A *Festschrift* Honoring the 90th Birthday on May 9, 1997, of Jonathan Evans Rhoads, M.D., Editor Emeritus of *Cancer*

***Cancer** special section*

A Review of the Possible Health Implications of Silicone Breast Implants

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BACKGROUND. The silicone gel breast implant has long been an important method of reconstruction for the mastectomy patient. Because of concerns about possible health implications of the implant, the Food and Drug Administration banned its use for augmentation mammaplasty and limited its use in the mastectomy patient to a research protocol study. This article reviews the recent literature about the possible health hazards of the silicone implant.

METHODS. In this review of the literature, specific attention was directed toward structural failure of the device as well as the diagnosis of rupture, tissue response to silicone, systemic immunologic response to silicone, the relationship of silicone to connective tissue diseases, and the association of the silicone implant with breast carcinoma in both the augmentation mammaplasty patient and the patient undergoing postmastectomy reconstruction. A total of 88 works were reviewed.

RESULTS. The literature fails to support an association between silicone gel breast implants and systemic diseases. Although implants may cause local symptoms, rupture over time, or be associated with an immunologic reaction, comprehensive epidemiologic studies have concluded that there is no connection between breast implants and the known connective tissue diseases or between the implants and breast carcinoma. There is no increase in the risk of recurrence in mastectomy patients reconstructed with implants and no delay in the detection of recurrences. Recent laboratory studies in animals suggest that silicone may have anticarcinogenic effects.

CONCLUSIONS. Silicone gel breast implants may rupture and cause local symptoms, but they have not been demonstrated to be a systemic health hazard for patients who have undergone augmentation mammaplasty or postmastectomy reconstruction. ***Cancer*** **1997;79:1747–56.** © *1997 American Cancer Society.*

KEYWORDS: breast, silicone, breast implants, breast reconstruction.

Although developed initially in 1962 for the purpose of breast enlargement, the silicone gel breast implant evolved to become a principal method for reconstruction after mastectomy. With improvement in reconstructive surgical techniques in the 1970s, the use of the breast implant for the mastectomy patient became an accepted practice, at first for delayed reconstruction and then for reconstruction at the time of mastectomy. The physical and psychologic benefits of the breast implant to the mastectomy patient have been well documented.[1,2] Although autogenous reconstructive techniques steadily improved during the 1980s and early 1990s, varieties of the breast implants remain a basic method of mastectomy reconstruction. The exact number of breast implant recipients is not known, with estimates ranging between 1 million and 2 million women, and it is generally accepted that approximately 20% have been used for mas-

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Received November 25, 1996; revision received January 23, 1997; accepted January 23, 1997.

tectomy reconstruction. Therefore, any potential systemic health effects of the implant would be of distinct interest to the mastectomy population. This article will review the evolution of concerns regarding the silicone implant, and will evaluate the current status of potential health hazards.

Federal Regulation of Silicone Implants

Originally used for lubrication, silicone, from a family of chemically related organo-silicon compounds, was first synthesized in 1938. It is derived from quartz rock (silica or SIO_2). When SIO_2 is heated in the presence of carbon, it produces elemental silicone. When methyl chloride is added, the resulting product is hydrolyzed to form low molecular weight polymers, which are linked to form linear silicone polymers and cross-linked to yield silicone rubbers or elastomers.[3] Depending on the degree of and speed of vulcanization of the polymer, it may exist in any state from a fluid to a solid. The compound polydimethylsiloxane is the silicone most widely used in medical implants and is the base material for silicone rubbers and the silicone gels used in breast implants.

A number of anecdotal reports regarding possible systemic symptoms related to patients who had silicone breast implants led to a reclassification of the implant by the Food and Drug Administration (FDA) in 1988. This reclassification, and the demand by the FDA that manufacturers obtain premarket approval of the implant before universal public consumption was allowed, led to a major controversy surrounding the implant in 1990–1991. The result of this controversy was a ban of the silicone gel implant for augmentation mammaplasty, and a restriction of the implant for mastectomy reconstruction patients to a research protocol, termed the Silicone Gel Adjunct Study. Also known as the Phase II Study, this study was authorized by the FDA in July 1992. The Mentor H/S Corporation (Santa Barbara, CA) was authorized to develop the study, which allows for implantation of gel-filled breast implants for reconstructive indications other than augmentation mammaplasty. Mastectomy patients who are included must be judged not suitable for saline-filled implants. The candidate for the Adjunct Study must be willing to sign the informed consent document, agree to complete all required 1-, 3-, and 5-year follow-up visits, and agree to conditions of the implant registry. The participating physician must obtain Institutional Review Board approval. Data from the study are currently being reviewed by the FDA.

Evaluation of Possible Health Hazards

A number of issues have been raised regarding possible adverse health implications of silicone gel implants by scientists, consumer groups, regulating agencies, the legal community, the media, and patient support groups. These center largely around harmful effects of implant rupture, the response of human tissue to silicone gel, a possible immune response stimulated by silicone, the development of connective tissue diseases in patients with implants, and the relationship of implants to breast carcinoma. These issues will be evaluated in subsequent sections of this article.

Implant Device Failure

Failures of reconstruction with the silicone implant may result from a variety of sources, including infection of the prosthesis, wound dehiscence and exposure of the implant, recurrent periprosthetic capsule formation (with its associated symptoms of pain, pressure, or chronic discomfort), an unsatisfying cosmetic result, or simply the request of a patient for removal of the implant. These events may or may not be associated with failure of the silicone device to maintain its integrity.

Escape of the silicone polymer, either by "bleeding" from the surface of the implant or by true rupture, has long been recognized, and measurement of the element silicon in the capsule surrounding the implant showed higher concentrations nearer the implant, with decreasing concentrations of silicon further into the capsule.[4] When elemental silicon levels in the blood are measured using atomic absorption spectrometry, whole blood levels in patients with silicone implants were significantly higher than those of controls.[5]

The silicone polymer has been found in multiple anatomic areas after leakage from breast implants, including transcutaneous extravasation,[6] occurrence in the pleural space,[7] chest wall muscles, axillae and upper extremity,[8] discharge from both nipples via intraductal spread,[9] brachial plexus extravasation and extracapsular siliconomas,[10] and other anatomic locations such as lymph nodes.

The actual incidence of silicone device bleed or rupture is not known, because the recent reports describe rupture rates in selected populations of patients who have had implants removed. The true incidence remains unknown because the cohort without explantation is not included. However, a number of reports document an incidence of implant rupture that correlates directly with duration of implantation. For example, Duffy and Woods[11] followed patients for a median of 49 months. There were 104 implant failures (15%) in 65 patients. With longer periods of follow-up, the incidence of implant rupture increases, with some reports of frequencies $> 55\%$ 10–15 years after implantation.[12–14] It appears that the frequency of rupture

begins to rise at the 12–13-year point.[15] When the relative strengths of the silicone implants were tested by breaking force or by computer-controlled tensiometer, significant correlations were determined between age of implantation and loss of strength in the shell of the implant.[16,17] Because of the relatively short life of the integrity of the implant in women with a normal life span, especially the young woman undergoing augmentation mammaplasty, it is incumbent on the surgeon to emphasize the probability of device failure in preoperative discussions. Young women need to be prepared for the eventuality of replacement surgery.

Clinical preoperative evaluation of device failure includes an observation of the change in the size, shape, or consistency of the implant or detection of palpable abnormalities. However, noninvasive imaging modalities are becoming more accurate in the diagnosis of implant rupture and of extracapsular extravasation of silicone. Mammography can be used to detect calcific or fibrous capsular contracture, contour changes, slippage of the implant, or free globules of silicone within the breast or axillary lymph nodes.[18,19] Irregularities of the implant contour or encapsulated implant ruptures are not well diagnosed by mammography, and the use of ultrasonography or magnetic resonance imaging (MRI) is most helpful. Although computed tomography is highly sensitive and specific, comparable to results with MRI, it is not used clinically because of the need for ionizing radiation.[20] Studies evaluating ultrasonography alone conclude that it is a very useful tool for diagnosing rupture.[21,22] Chung et al. studied 198 patients by ultrasonography prior to explantation, demonstrating a sensitivity for implant rupture of 74% and a specificity of 89%.[22] Studies of MRI alone demonstrate this modality to be a sensitive and specific technique in diagnosing loss of breast implant integrity. Sensitivities as high as 76%, with a specificity of 97%, have been reported.[23–25] Comparison of modalities demonstrate that MRI is more sensitive and specific than ultrasound if either is used alone, that there does not appear to be an added benefit to using ultrasound and MRI together, that mammography and ultrasound used together are a good screening tool for implant integrity, and the more expensive use of MRI is best reserved for when a diagnosis cannot be made with mammography and ultrasound as a screening modality.[26–28] Samuels et al.[28] completed a meta-analysis comparing the accuracy of various currently available modalities and described an algorithm that provides a guide to clinicians in the detection of breast implant rupture. They indicated that mammography, supplemented by ultrasonography, constitutes the most cost-effective initial study, followed by MRI if these are equivocal. The meta-analysis agreed that MRI is the most sensitive and specific study with which to evaluate breast implant rupture.[28]

Tissue Response to Silicone

Exposure of human tissue to any foreign body evokes an inflammatory process. With or without evidence of implant rupture or silicone gel bleed (considered by many to be a form of rupture), the tissues surrounding a silicone breast implant typically produce an inflammatory response. It is the degree of this response that may lead to local symptoms and objective physical findings. The cellular inflammatory response, including the production of macrophages, leads to the development of fibrosis around the implant. This fibrotic lining, or capsule, may elicit a contractile process similar to that observed in smooth muscle. The scar contracture that results from this process varies in degree from mild to severe and can produce firmness or hardness around the implant. The scar capsule contracture is a well known result of all foreign bodies and has been well recognized as the most common local adverse affect of the silicone implant. Contractures of the more severe form (Grades 3 and 4 of Baker) are frequently accompanied by local symptoms of pressure sensation and occasionally pain, in addition to the obvious aesthetic concerns that are produced and the frequent displacement of the implant by the contracting tissue. Contractures of long-standing duration frequently become calcified, in the presence or absence of rupture, leading to even more severe local symptoms. No specific etiology of the development of contracture has ever been firmly established.

Possible explanations for why contracture occurs in some patients and not in others include individual variations in reactions to silicone, perhaps based on genetic factors,[29] or the occurrence of subclinical infections. Treatment has involved removal of the scar tissue and replacement of the implant or reconstruction by autologous techniques. Other local responses to silicone gel breast implants have included the development of silicone granulomas outside the area of implantation, and involvement of regional lymph nodes with silicone. Such responses usually have resulted after rupture of the implants and extracapsular spread of the silicone.

Early reports that silicone is biologically inert in human tissue recently have been challenged. Because liquid silicone injected into laboratory animals elicited only a mild inflammatory response that was not dose-dependent, it was initially believed that silicone was a relatively inert substance.[30,31] This mild inflammatory response did not appear consistent with the clinical findings around gel-filled implants. Recently, it was shown that the intensity of the cellular and capsular response was lowest for silicone oil and increased as

the material's molecular weight increased and its compliance decreased.[32] It is now apparent that the polymer's molecular weight influences its migration, encapsulation, and intensity of cellular response.

Immune Response to Silicone

Symptoms similar to those observed with connective tissue disease have been reported by some patients with breast implants, especially since the FDA review became public in 1991. Such symptoms led investigators to consider an immunologic basis for a disease state related to silicone. As a long chain polymer with hydrophobic characteristics, electrostatic charges, and organic side groups, silicone is in theory a potentially ideal immunogen. A recent review article with 55 references of both in vivo and in vitro studies, case reports, and population studies resulted in the following conclusions: silicone is immunogenic; silicone is biodegradable and transported by way of the reticuloendothelial system to distant locations; silicone breast implants "leak" and in turn silicone migrates outside the breast tissues; case reports and population studies describe an autoimmune reaction and immunologic dysfunction in some patients with silicone breast implants; and improvement of vague symptoms not correlated with known connective tissue diseases has been reported after removal of the implants.[33]

Laboratory studies concluding that silicone was capable of eliciting a specific immune response[34–36] preceded the first clinical demonstration of an apparent specific antibody produced in response to silicone in two children with ventriculoperitoneal shunts made of silicone tubing.[37] This report stimulated a search for a relationship between autoantibodies and silicone gel implants. However, in a later study of 200 patients with breast implants compared with 100 controls, the prevalence of a positive antinuclear antibody (ANA) in the implant population was 26.5% compared with 28% for controls. Only 17.2% of the 29 patients with implant ruptures were ANA positive. ANA positive patients were tested to analyze titres of multiple autoantibodies, with the conclusion that there was no evidence that silicone gel implants were related to increased autoantibodies.[38] However, other investigators found that antibodies to silicone surface-associated antigens are elevated in symptomatic patients with breast implants and that the antibodies are associated with symptoms.[39] When the ANA was studied in a case series of breast implant patients compared with historic normal controls, a six-fold increase in the relative risk of a positive test was observed. This increased tendency was partially a function of duration of implant exposure and was not patient age-related.[40] A recent study failed to find a difference in antisilicone antibodies in test patients with silicone tissue expanders when compared with controls, calling into question the existence of specific antibodies to the silicone shell of an expander.[41] To date, no clinically applicable antibody test specific to silicone itself has been developed.

Although the question is still open whether silicone alone elicits a specific immune response, the possibility exists that silicone gel can act as an adjuvant, and thereby induce autoimmunity. By comparison, silicone gel has been found to be a more potent immunologic adjuvant than Freund's complete or incomplete adjuvant.[42] The adjuvant effect of silicone was examined by analyzing the frequency of autoantibodies to Type I and II collagen in patients with breast implants.[43] Seventy women with implants and without a specific autoimmune disease were studied, with the result that sera from the women reacted with multiple peptides of Type I collagen but reacted weakly against Type II collagen, suggesting that silicone can act as an adjuvant to enhance the immunogenicity of Type I collagen.[43]

In a review article on the potential relationship between breast implants and autoimmune connective tissue disease, Peters suggested possible mechanisms for an immunologic response.[44] These include 1) silicone from the gel or the shell of a saline implant may act as hapten-like substance that combines with other molecules to form an antigenic complex; 2) silicone ingested by macrophages may be converted to silica, thereby activating the macrophage to produce cytokines that are capable of producing fibrosis; and 3) silica itself may be released from the implants, directly stimulating macrophage activity.

Silicone and Connective Tissue Diseases

The question of whether silicone breast implants are associated with or cause connective tissue diseases has been the subject of increased scrutiny in recent years and isolated case reports have finally been supplanted by epidemiologic studies. Scleroderma (systemic sclerosis) is the rheumatic disease most frequently reported to occur in conjunction with paraffin or silicone injection, or silicone breast implants.[45–48] However, these isolated case reports, which increased in frequency since the publicity in 1991, have not been viewed in the context of epidemiologic studies and fail to take a placebo effect into account. It was not until 1992 that case–control studies evaluating the association of augmentation mammaplasty with scleroderma were performed. Wigley et al., studying 741 patients with scleroderma, found 7 who had undergone augmentation mammaplasty, concluding that the incidence of augmentation mammaplasty prior to scleroderma was 0.66%. This did not differ significantly from

the incidence of augmentation mammaplasty in the adult female population, estimated at 0.65%–2%.[49] Hochberg studied 869 women with scleroderma matched with 2061 controls. Augmentation mammaplasty was reported in 1.4% of the cases who subsequently developed scleroderma, compared with 1.1% of the controls. The odds ratio for association of augmentation mammaplasty with systemic sclerosis was 1.25, leading to a conclusion that there was no significant causal association between the two.[50] Hochberg and Perlmutter further published a meta-analysis of the silicone-augmentation issue, reviewing 28 references, and coming to the conclusion that there is no evidence of a significant association between augmentation mammaplasty and the development of a definite connective tissue disease, including systemic sclerosis.[51] No conclusions could be drawn in the analysis regarding the association of rupture or leakage of the implants with subsequent connective tissue disease, because adequate data were not available.

Connective tissue diseases other than scleroderma that have been reported to be possibly associated with breast implants include fibromyalgia, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome.[52–54] Most reports come to a general conclusion that no cause and effect relationship could be established. It remained for the large epidemiologic study by Gabriel et al. in 1994 to place strong credence on the conclusion that no association between breast implants and the known connective tissue diseases can be made. This study, a population retrospective review, examined the risk of a variety of connective tissue diseases after breast implantation. Two controls of the same age were matched with all women who received breast implants in Homestead County, Minnesota between 1964 and 1991. Seven hundred forty-nine women with breast implants were matched with 1498 community controls. After a mean of 7.8 years, only 5 cases, compared with 10 controls, had a specified connective tissue disease diagnosed (relative risk, 1.06).[55] This well done epidemiologic study confirms the lack of association between silicone implants and the known connective tissue diseases.

In a review article, Sanchez-Guerrero et al. found little or no association between silicone breast implants and any connective tissue disease or to a unique arthralgia/myalgia/fibromyalgia syndrome.[56] The authors agreed that silicone elicits a local inflammatory response and reported that any association between silicone breast implants and connective tissue disease should remain speculative. A meta-analysis by Perkins et al. reviewed more than 2600 articles, abstracts, and dissertations, including 13 epidemiologic studies. The analysis summarized a relative risk of 0.76 for connective tissue disease in general and 0.98 for scleroderma, in patients with breast implants.[57] Irrespective of which studies were aggregated in the meta-analysis, there was no significant increased risk for scleroderma, rheumatoid arthritis, or connective tissue diseases in general in breast implant patients. Sanchez-Guerrero et al. analyzed data from 14 years of follow-up from the Nurses Health Study cohort. Women who were free from connective tissue disease in June 1976 were followed through May 1990, before the widespread media coverage of the possible association. Among 87,501 women who were eligible for follow-up, 516 were confirmed as having definite connective tissue diseases and 1183 as having breast implants. The age-adjusted relative risk of a definite connective tissue disease among women with any type of implant was 0.6 compared with women without implants. The relative risk of self-reported signs or symptoms of connective tissue disease for women with implants was 1.5. The conclusion of this large cohort study was that no association between silicone breast implants and connective tissue diseases could be made.[58]

A comprehensive literature search of 15 epidemiologic studies on breast implants and connective tissue disease was reported by Silverman et al.[59] The results of these studies, especially those reported in case–control studies, were strikingly consistent. Meta-analyses of rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus were performed from a combined database of approximately 4000 cases. The relative risks in implant patients were 0.85 for rheumatoid arthritis, 0.62 for systemic sclerosis, and 0.35 for systemic lupus erythematosus, indicating that there was no increased risk of connective tissue diseases associated with breast implants.

A retrospective cohort study of 399,543 female health professionals who participated in the Women's Health Study was reported by Hennelkens et al.[60] A total of 10,830 women reported breast implants and 11,805 reported connective tissue diseases during the study. The relative risk of connective tissue disease among reported breast implant recipients was 1.24. These data were self-reported and are compatible with prior reports from other cohort studies that exclude a large hazard of connective tissue disease in breast implants.

Although the above epidemiologic studies support no association between silicone breast implants and the known connective tissue diseases, clinical series of patients with breast implants and symptoms mimicking connective tissue diseases continue to be reported.[54,61–64] These articles have a common theme of large series of patients with silicone implants reporting symptomatic complaints similar to those observed

with connective tissue diseases. Such symptoms may represent an undifferentiated connective tissue disease, and therefore would not be studied in the above epidemiologic reviews, or possibly could represent an as yet undiagnosed syndrome, referred to variably as "siliconosis," "silicone reactive disorder," or "silicone implant associated syndrome." This unique arthralgia/myalgia/fibromyalgia-type syndrome, given the vague, subjective nature of the symptoms, is difficult to study. To date, there is no association that has been epidemiologically proven between those symptoms and the silicone breast implant. In addition, there is no cause and effect relationship between silicone implants and neurologic diseases.[65] In conclusion, the clinical, immunologic, and epidemiologic evidence to date suggest little or no association between silicone breast implants and connective tissue diseases. A consistent pattern of immune response has also not been identified.

Silicone and Breast Carcinoma

Several questions have been raised regarding the relationship of the silicone implant with breast carcinoma, including: 1) does the silicone implant increase the risk of breast carcinoma in the augmentation mammaplasty patient?; 2) are carcinomas that arise in augmentation patients diagnosed at a later stage than those in nonaugmented patients?; 3) does a silicone implant increase the recurrence rates of patients who have reconstruction, or inhibit the detection of recurrences?; and 4) is there, theoretically, a protective mechanism against the development of breast carcinoma produced by the immunologic response to a silicone implant?

Isolated case reports of breast carcinoma among women with silicone gel implants are an unreliable source of determining the incidence. In addition, surveys of plastic surgeons, although interesting, are limited by the fact that they did not compare carcinoma incidence among women who did not receive silicone breast implants and who were treated by the same surgeons. These surveys found no evidence that women with breast implants are at any increased risk of breast carcinoma.[66,67] Two case–control studies of breast carcinoma in the state of Washington in which information on the use of breast implants for augmentation was obtained showed no increase in the risk of breast carcinoma for women aged 21–24 years (relative risk, 0.8) or for women aged 50–64 years (relative risk, 0.2).[68] However, the best available epidemiologic studies on this issue are cohort studies evaluating such a risk. Deapen et al. have retrospectively studied more than 3000 patients in Los Angeles County who underwent augmentation mammaplasty. They compared the incidence of breast carcinomas in those patients to an expected incidence (based on Los Angeles County incidence rates), with the conclusion that there was no increase in breast carcinoma after augmentation mammaplasty.[69,70] They also noted an earlier diagnosis of carcinoma in the patients who had implants. In a population-based cohort study in Alberta, Canada, Berkel et al. followed 11,676 augmentation mammaplasty patients who underwent surgery between 1973 and 1986. This group was compared with all women in Alberta with breast carcinoma (n = 13,557) in the same time frame. Forty-one patients with implants were subsequently found to have breast carcinoma, compared with an expected 86.2 cases with an average follow-up of 10.2 years. They concluded that there was a lower risk of breast carcinoma in these women than in the general population, and suggested that women who have augmentation mammaplasty are probably drawn from a population already at low risk.[71] These data were reviewed by Bryant and Brasher in 1995, resolving some problems that had been later identified with the study methods.[72] This reanalysis resulted in a higher standardized incidence ratio than in the original analysis, leading to the conclusion that the incidence of breast carcinoma could not be said to be either significantly higher or lower than among the general population. A population-based case control study of breast carcinoma that included 2174 cases and 2009 population controls younger than 55 years demonstrated prior breast implants in 36 cases versus 44 in a community control group.[73] The relative risk of breast carcinoma associated with a prior implant was 0.6. This reduced risk persisted with an increasing interval since surgery. This study confirmed the other record linkage studies that concluded that there was not an elevation in breast carcinoma risk after a breast implant.

Several studies evaluated the potential delay in the early detection of breast carcinoma because of a mammary implant or capsular interference with mammography. Two studies demonstrated that mammography can detect occult breast carcinomas in women with breast implants, but they provided no estimates of the proportion of breast carcinoma that might have been missed due to the presence of implants. Destouet et al. analyzed the screening mammagrams of 350 consecutive women with breast implants. After biopsy, breast carcinoma was diagnosed in three women who had parenchymal abnormalities.[19] Mitnick et al. studied 75 patients with breast implants with routine screening mammography and found 2 patients with microcalcifications that were confirmed to be intraductal carcinomas on biopsy.[74] The extent to which parenchyma is obscured by an implant varies among

patients and the technique used. Leibman and Kruse reviewed the mammagrams, sonograms, and clinical history of 25 women with breast implants and carcinoma.[75] One or the other imaging techniques was positive in 22 of 25 patients. The authors indicated that modified position views are essential in augmented breasts and sonography should be used to image palpable masses even when mammograms are normal. In a series of 35 patients treated for 37 breast carcinomas after augmentation mammaplasty at the M. D. Anderson Cancer Center, abnormalities were observed in 54.8% of 31 patients who had mammography before biopsy. However, palpable lesions were visualized in only 38.7% of patients. The pathologic staging of the tumor indicated that clinical detection of carcinoma was not delayed by the implants.[76] Cahan et al. confirmed that prepalpable and preinvasive breast carcinoma can be detected in the augmentation mammaplasty patient by mammography and that the stage of presentation in this group is not significantly different than in nonaugmented patients.[77] Although these studies show that carcinoma can be detected in the augmented patient, epidemiologic studies have not been performed to determine whether they are as easily detected as in the nonaugmented patient. Therefore, the search continues for the ideal implant material that would be radiolucent on mammography. Silicone shells filled with peanut oil, sunflower oil, and soybean oil allow the best visualization.[78,79]

Recent studies have reassured patients, oncologic surgeons, and reconstructive surgeons that use of the silicone implant at the time of mastectomy or in delayed reconstruction does not affect the incidence, detection, or management of breast carcinoma recurrence. Noone et al. reviewed 306 patients reconstructed immediately after mastectomy, finding a 19.6% overall recurrence rate and a 5.2% local recurrence rate during a mean follow-up of 6.4 years. Stage of disease comparisons with literature recurrence data showed no difference in the rate of recurrences. In addition, the detection and treatment of recurrences were not inhibited by the implants.[80] Wang et al. performed a retrospective case–control study, matching 172 consecutive mastectomy reconstruction patients against nonreconstructed mastectomy patients in the same institution, finding no statistical difference in the 10-year disease free survival rates for the reconstructed versus control group, and showing no difference in the disease free survival at 5 years between patients reconstructed with implants versus autogenous flap reconstruction.[81]

Some recent experimental reports support a possible protective mechanism against the development of breast carcinoma by a silicone implant. A decreased incidence of breast carcinoma development in rats who had received silicone implants before carcinogen stimulation was reported by Dreyfuss et al.[82] Additional work in the same laboratory showed that animals with silicone implants beneath the mammary gland had a statistically significant lower incidence of breast carcinoma formation (11.5%) compared with dorsally implanted animals (45.8%) and sham controls (64%). In carcinogen-stimulated mice, the carcinoma incidence with silicone implants was 17% compared with 50% in sham controls when the animals were sacrificed at 50 weeks.[83] A possible explanation for this anticarcinogen affect may be the cytotoxicity of the macrophage stimulated by silicone, as presented from the authors' laboratory by Sigal et al.[84] They demonstrated that murine macrophages were activated by silicone, producing more superoxide than controls. The cytocidal metabolite nitric oxide produced by the macrophage may offer one explanation, although it is possible that toxic cytokine production, such as the antitumor interleukin-6 (IL-6) may also play a role. Expansion of these studies demonstrated increased levels of IL-6 and a suppression of colon carcinoma in rats injected with silicone compared with controls.[85]

Because any foreign material placed in a laboratory animal may lead to sarcoma, representing the so-called "Oppenheimer effect," concerns have been expressed regarding the possible development of sarcomas in humans implanted with silicone.[86] To date, there have been no documented reports of any sarcoma in studies of women who used silicone gel breast implants. The study by Engel and Lamm confirmed this lack of association.[87]

The literature to date, including case reports, case series, physician surveys, case–control studies, and cohort studies failed to produce evidence associating the use of silicone breast implants with either an increased risk of breast carcinoma, an increased risk of more advanced carcinoma at the time of diagnosis, an increase in the rate of recurrence after reconstruction after mastectomy, or a decreased ability to detect and treat such recurrences. In addition, recent laboratory studies support a hypothesis that the silicone implant may in some way produce tumoricidal effects or some other mechanism of tumor suppression in laboratory animals.[88]

SUMMARY

This article reviewed the available pertinent literature evaluating the health implications of the silicone gel breast implant, a device that has been a mainstay of reconstruction for the mastectomy patient.

Local effects of the silicone implant such as discomfort, possible infection and extrusion, and scar

capsule contracture have long been recognized and have been mentioned briefly in this review. Eventual failure of the implant device by rupture of the shell or leaking of the silicone is correlated with duration of implantation, with the majority of explanted implants demonstrating rupture, usually between 10 and 15 years after implantation. Diagnosis of implant rupture is made by clinical examination and by imaging studies, including mammography, ultrasonography, and MRI. MRI is the most sensitive and specific imaging modality. However, the combination of mammography and ultrasonography can be recommended as initial imaging techniques.

Basic science as well as clinical information suggest a possible link between silicone implants and systemic immunologic reactions. Anecdotal case reports and case series report connective tissue diseases in patients with implants. However, recent large epidemiologic studies fail to support an association between silicone breast implants and the known connective tissue diseases.

There is no association between silicone breast implants and the subsequent development of breast carcinoma. When proper mammographic imaging is used, the diagnosis and treatment of breast carcinoma in augmentation patients is not delayed. In the mastectomy reconstruction patient, the presence of a silicone implant, placed either at the time of mastectomy or at a later procedure, does not increase the incidence of local recurrence or inhibit the detection or treatment of a local recurrence or systemic disease. Recent laboratory research suggests a protective mechanism of the silicone implant in carcinogen-treated animals.

REFERENCES

1. Schain WS. Psychosocial factors in mastectomy and reconstruction. In: Noone RB, editor. Plastic and reconstructive surgery of the breast. Philadelphia: B.C. Decker, 1991:327–43.
2. Spear SL. Reconstruction with implants. In: Noone RB, editor. Plastic and reconstructive surgery of the breast. Philadelphia: B.C. Decker, 1991:372–86.
3. Yoshida SH, Chang C, Teuber SS, Gershwin ME. Silicon and silicone: theoretical and clinical implications of breast implants. *Regul Toxicol Pharmacol* 1993;17:3–18.
4. Jennings DA, Morykwas MJ, DeFranzo AJ, Argenta LC. Analysis of silicon in human breast and capsular tissue surrounding prostheses and expanders. *Ann Plast Surg* 1991; 27:553–8.
5. Peters W, Smith D, Lugowski S, McHugh A, Barnes C. Do patients with silicone gel breast implants have elevated levels of blood silicon compared to control patients? *Ann Plast Surg* 1995;34:343–7.
6. Erdmann MWH, Asplund O, Bahnasy H. Transcutaneous extravasation of silicone following breast augmentation. *Br J Plast Surg* 1992;45:479–80.
7. Hirmand H, Hoffman LA, Smith JP. Silicone migration to the pleural space associated with silicone gel augmentation mammaplasty. *Ann Plast Surg* 1994;32:645–7.
8. Ahn CY, Shaw WW. Regional silicone gel migration in patients with ruptured implants. *Ann Plast Surg* 1994;33:201–8.
9. Holten INR, Barnett RA. Intraductal migration of silicone from intact breast prostheses. *Plast Reconstr Surg* 1995;95: 563–6.
10. Shermak MA, Chang BW, Soto A, VanderKolk CA. A retrospective analysis of contracture and rupture in 379 breast implants. Presented at the 74th Annual Meeting of the American Association of Plastic Surgeons, San Diego, California, May 2, 1995.
11. Duffy MJ, Woods JE. Health risks of failed silicone gel breast implants: a 30-year clinical experience. *Plast Reconstr Surg* 1994;94:295–9.
12. deCamara DL, Sheridan SM, Kammer BA. Rupture and aging of silicone breast implants. *Plast Reconstr Surg* 1993;91:828–34.
13. Peters W, Keystone E, Smith D. Factors affecting the rupture of silicone gel breast implants. *Ann Plast Surg* 1994;32:449–51.
14. Jacobs JC, Imundo L, Robinson OG, Bradley EL, Wilson DS. Analysis of explanted silicone implants: a report of 300 patients. *Ann Plast Surg* 1995;34:1–7.
15. Young VL, Schorr MW. Analysis of 100+ consecutive breast implants for integrity and mechanism of failure. Presented at the 74th Annual Meeting of the American Association of Plastic Surgeons, San Diego, California, May 2, 1995.
16. Phillips JW, deCamara DL, Lockwood MD, Grebner WCC. Strength of silicone breast implants. *Plast Reconstr Surg* 1996;97:1215–25.
17. Greenwald DB, Randolph M, May JW. Mechanical analysis of explanted silicone breast implants. *Plast Reconstr Surg* 1996;98:269–72.
18. Leibman AJ. Imaging of complications of augmentation mammaplasty. *Plast Reconstr Surg* 1994;93:1134–40.
19. Destouet JM, Monsees BS, Oser RF, Nemecek JR, Young VL, Pilgram TK. Screening mammography in 350 women with breast implants: prevalence and findings of implant complications. *A J R Am J Roentgenol* 1992;159:973–8.
20. Ahn CY, DeBruhl ND, Gorczyca DP, Bassett LW, Shaw WW. Silicone implant rupture diagnosis using computed tomography: a case report and experience with 22 surgically removed implants. *Ann Plast Surg* 1994;33:624–8.
21. Petro JA, Klein SA, Niazi A, Salzburg CA, Byrne D. Evaluation of ultrasound as a tool in the follow-up of patients with breast implants: a preliminary prospective study. *Ann Plast Surg* 1994;32:580–7.
22. Chung KC, Wilkins EG, Beil RJ, Helvie MA, Ikeda DM, Oneal RM, et al. Diagnosis of silicone gel breast implant rupture by ultrasonography. *Plast Reconstr Surg* 1996;97:104–9.
23. Dobke MK, Middleton MS. Clinical impact of breast implant magnetic resonance imaging. *Ann Plast Surg* 1994;33:241–6.
24. Ahn CY, DeBruhl ND, Gorczyca DP, Shaw WW, Bassett LW. Comparative silicone breast implant evaluation using mammography, sonography, and magnetic resonance imaging: experience with 59 implants. *Plast Reconstr Surg* 1994;94: 620–7.
25. Frankel S, Occhipinti K, Kaufman L, Kramer D, Carlson J, Mineger M, et al. MRI findings in subjects with breast implants. *Plast Reconstr Surg* 1995;96:852–9.

26. Reynolds HE, Buckwalter KA, Jackson VP, Siwy BK, Alexander SG. Comparison of mammography, sonography and magnetic resonance imaging in the detection of silicone gel breast implant rupture. *Ann Plast Surg* 1994;33:247–55.
27. Weizer G, Malone RS, Netscha DT, Walker LE, Thornby J. Utility of magnetic resonance imaging and ultrasonography in diagnosing breast implant rupture. *Ann Plast Surg* 1995; 34:352–61.
28. Samuels JB, Rorhich RJ, Weatherall PT, Ho AMW, Goldberg KL. Radiographic diagnosis of breast implant rupture: current status and comparison of techniques. *Plast Reconstr Surg* 1995;96:865–77.
29. Young VL, Nemecek JR, Schwartz BD, Phelan DL, Schorr MW. HLA typing in women with breast implants. *Plast Reconstr Surg* 1995;96:1497–1519.
30. Rees TD, Platt J, Ballantyne DL Jr. An investigation of cutaneous response to dimethylpolysiloxane in animals and humans. *Plast Reconstr Surg* 1965;35:131–40.
31. Rees TD, Ballantyne DL Jr., Seidman I, Hawthorne GA. Intraperitoneal injections of silicone in mice. *Plast Reconstr Surg* 1967;39:402–10.
32. Picha GJ, Goldstein JA. Analysis of the soft tissue response to components used in the manufacture of breast implants: rat animal model. *Plast Reconstr Surg* 1991;87:490–500.
33. Brauber N, Campbell A, Vojdani A. Silicone breast implants and autoimmunity: causation, association, or myth? *J Biomater Sci Polym Ed* 1995;7(2):133–45.
34. Heggers JP, Kossovsky N, Parson RW, et al. Biocompatibility of silicone implants. *Ann Plast Surg* 1983;11:38.
35. Kossovsky N, Heggers JP, Robson MC. Experimental demonstration of the immunogenicity of silicone-protein complexes. *J Biomed Mater Res* 1987;21:1125.
36. Smith DJ, et al. Immunogenic potential of carpal implants. *J Surg Res* 1990;48:13.
37. Goldblum RM, et al. Antibodies to silicone elastomers and reactions to ventriculo-peritoneal shunts. *Lancet* 1992; 340:510.
38. Peters W, Keystone E, Snow K, Rubin L, Smith D. Is there a relationship between autoantibodies and silicone-gel implants? *Ann Plast Surg* 1994;32:1–5.
39. Kossovsky N, Conway D, Kossovsky R, Petrovich D. Novel anti-silicone surface-associated antigen antibodies (anti-SSAA(x)) may help differentiate symptomatic patients with silicone breast implants from patients with classical rheumatological disease. *Curr Top Microbiol Immunol* 1996; 210:327–36.
40. Lewy RI, Ezrailson E. Laboratory studies in breast implant patients: ANA positivity, gamma globulin levels, and other autoantibodies. *Curr Top Microbiol Immunol* 1996;210:337–53.
41. Rohrich RJ, Holier LH, Robinson JB. Determining the safety of the silicone envelope: in search of a silicone antibody. *Plast Reconstr Surg* 1996;98:455–8.
42. Naim JO, Lanzafame RJ. The adjuvant effect of silicone gel on antibody formation in rats. *Immunol Invest* 1993;22:151–61.
43. Rowley MJ, Cook AD, Mackay IR, Teuber SS, Gershwin MD. Comparative epitope mapping of antibodies to collagen in women with silicone breast implants, systemic lupus erythematosus and rheumatoid arthritis. *Curr Top Microbiol Immunol* 1996;210:307–15.
44. Peters W. Silicone breast implants and autoimmune connective tissue disease. *Ann Plast Surg* 1995;34:103–9.
45. Miyoshi K, et al. Hypergammaglobulinemia by prolonged adjuvanticity in man: disorders developed after augmentation mammaplasty. *Ijishimpo* 1984;2122:9.
46. Kumagai Y, et al. Clinical spectrum of connective tissue disease after cosmetic surgery. *Arthritis Rheum* 1984;27:1.
47. Speira IL. Scleroderma after silicone augmentation mammaplasty. *JAMA* 1988;260:236.
48. Varga J, et al. Systemic sclerosis after augmentation mammaplasty with silicone implants. *Ann Intern Med* 1989; 111:377.
49. Wigley FM, et al. Augmentation mammaplasty in patients with systemic sclerosis. Data from the Baltimore Scleroderma Research Center and Pittsburgh Scleroderma Data Bank, [abstract]. *Arthritis Rheum* 1992;35:546.
50. Hochberg MC. Progress Report at the American College of Rheumatology Annual Meeting, November 1994, on a large scale examination of the association of silicone breast implants in augmentation mammaplasty with systemic sclerosis. *Arthritis Rheum* 1994;37:5369.
51. Hochberg MC, Perlmutter DL. The association of augmentation mammaplasty with connective tissue disease, including systemic sclerosis (scleraderma): a meta-analysis. *Curr Top Microbiol Immunol* 1996;210:411–7.
52. Vasey FD, et al. Clinical manifestations of 50 consecutive women with silicone breast implants and connective tissue disease [abstract]. *Arthritis Rheum* 1992;35:R7.
53. Spiera RF, Jibofsky A, Spiera H. Silicone gel-filled breast implants and connective tissue disease: an overview. *J Rheumatol* 1994;21:239–45.
54. Giltay EJ, Moens HJB, Riley AH, Tan RG. Silicone breast prostheses and rheumatic symptoms: a retrospective follow up study. *Ann Rheum Dis* 1994;53:194–6.
55. Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE, Melton LJ. Risk of connective tissue diseases and other disorders after breast implantation. *N Engl J Med* 1994;330: 1697–1702.
56. Sanchez-Guerrero J, Schur PH, Sergeant JS, Liang NH. Silicone implants and rheumatic disease. Clinical, immunological and epidemiologic studies. *Arthritis Rheum* 1994;37:158–68.
57. Perkins LL, Clark BD, Klein PJ, Cook RR. A meta-analysis of breast implants and connective tissue disease. *Ann Plast Surg* 1995;35:561–70.
58. Sanchez-Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, Liang MH. Silicone breast implants and the risk of connective tissue diseases and symptoms. *N Engl J Med* 1995;332(25):1666–70.
59. Silverman BS, Brown SL, Bright RA, Kaczmarek RS. A critical assessment of the relationship between silicone breast implants and connective tissue diseases [review]. *Regul Toxicol Pharmacol* 1996;23(1 Pt 1):74–85.
60. Hennelkens CH, Lee IM, Cook NR, et al. Self-reported breast implants and connective tissue diseases in female health professionals. A retrospective cohort study. *JAMA* 1996; 275(8):616–21.
61. Borenstien D. Siliconosis: a spectrum of illness. *Semin Arthritis Rheum* 1994;24:1–7.
62. Vasey FB, Havice DL, Bocanegra TS, Seleznick MJ, Bridgeford PH, Martinez-Osuna P, et al. Clinical findings in symptomatic women with silicone breast implants. *Semin Arthritis Rheum* 1994;24:22–8.
63. Freundlich B, Altman C, Snadorfi N, Greenberg M, Tomaszewski J. A profile of symptomatic patients with silicone breast implants: a Sjögren's-like syndrome. *Semin Arthritis Rheum* 1994;24:44–53.

64. Bridges AJ. Rheumatic disorders in patients with silicone implants: a critical review. *J Biomater Sci Polym Ed* 1995; 7(2):147–57.
65. Rosenberg NL. The neuromythology of silicone breast implants. *Neurology* 1996;46(2):306–14.
66. Harris HI. Survey of breast implants from the point of view of carcinogenesis. *Plast Reconstr Surg* 1961;28:81–3.
67. deCholonoky T. Augmentation mammaplasty. Survey of complications in 10,941 patients by 265 surgeons. *Plast Reconstr Surg* 1970;45:573–7.
68. Malone KE, Stanford JL, Daling JR, et al. Implants and breast cancer [letter]. *Lancet* 1992;339:1365.
69. Deapen DM, Pike MC, Casagrande JT, Brody GS. The relationship between breast cancer and augmentation mammaplasty: an epidemiologic study. *Plast Reconstr Surg* 1986; 77:361–7.
70. Deapen DM, Brody GS. Augmentation mammaplasty and breast cancer: a five-year update of the Los Angeles Study. *Plast Reconstr Surg* 1992;89:660–5.
71. Berkel H, Birdsell DC, Jenkins H. Breast augmentation: a risk factor for breast cancer? *N Engl J Med* 1992;326:1649–53.
72. Bryant H, Brasher P. Breast implants and breast cancer—reanalysis of a linkage study. *N Engl J Med* 1995;332(23): 1535–9.
73. Brinton LA, Malone KE, Coates RJ, et al. Breast enlargement and reduction: results from a breast cancer case controlled study. *Plast Reconstr Surg* 1996;97:269–81.
74. Mitnick JS, Harris MN, Rocs DF. Mammographic detection of carcinoma of the breast in patients with augmentation prostheses. *Surg Gynecol Obstet* 1989;168:30.
75. Leibman AJ, Kruse BD. Imaging of breast cancer after augmentation mammaplasty. *Ann Plast Surg* 1993;30:111–5.
76. Carlson GW, Curley SA, Martin FE, Fornage BD, Ames FC. The detection of breast cancer after augmentation mammaplasty. *Plast Reconstr Surg* 1993;91:837–40.
77. Cahan AC, Ashikari R, Pressman P, Cody H, Hoffman S, Sherman JE. Breast cancer after breast augmentation with silicone implants. *Ann Surg Oncol* 1995;2(2):121–5.
78. Gumico CA, Pin P, Young VL, Destouet J, Monsees B, Eichling J. The effect of breast implants on the radiographic detection of microcalcifications and soft-tissue masses. *Plast Reconstr Surg* 1989;84:772–8.
79. Handel N, Silverstein MJ, Gamagami P, Collins A. An in vivo study of the effect of various breast implant filler materials on mammography. *Plast Reconstr Surg* 1993;91:1057–62.
80. Noone RB, Frazier TG, Noone GC, Blanchet NP, Murphy JB, Rose D. Recurrence of breast carcinoma following immediate reconstruction: a 13-year review. *Plast Reconstr Surg* 1994;93:96–106.
81. Wang EH, Chang BW, Dooley WC, Chang LD, et al. Breast cancer recurrence following mastectomy with reconstruction. Presented at the 74th Annual Meeting of the American Association of Plastic Surgeons, San Diego, California, May 2, 1995.
82. Dreyfuss DA, Singh S, Dowlatshani K, Krizek TJ. Silicone implants as an anti-carcinogen. *Surg Forum* 1987;38:587.
83. Su CW, Dreyfuss DA, Krizek TJ, Leoni KJ. Silicone implants and the inhibition of cancer. *Plast Reconstr Surg* 1995; 96:513–8.
84. Sigal RK, Naama H, Noone RB, Daly JM. Silicone increases murine macrophage cytotoxicity. Presented at the 73rd Annual Meeting of the American Association of Plastic Surgeons, St. Louis, Missouri, May 3, 1994.
85. Noone RB, Sigal RK, Naama H, Daly JM. Silicone increases murine macrophage cytotoxicity. 1994 International Symposium on Plastic Surgery, Florence, Italy, May 23, 1994.
86. Dunn KW, Hall PN, Khoo CTK. Breast implant materials: sense and safety. *Br J Plast Surg* 1992;45:315.
87. Engel A, Lamm SH. Risk of sarcomas of the breast among women with breast augmentation. *Plast Reconstr Surg* 1992; 89:571.
88. Edelman DA, Grant S, van Os WA. Breast cancer risk among women using silicone gel breast implants. *Int J Fertil Menopausal Stud* 1995;40(5):274–80.