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Effect of Breast Silicone Implant Topography on Bacterial Attachment and Growth: An *In Vitro* Study

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Abstract. *Background/Aim: The mechanisms underlying capsular contracture remain unclear. Emerging evidence supports the inflammation hypothesis, according to which bacteria from an adherent biofilm cause chronic inflammation and collagen deposition on the implant and trigger capsular contracture. Our goal was to evaluate the effect of different types of breast implants on the growth of Staphylococcus aureus, S. epidermidis, and Pseudomonas aeruginosa, which are commonly found in biofilms in infection. Materials and Methods: Bacteria were grown in tryptic soy broth at 37˚C for 2, 6, and 24 h and subsequently incubated for 24 h on 12 shell sections of smooth, nano-, and macrotextured breast implants. After incubation, the solutions were ultrasonicated and bacterial numbers were determined by serial dilution. S. aureus were fixed, washed with phosphate-buffered saline, dehydrated in ethanol, and coated with a platinum film to visualize the presence of biofilms by scanning electron microscopy. Results: The numbers of S. aureus and S. epidermidis attached to the smooth and nanotextured surface implants were significantly lower than those on the macrotextured surface for all incubation times, whereas the number of P. aeruginosa was non-significantly lowest on the nanotextured surface after 24-h incubation. Biofilms on smooth and nanotextured implant surfaces showed patchy patterns on scanning electron microscopy in contrast to the continuous pattern detected on macrotextured implants. Conclusion: Nanotextured breast implants may limit bacterial growth and thus prevent capsular contracture.*

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Key Words: Smooth breast implant, nano-textured breast implant, macrotextured breast implants, biofilm, breast implant infection, scanning electron microscopy.

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Biofilms are microbial communities that attach to the surfaces of tissues, implants, and medical equipment, and are responsible for a considerable number of human microbial infections (1). Biofilm formation occurs in three stages: Attachment, maturation, and dispersion (2). Attachment is the initial stage in which bacteria interact with the implant surface to adhere to it and become embedded. During maturation, bacteria grow and multiply to reinforce the anchoring to the implant and to each other. Eventually, the bacterial cells detach from the biofilm and spread throughout the environment/host in a stage called dispersion (3). In humans, biofilm-related infections are abundant, and because they are difficult to treat, they become chronic. Evidence indicates that the presence of biofilms on medical devices is related to persistent inflammation of the surrounding tissue. This problem is accentuated by the fact that all medical devices, including breast implants, are vulnerable to bacterial colonization and biofilm formation (4). Therefore, determining the conditions that can reduce the chances of bacterial growth on medical devices would be beneficial.

Breast reconstruction using breast implants is one of the most common procedures performed in both plastic and reconstructive surgery. The surface of the shell covering a breast implant acts as a connection between the breast tissue

and the medical device and constitutes an important area of study in the field of implantation (5). Although the mechanism of capsular contracture (CC) is not well known, studies have shown a relationship between biofilm infections and the development of CC around breast implants (6).

According to the inflammation hypothesis of CC, biofilms growing on a breast implant surface induce chronic inflammation, which subsequently causes thickening of the collagen capsular membrane, additional fibrosis, and bacterial trapping, ultimately leading to contracture, hardness, and breast deformities (7). In an effort to understand the mechanisms leading to CC, previous studies focused on identifying the physical and chemical characteristics of implant surfaces that promote this condition.

Various types of breast implants are available, and the main differences between them are based on physical aspects, such as their shape, size, material, and surface texture (8). There are two types of implants: Smooth and macrotextured. Smooth-surface implants are used worldwide; however, the incidence of CC using these implants is higher than that in textured implant types when placed in the subfascial plane (9). Macrotextured surface implants, which can disrupt contractile forces, have been developed to minimize CC (10). Breast implant developers continue to use diverse techniques to advance new implant surface textures, to stabilize implants in the pocket through increased coefficients of friction and enhance integration of the implant with breast tissue. Recently, numerous articles have proposed the use of nanometric surface topographies to induce specific cellular behaviors, such as cell proliferation, attachment, migration, and differentiation, which are factors that affect the prevalence of CC (11-13). Surfaces with nanoscale roughness closer to cellular dimensions are known to exhibit profound effects on cells and produce a reduced foreign-body response (14).

Causative organisms that are principally involved in breast implant-related infections include *Staphylococcus aureus, S. epidermidis, Pseudomonas aeruginosa, Cutibacterium spp. (i.e., Propionibacterium),* and *Corynebacterium spp.* (15). Infections by these diverse group can be especially difficult to treat empirically in the absence of characterization of the local microbiome. A better understanding of these causative organisms and their aspects of biofilm formation can lead to better prevention, more effective salvage rates, and treatment of active infections.

The relationship between implant surface texture and microbial biofilm formation has not been sufficiently evaluated. In this study, we examined the microbial activity after bacterial incubation on different types of silicone breast implants. The attachment and growth of *S. aureus*, *S. epidermidis*, and *P. aeruginosa* were compared using implants with three different types of surfaces: smooth, nanotextured, and macrotextured. We also visualized the bacteria grown on the three types of surfaces using scanning electron microscopy (SEM) to provide a detailed morphological investigation of the biofilms at a high magnification.

Materials and Methods

Breast silicone implants. Specially manufactured hemispherical implants with three different types of topographies (smooth, nanotextured, and macrotextured surfaces) were cleanly cut into shell sections of 2-cm in diameter (Figure 1). The implants were prepared using Hans Smooth, Hans SmoothFine, and Hans Textured (Hansbiomed Co., Ltd., Seoul, Republic of Korea) to produce smooth, nanotextured, and macrotextured surfaces, respectively. Hans Smooth exhibits a relatively flat surface (0.40 μm), whereas the surface roughness values for Hans SmoothFine and Hans Textured are 5.96 μm and 100.10 μm, respectively.

In vitro bacterial attachment assay. A total of 36 miniature implants, comprising 12 2-cm diameter miniatures each of smooth, nanotextured, and macrotextured implants, were incubated in 10 ml of tryptic soy broth (BD Biosciences, Franklin Lakes, NJ, USA) containing 3.9×10^8 colony forming units (CFU)/ml of *S. aureus*, *S. epidermidis,* and *P. aeruginosa*. These strains were maintained at –70˚C as frozen stock cultures prior to the experiment. After incubation at 37˚C for 2, 6, and 24 h, each sample was placed in 15 ml of sterile 0.85% saline after washing and vortex mixing for 15 s, ultrasonication for 10 min at 40 kHz, and washing again by vortex/mixing for 15 s, as previously described (8). The procedure, which was triplicated, provides a distinct advantage over culture plates in helping to measure only the remaining adherent bacteria in the growth phase. Bacteria attached to whole implants were quantified by performing 10-fold serial dilutions and subsequently plating 100 μl of the diluted cultures on tryptic soy agar (BD Biosciences). All treatments were repeated three times, and the CFU counts were averaged (Figure 2).

SEM of S. aureus. The presence of biofilms was visually confirmed by SEM in all implants incubated with *S. aureus*. After 24 h of incubation, *S. aureus* was fixed overnight in a 2% glutaraldehyde solution, washed once with phosphate-buffered salin, and dehydrated in stepwise, increasing ethanol concentrations of 30%, 50%, 70%, 90%, 100%, and additional 100% for 10 min each. The samples were critical point-dried, coated with platinum, and qualitatively examined using SEM (SU8220; Hitachi Co., Hitachi, Japan).

Statistical analysis. Statistical analysis was performed using SPSS version 25 software (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). To determine differences in bacterial growth under different conditions (incubation times) for each implant, as well as to compare growth between implants, CFU counts were analyzed by one-way analysis of variance, and statistical significance was considered at a value of $p<0.05$. *Post-hoc* Bonferroni correction was used for multiple comparisons. The analysis of variance included "experiment" as the random effect; "species", "implant type", and the two-way interaction were included as fixed effects. Because the interaction plots and tests suggested an interaction between species and implant type, we investigated this interaction by analyzing the log differences for each species and time point separately.

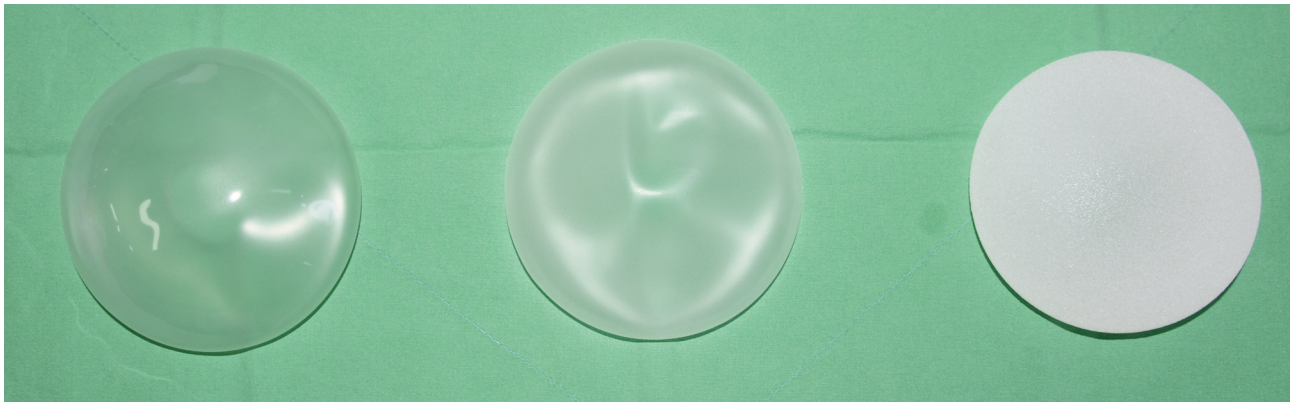

Figure 1. *The three different types of implant shells used in this study. Samples were prepared in the form of a disc with a diameter of 2 cm on three different implant surfaces: Smooth type (left), nanotextured type (center), and macrotextured (right) type. Each miniature disc shell was incubated in 10 ml of tryptic soy broth (BD Biosciences) containing 3.9×10^8 colony-forming units/ml of either Staphylococcus. aureus, S. epidermidis, or Pseudomonas aeruginosa.*

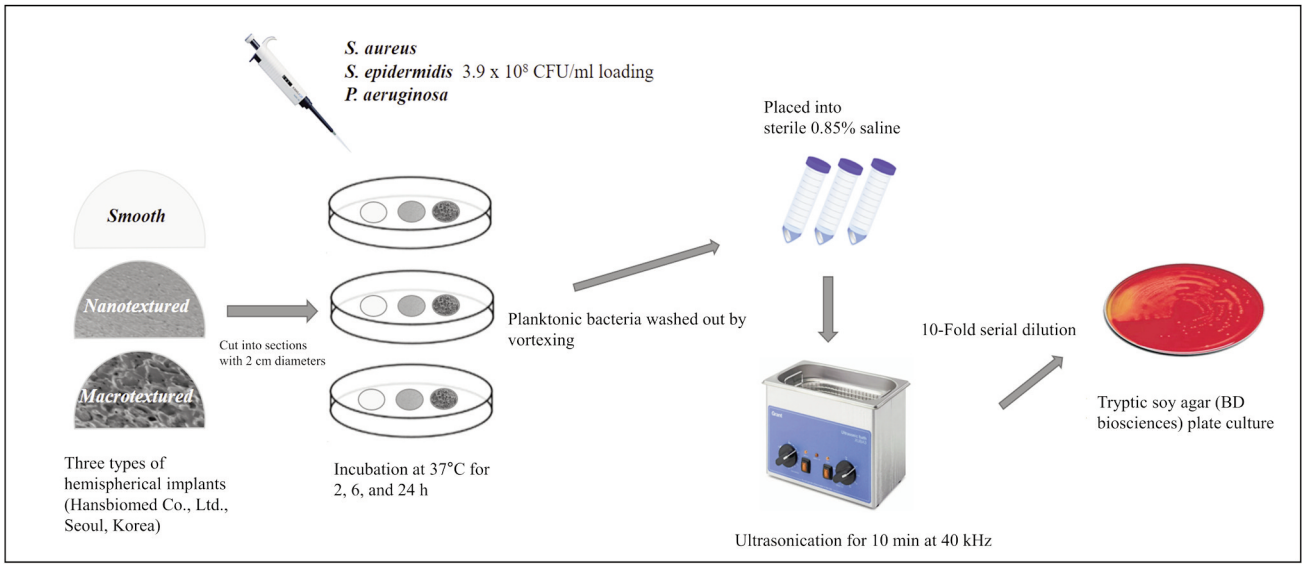

Figure 2. *In vitro bacterial-attachment assay. Miniature implant shells were cut into 2-cm diameter and incubated in 10 ml of tryptic soy broth (BD Biosciences) containing 3.9×10^8 colony-forming units (CFU)/ml of Staphylococcus. aureus, S. epidermidis, or Pseudomonas aeruginosa. After incubation for 2, 6, and 24 h, samples were placed into 15 ml of sterile 0.85% saline after washing by vortex mixing for 15 s and ultrasonicated for 10 min at 40 kHz. Bacteria attached to implant surfaces were measured by performing serial dilutions and counting CFU on tryptic soy agar (BD Biosciences).*

Results

In vitro bacterial attachment assay. S. aureus. The mean CFU value was used to measure the number of bacteria attached-the implants. The CFU values of *S. aureus* attached-the smooth, nanotextured-, and macrotextured implants after the 2-h incubation were 0.28×10^6 [95% confidence interval (CI)=0.08-0.62×10^6], 0.30×10^6 (95% CI=0.08-0.67×10^6) and 1.8 (95% CI=0.4-4.4) ×10^6), respectively; those after the 6-h incubation were 7.0×10^6 (95% CI=1.0-14.0×10^6), 7.3×10^6 (95% CI=1.5-13×10^6) and 25.0×10^6 (95% CI=4.6-73.0×10^6), respectively; and those after the 24-h incubation were 12.0×10^6 (95% CI=1.8-32.0×10^6), 8.6×10^6 (95% CI=1.6-20.0×10^6) and 110.0×10^6 (95% CI=1.8-400×10^6),

respectively. The numbers of *S. aureus* that grew on the nanotextured and smooth-textured implants were significantly lower than those recovered from the macrotextured implants for all incubation times ($p<0.05$). Moreover, the number of *S. aureus* on the nanotextured implants was the lowest of all implants after incubation for 24 h.

S. epidermidis. The mean CFU values of *S. epidermidis* attached-the smooth, nanotextured, and macrotextured implants after the 2-h incubation were 0.4×10^6 (95% CI=$0.07\text{-}1.1\times10^6$), 0.7×10^6 (95% CI=$0.2\text{-}1.3\times10^6$) and 10.0×10^6 (95% CI=$3.1\text{-}30.0\times10^6$), respectively; those after the 6-h incubation were 1.1×10^6 (95% CI=$0.3\text{-}2.1\times10^6$), 1.5×10^6 (95% CI=$0.7\text{-}3.1\times10^6$) and 19.0×10^6 (95% CI=$6.5\text{-}42.0\times10^6$), respectively; and those after the 24-h incubation were 1.2×10^6 (95% CI=$0.5\text{-}2.0\times10^6$), 3.5×10^6 (95% CI=$1.6\text{-}6.5\times10^6$) and 46.0×10^6 (95% CI=$14.0\text{-}88.0\times10^6$) respectively. The CFU of *S. epidermidis* quantified from the nanotextured and smooth implants were significantly lower than those recovered from the macrotextured implants for all incubation times ($p<0.05$).

P. aeruginosa. The mean CFU values of *P. aeruginosa* attached-the smooth-, nanotextured, and macrotextured implants were 0.9 (95% CI=0.3-3.2) $\times10^6$, 2.1 (95% CI=1.0-4.5) $\times10^6$, and 4.5 (95% CI=1.5-9.2) $\times10^6$, respectively, after 2-h incubation; 2.6 (95% CI=0.5-13.0) $\times10^6$, 2.7 (95% CI=0.7-7.0)$\times10^6$ and 7.7 (95% CI=2.2-28.0) $\times10^6$, respectively, after 6-h incubation; and 4.5 (95% CI=0.9-14.0) $\times10^6$, 3.6 (95% CI=0.4-7.4) $\times10^6$ and 17.0 (95% CI=3.7-93.0) $\times10^6$, respectively, after 24-h incubation. Although the numbers of *P. aeruginosa* CFU recovered from the nanotextured and smooth implants were lower than the bacterial load recovered from the macrotextured implant after all incubation times, there were no significant differences among the three implants at 2, 6, and 24 h. The number of *P. aeruginosa* on smooth implants was significantly higher after 24 h of incubation than after 2 and 6 h of incubation ($p<0.05$). Although the bacterial count on the nanotextured implants was the lowest, the bacterial counts on the three different implants were not significantly different after 24 h.

SEM. SEM images of the smooth, nanotextured, and macrotextured outer shells after 24 h of incubation with *S. aureus* showed dense and thick biofilms on the surface of the macrotextured implants and patchy biofilms on the surface of the smooth and nanotextured implants (Figure 3). Biofilms on the smooth and nanotextured implant surfaces showed a dispersed distribution.

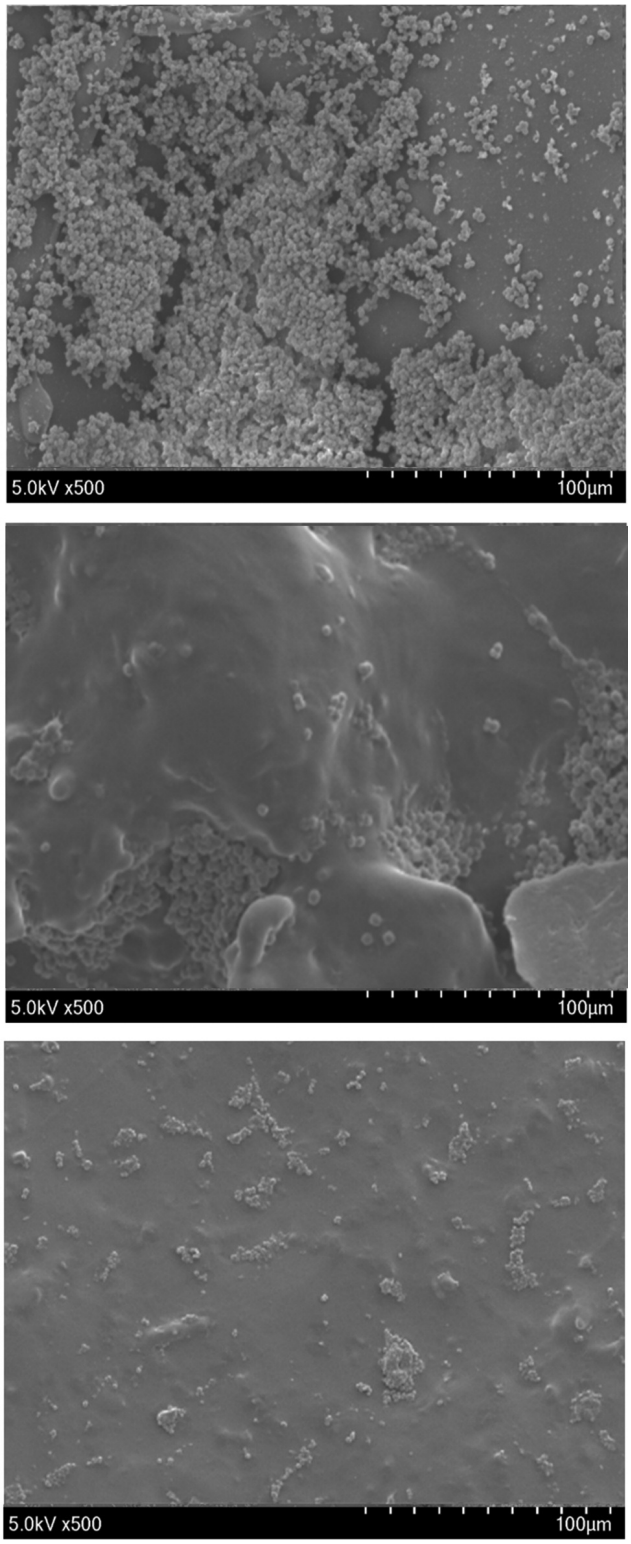

Figure 3. *Scanning electron microscopy (SEM) image of Staphylococcus aureus after 24 h of incubation on macrotextured (left), nanotextured (center) and smooth (right) silicone implants. The samples were critical point-dried, coated with platinum, and examined by SEM (Hitachi, SU8220) (original magnification ×1,000).*

Discussion

Silicone implants for long-term transplantation cause CC, which is undesirable after breast surgery (16). Contracture

of the collagen capsule formed around the breast may be uncomfortable and can distort the breast structure. Capsule formation is a natural reaction to foreign bodies. Its etiology is not entirely known. The process of bacterial adherence to an implant is affected by several factors, including implant surfaces, physiological signaling, and bacterial species and their interactions with the host environment. Implants can markedly alter the pathophysiology and directly influence cellular biology, body tissues, and fibrous capsule development, especially the adherence of the tissue to the breast implant and the alignment of collagen fibers (17). Microbial biofilms present on breast implants might contribute to a chronic inflammatory response, and thus, the formation of capsular fibrosis and subsequent contracture (18-20). Although bacterial growth depends on several factors, the implant surface topography has a significant effect on bacterial attachment. Clinical studies have confirmed a significant correlation between bacterial contamination and increased CC grades (21).

A previous study suggested that a higher surface area and roughness provide a more favorable environment for bacterial colonization (21). Furthermore, bacterial colonization promotes biofilm formation and infection at implant sites.

The presence of bacteria on an implant's surface has been shown to be a significant predictor of CC formation in clinical and laboratory studies (22, 23). Studies on pigs have confirmed a significant correlation between bacterial contamination and increased CC grade (24). Furthermore, translational research findings support the use of antibacterial mitigation to reduce CC, thus linking the surface area and bacterial growth relationship directly to functional clinical outcomes (25, 26). Strategies to prevent implant contamination help reduce the number of bacteria and keep contamination below a threshold (27). Smooth surfaces are known to be associated with a high prevalence of CC because fibroblasts that are in direct contact with the smooth implant surface produce collagen fibers that align within the capsule next to the implant in response to shearing motion within the implant pocket (28, 29). Indeed, continual rubbing between a smooth-surfaced implant and its non-adherent capsule plays a key role in causing a thick capsule and an acute, active tissue response (30). In contrast, textured surfaces disrupt the collagen alignment of the surrounding capsule by inhibiting micromotion at the implant/host interface (31). At the clinical level, nanotextured surfaces have demonstrated excellent safety outcomes and reduced serious adverse events, such as double capsules, CC, implant rupture or device failure, and late seromas (32, 33). Our study showed that the adherence of *S. epidermidis* was greatest on the macrotextured surface and lowest on the smooth surface. However, while a previous study indicated that a greater surface area and roughness provided a more favorable environment for colonization (34), our results indicated the lowest bacterial count on nanotextured implants after 24-h incubation in both the *S. aureus* and *P. aeruginosa* bacterial-attachment assays. Although in our study, each bacterial type had a different growth pattern on the three silicone materials, the bacterial count on the nanotextured surface was the lowest at all incubation times.

Multiple clinical studies have demonstrated a significant correlation between the presence of biofilms and the CC of breast implants. Dobke *et al*. examined 150 silicone wall-mammary implants (35). In their study, 76% of contracted capsules harbored bacteria. Pajkos *et al*. evaluated 19 contracted and eight non-contracted breast implants and capsules for bacterial presence (36). Bacteria were detected in 17 out of 19 of the breast implants with CC, of which 11 samples had biofilms. In contrast, bacteria were present in only one out of eight of the non-contracted implants. Interestingly, Jacombs *et al*. showed different aspects of bacterial growth depending on the implant surface and surrounding capsular tissue (22). In their *in vivo* experiment using 16 adult female pigs with 121 implants, including textured and smooth implants, 20-fold higher bacterial numbers were found on the textured implants than the smooth implants, whereas no significant difference in bacterial numbers was detected in the surrounding capsular tissue. Based on the inflammation theory, this study indicated that there is a bacterial load threshold associated with each type of implant surface which is necessary to lead to the development of CC on the implant surface. Although the cause of CC is multifactorial, this finding could help to untangle why textured implants are associated with lower rates of CC while resulting in higher bacterial counts on the surface, which is in agreement with previous findings that showed enhanced tissue ingrowth on texturized surface and subsequent disturbance in fibrotic tissue arrangements (37). In the current study, nanotextured and smooth-surface implants showed relatively patchy and dispersed biofilm formation. *P. aeruginosa* numbers were not significantly affected by the incubation times, but their bacterial load recovered from the nanotextured implants was the lowest of the three implant types tested. It has been suggested that nanotexturization mimicking the size of the bacteria promotes bactericidal effects by reducing the area of contact with the bacteria, as revealed in a previous study (38). Because of the surface texturization and reduced and patchy biofilm formation on the surface, nanotextured surface implants might be the implants of choice to reduce CC in clinical implant-based breast surgery.

Our study has several limitations. We only examined biofilm distribution by SEM for *S. aureus* cultures; therefore, the results cannot be generalized to other species. Given the *in vitro* nature of the study, we were unable to analyze the friction between the convex area of the nanotextured and macrotextured surfaces and surrounding soft tissue. In

addition, as each bacterial incubation was performed horizontally in tryptic soy broth, the method did not mimic the actual three-dimensional interference between an implant surface and breast tissue.

Our study estimated the numbers of three bacterial species commonly found in biofilms attached to different breast implant types after 2, 6, and 24 h of incubation. We speculate that an increased number of bacteria would increase the chances of biofilm formation and that the biofilm distribution pattern (*i.e.,* continuous or patchy) may also affect capsule formation. Further studies are needed to investigate this at the molecular level.

In conclusion, the topography of breast implants significantly contributes to the growth and adhesion of bacterial pathogens. Our findings revealed differences in biofilm attachment between smooth, nanotextured, and macrotextured surfaces of silicone implants. The nanotextured surface led to production of a patchy *S. aureus* biofilm, concentrated on the concave area, whereas few biofilms were detected in the convex area. With a texturized surface and less biofilm formation on the surface, nanotextured implants may prevent CC in implant-based breast surgery.

Conflicts of Interest

The Authors declare that they have no conflicts of interest to disclose.

Authors' Contributions

Jong Ho Lee, Koeun Kim, Young Ju Lee, Hee Kyung Jin and Jung Dug Yang contributed to conception and design of the study. Koeun Kim and Jae sung Bae organized the database and performed the statistical analysis. Jong Ho Lee wrote the first draft of the manuscript. Jeong Yeop Ryu, Joon Seok Lee, Kang Young Choi, Ho Yun Chung and Byung Chae Cho wrote sections of the article. All Authors contributed to article revision, and read, and approved the submitted version

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