The Safety of Silicone Gel–Filled Breast Implants

A Review of the Epidemiologic Evidence

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Abstract: Few implantable medical devices have been studied for their safety more extensively than silicone gel–filled breast implants. We summarize the epidemiologic evidence on the safety of breast implants, most of which is drawn from large cohort studies with long-term follow-up. The topics addressed in this report include cancer, breast cancer detection, connective tissue disease, suicide, offspring effects, neurologic disease, implant rupture, and local perioperative complications and additional surgery. We conclude that the weight of the epidemiologic evidence does not support a causal association between breast implants and breast or any other type of cancer, definite or atypical connective tissue disease, adverse offspring effects, or neurologic disease. Women with breast implants do not present with more advanced stages of breast cancer or suffer impaired survival after breast cancer diagnosis. The only study to examine an actual incidence rate of breast implant rupture reported rupture-free survival of 98% at 5 years and 83%–85% at 10 years for newer "third-generation" implants. Future studies are needed to determine whether the consistently observed excess of suicide among women with implants reflects underlying psychiatric illness prior to breast augmentation surgery or other factors.

Key Words: breast implants, epidemiology, review, safety

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Few medical devices have been studied for their safety more rigorously and for more adverse outcomes than silicone gel–filled breast implants. Although their design has been altered over the years, including changes to the cohesiveness of the silicone gel filler and texturing of the shell, the basic device design remains a clinically qualified silicone elastomer shell surrounding a viscous crosslinked silicone gel.

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Beginning in the 1980s through the early 1990s, concerns were raised by public advocates and regulatory agencies that insufficient information existed on the safety of silicone gel–filled breast implants. This culminated in a virtual ban on silicone breast implants by the US Food and Drug Administration in 1992, until there was sufficient evidence that the device was safe. In 1999, the Institute of Medicine (IOM), which was established by the National Academy of Sciences to examine policy matters pertaining to the health of the public, published a review of the safety of silicone breast implants.[1] The IOM specifically examined the safety concerns that had been raised about implants up to that time. These included cancer and effects on breast imaging; connective tissue or rheumatic disease; neurologic disease; effects on pregnancy, lactation, and offspring; risk for reoperations; and specific local and perioperative complications.

The release of the IOM report did much to clarify the extent of knowledge and to identify gaps in information about the safety of silicone gel–filled breast implants. Since then, research on the safety and performance of these devices has continued, especially as new device designs, such as cohesive silicone gel–filled implants, were being tested and marketed. Extensive additional data are now available on safety issues already identified, as well as on more recent concerns such as incidence and consequences of breast implant rupture and risk of suicide.

This report summarizes the epidemiologic evidence regarding the safety of silicone gel–filled breast implants through September 2007. The specific safety issues addressed in this review include (1) cancer, (2) breast cancer detection, (3) connective tissue disease (CTD), (4) suicide, (5) offspring effects, (6) neurologic disease, (7) implant rupture, and (8) local perioperative complications and additional surgery. These issues represent those for which there has been considerable scientific investigation and which appear to be of greatest interest to regulatory agencies.

Cancer

More than a dozen epidemiologic studies, many of which have been large and able to assess long-term risks, have been conducted in North America and Europe to evaluate the potential association between cosmetic breast implants and the incidence of breast and other cancers.[2–17] The primary concern among breast implant patients, the medical community, and regulatory agencies was breast cancer risk

because of the location of the implants, their use for reconstruction following breast cancer, and the hypothesis that they may interfere with mammographic detection of breast cancer. Epidemiologic studies have been remarkably consistent in finding no evidence of increased breast cancer risk among women with breast implants.[3,4,6,7,9–20] Indeed, in 1999, the International Agency for Research on Cancer (IARC)[19] took the unusual step of concluding that there was evidence of a lack of breast carcinogenicity in women with silicone breast implants, and this conclusion was supported by that of the independent report of the IOM Committee on the Safety of Silicone Breast Implants.[1]

Some early reports also raised concern that women with silicone gel–filled breast implants may be at increased risk of developing other cancers, including lung cancer, cancers of the cervix and vulva, leukemia, and multiple myeloma. However, the weight of the epidemiologic evidence is consistent with there being no causal association between breast implants and any other type of cancer. Accordingly, independent scientific review bodies have unanimously concluded that there is no demonstrated excess of cancer of any type among women with silicone breast implants.[1,18–20]

Since publication of these independent reviews, numerous epidemiological studies have continued to evaluate risk of breast and other cancers in women with silicone gel–filled breast implants.[4,5,13–17] In the most recent updates of a nationwide Swedish cohort of 3486 women who received cosmetic breast implants, with an average follow-up of 18.4 years (range up to 37.8 years),[16] and a cohort of 2736 Danish women with cosmetic breast implants, with an average follow-up of 14.4 years (range up to 30 years),[15] there was no statistically significant increase in cancer incidence overall compared with the general population of age-matched women. Similarly, Pukkala et al[14] conducted a cohort study of 2171 Finnish women with cosmetic breast implants, with a mean length of follow-up of 8.3 years. Cancer incidence overall was similar to that expected in the general population. Brinton et al[4,5] conducted a retrospective cohort study of the incidence and mortality of cancers of various types among 13,488 women with silicone breast implants compared with 3936 women who had other types of plastic surgery, as well as with women in the general population. There was a slight excess of cancer incidence overall among women with implants (standardized incidence ratio [SIR] = 1.2; 95% CI, 1.1–1.4) when compared with women in the general population, but not when compared with other plastic surgery patients.[5] In a recent, large, Canadian, cohort study, the incidence rate for cancer at all sites combined was significantly reduced among 24,558 women with implants compared with the general population (SIR = 0.75; 95% CI, 0.70–0.81) and was similar to that among other plastic surgery patients.[17]

The incidence of breast cancer was below expectation in virtually all studies,[3–11,14–20] with risk ratios suggesting a reduction of 10% to 50%. Few statistically significantly increased or decreased SIRs were observed for other types of cancers in any of the studies. A significant increase in lung cancer (SIR = 2.2; 95% CI, 1.3–3.4) was observed among women with implants in the Swedish study.[16] An earlier survey based on a randomly selected subset of these Swedish women with breast implants found that they were 2.8 times more likely to be current smokers than the general female population.[21] This difference in smoking habits is likely to explain the increase in lung cancer risk among women in this study, as well as the excesses of lung cancer mortality among women with breast implants in the recent Swedish mortality study.[22] The slight excess of cancer overall in the study by Brinton et al[5] was due primarily to statistically significant increased risks of cervical, vulvar, and brain cancer and leukemia compared with the general population. In addition to concerns about selection bias and validation of cancer diagnoses in this US study, substantial differences in demographic, lifestyle, and/or reproductive characteristics between women with implants and both women with other types of cosmetic surgery and women in the general population have been reported in several epidemiologic studies[21,23–25] and are likely to account for these sporadic excesses of cancer, in particular vulvar, cervical, and lung cancer.

Epidemiologic studies do not support the speculation, based on animal results, that silicone may be related to an increase in a precursor condition for multiple myeloma. In the Swedish study by McLaughlin et al,[16] 1 case of multiple myeloma was observed among women with breast implants compared with 1.4 expected. In both the Danish[15] and the Finnish[14] breast implant cohorts and in the US study,[5] no cases of multiple myeloma were observed (versus 0.6, 0.2, and 1.73 expected, respectively), and in the Canadian study 3 were observed versus 6.5 expected.[17]

Brain cancer has been studied quite extensively in several large-scale incidence studies,[14–17,26] as well as in 5 mortality studies,[22,27–31] all of which consistently failed to demonstrate any significant excess among women with cosmetic breast implants. Only 1 study to date has reported a significant excess of brain cancer among women with breast implants,[28] and interpretation of this finding is hampered by the fact that the diagnostic accuracy of death certificates for the ascertainment of brain cancer deaths often reflects metastases from other sites.[26] Moreover, no additional deaths from brain cancer were observed in the most recent updated follow-up of this study,[29] yielding a nonsignificant standardized mortality ratio (SMR) of 1.4 (95% CI, 0.8–2.5) after an average of 20 years of follow-up.

In summary, large-scale incidence studies have consistently found no credible evidence of a causal association between breast implants and any type of cancer. Sporadic lung or cervical cancer mortality and incidence excesses are likely due to confounding by lifestyle and behavioral factors and/or reproductive characteristics, which have been shown to differ between women with implants and women with other types of cosmetic surgery and women in the general population.

Breast Cancer Detection

The IOM[1] suggested that implants may make screening mammography more challenging by obscuring a variable part of breast tissue. Based on the findings of a few case series,[32–35] many originating from the same clinic, a hypothesis

was generated that opaque breast implants may interfere with physical breast examination or mammographic visualization of breast tumors, leading to delays in breast cancer diagnosis and worse prognosis among women receiving implants. However, the interpretation of these clinical case series is hampered by potential referral or ascertainment bias, small sample size, and absence of a control group. Furthermore, many of the women included in these case series underwent their mammograms prior to the implementation of the Eklund et al[36] implant displacement technique, which improved the accuracy of mammograms for women with breast implants.

The findings of epidemiologic studies, which employed control groups to provide comparison data, consistently indicate that, although the sensitivity of mammography may be reduced somewhat in women with breast implants, these women do not in fact present with more advanced stages of breast cancer or suffer from lower survival rates after breast cancer diagnosis, thus providing no evidence of a delay in breast cancer detection following breast augmentation.[15,16,37–40] Moreover, none of the mortality studies to date has demonstrated an increased risk for death from breast cancer among women with implants compared with women in the general population.[22,27,29,31]

CTD

Since the publication of anecdotal reports of autoimmune disorders among women with breast implants in the 1980s and early 1990s, more than 2 dozen case-control and cohort studies have been conducted throughout North America and Europe to evaluate in a systematic fashion the association between cosmetic silicone breast implants and the occurrence of various CTDs, including systemic sclerosis, fibromyalgia, systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjögren syndrome. Data from studies published through 2004 have been summarized in numerous meta-analyses, weight-of-the-evidence, and critical reviews, which have unanimously concluded that there is no evidence of an association between breast implants and any of the traditional CTDs evaluated individually or combined, or atypical CTD.[1,41–51]

The only finding of a relationship between CTDs and breast implants comes from a single large retrospective cohort study of female health professionals in the Women's Health Study.[52] This study found a small increased risk of self-reported (not validated) CTDs overall among women with breast implants. Compared with women without implants, the relative risk (RR) for any self-reported CTD combined was 1.24 (95% CI, 1.08–1.41). For individual diseases, an increased risk was found for the category of "other CTDs (including mixed)" (RR 1.30; 95% CI, 1.05–1.62). The individual RRs for self-reported rheumatoid arthritis, polymyositis or dermatomyositis, scleroderma, and Sjögren syndrome were all slightly but not significantly elevated. The authors concluded that their data were reassuring in ruling out a large hazard of CTDs. This study used outcome data that were self-reported by female health professionals in a mailed questionnaire. In a subsequent medical record validation of these data by the same research group, evidence of overreporting of disease by the subjects was observed, as only 22.7% of self-reported cases of definite CTD could be confirmed.[53] Such overreporting could easily have accounted for a slight excess of CTDs among women with implants.

A recent CTD report of the US cohort study of 7234 women with breast implants[54] also showed reporting and diagnostic biases inherent in self-reports of illness, as evidenced by the overreporting of CTDs by both implant and comparison patients and by the difficulty of confirming conditions according to predefined clinical criteria. In particular, only a minority of self-reports, particularly among women with implants, of rheumatoid arthritis, scleroderma, and Sjögren syndrome were considered "likely" after medical record review by expert rheumatologists. Based on the "likely" diagnoses by the study rheumatologists, RRs among women with implants were not significantly elevated for the 3 CTD disorders combined (RR = 2.5; 95% CI, 0.8–7.8) or for rheumatoid arthritis alone (RR = 1.9; 95% CI, 0.6–6.2).

Most recently, Fryzek et al[55] reported on the occurrence of CTD in an extended follow-up of 2761 Danish women with breast implants and 8807 comparison subjects who underwent breast reduction surgery from plastic surgery private clinics and public hospital plastic surgery departments. All CTD outcomes were based on hospital records and were medically verified through medical chart review. Compared with general population rates, there was no significant increase in the incidence of any specific definite CTD or combined CTDs in either the implant or comparison cohorts, after a mean follow-up time of 13.4 years. With respect to other rheumatic conditions, unspecified rheumatism, which included fibromyalgia, was similarly elevated in both the implant and the control cohorts. After validating the diagnosis of fibromyalgia through medical records, direct comparison of the implant and comparison cohorts showed no relation between breast implants and confirmed fibromyalgia (RR = 1.2; 95% CI, 0.6–2.1). The US study by Brinton et al[54] also found that women with breast implants were not more likely to have fibromyalgia than women with other types of plastic surgery, although based on self-reports (RR = 1.3; 95% CI, 0.9–1.7).

In a subsample of women from the Danish implant cohort who were chosen to undergo magnetic resonance imaging (MRI) to detect rupture, Holmich et al[56] evaluated risk of CTD by rupture status among 238 women with cosmetic silicone breast implants. Ninety-two of the women had MRI-diagnosed ruptures, of which 69 were intracapsular and 23 were extracapsular, and 146 had intact implants. Overall, there were no statistically significant differences in self-reported definite CTD between women with intact implants and either women with ruptured implants overall (odds ratio [OR] = 0.9; 95% CI, 0.1–6.7) or women with extracapsular ruptures (OR = 3.8; 95% CI, 0.4–35.1).

In an earlier MRI study by Brown et al,[57] 236 of 344 women with primarily second-generation implants had at least 1 ruptured implant; 73 of these 236 women had an extracapsular rupture. Women with breast implant rupture were no more likely than women with intact implants to report a diagnosis of any of the definite CTDs studied. When women with extracapsular silicone were compared with a

combined group of women with intracapsular rupture and women with no ruptures, excesses were found for self-reported Raynaud syndrome (OR = 4.2; 95% CI, 1.1–16.0) and "other CTD" (OR = 2.7; 95% CI, 0.8–8.5). However, the study had considerable potential for selection bias due to recruitment procedures, failed to use the proper control groups in the above comparison, and could not determine whether disease onset occurred before or after breast augmentation.[58]

An association has also been conjectured between silicone breast implants and the existence of a new disease, which does not fulfill established diagnostic criteria for any known CTD. It has been suggested that breast implant recipients experience symptoms of apparent connective tissue, rheumatic, or autoimmune origin that do not fit the profile for a defined CTD, including cognitive dysfunction, severe joint and muscle pain, incapacitating fatigue, and skin abnormalities. Attempts have been made to define these syndromes, which may be referred to as "undifferentiated," "atypical," or "mixed" CTD,[59] and it has been suggested that the symptomatology of the proposed new disease bears some resemblance to fibromyalgia.[60] Most of the published epidemiologic studies to date evaluated traditional CTDs rather than atypical symptoms; however, those studies that did attempt to include a category for undefined or atypical CTD as an outcome have been remarkably consistent in finding no convincing evidence of an association between silicone breast implants and atypical connective tissue or rheumatic disease.[1,41,50] The IOM[1] report found no "convincing evidence for atypical connective tissue or rheumatic disease or a novel constellation of signs and symptoms in women with silicone breast implants." More recently, Tugwell et al[50] conducted a systematic review for a US Federal Court–appointed National Science Panel of the relevant literature regarding breast implants in relation to rheumatologic disorders. The authors specifically evaluated atypical presentations of CTDs and concluded that there was no evidence of an association between breast implants and "undifferentiated CTD." Undifferentiated CTD was accepted by the authors as the term for atypical CTD because it has a clear case definition, is distinct from the other established CTDs, and has substantive symptoms.[61] Lipworth et al[41] performed an updated review of the results of epidemiologic studies published since 1999[2,55,62–66] and concluded that the results of several studies provide no evidence of a higher frequency of undefined CTD among women with cosmetic breast implants or of a rheumatic symptom profile unique to these women and/or indicative of a specific atypical CTD.

In the recent analysis of CTDs by Brinton et al[54] in their US cohort, the authors included a category of self-reported conditions termed *other disorders*. The risk ratio for these self-reported disorders among women with implants compared with other plastic surgery controls was 1.4 (95% CI, 0.8–2.6) for the period before 1992 and 3.6 (95% CI, 1.9–7.0) for the period after 1992, during which breast implant litigation was widespread in the United States, providing clear evidence of reporting bias inherent in these self-reports of CTDs, particularly in the United States. Moreover, as the authors indicate, most of these "other CTDs" were "vaguely defined or should not have been considered CTDs."

In the most recent CTD update of the earlier Danish follow-up study,[55] unspecified rheumatism (including fibromyalgia and myalgia) was similarly increased in both the implant and comparison cohorts. For ill-defined rheumatic conditions other than unspecified rheumatism, the SIR was 0.7 (95% CI, 0.4–1.2) among women with implants and 1.2 (95% CI, 1.0–1.5) among comparison women. These results suggest that women undergoing breast implantation are not at increased risk for these conditions.

In summary, the results of the most recent investigations are remarkably consistent with earlier epidemiologic evidence in demonstrating that cosmetic breast implants are not associated with an excess of any individual established CTD or all CTDs combined. Moreover, based on several well-conducted epidemiologic studies, there is no credible evidence for the conjectured excess of atypical or undefined CTD among women with cosmetic breast implants.

Suicide

Five large-scale epidemiologic mortality studies conducted in various populations during the past few years have reported that women with cosmetic breast implants have a 2- to 3-fold higher rate of suicide than similar-aged women in the general population.[22,27–31] To our knowledge, prior to these recent mortality studies, there were no reports, even case reports, in the literature indicating a suicide excess among women with cosmetic breast implants.

Three nationwide cohort studies have been conducted in Scandinavia to evaluate cause-specific mortality among women with breast implants, with similar results. Lipworth et al[22] examined causes of death among a cohort of 3527 Swedish women who had breast augmentation surgery between 1965 and 1993. The subjects were followed for an average of 18.7 years (range, 0.1–37.8 years) after implantation. Twenty four women who had breast implants committed suicide compared with 5.2 expected suicides, based on the national Swedish statistics, resulting in an SMR of 3.0 (95% CI., 1.9–4.5) for suicide among implanted women compared with the general female Swedish population.

Pukkala et al[30] examined a cohort of 2166 Finnish women who had cosmetic breast implantation from 1970 through 2000. Women were followed for a mean of 10.3 years (range, 1 month to 30 years). Women with cosmetic breast implants did not experience a higher overall rate of mortality when compared with the general Finnish female population. However, a statistically significantly increased SMR for suicide was observed among implanted women compared with the general Finnish female population (SMR = 3.2; 95% CI, 1.53–5.86, based on 10 suicides compared with an expected 3.1).

Jacobsen et al,[27] examining mortality outcomes in the Danish implant cohort, found an increased risk of suicide in this population (SMR = 3.1; 95% CI, 1.7–5.2, based on 14 suicides compared with an expected 4.5). This was the first mortality study to explore underlying psychopathology among women undergoing cosmetic breast implant surgery, by examining their preoperative history of hospitalization for

psychiatric illness. The results of this study indicate that the Danish women who underwent breast implantation had a higher prevalence of psychiatric admission prior to cosmetic surgery (8.0%; 95% CI, 7.0%–9.0%) than women who underwent breast reduction (4.7%; 95% CI, 4.2%–5.2%) or other types of cosmetic surgery (5.5%; 95% CI, 4.5%–6.7%). When compared with all control groups, the OR for prior psychiatric admission was 1.7 (95% CI, 1.4–2.0). In fact, 7 of 14 women with breast implants who committed suicide had a history of preoperative psychiatric hospitalization.

Brinton et al[28,29] recently updated the US cohort of women for mortality. The average follow-up for mortality was 20.5 years for implanted women and 18.9 years for the other cosmetic surgery cohort. Risk of suicide was increased (SMR = 1.6; 95% CI, 1.1–2.3, based on 29 observed suicides) among implanted women compared with the general population. The RR of suicide for implanted women compared with other cosmetic surgery patients was elevated but not statistically significant (RR = 2.6; 95% CI, 0.9–7.8).

Villeneuve et al[31] recently examined mortality in a large cohort of 24,558 Canadian women with breast implants and 15,893 women who underwent other plastic surgery procedures between 1974 and 1989. Higher rates of suicide were observed in both the implant (SMR = 1.7; 95% CI, 1.3–2.2) and other plastic surgery groups (SMR = 1.6; 95% CI, 1.1–2.2) compared with the general population, based on 58 and 33 observed suicides, respectively.

The reason for the consistently higher risk of suicide among women with cosmetic breast implants, and whether or not it represents a causal link or reflects increased prevalence of prior underlying psychopathology and other risk factors for suicide among these women, remains unclear.[67] The strongest risk factor for suicide, particularly among women, appears to be psychiatric diagnosis requiring hospital admission,[68–72] with a nationwide study of suicide in Denmark reporting that almost 50% of individuals who committed suicide had been or currently were psychiatric inpatients.[73] Moreover, risk ratios for suicide of 337 (95% CI, 136–825) and 68.4 (95% CI, 39.5–118) were reported for those who had been discharged <8 days and 8–30 days, respectively, from a psychiatric hospital.[73] The results of the Danish breast implant mortality study,[27] in particular the higher prevalence of prior hospitalization for psychiatric disorders among women who choose to undergo cosmetic breast implantation compared with women undergoing breast reduction and other types of cosmetic surgery, support the notion that the excess of suicide among these women is unlikely to represent a causal association but rather reflects confounding by underlying psychiatric morbidity prior to implant surgery among a subset of these women. The prevalence and severity of pre- and postimplant psychiatric disorders among women who choose to undergo breast implantation needs to be further investigated to assess the need for psychologic or psychiatric screening and perhaps postimplant counseling or monitoring. Moreover, future mortality studies of women with cosmetic breast implants should closely examine other causes of death besides suicide to more completely capture possible psychiatric morbidity and misdiagnosed suicides in such women.

The epidemiologic evidence regarding suicide among women with breast implants is remarkably consistent, as is the strength of the general association between prior psychiatric illness and suicide. Therefore, further etiologic epidemiologic studies are needed to identify whether history of psychiatric illness or other factors prior to breast augmentation surgery may place some women with cosmetic breast implants at high risk of suicide.

Offspring Effects

The concern that children born to mothers with silicone breast implants are at risk for developing adverse health outcomes stems from isolated case reports of children born to or breast-fed by such women who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms.[74–79] Besides the lack of a control group, these case series or small clinical studies suffer from serious selection bias. In particular, the referral of children to a gastroenterology clinic because of a concern about breast implants is likely to introduce selection bias. In addition, some of the children were born to families with a history of scleroderma and esophageal dysmobility, so genetic or familial factors cannot be ruled out, and sedation of the children during testing may have affected esophageal pressures. The methods of one study[74] have been seriously criticized, particularly with respect to selection bias generated by the fact that, of 67 consecutive children born to mothers with silicone breast implants who were referred to the authors, only 11 were evaluated, as well as by the inclusion of children of mothers who were involved in anti-implant litigation.[80–83]

To date, 4 population-based retrospective cohort studies have examined health outcomes among children born to mothers with silicone breast implants, and none has found evidence of such a relationship. Kjoller et al[84] examined the occurrence of esophageal disorders, CTD, and congenital malformations in children of Danish mothers who received breast implants at public hospitals between 1977 and 1992. They compared 939 children of mothers with breast implants to 3906 children of mothers who had undergone breast reduction. After a mean follow-up of 5.5 years (range up to 15.7 years), higher than expected rates of esophageal disorders were found among children born to mothers with implants compared with the general population; however, similar excesses were observed among the control group of offspring born to mothers with breast reduction surgery, and excesses were also observed among children born prior to their mother's breast implant surgery. The observation of an increased occurrence of esophageal disorders among the offspring of women with breast implants and women with breast reduction suggests confounding by some characteristics of women who undergo cosmetic breast operations in general as a likely explanation for the observed excesses. There were no significant increases in CTD or congenital malformations in either the breast implant or breast reduction cohorts.

Kjoller et al[85] reported on an additional cohort of children of Danish women who received breast implants at private plastic surgery clinics between 1973 and 1995 and updated the follow-up of the earlier public hospital breast

implant and reduction cohorts.[84] The mean follow-up after breast implantation for the private clinic and public hospital cohorts combined was 6.0 years (range up to 19 years). Esophageal disorders, rheumatic disease, and congenital malformations were examined among 2854 children born to Danish women with breast implants and 5805 children born to women who underwent breast reduction or other plastic surgery. Significantly higher than expected rates of esophageal disorders were observed for children born before (observed/expected [O/E] = 2.0; 95% CI, 1.3–2.8) but not after (O/E = 1.3; 95% CI, 0.5–2.9) maternal implant surgery; similar excesses were observed among children born before (O/E = 2.1; 95% CI, 1.5–2.8) and after (O/E = 1.6; 95% CI, 1.1–2.3) maternal breast reduction surgery. Risks of rheumatic disease were not significantly elevated and were similar among children born before and after maternal breast implant surgery. A marginally significant excess of congenital malformations of the digestive organs was observed among children born after maternal implant surgery (O/E = 1.8; 95% CI, 1.0–3.1), but a similar excess was observed among children born to women in the breast reduction cohort after their surgeries (O/E = 1.9; 95% CI, 1.4–2.4). The risk of malformations overall was not statistically significantly higher than expected among children born after breast surgery. Any observed elevated risks of adverse health outcomes appear unrelated to breast implants per se because similar findings were observed among children born both before and after the mother's implant surgery, as well as among children born to control mothers in the breast reduction cohort.

Similarly, a retrospective cohort study conducted in Sweden found no evidence of increased risk of adverse health outcomes among children born to women with breast implants, after a mean follow-up of 8.9 years (range up to 24 years).[86] The investigators evaluated hospitalization rates for rheumatic and esophageal disorders, incidence rates for cancer, and prevalence rates for congenital malformations among 5874 children born to women with cosmetic breast implants compared with 13,274 children born to women who had undergone breast reduction surgery. Compared with children of women who had undergone breast reduction, children of women with cosmetic breast implants were not at increased risk for rheumatic disease (RR = 1.1; 95% CI, 0.2–5.3), esophageal disorders (RR = 1.0; 95% CI, 0.7–1.6), congenital malformations overall (RR = 1.0; 95% CI, 0.6–1.5), congenital malformations specifically involving the digestive organs (RR = 0.5; 95% CI, 0.2–1.3), cancer (RR = 0.3; 95% CI, 0.0–2.5) or perinatal death (RR = 0.9; 95% CI, 0.5–1.8). The rates of these outcomes among children born after the mother's implant surgery were also not statistically significantly higher than among children born before a mother's implant surgery.

A recent fourth study, conducted in Finland by Hemminki et al,[87] attempted to evaluate perinatal health outcomes among infants born to women with silicone breast implants, as well as pregnancy and birth patterns among these women. In general, this study suffered from serious methodological flaws, including inadequate control selection and serious confounding, and the unsupported speculation of the authors based on their null findings, which provided no evidence of an association between implants and adverse perinatal health.

In summary, the epidemiologic evidence indicates that offspring of women with breast implants are not at increased risk for esophageal disorders, rheumatic diseases, or congenital malformations.

Neurologic Disease

Sporadic case reports have described neurologic disorders, including a multiple sclerosis–like syndrome and motor and peripheral neuropathies, among women with cosmetic breast implants. To date, 3 large, population-based cohort studies have been conducted to evaluate risk for neurologic disease among women with cosmetic breast implants,[88–90] and an association has consistently failed to emerge.

Nyren et al[88] examined hospitalization for selected neurologic disease among 7433 Swedish women who underwent cosmetic breast augmentation between 1965 and 1993 (3502 cosmetic, 3931 reconstruction) and 3351 breast reduction controls matched on hospital, age, and calendar year at operation. Women in the breast implant and breast reduction cohorts were followed for an average of 8 and 9.9 years, respectively. When the general female population of Sweden was used as a comparison, a small and similar excess of neurologic disorders was observed in both the cosmetic breast implant (RR = 1.7; 95% CI, 1.1–2.6) and breast reduction (RR = 1.5; 95% CI, 0.9–2.4) cohorts. As observed in the mother-offspring results, these findings indicate that the higher rate of neurologic disorders among women with breast implants is not causally related to silicone breast implants themselves, but rather reflects certain characteristics or increased medical surveillance among women undergoing elective types of breast surgery. Indeed, in a direct comparison of implanted women with breast reduction women, which used medical record data to correct for all misclassified and preexisting (prevalent) diagnoses in both cohorts, the overall RR for neurologic disease among women with cosmetic and reconstructive breast implants was 0.8 (95% CI, 0.5–1.4), based on 25 cases in the breast implant group. There were deficits of multiple sclerosis (RR 0.5; 95% CI, 0.2–0.9) and of mononeuritis of the upper limb (RR 0.5; 95% CI, 0.2–1.0) among implant patients and a nonsignificant excess of diseases of the nerve roots and plexuses (RR 1.5; 95% CI, 0.6–3.9). The results of this study suggest that women with breast implants have no excess risk of neurologic conditions.

A nationwide study was conducted in Denmark among 1135 women who underwent cosmetic breast implantation and 7071 control women undergoing breast reduction surgery between 1977 and 1992 at public hospitals.[89] As in the Swedish study, when compared with the general population, rates of hospitalization for neurologic disease were about 70% higher among both women with cosmetic breast implants and women who had undergone breast reduction. A later report by the same authors[90] examined the occurrence of neurologic disorders among 1653 women who received cosmetic breast implants and a comparison cohort of 1736 women who underwent other types of cosmetic surgery at private plastic surgery clinics in Denmark between 1973 and 1995; they also expanded the follow-up through 1996 of the

original public hospital cohorts studied earlier[89] and included outpatient data for the last 2 years of follow-up. The average follow-up time was 8.7 years for the combined public and private hospital implant cohorts and 9.8 years for the combined breast reduction and other cosmetic surgery cohorts, with some subjects being followed for up to 20 years. The occurrence of neurologic disease among women who underwent breast augmentation or other cosmetic surgery at private clinics was comparable to that observed in the general Danish population. When data for the private and updated public hospital cohorts were combined, a slightly elevated RR for neurologic disorders overall was observed in the implant cohort (RR 1.3; 95% CI, 0.8–1.9), but once again a larger excess risk was observed in the control cohort of women with other types of cosmetic surgery (RR 1.7; 95% CI, 1.4–2.0); the excess was statistically significant only in the control cohort. The 30% excess risk of neurologic disease in the implant cohort was almost entirely due to a nonsignificant 50% excess risk of peripheral neuropathies; a significant 70% excess risk of peripheral neuropathies was observed in the comparison cohort.

Prior to the publication of the 3 large epidemiologic studies on neurologic disease among women with breast implants, the American Academy of Neurology[91] published a report which concluded that the existing case reports concerning allegations of neurologic symptoms were insufficient to establish a causal association with silicone, given the methodologically unsound nature of such reports. In 1998, in an editorial[92] accompanying the Swedish[88] and Danish[89] studies published in *Neurology*, Ferguson concluded that these studies "offer the best epidemiologic data to date of the lack of association between breast implants and neurologic disease."

In summary, 3 large, nationwide cohort studies with long-term follow-up have found no evidence of a causal association between silicone breast implants and neurologic disease. Any excesses of neurologic disorders observed among women with breast implants were similarly observed among comparison cohorts of women with breast reduction or other types of cosmetic surgery, indicating that women who undergo cosmetic surgery may have certain characteristics related to disease occurrence and diagnosis that differ from women in the general population. In short, there is no credible scientific evidence indicating that silicone gel–filled breast implants cause neurologic disease.

Implant Rupture

In 1999, the IOM defined silicone breast implant rupture as a breach of any size in the implant shell and reported that all silicone gel implants were susceptible to silicone bleed through the implant shell.[1] However, because the larger-weight molecules of the silicone gel cannot diffuse through the shell, gel does not appear outside the implant unless the shell has ruptured. Rupture has been suspected to occur as a result of biochemical degradation of silicone, physical trauma to the elastomer at the time of implantation, "fold-flaw" failures, or as a result of mechanical injury, eg, during mammograms, closed capsulotomies, or accidents.[93]

Intracapsular rupture, which is most commonly identified via MRI, represents a loss of integrity of the implant shell and is diagnosed when silicone gel is present outside the implant but within the intact fibrous capsule. Intracapsular rupture can go unrecognized as there may be no accompanying change in the configuration of the breast, no patient complaints, and no physical diagnostic finding. Leakage of gel outside the fibrous capsule surrounding an implant, or extracapsular rupture, is typically identified by MRI or at explantation surgery.

Estimates of breast implant rupture prevalence range widely from 0.3% to 77%, in part because the methods of estimating rupture prevalence rates differ among studies.[1,94–98] Determination of the frequency of gel migration is more difficult than ascertainment of rupture prevalence, unless there is implant retrieval (which is usually done in symptomatic women) and examination of explant and tissue.

The IOM concluded that quantitative data on rupture incidence over time were lacking for all breast implant types, including third-generation implants.[1] Several studies of silicone gel–filled breast implant rupture have been published since the IOM report, but only 1 of these has been a valid study of rupture incidence.[99]

Marotta et al[96] conducted a retrospective failure analysis for explanted silicone gel–filled breast implants (8000 explants from 35 studies) and found a statistically significant correlation between implant duration and elastomer shell failure (25% within 3.9 years and 71.6% at 18.9 years). An update of that analysis (9774 explanted implants from 42 studies) revealed 26% failure at 3.9 years, 47% at 10.3 years, and 69% at 17.8 years.[100] These percentages were arrived at by studying only women who elected to undergo explantation. Because women with severe enough complaints to undergo explantation likely have much higher rupture rates than asymptomatic women, the reported rupture rates overestimate the rupture rate for all women with implants, as asymptomatic women are not typically part of the studies. Marotta et al[96] found a general reduction in tensile strength, tear strength, and elongation of explanted silicone elastomer shells and concluded that their explant rupture data are representative of the implant aging properties and rupture characteristics of the general population of silicone gel–filled breast implants that remain implanted. The fact that prevalence of rupture increases over time is not surprising since prevalence is a cumulative measure at a given moment in time. This, however, does not imply that the *probability* of rupture during a specified time period (incidence) increases with increasing implant age, a conclusion that cannot be drawn from the selected cross-sectional data analyzed by Marotta et al. Finally, damage to implants during explantation can also lead to an overestimation of in vivo failure prevalence; in one report, as many as 24% of ruptures identified at time of explantation occurred as a direct result of the procedure to remove the implant.[101]

Brown et al[95] determined the prevalence of rupture diagnosed by MRI in a group of 344 women (687 implants) with breast implants. Overall, 265 (77%) of the women had at least 1 breast implant that was rated by radiologists as being

ruptured or indeterminate (55% of implants were ruptured, affecting 69% of women). The median implant age at rupture was estimated to be 10.8 years, and over 90% of the implants included in the study were the less durable second-generation implants. Extracapsular migration of gel was seen in 85 (12.4%) breasts in 73 (21.2%) of the women.

Kjoller et al[102] examined the occurrence and severity of recorded postoperative local complications, including rupture, in a group of 754 Danish women (1572 implants) who had undergone breast implantation. The average follow-up was 7 years, ranging from 0 to 23 years. Implant rupture was observed in 0.3% of breasts (0.5% of implantations) on average 1463 days (range, 900 to 2160 days) postoperatively. The rupture rate reflects the prevalence of symptomatic ruptures only as no attempt was made to identify silent ruptures (eg, by MRI).

In a study of implant rupture identified by MRI in a group of 271 Danish women (533 implants) who had received cosmetic breast implants, Holmich et al[97] found that 141 (26%) implants in 97 (36%) women were ruptured, with a median follow-up after implantation of 12 years (range, 3 to 25 years). Of the ruptures, 31 (22%) were extracapsular, affecting 23 women (8%) in the study group. Extracapsular rupture was significantly associated with a prior closed capsulotomy.

Handel et al[98] conducted a study of 1529 consecutive women who received 3494 implants (1137 saline-filled, 778 double lumen, 1537 silicone gel–filled, 38 other) for augmentation, reconstruction, or revision at a clinical practice between 1979 and 2004. Rupture diagnosis was based on clinical confirmation at the time of explantation and not on the basis of mammography, ultrasound, or MRI findings. After a mean follow-up of 37.4 months (range, 0–23.3 years), silicone implant ruptures occurred in 14 of 1123 smooth implants, 6 of 618 textured implants, and 8 of 568 polyurethane foam–covered implants, yielding crude prevalence rates of 1.2%, 1.0%, and 1.4%, respectively.

Finally, MRI rupture screening of 144 Swedish women with 286 fourth-generation cohesive silicone breast implants yielded a rupture prevalence of 0.3%-1.0% at an average of 6 years postimplantation.[103] In a recent multicenter European study, MRI examination of rupture in women with 199 third-generation silicone gel–filled breast implants with a median implantation time of almost 11 years revealed a rupture prevalence rate of 8%.[104]

It is difficult to compare the results of these cross-sectional rupture prevalence studies for several reasons. Studies often include women with first-, second-, and third-generation implants, saline and silicone implants, and implants made by different manufacturers. The study populations in many reports of rupture prevalence are likely biased in favor of higher rupture prevalence since many publications present rupture data for implants that had already been explanted because rupture was suspected. As a result, findings cannot be generalized to the universe of all women with breast implants. Moreover, studies present data on women with different follow-up periods, and determination of rupture has been based on different detection methods (eg, explantation, ultrasound, mammography, MRI, clinical survey results in patient cohorts), with varying sensitivity and specificity. As a result of this considerable heterogeneity, it is impossible to extrapolate from the available prevalence data and to assess the potential for rupture of third-generation, single-lumen, silicone gel–filled implants currently in use.

There has been only one published study to date that directly examined the incidence rate of breast implant rupture by repeated MRI.[99] In a follow-up to the rupture prevalence study[97] in which 271 Danish women had a baseline MRI in 1999, a repeat MRI was performed 2 years later. A rupture incidence analysis was performed based on 317 implants (in 186 women) that were intact at the baseline MRI (n = 280) or were intact at baseline but removed before the second MRI (n = 37). The authors found an overall incidence rate for definite ruptures of 5.3% per year. The rupture rate increased significantly with implant age. For third-generation implants (barrier-coated, low-bleed implants available since 1988), the rupture-free survival was estimated as 98% at 5 years and 83%-85% at 10 years.[99]

Implant age has been commonly noted in the literature as a determinant of rupture, with risk of implant rupture increasing with implant age.[99,105–107] Holmich et al[97] found that age of implant was significantly associated with rupture prevalence among second- and third-generation implants. However, the prevalence of rupture among first-generation implants, which had thick shells and highly viscous gel, was substantially lower than among thin-shelled second-generation implants, despite the longer implantation time, although this observation suffered from the small numbers of first-generation implants.

Only 1 prospective study to date has been conducted to address the possible health implications of ruptured, in situ silicone breast implants. In this unique study, Holmich and colleagues[108] examined the possible health implications, including changes over time in MRI findings, serological markers, or self-reported breast symptoms, of untreated silicone breast implant ruptures. Sixty-four women with implant rupture diagnosed by MRI were followed for 2 years, and a second MRI was performed. A control group of women with no evidence of rupture on either MRI was used for comparison. The majority of women had no visible MRI changes of their ruptured implants. Progression of silicone leakage (either herniation of silicone within the fibrous capsule, migration from the intracapsular space into the surrounding tissue, or progression of extracapsular silicone) was observed in 11 implants (11%) in 10 women; in most cases the changes were small. There was no increase in autoantibody levels and no increase in reported breast hardness. Women did report a significant increase in nonspecific breast changes compared with women in the control group. The authors concluded that, for most women, rupture is a harmless condition which does not appear to progress or to produce significant clinical symptoms. Based on their findings, they argue against routine explantation in asymptomatic women with ruptures. Instead, they recommend that these women be followed regularly by clinical examination. This advice has been advocated by others, such as Rohrich et al,[106] since rupture is not always or

necessarily associated with clinical symptoms and the long-term risk of untreated rupture has yet to be fully assessed.

Local Complications

Women with silicone gel–filled breast implants sometimes develop local and perioperative complications, including serious infections, severe or chronic breast pain, hematoma, and the need for additional surgery. Many of these postoperative complications are not unique to breast implantation but occur following various types of surgery in general.

The reported frequency of local complications among silicone breast implant patients ranges between 17% and 36%. This variability among studies likely reflects differences in patients' physical conditions and comorbidities, implant design, and surgical technique. Typically, the most frequent local complication is capsular contracture, while complications such as pain, hematoma, and wound infection are substantially less common.

Cohort studies conducted in Denmark,[102,109,110] Sweden,[111] and Finland[112] have investigated local complications among women with cosmetic breast implants. In the study by Kjoller et al,[102] of 754 Danish women who received cosmetic breast implants, 22.2% of implantations were followed by complications. Capsular contracture was the most common complication, occurring in 11.4% of implantations (7.9% of breasts), on average 621 days postoperatively. Other complications were rare; for instance, hematoma and infection occurred in 2.3% and 2.0% of implantations, respectively. Seroma was observed in 0.2% of all implantations. Additional hospitalizations were recorded as a result of complications in only 5.4% of implantations. In 89.1% of implantations, no additional surgery was required because of complications. Capsular contracture was the most frequent reason for additional surgery in women with breast implants.

A study by Henriksen et al[109] presented prospectively acquired data from the nationwide Danish Registry for Plastic Surgery of the Breast. The incidence and severity of short-term complications was examined in 1090 women with breast implants (2141 implants) between 1999 and 2002, with a mean follow-up of 15 months (range up to 23 months). After initial implantation, 19% of 971 women developed at least 1 adverse effect. Forty percent occurred within 3 months of implantation and 79% within 6 months. Infection, hematoma, seroma, wound rupture, and prolonged pain in the breast were all rare events, each occurring in less than 1% of implantations within the follow-up period. Capsular contracture grade II-IV occurred among 4.1% of women during the 2-year follow-up period after initial implantation. Overall, 97 (29%) of 344 adverse events among 55 (6%) of 971 women with initial breast implant surgery required surgical intervention. Compared with initial implantation, the frequency of most complications was slightly higher for subsequent implantations, largely due to higher rates of capsular contracture (5.0%), infection (3.4%), and hematoma (3.4%). Following subsequent implantation, 24% of 119 women developed at least 1 adverse event. These authors conclude that most short-term adverse effects following cosmetic breast augmentation are considered clinically insignificant and do not require treatment.

A more recent report from the Danish Implant Registry examined determinants of surgery-requiring complications and capsular contracture among 2277 women who underwent cosmetic breast implantation from 1999 through 2003.[110] Most implants (76%) contained soft silicone gel (third-generation implants), while 22% contained firm, cohesive gel (fourth-generation implants). During an average follow-up of 19.5 months (range, 3–50 months), 12% of implants (17% of women) had short-term complications, of which 136 (3.0%), corresponding to 4.3% of women, required surgical intervention. Capsular contracture grades III through IV was registered among 30 women, 9 of them bilaterally. The most frequent clinical indications for surgical intervention were asymmetry/malposition of implant (38% of surgeries) and capsular contracture grades III to IV (16%). Other less common implant-related complications requiring surgery included periprosthetic infection (1.5%) and breast pain (3.7%). Unsatisfactory cosmetic result was an indication for 51% of the 136 revision procedures.

Fryzek et al[111] analyzed local complications among 1280 Swedish women with cosmetic breast implants and a comparison cohort of 2211 women who had breast reduction surgery. Based on medical record review, they found that 69% of women with cosmetic breast implants had no local complications, while 31% had an implant change, implant leakage, or capsulotomy.

The occurrence of local complications was examined among 685 Finnish women with cosmetic breast implants, with a mean follow-up of 10.9 years (range up to 34 years).[112] Overall, 64% of women had no local complications diagnosed in their medical records. Again, the most common complication was capsular contracture, occurring in 17.7% of women and 15.4% of implants. Wound and skin problems, infection, and hematoma were diagnosed in 2.8%, 2.5%, and 1.8% of women, respectively. Seventy-four percent of women needed no postoperative treatment, while 22% required surgery after primary implantation.

There have been a few additional recent reports on the occurrence of specific local complications following breast implantation. Breiting et al[2] conducted a study of 190 Danish women with long-term cosmetic silicone breast implants compared with 186 women who had undergone breast reduction surgery. Eighteen percent of women with implants self-reported chronic breast pain compared with 8% among women with breast reduction. In their recent clinical practice–based study, Handel et al[98] reported that the rate of capsular contracture grade III or IV was 1.99 per 1000 patient-months after augmentation and 4.36 per 1000 patient-months after implant revision surgery. The frequency of hematoma and infection ranged between 1.5% and 2.1% following augmentation or revision surgery. For breast augmentation, 248 of 1601 (15.5%) implants required subsequent reoperation, while 21.9% of implants used for revision surgery required subsequent reoperation. The most common reason for reoperation was capsular contracture (56% of patients requiring additional surgery). Pittet et al[113] reported that the rate of infection after silicone gel–filled breast implantation is 2%–2.5%, and that two thirds of infections occur within the acute

postoperative period. The risk of infection was higher in women who had breast reconstruction after mastectomy and radiotherapy for cancer than in augmentation patients.

Thus, the epidemiologic evidence, largely deriving from several recent cohort studies conducted in Scandinavia, consistently demonstrates that the incidence of short- and long-term local complications following breast implantation is low and does not typically require additional surgery. Surgical intervention occurs most frequently as a result of capsular contracture.

Summary

The safety of silicone gel–filled breast implants has been studied extensively. Much of the epidemiologic evidence to date is drawn from large cohort studies with long-term follow-up, often longer than 3 decades. Based on our review of the published epidemiologic literature, through September 2007, on the safety of breast implants, we conclude that the weight of the epidemiologic evidence does not support a causal association between breast implants and breast or any other type of cancer, definite or atypical CTD, adverse offspring effects, or neurologic disease. Women with breast implants do not present with more advanced stages of breast cancer or suffer from impaired survival after breast cancer diagnosis. Future studies are needed to determine whether the consistently observed excess risk of suicide among women with implants reflects underlying psychiatric illness that is present prior to breast augmentation surgery or develops postimplantation.

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