

Breast cancer following augmentation mammoplasty (United States)

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Abstract

Objective: Although clinical reports have raised concern that breast implants may either increase the risk of breast cancer or delay its diagnosis, epidemiologic studies have generally shown implant recipients to be at a reduced risk of subsequent breast cancer. A large retrospective cohort study was undertaken to clarify effects of cosmetic breast implantation.

Methods: Medical records of 13,488 women receiving cosmetic implants at 18 plastic surgery practices and a group of 3936 patients who received other types of plastic surgery at the same practices were reviewed and information abstracted. Questionnaires were sent to all subjects located as alive, with 71% being completed. Attempts were made to obtain medical verification for all reported cancers and to obtain death certificates for deceased subjects.

Results: A total of 136 breast cancers were observed among the breast implant patients. External analyses, using general population rates from the Surveillance, Epidemiology and End Results (SEER) program, resulted in 152.2 cases expected and a standardized incidence ratio (SIR) of 0.9 (95% CI 0.8–1.1). A comparable SIR was found for the other plastic surgery patients (SIR = 1.0, 95% CI 0.7–1.2). Internal analyses, directly comparing the implant patients with the other plastic surgery patients, showed a RR of 0.8 (95% CI 0.6–1.1). In neither the external nor internal analyses was there any systematic variation in risk by age or calendar year of initial implant. Risk also did not vary by years of follow-up or by type of implant. Risk was not affected by exclusion of patients who received their implants following surgery for benign breast disease. Although breast tumors tended to be detected at a somewhat later stage among the breast implant than the comparison patients, the difference was not statistically significant, nor was there any significant difference in breast cancer mortality between the two groups.

Conclusions: Breast implants do not appear to alter the risk of subsequent breast cancer.

Introduction

Silicone breast implants, first marketed in the United States in 1962, became widely sold during the next three decades, with estimates that between 800,000 and 1 million women received the devices [1, 2]. Early reports of breast cancer occurring among women whose breasts had been injected with free silicone raised concern about a possible link with the disease [3–6]. A number of clinical studies also reported the occurrence of breast cancers among women with silicone breast implants [4, 7–11], although the absence of appropriate comparison

groups prevented any etiologic inferences. Questions have also been raised regarding whether silicone breast implants might affect the prognosis of breast cancer, given studies showing that radiologically opaque silicone may interfere with complete imaging of the breast [12–15].

A number of cohort [16–20] as well as case-control investigations [21–23] have assessed the relationship of breast implants to subsequent breast cancer risk. With one exception [19], all have shown breast cancer incidence to be *reduced* among women with implants as compared to either the general population or women

without implants. In several of these investigations the magnitude of reduced risk was relatively large, on the order of 50–60%. However, these studies generally did not have detailed information on patient characteristics that could affect disease status – of importance since women with implants have been shown to differ substantially from others on a variety of lifestyle factors [24].

To clarify the relationship of breast implants to subsequent breast cancer, as well as other cancers, we undertook a large retrospective cohort study that involved detailed abstraction of medical records and administration of questionnaires to study subjects to obtain information on health status as well as lifestyle factors. We report here the results pertaining to breast cancer risk.

Materials and methods

This retrospective cohort study identified patients from 18 plastic surgery practices in six geographic areas (Atlanta, GA; Birmingham, AL; Charlotte, NC; Miami and Orlando, FL; and Washington, DC). These practices were chosen on the basis of having performed large numbers of cosmetic breast implant surgeries prior to 1989 and willingness to give us unrestricted access to their records for purposes of subject identification and medical record abstraction. In order to maximize opportunities for assessing long-term effects, all female subjects who had a first bilateral augmentation mammoplasty at these practices prior to 1989 were eligible for study inclusion. Since a determination of the development of breast cancer was a primary goal of the study, patients receiving a breast implant following a diagnosis of breast cancer were not included. A total of 13,488 subjects, composed of all augmentation mammoplasty patients at each practice meeting eligibility criteria, were identified for study. In addition, attempts were made, after identification of approximately every third to fourth eligible breast implant patient, to identify a similarly-aged comparison subject who had some other type of plastic surgery (not involving silicone) during the same time period in all but one practice (where permission for access to records of such patients was not obtained). A total of 3936 comparison subjects were identified for study. Some patients had more than one operation. Prioritizing operations according to the following categories showed that 20.5% had abdominoplasty or liposuction; 34.2% blepharoplasty or rhytidectomy (operations for removal of wrinkles of the face and neck); 28.1% rhinoplasty, otoplasty, mentoplasty or genioplasty (operations involving the nose, ear or chin); and 17.2% other types of plastic surgery.

Trained medical records abstractors reviewed medical charts for eligibility. Using standardized software, data were directly entered into laptop computers. This included patient identifiers as well as details on the types of surgery obtained (including implant type, manufacturer, catalog number), any noted complications, and other factors that might affect health status (*e.g.* weight).

Vital status as well as location information was sought through a variety of tracing sources, including telephone directories, credit bureaus, motor vehicle administration records, postmasters, and the National Death Index. A total of 10,778 (79.9%) of the implant patients and 3214 (81.7%) of the comparison subjects were successfully traced, with 364 subjects identified as deceased (245 implant patients, 119 controls) (Table 1). Location rates varied by plastic surgery practice as well as by age, year of initial implant, and race, with the highest rates achieved for subjects who were white, were older at their initial surgery, or had more recent dates of surgery. In order to identify causes of death, copies of death certificates were sought and successfully obtained for 91.4% for the implant and 95.8% of the comparison patients. Questionnaires were mailed to all alive, located subjects to obtain information on demographic factors, subsequent plastic surgeries, updated health status, and lifestyle factors that could affect health. Lifestyle factors included menstrual, pregnancy and breastfeeding history; use of exogenous hormones; anthropometric factors; cigarette smoking; alcohol consumption; and breast screening history. Non-respondents to several mailings were telephoned and given the opportunity to complete their interviews by telephone. Completed questionnaires were obtained from 7447 (70.7%) of the implant patients from whom this information was sought, and from 2203 of the comparison subjects (71.2%) (Table 1). As with location rates, questionnaire response rates varied by a number of other factors, being highest for white patients and those who received their implants at older ages or in later time periods.

Table 1. Status of patients identified as eligible for study

	Breast implant patients	Other plastic surgery patients
Eligible patients (received cosmetic surgery between 1962 and 1988)	13,488	3936
Traced	10,533 alive; 245 dead	3095 alive; 119 dead
Completed questionnaires	7447	2203
Identified breast cancers	116 alive; 20 dead	52 alive; 8 dead

Cancer events were defined on the basis of information contained in either completed questionnaires or obtained death certificates. Attempts were made to confirm all cancers reported in the questionnaires by obtaining medical verification (discharge summaries, operative reports, pathology reports) from the institutions where the diseases had been diagnosed and/or treated. Since the events occurred over a wide period of time, some of the requested records were no longer available. It was not possible to further validate deaths from breast cancer since contact with individuals other than patients was not attempted.

Statistical methods

Person-years were accrued beginning 1 year after the date of initial plastic surgery and continuing through the earliest of date of cancer occurrence or death, or date last known alive and free of cancer. For the incidence analyses, 12 breast cancer cases (seven among implant patients) that were detected during the first year of follow-up were excluded. Death certificates which noted cancer as a cause of death were searched for information on the duration of the disease, to more precisely define a diagnostic date; 31 December 1996 defined the end of the study period. Non-located subjects as well as living located subjects who did not complete a questionnaire did not contribute person-years or events to the analysis of cancer incidence.

Two statistical approaches were used to analyze the cohort data. A standardized incidence ratio (SIR) was computed as the number of observed breast cancer events divided by the expected number of events based on age, race and calendar year-specific incidence disease rates for females from cancer registry rates available through the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI) [25]. The majority of analyses used rates derived from the Atlanta SEER area, given that the practices from which patients were derived were all located in the southeastern part of the US. A SIR greater than one indicates the breast cancer rate in the study group exceeds that expected in the SEER area, while a SIR less than one indicates a deficit in the breast cancer rate in the study population compared to that expected. We also computed asymptotic 95% confidence intervals (CI) for the SIRs. Comparisons of SIRs across categories of other factors, such as age at risk, calendar year and type of breast implant, were based on a test of homogeneity, with a significant p -value ($p < 0.05$) indicating the differences among SIRs were not likely to be due to chance alone [25].

We also conducted extensive internal analyses based on the relative risk (RR) of breast cancer in the breast implant patients compared to that in the other plastic surgery patients [25]. Poisson regression methods, as implemented in the AMFIT module in the Epicure analysis package [26], were used to calculate RRs and compute 95% CIs. For all analyses the RR of implant status was adjusted for age at risk (5-year intervals through age 85), calendar year of follow-up (1960–1964, ..., 1990–1994, 1995–1996), and race (white or black). Other factors, such as age at surgery, year of surgery, time since surgery or specific predictors of breast cancer risk, were included in the regression models, as necessary, to evaluate their roles as potential confounding factors or to examine variations of the RR. Breast cancer risk factor information was derived from questionnaires, if available, or from information abstracted from the medical records of the plastic surgeons.

Standardized mortality ratios (SMRs) were also calculated, using US mortality rates to generate expected values. For this analysis, subjects who were located but did not respond to the questionnaire were assumed alive at the end of follow-up and their person-years accrued up to this time.

Results

Table 2 shows descriptive characteristics of the implant and comparison patients. Implant patients were somewhat younger than the comparison subjects at the time of study entry (34.8 vs. 42.0 years). This was primarily due to a preponderance in the comparison group of women who had undergone abdominoplasties, liposuction, blepharoplasties or rhytidectomies at older ages. The remaining comparison subjects (those with facial and other types of surgery) had a comparable mean age at operation as the breast implant patients. The mean year of initial surgery was similar for the implant and comparison subjects. The average length of follow-up was 12.9 years among the implant patients versus 11.6 years among the comparison patients. The maximum lengths of follow-up were 30.6 and 29.0 years, respectively, among the implant and comparison patients.

Validation of reported events

Twenty-three of the implant patients versus eight of the comparison patients died with breast cancer. Two of the implant patients completed questionnaires indicating the development of breast cancer prior to their deaths, while one implant patient developed breast cancer

Table 2. Descriptive information regarding breast implant and other plastic surgery patients

Age at entry or breast cancer	Breast implant patients (n = 13,488)		Other patients (n = 3936)	
	At entry	At breast cancer	At entry	At breast cancer
< 30	5028	1	871	1
30-34	3683	5	514	1
35-39	2496	14	554	3
40-44	1282	27	595	4
45-49	638	37	582	11
50-54	241	28	512	10
≥55	94	24	306	30
Unknown	26		2	
Mean ages	34.8	48.0	42.0	54.6
<i>Additional characteristics of study cohort</i>				
Person-years of follow-up	96,675		26,151	
Mean year of study entry	1982.9		1984.1	
Mean years of follow-up	12.9		11.6	
Mean year at cancer development	1990.5		1991.0	

within 1 year of her implant surgery. Thus, 20 implant and eight comparison patients were identified for the incidence analyses on the basis of death certificates. In addition, 116 implant patients and 52 of the comparison patients reported breast cancers on their questionnaires. Medical records from diagnosing and/or treating physicians (including pathology and operative reports) were obtained for 67.2% and 69.2%, respectively, of the breast cancers reported by the implant and comparison patients. All of the records confirmed reported events as breast cancers.

Analyses based on external rates

For initial analyses comparing breast cancers (invasive and *in situ*) among cohort members to Atlanta SEER rates, we observed SIRs of 0.89 (95% CI 0.8-1.1) (136 observed cases versus 152.2 expected) for implant patients and 0.96 (95% CI 0.7-1.2) for the comparison group (60 observed cases versus 62.7 expected). SIRs using incidence rates from all SEER areas were similar to those derived using only Atlanta rates (SIR for breast implant patients = 0.96, 95% CI 0.8-1.1).

Breast cancer risks were examined further according to duration of follow-up and age and calendar year in which implants were first received (Table 3). A slight decrease in risk during the initial 10-year period

Table 3. Standardized incidence ratios (SIR) of breast cancer for breast implant patients (n = 13,488) according to duration of follow-up and age and calendar year of initial implant; comparison based on Atlanta SEER rates, 1973-1995

	Breast cancers		SIR ^a	95% CI
	Observed	Expected		
Years of follow-up				
< 5	19	26.92	0.71	0.4-1.1
5-9	40	49.38	0.81	0.6-1.1
10-14	46	45.14	1.02	0.8-1.4
15+	31	30.76	1.01	0.7-1.4
Age of initial implant (years)				
< 30	16	21.79	0.73	0.4-1.2
30-34	37	36.84	1.00	0.7-1.4
35-39	45	39.42	1.14	0.8-1.5
40+	38	54.15	0.70	0.5-0.9
Calendar year of initial implant				
< 1975	16	21.31	0.75	0.5-1.2
1975-1979	63	56.83	1.11	0.9-1.4
1980-1984	47	50.18	0.94	0.7-1.2
1985-1988	10	23.88	0.42	0.2-0.8

^a SIRs adjusted for age at risk, calendar year of follow-up, and race.

(SIRs = 0.71-0.81) did not persist with increasing follow-up time, with the remaining subjects showing no substantial alteration in risk. There were no distinctive trends in risk by either age or calendar year, and tests for homogeneity of SIRs were non-significant. However, subjects who received their implants during the most recent calendar time period (1985-1988) were at a significantly reduced risk (SIR = 0.42, 95% CI 0.2-0.8). Risks were also examined according to cross-classifications of the timing parameters, which did not reveal any distinctive patterns. For instance, among subjects who had their implants inserted prior to 1980, the risks were 0.72 and 1.13, respectively, for patients with < 10 and 10+ years of follow-up. SIRs were also examined among implant patients according to age at which the breast cancers developed, being similar for cancers that developed prior to and after 50 years of age (respective SIRs of 0.90 and 0.88).

A total of 6.7% of the implant patients considered in the analyses had notations in their plastic surgery records that they had received their implants in conjunction with surgery for fibrocystic disease, while 0.5% had notations that implants were received following a mastectomy for benign disease. Removal of these patients from analysis had minimal impact on the observed breast cancer risk (SIR = 0.93, 95% CI 0.8-1.1).

A total of 49.7% of the patients received silicone gel implants, 34.1% double-lumen implants, 12.2% saline-filled implants, 0.1% other types of implants, and 3.8% unspecified types of implants. Risks did not vary

substantially by the type of implant, the SIRs being 0.95 for silicone gel implants, 0.72 for double-lumen implants, 1.21 for saline-filled implants, and 0.83 for unspecified types of implants (no cases of breast cancer occurred among subjects with other types of implants). None of these estimates was statistically significantly different from the others or from 1.0. Attempts were also made to evaluate whether risk was affected by the type of implant cover, with a specific interest in polyurethane-foam-coated implants, which have been found to leak chemicals shown to be carcinogenic in laboratory animals [27]. However, only 1.3% of the implants were found to have such covers. Among women with these implants, four cancers were noted, two of which were breast cancers (SIR = 1.99, 95% CI 0.5–8.0).

To address potential reporting or selection biases, we performed several analyses focusing on practices with differential location or questionnaire response rates, as well as on whether events occurred prior to or after 1992, the date when publicity regarding potential adverse effects of breast implants became widespread. When analyses grouped practices according to their combined location and response rates, the SIRs ranged from 1.11 for the practices with the lowest rates (questionnaire response rate of < 52% among all eligible study subjects) to 0.90 for those with intermediate rates (52–59%) to 0.81 for those with the highest rates (62–75%). A test for homogeneity of these SIRs was non-significant. SIRs for practices grouped by either location or response rates showed no further distinction. In addition, breast cancer risk was examined for the subgroup for whom there was the greatest success in obtaining questionnaires (70% questionnaire response rate among eligibles), namely white subjects who obtained their surgery at 40 years of age or older during calendar years 1982 or later; the breast cancer SIR among these subjects was 0.61 (95% CI 0.4–1.0). The SIRs were also not substantially different by whether breast cancers were diagnosed prior to or after 1992.

Analyses based on internal comparisons

The relative risk of breast cancer derived when implant patients were compared with the patients with other types of plastic surgery was 0.79 (95% CI 0.6–1.1). Similar to the SIRs, there were no significant trends by either duration of follow-up, or age or year of initial implantation (Table 4). However, reductions in risk were seen for women who had their implants inserted while young (< 30 years of age), or who received them in either early (prior to 1975) or late (after 1984) time periods; this latter risk was statistically significant

Table 4. Relative risks (RR) of breast cancer for breast implant patients (n = 13,488) according to duration of follow-up and age and calendar year of initial implant, comparison based on internally derived rates from the other plastic surgery patients (n = 3936)

	Breast cancers		RR ^a	95% CI
	Implant patients	Other patients		
Years of follow-up				
< 5	19	13	0.76	0.3–1.7
5–9	40	17	0.85	0.4–1.6
10–14	46	17	0.91	0.5–1.7
15+	31	13	0.48	0.2–0.9
Age of initial implant (years)				
< 30	16	4	0.42	0.1–1.3
30–34	37	5	0.83	0.3–2.1
35–39	45	10	0.83	0.4–1.7
40+	38	41	0.86	0.6–1.4
Calendar year of initial implant				
< 1975	16	5	0.51	0.2–1.7
1975–1979	63	21	0.82	0.5–1.4
1980–1984	47	17	1.17	0.6–2.2
1985–1988	10	17	0.36	0.2–0.8

^a RRs adjusted for age at risk, calendar year of follow-up, and race.

(RR = 0.36, 95% CI 0.2–0.8). Patients with 15 or more years of follow-up since initial implantation were also at reduced risk (RR = 0.48, 95% CI 0.2–0.9).

Comparisons with specific subgroups of the other plastic surgery patients showed RRs of 0.94 (95% CI 0.5–1.8) based on the abdominoplasty/liposuction controls, 0.83 (0.5–1.3) based on the blepharoplasty/rhytidectomy controls, and 0.63 (0.4–1.0) based on the other controls.

Assessment of confounding and interactive effects

Among the breast implant patients it was possible to evaluate breast cancer risk by pre-implantation breast size. There was no significant variation across different chest sizes, with the SIRs being 0.72, 0.96 and 0.72 for bra sizes of < 33, 33–34 and 35+, respectively. Breast cancer SIRs also did not vary by cup size, being 0.84 for subjects with A cups and 0.87 for those with B cups. A non-significant reduction in risk was observed for those with C or larger cup sizes (SIR = 0.48, 95% CI 0.2–1.1), although this estimate was based on only six observed breast cancers.

Factors which appeared to increase breast cancer risk among the breast implant patients were higher education, nulliparity or a late age at first birth, large body sizes, and a family history of breast cancer in a first-degree relative (data not shown). Given differing characteristics of the implant and comparison patients [28] (with the implant patients more likely to have less years

of education, have earlier ages at first birth, and be thinner), we adjusted the RR associated with breast implants for these factors. However, the RR estimates were not substantially changed by adjustment for any of the factors. The adjusted estimates ranged from a low of 0.68 (after adjustment for income) to a high of 0.83 (after adjustment for either education or body mass index).

Internal analyses also considered whether breast cancer risk related to implants differed within subgroups defined by a variety of established breast cancer risk factors (Table 5). Breast cancer risks did not vary in any systematic way by these factors, including years of education, household income, age at first birth, family history of breast cancer, body size, alcohol consumption, or use of exogenous hormones.

Stage of disease at diagnosis and mortality analyses

Among the breast cancer cases for which medical records were obtained, the stage distribution at diagno-

sis was as follows: *in-situ* cancers (15.4% of implant patients versus 27.8% of comparison patients), local disease (41.0% vs. 52.8%), distant or regional (34.6% versus 16.7%), unknown stage (9.0% versus 2.8%) (Table 6). Although these differences were not statistically significant, they persisted after adjustment for other factors, including those related to access to medical care.

A total of 23 implant patients died with breast cancer, vs. 37.9 expected, resulting in a SMR of 0.61 (95% CI 0.4–0.9). This was somewhat higher than the SMR observed for the patients with other types of plastic surgery, based on eight deaths (SMR = 0.45, 95% CI 0.2–0.9). The mortality ratio of the breast implant patients compared with the other patients was 1.15 (95% CI 0.5–2.8). When compared to the general population, the risks among the implant patients would be expected to be low since patients with historical or pre-existing breast cancer at the time of implantation were not included in the cohort (*i.e.* prevalent cases of breast cancer were excluded). Since the artifact should be most apparent early in the follow-up, risks were investigated by duration of follow-up. Risks among the implant patients increased with follow-up time to a SMR of 1.04 (95% CI 0.6–1.9) after 15 years of follow-up (based on 10 deaths). Among the comparison patients, the SMR after extended follow-up was 0.74 (0.2–2.9) (based on two deaths).

Discussion

Although several studies have noted that women with breast implants are at a reduced risk of subsequent breast cancer [16–18, 20], we found no substantial alteration in risk, in agreement with a recent study on the issue [19]. Based on standardized population rates we found breast implant recipients to have a SIR of 0.89, a risk comparable to that obtained when these

Table 5. Relative risks (RR) of breast cancer associated with breast implants by selected breast cancer risk factors

Breast cancer risk factors ^a	No. of breast cancers among implant patients	RR ^b	95% CI
Years of education			
High School or less	23	0.66	0.3–1.4
Some college	49	1.05	0.6–1.9
College graduate or beyond	44	0.76	0.4–1.3
Household income (\$1000)			
< 35	23	0.53	0.3–1.0
35–69	26	0.72	0.4–1.4
70+	46	0.77	0.4–1.4
Age at first birth (years)			
< 20	20	1.26	0.4–3.7
20–24	43	0.86	0.5–1.5
25–29	24	0.87	0.4–1.9
30+	9	0.76	0.2–2.5
Nulliparous	14	0.48	0.2–1.1
Family history of breast cancer in first-degree relative			
No	113	0.78	0.5–1.1
Yes	23	1.06	0.5–2.4
Body mass index			
< 20.5	31	0.76	0.4–1.6
20.5–22.4	37	0.61	0.3–1.1
22.5–24.4	32	1.38	0.6–3.0
24.5+	30	0.85	0.5–1.6
Alcohol use			
No	21	0.76	0.3–1.7
Yes	85	0.75	0.5–1.1

^a The inconsistency in numbers of cases was due to information being unavailable from either questionnaires or the medical records of the plastic surgeons. No information on either income or alcohol usage was abstracted from the medical records.

^b RRs adjusted for age at risk, calendar year of follow-up, and race.

Table 6. Stage distribution of the observed breast cancer patients by implant status^a

Stage of disease at diagnosis	Implant patients		Comparison patients	
	No.	Percentage	No.	Percentage
<i>In-situ</i>	12	15.4	10	27.8
Local	32	41.0	19	52.8
Distant or regional	27	34.6	6	16.7
Unknown	7	9.0	1	2.8

^a Pertains only to those subjects for whom medical verification of reported breast cancers was obtained (78 implant versus 36 comparison patients).

patients were contrasted to a group of women with other types of plastic surgery (RR = 0.79 based on internal analysis).

By virtue of the size of our study, and length of follow-up, we had the advantage over previous studies in being able to evaluate a number of time-related parameters, including effects by duration of follow-up and age and calendar year of implantation. The external analyses showed a slight decrease in breast cancer risk in the period immediately following implantation, an effect that would have been even stronger had we included the first year following implantation in our analyses. This would be consistent with women considering the operation having received intensive pre-implantation screening for potential breast problems. There were no consistent trends across any of the time-related variables examined, including age and calendar year of initial implantation or duration or follow-up. The failure to detect trends by calendar year of implantation is noteworthy given changing "generations" of implants over time, with those implanted prior to 1975 associated with thicker gel and less likely to break or leak. Implants used after 1984 were also thicker and generally "low bleed", although to a lesser extent than those used prior to 1975.

The studies that have suggested that breast implants lead to a reduction in breast cancer have all used general population rates to derive expected values. In our attempts to reconcile our findings with those of others, we sought to confirm that our estimates were not biased by the inclusion in our implant series of a considerable number of women who had mastectomies for benign breast disease, a condition associated in many studies with an increase in subsequent breast cancer risk [29]. Exclusion of these women failed to alter substantially the previously observed breast cancer risk associated with breast implants. Had we restricted our series to women with relatively short follow-up (< 10 years), we might have concluded that implants are associated with a slightly beneficial effect on risk. The previous studies have for the most part had limited follow-up, which may contribute to the differences in conclusions derived.

The reduced risk of breast cancer observed in some investigations has been proposed as possibly reflective of a biologic effect, mediated through either interference with blood supply, a compressive effect on surrounding breast tissue, or advantageous immunologic factors [18, 21]. However, it has also been recognized that unique characteristics of the breast implant patients could predispose to a low risk of breast cancer. In particular, it has been suggested [30] that the smaller breasts, thinness or early ages at first birth of breast implant patients could explain their low breast cancer risks. The relationship of breast size to breast cancer risk is

complex [31], and may depend more on glandular size than on total breast mass [32]. Given some evidence that women with smaller breasts experience a reduction in breast cancer risk [33], we attempted to determine whether breast size affected our observed relationship. However, we failed to find any difference in breast cancer risk according to breast size, as measured by either chest or cup sizes. It is of interest that when we adjusted in our internal analyses for either body size or education, we did note a slight increase in the risks associated with breast implants. Thus, it may be that part of the reduced breast cancer risk previously noted for breast implant patients may also be due to unique characteristics of the patients, including body size and socioeconomic background.

In addition to concerns about whether breast implants affect the incidence of breast cancer, there have also been suggestions that breast implants might result in a poor prognosis, especially if mammographic interference by breast implants leads to tumors being detected at late stages. A number of previous epidemiologic studies have failed to find that women with augmented breasts have unusually late detection of tumors [18, 21, 34, 35] or poorer survival [35, 36] as compared to the general population. However, in our study there was some indication of a shift toward later detection of breast cancers among the implant as compared to the other plastic surgery patients, although the differences were not statistically significant. The rarer detection of *in-situ* tumors among implant patients is consistent with at least one previous investigation in which comparisons were made with the general population [21]. Some of the shift toward later detection of breast cancers in our study may have resulted from pre-implantation screening, although it is of note that the deficit of *in-situ* breast cancers persisted over time. Breast cancer mortality was not significantly different between the implant and comparison patients, a finding consistent with the one other epidemiologic investigation in which this issue was examined [20]. Our findings, however, may have been influenced by the tendency of breast implant patients to be thin [28], which has been found to impart a beneficial effect on breast cancer mortality [37, 38]. Thus, continued surveillance of mortality risk among implant patients appears warranted, particularly given the observed stage at diagnosis differences between the implant and comparison patients.

Some limitations of our study warrant attention. Our location, response and validation rates were less than we had desired. Thus, a number of systematic and subject-related opportunities for bias must be considered. Searches through the National Death Index enabled a substantial opportunity for identifying deaths among

subjects whose records contained extensive identifiers. Deceased subjects will obviously include a disproportionate number of individuals with breast cancer compared with the cohort as a whole. Thus, including in the incidence analysis cases identified via a death search, but excluding the person-years of follow-up of all who declined to respond, could lead to an overestimate of the SIR. Conversely, subjects who were untraceable and for whom extensive identifiers were not available undoubtedly included a disproportionate number who were untraceable because they had died. Exclusion of these deaths could have led to an underestimate of the SIR. Additionally, for 30% of breast cancers in the analysis, medical records were unavailable. If any of these reports were actually not breast cancer, then the SIR could have been overestimated. Since the available medical records confirmed all self-reports of breast cancer, we feel that the likelihood of this latter bias is small. Each of these biases is also likely to have operated equally among the comparison and implant patients. Thus, it would seem prudent to pay particular attention to results of the SIR analysis that are similar to those obtained from internal comparison of risks in the study groups. Fortunately, these two analyses yielded similar conclusions for virtually every consequential result.

In studies of health outcomes in implant patients there has also been substantial concern over the possibility of differential reporting between implant and comparison patients. Much of this is based on the widespread publicity and legal actions surrounding the issues. We tried to assess the likelihood of any such biases through several analyses, including comparison of results in higher versus lower responding groups defined by medical practice and demographic characteristics, and by whether breast cancer occurred before or after the early 1990s, when the adverse publicity and legal actions dramatically increased. These analyses did not raise any hints of underlying bias. At best, however, these are imperfect solutions. While the overall cooperation rates for the implant and comparison groups are the same, the reasons for compliance could be different. In addition, the various subtle and not so subtle opportunities for bias in such a highly polarized and controversial area could interact in ways that are beyond our abilities to address. If such complex biases exist, we do feel that their impact will vary by outcome. While cancer in relation to silicone exposure has been of scientific interest, it has received little attention in the public, regulatory, and judicial controversies that have occurred. For this reason, we suspect that the lack of any apparent evidence of bias in our attempts to assess it indicates that, at least for breast cancer, important consequences are unlikely.

In summary, our findings do not support clinical reports that breast implants might lead to an enhanced risk of breast cancer. Our findings also did not provide support to epidemiologic findings of a decreased risk of breast cancer among patients with breast implants. It appears likely that previously reduced risks were reflective of either pre-implantation screening biases or favorable breast cancer risk characteristics of implant patients, rather than an effect of the implants. Although our findings were reassuring regarding whether breast implants affect the incidence of subsequent breast cancer, further attention should be focused on their effects on stage at diagnosis.

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