REVIEW

Breast Implants and Cancer

*Louise A. Brinton, S. Lori Brown**

Background: **Although silicone breast implants have been linked to various short-term complications, less is known about their long-range effects. Most attention has focused on connective tissue disorders, but the range of immunologic disturbances observed in women with implants suggests that consideration also be given to other chronic diseases, including cancer. The greatest attention has focused on breast cancer, given clinical reports suggesting an association and observations that mammographic visualization is deterred by implants. Findings from epidemiologic studies, however, actually suggest that breast cancer risk might be reduced among women with implants, although the biologic mechanism remains undefined. In addition, most studies do not suggest that women with breast implants have more advanced breast cancer at diagnosis or a worse prognosis than those without implants. The majority of studies have focused on women who received implants for cosmetic reasons, with little previous investigation of women who received implants for breast reconstruction following cancer surgery. In terms of other cancers, animal as well as clinical data suggest potential risks of sarcomas and hematologic cancers, including multiple myeloma. The risk of these cancers has not yet been adequately addressed by epidemiologic studies, although several ongoing studies should provide insights. It will be important for studies to consider effects of other lifestyle factors as well as to analyze relationships according to duration of implantation, a demonstrated determinant of implant deterioration. In addition, consideration should be given to type of implant, including implants with polyurethane foam covers, which can leak toluene diamine, a demonstrated carcinogen in animals. [J Natl Cancer Inst 1997;89:1341–9]**

Silicone breast implants, first marketed in 1962, received widespread acceptance, with estimates that between 800 000 and 1 million women received the devices by 1989 *(1,2)*. The majority of devices implanted prior to restricted usage guidelines issued by the U.S. Food and Drug Administration (FDA) in 1992 were for cosmetic reasons, with only approximately 20% having been used for reconstruction following mastectomy.

The long-term safety of the use of these devices in women has generated considerable controversy, accompanied by numerous legal actions. A number of complications as a result of these devices have been noted, including infection and contracture of the tissue surrounding the breast implants, often leading to discomfort, pain, and an abnormal appearance of the breast. Implant rupture has been well documented, with the effects ranging from focal problems, to clearly visible tears, to complete disintegration of the implant shell. Rupture and leaking (not related to ''bleed'' of silicone through the silicone elastomer shell) have been estimated to occur in 23%–64% of implants in series of patients in which explanted devices have been examined *(3–7)*. More precise estimates await studies in nonreferred populations of women. It will also be important to account for the duration of implantation, since there is evidence that implant age is a prime factor in the occurrence of rupture *(3,6)*. In addition to rupture, gel bleed, or the escape of silicone from an implant with an intact envelope in the absence of gross holes or tears, has been documented. Gel bleed is ubiquitous and is observed even in ''low bleed'' implants *(8–10)*.

Silicone gel has been found to migrate into both surrounding and distant tissues as a result of rupture or bleed, with reports of evidence of silicone found in the breast *(11)*, implant capsule *(9)*, axillary lymph nodes *(12)*, arms, fingers, and groin *(13,14)*, blood *(15)*, and liver *(16)*. However, the consequences of such exposures remain undefined. Silicone was initially thought to be an inert substance *(17)*. Recent evidence *(18)*, however, has documented that it is immunogenic; the range of repercussions remains to be defined.

The antibody response to silicone has been an area of major interest as an indication that silicone is not biologically inert. A great deal of the research has focused on whether antibodies to silicone are present in women with silicone implants and whether there is an increased incidence of autoantibodies in women with silicone implants. Wolf et al. *(19)* reported the development of an immunoglobulin G (IgG) antibody to polydimethylsiloxane (silicone) that is found in high levels in women with breast implants; however, antibodies have also been noted in women without breast implants. The ubiquitous occurrence of this antibody is attributed to the widespread use of silicone in a variety of common over-the-counter remedies and household products. The highest levels of anti-silicone antibodies have been found in

**Affiliations of authors:* L. A. Brinton, Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; S. L. Brown, Office of Surveillance and Biometrics, Center for Devices and Radiological Health, Food and Drug Administration, Rockville, MD.

Correspondence to: Louise A. Brinton, Ph.D., National Institutes of Health, Executive Plaza North, Rm. 443, Bethesda, MD 20892-7374.

See ''Note'' following ''References.''

women with ruptured silicone gel breast implants *(19)*. Recently, the results of an antipolymer antibody test, which are reportedly associated with the severity of local and systemic complications in breast implant recipients, have been described *(20)*. Although the results indicate that some individuals may mount a specific antipolymer immune response, the findings do not establish that these antibodies induce complications.

The high rate of occurrence of antinuclear antibodies in patients with autoimmune diseases like systemic lupus erythematosus or scleroderma has prompted use of the antinuclear antibody test along with clinical assessments as a diagnostic tool among implant patients *(21)*. However, these antibodies may occur in unaffected women. Claman and Robertson *(22)* reported that the proportion of positive antinuclear antibodies is greater in women with breast implants than in control subjects, but Peters et al. *(5)* reported that implant patients have levels similar to those of age-matched control subjects. The discrepant findings may be explained by the fact that the study by Claman and Robertson *(22)* had a relatively high rate of diagnosed connective tissue diseases and a low prevalence of positive antinuclear antibodies in the nonaugmented control group [0% versus 28% in the study by Peters et al. *(5)*]. Neither of these studies observed an association between the antinuclear antibody test results and breast implant rupture, but ascertainment of rupture was not complete. Another group of investigators *(23)* observed an increase in anti-collagen autoantibodies in women with breast implants when compared with those in age-matched control women. It has been suggested that silicone may act as an adjuvant, i.e., that it is a depot for antigen, which results in enhanced presentation and inappropriate response to native antigens *(24)*.

While positive test results have been reported in a number of assays used to assess various aspects of the immune response, the clinical relevance or reproducibility of these results is not clear. For instance, the proliferative response of mononuclear cells stimulated with silicone dioxide has been reported to be enhanced greatly in women with breast implants compared with control subjects without implants *(25)*. False-positive results from tests for cell-mediated immunity to silicone were reported to be a major concern in a blinded study of this test *(26)*. There is little doubt, however, that silicone bleeding from breast implants may cause local inflammation in some women *(27)* and that this inflammation may become chronic, which is of concern because chronic inflammation has been implicated in tumor formation. Other perturbations to the immune system that might influence the development or progression of cancer are under investigation *(28)*. Given that women with implants have been reported to have diminished natural killer cell activity *(29)*, control of tumor cell growth might also be involved.

While the extent and the consequences of silicone on the immune system are not known, the evidence that silicone is not inert and may act on the immune system has provoked much interest in the possibility that patients with silicone breast implants have increased rates of connective tissue disorders as well as less defined conditions *(30)*. A recent, large retrospective cohort study of female health professionals *(31)* suggested a small increased risk of connective tissue diseases in women with silicone breast implants, although other prospective studies *(32,33)* have failed to detect any such increases. The issue of an atypical disorder or syndrome related to silicone breast implants has not been resolved. Recent research *(34)* suggested that the human leukocyte antigen (HLA) DR53 may be a marker in women with breast implants for susceptibility to development of symptoms that have been likened to fibromyalgia or chronic fatigue syndrome.

Although most attention has focused on the long-term effects of silicone implants on these connective tissue disorders, the range of complications suggests that consideration be given to effects on other chronic diseases, most notably cancers that may arise as a result of immunologic disturbances. Furthermore, it is well recognized that implants can interfere with the visualization of breast tumors, leading to concerns that there may be resultant delays in diagnosing breast cancers. Concern regarding cancer risk in women with implants is further raised by findings that the polyurethane foam cover used to coat some implants has been found to have the potential for releasing 2,4-toluene diamine, a demonstrated carcinogen in laboratory animals *(35)*. Thus, the issue of whether silicone breast implants may alter cancer risk certainly warrants serious consideration.

This review will attempt to address those cancer sites that have received some attention with respect to silicone breast implants. Although most attention has focused on breast cancer, there has been additional interest in the risks of sarcomas as well as selected hematopoietic cancers, including multiple myeloma. Although the relationship of breast implants to breast cancer risk has been reviewed previously *(36,37)*, with varying conclusions, there has not been, to our knowledge, a comprehensive review of other cancer sites. We have searched the medical literature to identify and provide a comprehensive review of case reports, descriptive studies, and analytic investigations (case–control and prospective studies) that could offer some insights regarding potential relationships. Anecdotal reports must be interpreted cautiously, but they can often provide important clues for future research directions. More major emphasis is placed on analytic studies, whose strengths and limitations are discussed.

Breast Cancer

With respect to cancer risk, the greatest attention has focused on whether silicone breast implants might alter the risk of subsequent breast cancer. Initial concern regarding possible effects on breast cancer risk arose following reports of the development of breast cancers among women whose breasts had been injected with free silicone *(38–41)*. A number of studies *(39,42–46)* also reported the occurrence of breast cancers among women with silicone breast implants, although the absence of appropriate comparison groups prevented any etiologic inferences. Observations that mammographic visualization was deterred by silicone breast implants led to additional concerns that the devices might result in delays in diagnosis of breast cancer.

Interference With Mammographic Visualization

A number of studies *(47–50)* have shown that the presence of a radiologically opaque silicone breast implant interferes with complete imaging of the breast. Displacement of the silicone implant posteriorly during mammography, a technique introduced by Eklund and colleagues in 1988 *(51)*, has been proposed to improve visualization of breast tissue over the standard compression technique. However, Silverstein et al. *(52)* found that

much of the breast tissue was obscured using either technique, and the decrease in visible area was 35% for the compression technique and 25% for the displacement technique. The best images have been found to be obtained from women with submuscular implants who have no substantial capsular contracture *(52)*. It has also been found that imaging can be improved by use of both the compression and displacement methods, since the posterior breast can be visualized best with standard compression while the anterior breast can be seen best with the displacement technique *(53)*.

Postsurgical contracture further complicates mammographic interpretation *(53,54)*. Capsular contracture is often accompanied by calcification, it interferes with compression of the breast tissue to a uniform thickness, and it prevents displacement of breast tissue for modified compression views. Thus, the area of the breast visualized by mammography may be substantially reduced *(50,55)*.

Current recommendations are that implant patients have mammograms according to the same schedule as recommended for women without implants *(51)*. It has also been suggested that women older than 30 years of age who are considering augmentation mammoplasty have mammography before *(56,57)* and after *(56)* implantation. Current screening guidelines stress that at least four views (two compression and two displacement techniques) be done. This of course will mean that these women will have higher radiation exposures over time, which may be of some concern. Also of concern is the possibility of breast implant rupture or conversion of an intracapsular rupture to an extracapsular rupture with subsequent silicone gel migration during compression mammography *(3,58)*. In certain circumstances, other detection methods, including sonography and magnetic resonance imaging, may also be considered, although for now they should be considered secondary approaches to routine mammography *(50,59)*.

Stage of Breast Cancer Diagnosis Among Patients With Breast Implants

Several clinical studies *(52,56)* have suggested that women with breast implants present with more advanced breast cancer. Although it has been speculated that this is due to their tumors being more difficult to detect mammographically, in one of the studies *(52)* it was noted that none of the women had previous mammograms. Furthermore, not all studies have found that women with implants present with more advanced breast cancer than other patients *(60–62)*.

Interpretation of results from the clinical studies is hampered by small sample sizes and questions regarding the influence of potential biases in the referral of patients. Thus, of interest are results regarding stage at detection of breast cancers arising in subjects from two large cohort studies, in Los Angeles and Alberta, Canada (*see* next section on analytic studies of breast cancer for methodologic details of these studies). In the Los Angeles study *(63,64)*, the stage distribution of breast cancer occurring among the patients who had breast implants was nearly identical to that observed among women living in Los Angeles County. The issue of whether patients with implants are diagnosed with breast cancer at later stages was also pursued in the study in Alberta, Canada, by comparing breast cancer survival rates among patients who had implants with those among other patients; no apparent differences were observed *(65)*. Thus, neither of these epidemiologic studies has provided support to the notion that breast cancer diagnosis in patients with implants is delayed.

Analytic Studies of Breast Cancer Associated With Breast Implants

Two large-scale follow-up studies—one in Los Angeles *(64)* and the other in Alberta, Canada *(66)*—have been conducted to address effects of breast implants on breast cancer risk (Table 1). Both studies used record linkage techniques to assess cancer outcomes among cohort members.

The Los Angeles cohort consisted of 3182 women who received mammoplasty during the period from 1953 through 1980 from a number of board-certified plastic surgeons in the Los Angeles area *(67)*. The mean age of the subjects was 31.4 years at implantation. The majority (75%) of implants were silicone gel; 9% were saline, and 16% were of other or unknown types. Subjects were followed through the Los Angeles Cancer Registry. In the latest report of the study *(64)*, based on follow-up through 1991 (median follow-up, 14.4 years), 31 patients with breast cancer were identified versus 49.2 expected (standardized incidence ratio [SIR] = 0.63; 95% confidence interval [CI] = 0.4–0.9). Apart from age, race, and socioeconomic status (as measured by census tract of residence), this study could not

Table 1. Follow-up studies evaluating breast cancer risk among patients with augmentation mammoplasties

First author (reference No.)	Study site	No. of patients	Person-years*	Date of implants	Average years of follow-up	Breast cancers†		
						Obs	Exp	SIR (95% CI)
Deapen *(64)*	Los Angeles County	3182	37 439	1953–1980	14.4	31	49.2	0.63 (0.4–0.9)
Berkel *(66)*	Alberta, Canada	11 676	124 494	1973–1986	10.2	41	86.2	0.48 (P<.01)
Bryant *(68)*	Alberta, Canada	10 835	89 219	1973–1986	11.2	45‡	59.2	0.76 (0.6–1.0)
						41§	56.9	0.72 (0.5–0.9)
McLaughlin *(70)*	Sweden	1756	20 610	1965–1983	11.7	7	11.2	0.63 (0.3–1.3)
McLaughlin *(71)*	Denmark	824	NA	1977–1989	6.9	1	4.2	0.24 (0.0–1.3)
Friis *(72)*	Denmark	1135	NA	1977–1992	8.4	8	7.8	1.0 (0.4–2.0)

*NA = not available.

†Obs = observed; Exp = expected; SIR = standardized incidence ratio; CI = confidence interval.

‡Includes both *in situ* and invasive cases.

§Limited to invasive cases.

account for the influence of other predictors of breast cancer risk. Not surprisingly, patients were found to be of higher socioeconomic status than the general population.

In a second record linkage study *(66)*, computerized information on insurance payment claims made to the Alberta Department of Health was used to identify a cohort of 11 676 women who received breast implants in the province from 1973 through 1986. Approximately 85% of women received smooth-walled implants filled with silicone gel, and the remainder received saline-filled implants. Linkage of the cohort with the Cancer Registry of Alberta, Canada, allowed the identification of 41 patients with breast cancer. The expected number, based on general cancer incidence rates, was 86.2, resulting in a significantly low SIR of 0.48 ($P<.01$).

That study *(66)* was criticized on the basis of a number of methodologic limitations *(68)*. Notably, concerns were expressed that losses due to migration out of Alberta Province had been underestimated, person-years had been overestimated, and linkage methods were incomplete—all factors that should have underestimated the SIR. Additional analyses were undertaken to account for some of these problems *(69)*. Although these reanalyses found substantial differences in the numbers of person-years at risk, the risk ratio overall and for different induction periods all remained at less than unity (range, 0.68–0.85). The authors concluded that the incidence of breast cancer among women who had breast augmentation could not be said to be either significantly higher or significantly lower than that among the general population.

Two additional smaller record linkage studies in Scandinavia *(70,71)* also noted a decreased risk of breast cancer among augmentation mammoplasty patients (Table 1). Among a cohort of 1756 Swedish women, a total of seven breast cancers were observed versus 11.2 expected (SIR = 0.63; 95% CI = 0.3–1.3) *(70)*. In a follow-up study of 824 Danish women *(71)*, one case of breast cancer was observed versus 4.2 expected (SIR = 0.24; 95% CI = 0.0–1.3). However, an update of this study *(72)*, involving 1135 women, failed to confirm a reduced risk of breast cancer, with eight cases observed versus 7.8 expected (SIR = 1.0; 95% CI = 0.4–2.0).

Several case–control studies *(73–75)* have also assessed the relationship of breast implants to subsequent breast cancer risk (Table 2). In the large Cancer and Steroid Hormone (CASH) Study *(73)*, which involved study of 4742 case subjects with breast cancer and 4754 control subjects, 12 case subjects versus eight control subjects reported prior breast implants or injections to increase breast size, resulting in an adjusted relative risk (RR) of 1.0 (95% CI = 0.3–3.3). In a study of 1097 breast cancer patients and 1170 population control subjects in the state of Washington *(74)*, seven case subjects versus 15 control subjects reported a previous implant. The risk associated with breast implants was 0.8 (95% CI = 0.3–2.2) for women aged 21–44 years and 0.2 (95% CI = 0.1–1.3) for those aged 50–64 years. The small number of women with breast implants in this study precluded adjustment for potential confounders other than age.

In the latest study *(75)*, attempts were made to control for characteristics of the women with implants that could independently affect their breast cancer risk. Although this study noted that women with implants tended more often to be of higher socioeconomic status, to bear their children earlier, to be thin, and to have small breasts, adjustment for these factors had little impact on the risk of breast cancer associated with having had an implant, with the adjusted RR of 0.6 being nearly statistically significant (95% CI = 0.4–1.0). The authors also considered whether more pre-implant screening might have deterred women with breast problems from receiving implants. Such an effect should have resulted in the largest reduction in risk immediately following implantation; however, the greatest reduction in risk was observed among women who received their implants 10 or more years before the study. The reduced risk associated with implants was observed for all stages of breast cancer diagnosis and within nearly every subgroup of women examined, leading the investigators to question whether the effect of a reduced risk might have a biologic basis. Among possible mechanisms proposed were compressive effects of implants, interference of blood supply to surrounding breast tissue, and beneficial immunologic reactions to silicone; this latter explanation is consistent with at least one animal study *(76)*. Furthermore, since a reduced risk of breast cancer has also been observed following breast reduction surgery *(75,77,78)*, it is possible that breast tissue loss resulting from the surgical intervention of augmentation mammoplasty might be involved.

Although it appears from the available epidemiologic data that breast implants may lead to substantial reductions in subsequent breast cancer risk, further research is needed to assess how much of the reduction is real versus how much is due to methodologic biases of the studies conducted to date. In the cohort studies, an inability to fully control for predictors of breast cancer risk and losses to follow-up are of concern, particularly since survival among breast implant patients may be influenced by associated lifestyle factors. In case–control studies, the accuracy of the information on previous breast implants must be questioned. For instance, it is unclear whether the low

Table 2. Population-based case–control studies of breast cancer risk associated with breast implants

First author (reference No.)	No. of case subjects	No. of control subjects	Exposed subjects		RR (95% CI)*	Adjustment factors
			Case	Control		
Glasser *(73)*	4742	4754	12	8	1.0 (0.3–3.3)	
Malone *(74)*	1097	1170				Age
Aged 21–44 y	690	825	6	9	0.8 (0.3–2.2)	
Aged 50–64 y	407	345	1	6	0.2 (0.1–1.3)	
Brinton *(75)*	2174	2009	36	44	0.6 (0.4–1.0)	Study site, age, race, family history of cancer, body mass, and screening history

*RR = relative risk; CI = confidence interval.

rate of implants in the CASH Study *(73)* related to the earlier period of this study as compared with other investigations or whether underascertainment might have been involved. Both methodologic approaches are plagued by questions regarding the impact of pre-implant screening and uncontrolled predictors of breast cancer risk. Thus, future studies are needed to determine whether previous investigations may have overstated the inverse association between breast implants and breast cancer risk or whether there are unique biologic relationships that could fully explain the observed relationship.

Breast Cancers Following Reconstructive Implants

The analytic studies have focused on the risk of breast cancer following cosmetic augmentations, with much less known about the risk of breast cancer following reconstructive surgery. These risks are obviously important to define, given the much higher risk of breast cancer (i.e., of second primary cancers) among these patients and that they continue to have access to silicone gel implants.

In a study of 146 breast cancer patients with silicone implants following mastectomy and 146 matched mastectomy control subjects without implants, Petit et al. *(79)* found a lower risk of death due to breast cancer (RR = 0.5; 95% CI = 0.3–1.0), distant metastases (RR = 0.5; 95% CI = 0.3–0.8), and local recurrence (RR = 0.5; 95% CI = 0.3–1.1) and no increase in the development of a second primary breast cancer (RR = 1.1; 95% CI = 0.5–2.7) or other cancers (RR = 0.8; 95% CI = 0.2–2.5) in the women with the silicone implants. The small size of the study, however, limited the conclusions.

The risk of breast cancer as well as other cancers in women who receive reconstructive implants merits further investigation. Any such investigations, however, will need to account for unique confounding effects, including those relating to treatment. Such investigations might be best undertaken within the context of clinical trials, where treatment effects can be taken into account. Studies on the safety of silicone implants for breast cancer survivors should be encouraged, especially given that these devices can substantially contribute to the successful acceptance of a breast cancer diagnosis in many women *(80,81)*.

Sarcomas

For some time, there has been concern that sarcomas might result from a phenomenon of ''polymer'' or ''foreign-body carcinogenesis'' *(82)*. Specific concerns regarding the effects of silicone gel implants were raised in the late 1980s when a Dow Corning Corporation study noted a 23% development rate of sarcomas (mainly fibrosarcomas) in rats at the implant site of medical-grade silicone gel *(83)*. However, two expert committees commissioned by the FDA to review this issue concluded that the tumors were due to nonspecific solid-state carcinogenesis and that this phenomenon in rodents did not appear to be relevant in humans.

Two descriptive studies *(84,85)* have been undertaken to determine whether there have been changes in the incidence of sarcomas following the introduction of breast implants. No notable changes in incidence have been observed, although this methodologic approach would not be expected to have the power to detect associations unless exceedingly large effects were apparent.

Multiple Myeloma

The recognition that silicone is immunogenic and that it may be involved in the etiology of various immune disorders has led to concern regarding the effects of implants on hematologic cancers. Concern was heightened when Potter et al. *(86)* provided experimental evidence that plasma cell tumors can be induced in genetically susceptible substrains of BALB/c mice by the injection of silicone gels from mammary implants. Depending on the protocol and the specific lot of silicone gel used, plasmacytomas developed in up to 80% of genetically susceptible mice. This result led to concern regarding potential effects in humans, given that murine plasmacytomas have some features in common with human plasma cell neoplasms, including multiple myeloma and its precursor, monoclonal gammopathies of undetermined significance (MGUS). Given the postulated role of immune stimulation in the etiology of multiple myeloma *(87)*, the conduct of epidemiologic studies of monoclonal gammopathies, including MGUS, in relation to silicone exposure was encouraged *(88)*. However, because of the rarity of these conditions and their diagnostic complexities, it was recognized that the association would be difficult to resolve.

Several investigations *(89–91)* have assembled series of women with multiple myeloma who have had histories of breast implants. A registry of patients with multiple myeloma has also been established, and a total of 18 cases from four medical practices has been identified *(92)*. Although the etiologic relevance of these cases must be questioned, given potential referral biases and the absence of comparison groups, several observations are of interest: 1) Most of these multiple myelomas developed many years after the initial breast implantation, 2) a number of the cases occurred among women under the age of 45 (in contrast to the usual presentation after 60 years of age), and 3) disease prognosis often appeared to improve after explantation. In one investigation *(90)*, it was estimated that the observed number of subjects who had multiple myeloma and a history of breast implants was greater than that expected on the basis of population estimates. Attempts were also made in the registry to calculate expected values, and it appeared that there might be an excess risk of the disease among women under 45 years of age *(92)*.

Attempts have also been made in several of the cohort studies to evaluate the risk of multiple myeloma among women with breast implants. In the Los Angeles study, no cases of multiple myeloma or other plasma cell tumors were observed versus the 0.6 that was expected *(93)*. These tumors were also not observed in either the Swedish or Danish follow-up studies *(70,72)*.

It is obvious that resolution of whether an association exists between silicone implants and the occurrence of multiple myeloma will be dependent on having appropriate comparison groups as well as adequate statistical power (i.e., sufficient follow-up on a large number of study subjects) to evaluate effects. Given the rarity of multiple myeloma in the general population, however, appropriate investigations will be quite labor intensive. Thus, it may be informative for studies to also focus on rela-

tionships of silicone exposure to MGUS, which is estimated to have a prevalence of approximately 1% among persons 50 years of age and older *(94)*. One investigation *(90)* noted an increased prevalence of MGUS among symptomatic women with implants, but results must be interpreted cautiously, given the referral nature of the study population.

Lymphomas

There have been several reports of lymphomas occurring among women with silicone breast implants; these reports are of interest because of evidence that implants can affect T-cell-mediated autoimmune reactions. At least four cases of cutaneous T-cell lymphomas have been reported among women with silicone gel breast implants *(95,96)*. In several cases, the skin lesions began as eruptions overlying the implants, while in another instance a ruptured implant led to the diagnosis of pre-Sézary syndrome, which subsequently progressed to Sézary syndrome (a form of cutaneous T-cell lymphoma), leading to the suggestion that persistent antigenic stimulation might have been involved *(96)*. Another report *(97)* noted a follicular mixed lymphoma adjacent to a surrounding granulomatous response in a woman who had painful capsular contracture. An additional case has been reported of a primary effusion lymphoma developing between a silicone breast implant and its capsule in the absence of a mass lesion in a woman negative for the human immunodeficiency virus *(98)*. The histologic dissimilarity of the cancers in these reports argues against a common mechanism. Nonetheless, the risk of lymphomas among women with implants deserves further attention, given the reported immunologic disturbances following silicone exposure.

Other Cancers

Most attention has focused on breast and hematologic cancers and sarcomas, but it is possible that the risk of other cancers might also be affected by silicone breast implants. Local reactions, including chronic inflammation, granuloma/siliconoma formation, and epidermal hyperplasia *(99)*, suggest that some attention should be focused on skin cancers. Squamous cell carcinomas have been reported to arise from an implant capsule *(100,101)*, and a case was reported in which silicone granulomas were found to have a fibrous lining composed of squamous epithelium *(100)*. In particular, concern has been expressed that there may be a delay in the diagnosis of cancers under the false assumption that they merely represent diffuse nodularity from silicone granulomas *(40)*. There have also been several (at least four) instances of desmoid tumors of the breast among women with breast implants *(102,103)*. Although these tumors have been described as benign neoplasms originating from fascial or musculoaponeurotic structures, it is of interest that they resemble a low-grade fibrosarcoma. They rarely occur in the breast, and their etiology is unknown, but there is some speculation that they may be related to previous injury or surgery.

Epidemiologic investigations, because of their relatively small samples sizes and short follow-up times, have mainly had to focus on the most common cancer sites. One cohort study *(32)* combined all cancers other than breast cancer and found crude incidence rates for cancers other than breast cancer to be similar in women with breast implants compared with age-matched control subjects (rate ratio = 1.1; 95% CI = 0.5–2.1). Most studies have had insufficient power to evaluate risk of most cancer sites other than breast cancer. However, in the Los Angeles cohort, Deapen and Brody *(67)* did note significant excesses of both lung cancer (12 cases observed; SIR = 2.1; 95% CI = 1.1–3.7) and vulvar cancer (one case observed; SIR = 5.3; 95% CI = 1.7–12.3). Cervical cancer was more common than expected, but its frequency was not statistically significantly elevated. Since all three of these cancers have been noted to be more common among cigarette smokers, the excesses are difficult to evaluate in the absence of information regarding smoking history. This study highlights the need for future studies to collect sufficient information on variables that could affect cancers of many sites, particularly since several studies have now demonstrated that women seeking breast implants differ in many respects from women in the general population. Thus, women with implants have been noted to differ from other women in terms of selective residency patterns, being of relatively high socioeconomic status, bearing their children at young ages, having small breasts, being thin, and having more access to medical care *(1,74)*. These factors will need to be accounted for in future analytic investigations to determine the independent effects of exposure to silicone implants.

Polyurethane Foam-Covered Breast Implants

The relationship of polyurethane foam-covered implants to cancer risk bears special attention. These devices have been estimated to account for approximately 10% of all implanted silicone implants. Originally designed to decrease the risk of breast contracture, polyurethane implants were withdrawn from the market in 1991 when the FDA found that the polyurethane could degrade into 2,4- and 2,6-toluene-diisocyanate diamines (TDAs) *(104)*. TDAs have been shown to cause cancer in laboratory animals (mice: cancers of the liver, ovaries, spleen, subcutaneous tissue, and peritoneum; rats: cancers of the pancreas and liver and breast fibrosarcomas) and are recognized as animal carcinogens *(105)*. There is evidence of increased cancer rates when 2,4-TDA is injected subcutaneously *(106)*, painted on the skin *(107)*, or added to the diet *(108,109)*, and a statistically significant dose–response relationship between ingestion of 2,4-TDA and breast cancer in rats has been shown *(108)*. High rates of cancer have been found in rodents at the injection site and in the liver, lung, and breast *(104)*. Although these studies suggest that breakdown products may be human carcinogens, it must be noted that the dose from polyurethane implants is much lower than that used in these animal studies. Data on human consequences of polyurethane implants are limited to a follow-up study of 213 patients, whose exposure ranged from 1 year to 18 years *(110)*. Two patients developed breast adenocarcinomas, of questionable relevance given the absence of any comparison group.

Additional concern regarding the carcinogenic potential of TDA derives from the chemical being found in the urine of a patient several months following insertion of a polyurethane breast implant *(111)*. These breakdown products have also been found in the urine and plasma of subjects experimentally exposed to toluene diisocyanate and in workers in the polyurethane-manufacturing industry *(112)*. Two cohort studies

(113,114) of cancer risk among individuals occupationally exposed to diisocyanates in the production of polyurethane foam noted some excesses of cancers of the pancreas, rectum, and lung and of non-Hodgkin's lymphoma, despite overall cancer risks that were below unity. Both studies, however, were limited by the numbers of observed cancers and by an inability to control for extraneous factors, such as cigarette smoking.

Because of the uncertainty of the risk for humans, the manufacturer of polyurethane foam-covered implants suspended sales of these implants and performed a study to measure TDA levels in body fluids of women with the implants. Free TDA was detected in the urine of 80% of 61 women with the implants, compared with 13% of 61 women without the implants. On the basis of this information, the FDA estimated the risk of cancer from exposure to TDA from this type of implant to be about one in one million over the woman's lifetime, which was considered to be a negligible risk *(115,116).*

Conclusions

There is currently little evidence to support the notion that breast implants increase the risk of subsequent breast cancer. Although the diminished ability to mammographically visualize lesions in women with implants has been well documented, there is no conclusive evidence that the prognosis of the disease is affected. In contrast, evidence is accumulating that the risk of breast cancer may be reduced among women with implants. However, it remains unclear the extent to which some of this reduction in risk might relate to methodologic limitations of the previous epidemiologic studies, including potential selection, surveillance, and reporting biases. Furthermore, since a biologic mechanism for the reduced risk remains uncertain, the purported reductions in breast cancer risk experienced by breast implant patients must be cautiously interpreted.

Insufficient data are currently available to conclude whether silicone implants predispose to other cancers. However, experimental data would support the need for further evaluation of sarcomas and hematopoietic cancers, particularly multiple myeloma and lymphomas.

The relationship of breast implants to subsequent cancer risk should become clearer as results emerge from several ongoing follow-up studies, including one being conducted currently by the National Cancer Institute *(117).* Risks of cancer among women with silicone breast implants may be easier to resolve than those of many other diseases postulated to arise as a result of exposure to silicone implants, since reports of cancer can be validated against pathology reports and cancer incidence rates are readily available for the general population. However, it will be essential for these studies to have adequate statistical power for evaluating cancer relationships and to consider other lifestyle factors that could independently affect disease risk. A number of these lifestyle factors have recently been elaborated *(118).* It will also be important for these studies to consider latency effects, especially in view of evidence of deterioration of the implant capsule over time and its possible association with immunologic changes. Thus, studies involving observations on women with long durations since initial implantation (e.g., 10 or more years) and that can account for effects of explantation and reimplantation of different devices over time will be essential to providing useful data. Finally, an issue not addressed by most previous investigations is whether different types of implants have unique long-term effects. Of particular importance will be whether there are any unique effects of polyurethane foam-coated implants, given evidence that they have the potential for biodegradation to TDA. Such studies might be best addressed in Canada, given generally higher rates of usage of these devices in that country than in the United States.

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Note

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