the initial implant for the SCC to appear; however, as the disease progressed, it leads to 16% of death [12]. Meanwhile, FDA declares that its risk factors, etiological factors, and occurrence rate are still unidentified.

TABLE 4: SUMMARY CASES OF SCC REPORTED IN LITERATURE BY US FDA [93]

No. of cases*	19 cases		
Gender	Female = 17	Male = 1	Not specified = 1
Age at Diagnosis	40-81 years		
Type of Implant	Silicone = 9	Saline = 7	Not specified = 3
Texture of Implant	Textured = 4	Smooth = 4	Other & Not specified = 11
Time Until SCC Diagnosis	7-42 years		
Mortality	3 cases		

* The author acknowledges the limitations of the above-mentioned data, which might include some duplication of cases in the literature.

However, the Australian Society of Plastic Surgeons also revealed that TGA is not currently aware of any cases in Australia. [13].

1.1.4 The opinion of global specialized societies and associations in the breast implant

The American Society of Plastic Surgeons (ASPS) and Plastic Surgery Foundation (PSF) declare that there are 16 SCC cases along with breast implant reported in published case reports, the remaining 2 cases were reported by surgeons. When diagnosed, these patients were on average 56 years old. In both textured and smooth implants, SCC reported positive results. Breast implant-related SCC may be rare due to the 23-year time lag in disease onset. However, once diagnosed, it leads to 44% death within 6 months [8].

TABLE 5: SUMMARY CASES OF SCC REPORTED IN LITERATURE BY ASPS [8]

No. of cases*	18 cases	
Age at Diagnosis	40-81 years	
Type of Implant	Silicone	Saline
Texture of Implant	Smooth	Textured
Time Until SCC Diagnosis	11-40 years	
Mortality	43.8% at 6 months	

* The author acknowledges the limitations of the above-mentioned data, which might include duplication of cases in the literature.

1.1.5 The opinion of local societies and experts in the field of breast implant

1.1.5.1 Search criteria

The second suitable instrument used for data collection was a computer based self-administrated questionnaire. Combined with the data collection method, this methodology allows studying the determinant of the outcome (SCC) in relation to the exposure (breast implant capsule) in longitudinal nature.

The sampling technique implemented to obtain the sample size is a convenience sample. Where there was a predefined list of 283 HCPs in Saudi Arabia and 2 specialized societies; however, only 83 healthcare providers (HCP), 8 expert surgeons, and 1 specialized society were requested to fulfill the required questionnaire.

The questionnaire is segregated into two main sections: the first part covers 3 core inquiries about the association of breast implant and SCC, while the second part contains 1 specific query about reporting incidences. These questions structured by various format including open-ended, close- ended along with conditional questions.

1.1.5.2 Local experts

Surgeons from Saudi healthcare providers were consulted to provide the Post Market Clinical Evaluation Team (PMCE) at SFDA with their opinion regarding the safety of using breast implant, who provided the SFDA team the valuable points in the below sections.

The initial elements of the survey showed the demographics of the breast implant surgeries within the Saudi healthcare providers. An 8 surgeons from various healthcare providers fulfil the questionnaire. 25% of surgeons, does not performed breast implant surgery, while the other 75% implanted 1240 breast implants for breast reconstruction type of procedures.

Two of the survey elements were designed to discover issues related to breast implant in whether they affect patient safety after implementing the breast implant or not. Figure 2 demonstrates the responses of 6 surgeons, which reported that they performed multiple breast implantation procedures within the Saudi healthcare providers. All of them agreed that the SCC is rare since then they are not aware of SCC complaints related to breast implant capsule. However, figure 3 revealed that 33% of the surgeons, who performed an estimated 1000 breast implant surgeries, stated that they have faced couple of complaints related to breast implant rather than SCC, such as capsular contraction and late seroma. Whereas, 67% of the plastic surgeons, who implanted 240 devices, does not reported any complaints in relation to breast implantation procedures.

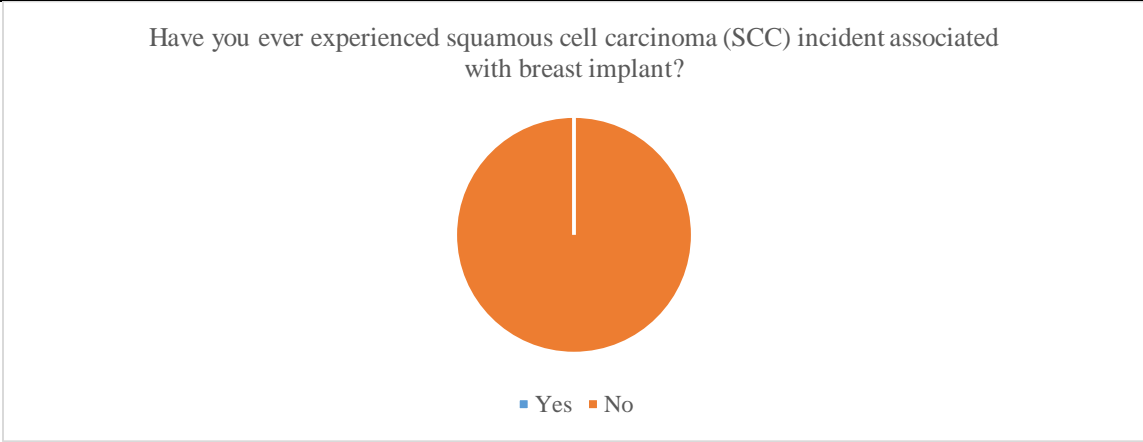


FIGURE 2: COMPLAINTS OF BREAST IMPLANT CAPSULE ASSOCIATED SCC.

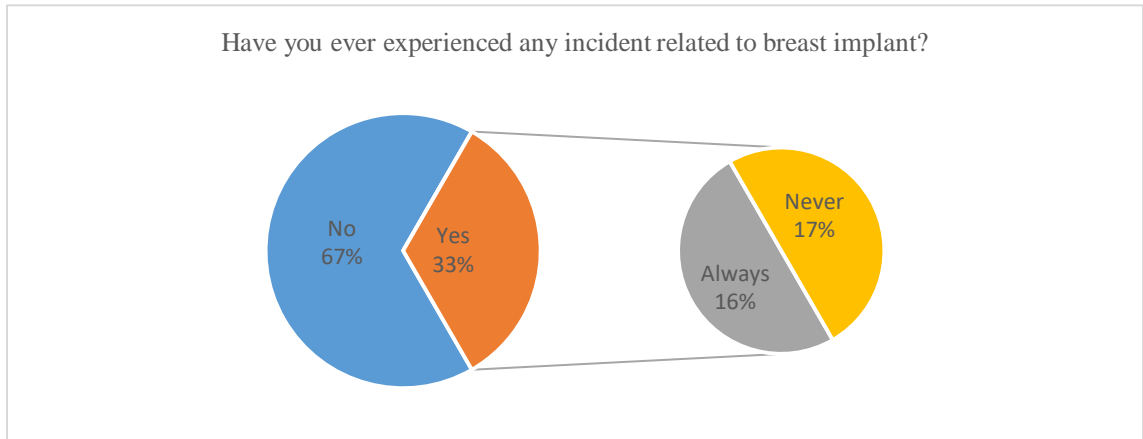


FIGURE 3: ANY INCIDENTS ASSOCIATED TO BREAST IMPLANT.

One element measured to disclose the realization of the healthcare community regarding the importance of Reporting complaints related to medical devices, which helps in taking immediate corrective action, elevating the awareness of the potential risks of the device, and the way to prevent reoccurrences. Nevertheless, figure 3, and as revealed by the respondents, demonstrate that 16 % of healthcare surgeons always report any complaints related to breast implants, which reflect that they are fully aware about the regulatory practice. While 17% of healthcare surgeons never reported any incidence related to breast implant to the SFDA NCMDR. The reason appears to be the” Usual expected side effect”, which does not need to be reported from their perspective. In fact, this element highlights the low level of awareness regarding regulatory practice.

1.1.5.3 Local society

Besides the expert healthcare provider's experience, a specialized society was consulted to reveal its members' opinions and clinical experiences regarding this issue. The president of Saudi Scientific Association of Plastic Surgery and Burns (SSAPSB) shared the following inputs:

- They agree that the risk of developing SCC is considered a safety concern for breast implant surgery, but data is very limited and not consistent, which we cannot draw conclusions on incident, risk factors and causation.
- They believe plastic surgeons need to be educated about it and how to deal with it. And just like BIA- ALCL, patients seeking breast implants need to be made aware of such an extremely rare condition.
- They have never experienced squamous cell carcinoma (SCC) complaints associated with breast implants in any patient.
- They would like to encourage and reinforce a reporting system for and BIA SCC/ BIA ALCL.

Discussion and conclusion

This systematic review addresses the association between breast implants and SCC across multiple sources globally and locally, but still the risk factors, etiological factors, and occurrence rate cannot be predicted.

During the search process, multiple cases of SCC were identified globally through a literature search, US FDA, and ASPS, respectively. As it was stated, the average age at diagnosis was in the late 50s, and since SCC is a rare disease usually diagnosed with an average of 25 years after implantation. There are several outcomes associated with the occurrence of SCC that were categorized into five categories: 33% of cases had no recurrence of disease, 11% of patients died due to disease, and 33% of complaints led to progress of disease with multiple metastasis, 16% death cases because of disease progression, and 44% of patients died within six months of diagnosis. Whilst, during the local investigation, there were no cases of SCC from any of the

implanted devices, neither from Saudi healthcare surgeons, who performed 1240 surgeries, nor from Saudi specialized societies.

There are several aspects of the conducted study need to be mentioned. First, the different data collection methods used in this systematic review yield some methodological issues that need to explain. Second, all included studies were either case reports or case series, which might decrease the certainty of the temporal relationship of associations explored. Another point of view is that the questionnaire is a common approach to studying specific trends or experts' opinions; however, it has survey needs to include more data. Finally, the data extracted from the literature and global experience review might include duplication of cases, as there are similarities in the number of cases, age at diagnosis, and time until SCC diagnosis.

In conclusion, this systematic review of a rare and poorly understood relationship between SCC and breast implant capsules needs additional surveillance globally and locally since it is important to improve the way of detection and management of SCC in order to obtain an optimum regulatory decision.

ACKNOWLEDGMENT

Thanks to the post-market clinical evaluation team for their supports in conducting this work. For further information or inquiries related to this study, you may contact us at: cia.md@sfd.gov.sa

REFERENCES

1. World Health Organization. WHO launches new roadmap on breast cancer [Feb 3, 2023]. Available from: <https://www.who.int/news/item/03-02-2023-who-launches-new-roadmap-on-breast-cancer>
2. American cancer Society. Key Statistics for Breast Cancer [Jan 12, 2023]. Available from: <https://www.cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html#:~:text=The%20American%20Cancer%20Society's%20estimates,will%20die%20from%20breast%20cancer.>

3. Bhosale, S. J., Kshirsagar, A. Y., Deshmukh, S. J., Jagtap, S. V., & Langade, Y. B. (2013). Squamous cell carcinoma of the breast. *The American journal of case reports*, 14, 188–190. <https://doi.org/10.12659/AJCR.883934>.
4. American Society of Plastic Surgeons. ASPS statement on Breast Implant Associated-Squamous Cell Carcinoma (BIA-SCC) [Sep 08, 2022]. Available from: <https://www.plasticsurgery.org/for-medical-professionals/publications/psn-extra/news/asps-statement-on-breast-implant-associated-squamous-cell-carcinoma>.
5. Yadav, S., Yadav, D., & Zakalik, D. (2017). Squamous cell carcinoma of the breast in the United States: incidence, demographics, tumor characteristics, and survival. *Breast cancer research and treatment*, 164(1), 201–208. <https://doi.org/10.1007/s10549-017-4251-3>.
6. U.S. Food and Drug Administration. Breast Implants: Reports of Squamous Cell Carcinoma and Various Lymphomas in Capsule Around Implants: FDA Safety Communication [Internet]. U.S. Food and Drug Administration; 2022 [updated – 2022 cited – 2023 May 11]. Available from: <https://www.fda.gov/medical-devices/safety-communications/breast-implants-reports-squamous-cell-carcinoma-and-various-lymphomas-capsule-around-implants-fda>
7. Saudi Food and Drug Authority. Overview. [Internet]. Saudi Food and Drug Authority; 2021 [updated – 2019; cited – 2023 May 11]. Available from: https://www.sfda.gov.sa/sites/default/files/2021-02/PM%20EVALUATION%20FOR%20THE%20SAFETY%20AND%20EFFECTIVENESS%20OF%20BREAST%20IMPLANTS_0.pdf.
8. American Society of Plastic Surgeons. ASPS statement on Breast Implant Associated-Squamous Cell Carcinoma (BIA-SCC) [Sep 08, 2022]. Available from: <https://www.plasticsurgery.org/for-medical-professionals/publications/psn-extra/news/asps-statement-on-breast-implant-associated-squamous-cell-carcinoma>.

9. Therapeutic Goods Administration. Breast implants: Report of squamous cell carcinoma and various lymphomas in scar tissue around breast implants [Internet]. U 8. Therapeutic Goods Administration; 2022 [updated – 2022; cited – 2023 May 11]. Available from: [https://www.tga.gov.au/news/safety-alerts/breast-implants-report-squamous-cell-carcinoma-and-various-lymphomas-scar-tissue-around-breast-implants#:~:text=The%20risk%20of%20squamous%20cell,Lymphoma%20\(BIA%2DALCL\).](https://www.tga.gov.au/news/safety-alerts/breast-implants-report-squamous-cell-carcinoma-and-various-lymphomas-scar-tissue-around-breast-implants#:~:text=The%20risk%20of%20squamous%20cell,Lymphoma%20(BIA%2DALCL).)
10. Zhou, Y. M., Chaudhry, H. E., Shah, A., & Andrews, J. (2018). Breast Squamous Cell Carcinoma Following Breast Augmentation. Cureus, 10(10), e3405. <https://doi.org/10.7759/cureus.3405>.
11. Prisma. (2021). Transparent Reporting of Systematic Reviews and Meta-Analyses. Available from: <https://www.prisma-statement.org/>.
12. U.S. Food and Drug Administration. UPDATE: Reports of Squamous Cell Carcinoma (SCC) in the Capsule Around Breast Implants - FDA Safety Communication [Internet]. U.S. Food and Drug Administration; 2023 [updated – 2023; cited – 2023 May 11]. Available from: <https://www.fda.gov/medical-devices/safety-communications/update-reports-squamous-cell-carcinoma-scc-capsule-around-breast-implants-fda-safety-communication>
13. The Australian Society of Plastic Surgeons. A BIA-ALCL, BIA-SCC, and other various cancers [Sep 14, 2022]. Available from: <https://www.plasticsurgery.org/for-medical-professionals/publications/psn-extra/news/asps-statement-on-breast-implant-associated-squamous-cell-carcinoma>.