ELSEVIER

Cancer Risk at Sites Other than the Breast Following Augmentation Mammoplasty

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PURPOSE: There has been limited investigation of cancer risk other than breast cancer among patients with breast implants, despite some clinical and laboratory evidence suggesting links with certain cancer sites, including hematopoietic and connective tissue malignancies.
METHODS: A retrospective cohort study of 13,488 patients who received cosmetic breast implants at 18 plastic surgery practices in six geographic areas was conducted to assess long-term health effects. After an average of 12 years of follow-up, questionnaires were administered to subjects located and alive (78% of eligible population). Attempts were made to obtain death certificates for deceased subjects and medical verification for all reported cancers. Expected numbers of cancers were derived using general population cancer incidence rates and an internal comparison series of 3936 patients who received other types of plastic surgery at the same practices as the implant patients.
RESULTS: A total of 359 malignancies was observed versus 295.95 expected based on general population rates, resulting in a standardized incidence ratio (SIR) of 1.21 [95% confidence interval (CI) 1.1–1.4]. Individual malignancies for which incidence was significantly elevated included cancers of the stomach (SIR = 2.65), cervix (SIR = 3.18), vulva (SIR = 2.51), brain (SIR = 2.16), and leukemia (SIR = 2.19). No excess risks were observed for other hematopoietic malignancies, including multiple myeloma. The internal analyses, however, based on cancer rates derived among the comparison patients, showed no increased cancer risk among the implant patients [relative risk (RR) = 1.00, 95% CI 0.8–1.2], as well as no statistically significant elevations for most individual sites. Cervical cancer continued to be elevated (RR = 1.78), although to a lesser extent than in the external analyses, while the risk for respiratory cancers was higher (RR = 2.40). Non-significant elevations in risk persisted in this analysis for liver cancer (RR = 2.65), brain cancer (RR = 2.83), and leukemia (RR = 1.83). Many of the cancers showing excesses were defined on the basis of death certificates, requiring caution in interpretation. The histologies of the leukemias were quite varied, which makes a biologic relationship appear unlikely. However, respiratory cancers showed some evidence of increasing risk with follow-up time and both respiratory and brain cancers were elevated in the mortality analyses.
CONCLUSIONS: Although excesses of cervical and vulvar cancer among implant patients might be attributable to lifestyle factors, reasons for excesses of respiratory and brain cancers were less apparent.
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KEY WORDS: Breast Implants, Cancer, Incidence, Epidemiology.

INTRODUCTION

Silicone breast implants were first introduced in the United States in the early 1960s and became widely sold during the next three decades. Although it has been estimated that between 800,000 and one million women received the devices (1, 2), there has been limited assessment of their long-term effects. Most attention has focused on connective tissue disorders, but the range of immunologic disturbances observed in women with implants suggests consideration of other chronic diseases, including cancer. The greatest attention regarding cancer risk has focused on breast cancer, given clinical reports of an association (3–8) and observations that mammographic visualization is compromised by implants (9–12). Some (13–18), although not all (19–20), epidemiologic studies have suggested that breast cancer risk might be reduced among women with implants, although the biologic mechanism remains undefined.

Other cancers have not been well evaluated, despite some animal as well as clinical data to suggest potential risks for selected sites, including sarcomas and certain hematopoietic malignancies (21, 22). There have only been limited attempts to address the relationships epidemiologically, and the available studies suffer from small numbers of events and absence of information on most potential confounding

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Selected Abbreviations and Acronyms

SIR = standardized incidence ratio
RR = relative risk
SEER = Surveillance Epidemiology and End Results
SMR = Standardized mortality ratio
CI = confidence intervals

variables (17, 19, 23). In particular, the absence of information on lifestyle factors that may contribute to cancer risk (e.g., socioeconomic status, sexual and reproductive behavior, cigarette smoking) complicates interpretation of findings from these studies, particularly observed excesses of cancers of the cervix, lung, and vulva (17, 23).

We undertook a large retrospective study to assess the potential long-term effects of breast implants. This study had an advantage over other studies in being specifically designed to address this issue, having large numbers of study subjects, extended follow-up, information on types of implants (as obtained through medical record abstraction), and information on other factors that could influence a woman's risk of subsequent disease (as obtained through detailed questionnaires administered to study subjects). Separate analyses have concentrated on breast cancer risk in this population, showing no significant association with breast implants (20). We address here risks for developing other cancers.

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 was 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 the study. Some subjects had multiple procedures. Prioritizing operations according to the following categories showed that 20.5% had abdominoplasty or liposuction; 34.2% blepharoplasty or rhytidectomy (operations for the removal of wrinkles of the face and neck); 28.1% rhinoplasty, otoplasty, mentoplasty, or genioplasty (operations involving the nose, ear, and chin); and 17.2% another type of plastic surgery.

Trained medical records abstractors reviewed the 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, catalogue number), any noted complications, and other factors which 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, postmasters, motor vehicle administration records, 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 identified as deceased (245 implant patients, 119 controls). 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 older at their initial surgery, those with more recent dates of surgery, and white patients. In order to identify causes of death, copies of death certificates were sought and obtained for 91.4% of the implant and for 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 reproductive and lifestyle factors that could affect health.

Reproductive and 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 questionnaires by telephone. Completed questionnaires were obtained from 7447 (70.7%) of the implant patients from whom this information was sought, and from 2203 (71.2%) of the comparison subjects. As with location rates, questionnaire response rates varied by a number of factors, being highest for white patients and those who received their implants at older ages or in later time periods.

Cancer events were defined on the basis of information in either completed questionnaires or obtained death certificates. 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. 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.

Statistical Methods

Person years were accrued beginning one year after the date of initial plastic surgery and continuing through the earliest date of cancer occurrence or death, or date last known alive and free of cancer. For the incidence analysis, 35 cancers (28 among implant patients) that were detected during the first year following surgery were excluded. December 31, 1996 defined the end of the study period. Non-located subjects as well as those not responding to the questionnaire did not contribute person-years or events to the cancer incidence analysis.

Two statistical approaches were used to analyze the incidence data. A standardized incidence ratio (SIR) (24) was computed as the number of observed 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 NCI. 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 U.S. A SIR greater than 1 indicates that the disease rate in the study group exceeds that expected in the SEER area, whereas a SIR less than 1 indicates a deficit in the disease rate in the study population compared to what is 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 that differences among SIRs were not likely due to chance alone (24).

We also conducted extensive internal analyses, based on the relative risk (RR), of cancer in the breast implant patients compared to that of the other plastic surgery patients (24). Poisson regression methods, as implemented in the AMFIT module in the Epicure analysis package (25), were used to calculate RRs, compute 95% CIs, and adjust for potential confounding variables. 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 (1960–64,. . ., 1990–94, 1995–96), and race (white or black). Other factors, such as age at surgery, year of surgery, time since surgery, or specific predictors of cancer risk, were included in the regression model, as necessary, to evaluate their roles as potential confounding factors or to examine variations of the RR. Risk factor information was derived from questionnaires, if available, or from the medical records of the plastic surgeons.

Standardized mortality ratios (SMRs) were also calculated, using U.S. 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

Implant patients were on average five years younger (34.8 vs. 42.0 years) than the comparison subjects at the time of study entry (Table 1). This was primarily owing to the relatively large number of patients in the comparison group with abdominoplasty/liposuction or blepharoplasty/rhytidectomy—operations which occurred at relatively late ages. The remaining comparison subjects had similar mean ages at surgery as the breast implant patients. The mean year of initial surgery was similar between the implant and comparison subjects. The average length of follow-up was 12.9 years among the implant patients versus 11.6 among the comparison patients.

Approximately one quarter of the cancers were defined on the basis of death certificates only (Table 2). Medical records (including pathology and operative reports) were obtained for 56.1% of the cancers reported among the augmentation patients and for 64.4% of those reported among the comparison subjects. The success in obtaining records was lower for reports of cervical, uterine, and thyroid cancers. Obtained documentation showed high confirmation rates for most reported cancer sites. Exceptions were cervical and vulvar cancers (for which 50% or fewer were confirmed). Some reports of melanoma were also confirmed only as epithelial cancers, resulting in confirmation rates for implant and comparison subjects of 65.0% and 80.0%, respectively. In addition, some reports of corpus uterine cancer were confirmed only as benign conditions (respective confirmation rates of 71.4% and 80.0%). The reported cancers that were not medically confirmed and the 22 breast cancers confirmed as *in situ* cancers (12 among implant patients and 10 among comparison patients) were excluded from subsequent analyses. In addition, the cancers that were documented as sites other than those reported were re-classified.

Among implant patients, 359 cancers were observed versus 295.95 expected on the basis of population rates (Table 3). Among comparison patients, 151 cancers occurred, versus 140.89 expected. Using incidence rates from the SEER Atlanta area to derive expected values resulted in an overall SIR of 1.21 (95% CI 1.1–1.4) for the implant patients and 1.07 (95% CI 0.9–1.3) for the comparison patients. Among the implant patients, statistically significant elevations were seen for cancers of the stomach (SIR = 2.65, 95% CI 1.0–7.1), cervix (SIR = 3.18, 95% CI 2.3–4.3), vulva (SIR = 2.51, 95% CI 1.1–5.6), and brain (SIR = 2.16, 95% CI 1.2–3.9), and for leukemia (SIR = 2.19, 95% CI 1.1–4.4). Non-significant excesses of two-fold or greater were noted for liver and gallbladder (2.56), laryngeal (2.19), and connective tissue (2.48) cancers, although each was based on small numbers of cases. Among the comparison patients, significant excesses were observed for kidney cancers (SIR = 3.22, 95% CI 1.5–6.7), melanoma (SIR = 1.88, 95% CI 1.0–3.4) and eye cancers (SIR = 7.38, 95% CI

TABLE 1. Descriptive information regarding breast implant and other plastic surgery patients

	Breast augmentation patients	Other plastic surgery patients
Number of eligible study subjects	13,488	3936
Number (percent of eligible) traced as alive	10,533 (78.1%)	3095 (78.6%)
Number (percent of eligible) deceased	245 (1.8%)	119 (3.0%)
Mean age at study entry (yrs.)	34.8	42.0
Person years of followup	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 diagnosis	1990.3	1991.1

1.8–29.5), although the latter estimate was based on only two observed cases.

Internal analyses, based on comparison subjects, showed no overall excess cancer risk (RR = 1.00, 95% CI 0.8–1.2). This primarily reflected a change in risk from the external analyses for cervical cancer (RR = 1.78, 95% CI 0.7–4.8). Non-significant excesses, however, persisted for cancers of the liver and gallbladder (RR = 2.65) and brain (RR = 2.83), and for leukemia (RR = 1.83). Respiratory cancer, which had not been significantly elevated when SEER rates were used to compute expected values, was significantly elevated in the internal analyses (RR = 2.40, 95% CI 1.2–4.7). The majority of these were lung cancers (SMR = 2.23, 95% CI 1.1–4.5).

RRs for cancers that persisted as elevated in the internal analyses were further examined according to a variety of characteristics, including age and calendar year of initial implantation, duration of follow-up, and type of implant (Table 4). There was no distinctive heterogeneity in the risks according to most of these parameters. However, the

TABLE 2. Recorded cancers as confirmed by either death certificates or medical records

	Augmentation patients				Comparison patients			
		Percentages				Percentages		
Cancer site	Recorded cancers	Death certificate	Record retrieval[a]	Medically validated[b]	Recorded cancers	Death certificate	Record retrieval[a]	Medically validated[b]
All cancers[c]	405	25.2	56.1	74.1	167	29.3	64.4	78.9
Buccal	4	25.0	100.0	66.7	4	25.0	100.0	66.7
Stomach	4	25.0	0.0	na[d]	1	100.0	na[d]	na[d]
Small intestine	1	0.0	100.0	100.0	0	na[d]	na[d]	na[d]
Large intestine	21	28.6	46.7	85.7	14	64.3	100.0	80.0
Rectum	3	33.3	100.0	100.0	3	33.3	50.0	100.0
Liver, gallbladder	4	25.0	66.7	100.0	1	100.0	na[d]	na[d]
Pancreas	4	75.0	0.0	na[d]	3	66.7	0.0	na[d]
Respiratory	37	75.7	44.4	100.0	13	69.2	50.0	100.0
Breast[e]	136	14.7	67.2	100.0	60	13.3	69.2	100.0
Cervix	56	3.6	38.9	19.0	7	14.3	50.0	33.3
Corpus & uterus	17	0.0	41.2	71.4	9	11.1	62.5	80.0
Ovary	19	36.8	66.7	75.0	6	83.3	0.0	na[d]
Vulva & vagina	10	0.0	60.0	50.0	1	0.0	0.0	na[d]
Kidney	2	100.0	na[d]	na[d]	7	28.6	40.0	100.0
Bladder	2	50.0	100.0	100.0	2	0.0	50.0	100.0
Melanoma	31	6.4	69.0	65.0	12	8.3	45.4	80.0
Eye	1	0.0	100.0	100.0	2	0.0	50.0	100.0
Brain	12	91.7	100.0	0.0	1	100.0	na[d]	na[d]
Thyroid	14	0.0	42.9	83.3	5	20.0	100.0	100.0
Endocrine	1	100.0	na[d]	na[d]	0	na[d]	na[d]	na[d]
Connective tissue	4	25.0	33.3	100.0	2	0.0	100.0	100.0
Hematopoietic	15	46.7	50.0	100.0	9	11.1	62.5	100.0

[a] Obtainment rate of medical records for cancers reported by interview.
[b] Rate of confirmation of reported cancers with available medical documentation.
[c] Unknown sites were reported by seven augmentation and five comparison patients.
[d] Not applicable.
[e] Includes both *in situ* and invasive breast cancers.

TABLE 3. Standardized incidence ratios (SIR) and relative risks (RR) of site–specific cancers among patients with augmentation mammoplasty; External analyses based on Atlanta SEER rates, 1973–1995, internal analyses based on comparison group of patients with other types of plastic surgery

	Observed cancers		External analyses—SIRs		Internal analyses
	Implant Pts.	Other Pts.	Implant Pts.	Other Pts	RRs
All cancers	359	151	1.21[a]	1.07	1.00
Buccal	3	3	0.61	1.07	0.43
Stomach	4	1	2.65[a]	1.03	1.25
Large intestine	16	13	1.23	1.45	0.84
Rectum	7	3	1.08	0.77	1.48
Liver, gallbladder	3	1	2.56	1.02	2.65
Pancreas	5	3	1.97	1.50	1.59
Respiratory	37	13	1.33	0.65	2.40[a]
Larynx	3	0	2.19	0.00	∞
Lung	33	13	1.27	0.70	2.23[a]
Breast (invasive)	124	50	0.99	0.96	0.84
Cervix	40	5	3.18[a]	1.43	1.78
Corpus and uterus	17	8	1.15	0.90	0.90
Ovary	16	6	1.12	0.90	1.92
Vulva and vagina	6	1	2.51[a]	0.93	1.24
Kidney	2	7	0.56	3.22[a]	0.37
Bladder	2	2	0.52	0.78	0.49
Melanoma	24	11	1.20	1.88[a]	0.64
Eye	1	2	1.93	7.38[a]	0.33
Brain	11	1	2.16[a]	0.49	2.83
Thyroid	13	5	1.19	1.78	0.66
Endocrine	1	0	2.75	0.00	∞
Connective tissue	4	2	2.48	3.95	0.59
Hematopoietic	15	9	0.94	1.10	0.63
Non-Hodgkins lymphoma	6	4	0.72	0.90	0.55
Hodgkins disease	1	2	0.46	3.63	0.11
Multiple myeloma	0	1	0.00	0.90	0.00
Leukemia	8	2	2.19[a]	0.99	1.83

[a] 95% CI excludes 1.0.

respiratory cancer excess was highest among those with extended follow-up, with the RR being 2.85 among patients with 15 or more years of follow-up. A total of 49.7% of the subjects received silicone gel implants, 34.1% double lumen implants, 12.2% saline implants, 0.1% other types of implants, and 3.8% unspecified types. There was no significant heterogeneity in the risks for all cancers or for individual sites according to type of implant. We also attempted to evaluate whether risks were affected by the type of implant cover, since polyurethane-foam coated implants have been shown to leak chemicals shown to be carcinogenic in laboratory animals (21). However, only 1.3% of the implants were noted to have such covers.

To address potential reporting or selection biases, we performed several analyses focusing on practices with higher 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. Risks did not vary substantially by categories of practices defined by location and questionnaire response rates. Similarly, interpretation of the results was not altered by restriction of events to those occurring prior to 1992.

The implant and comparison patients demonstrated a number of differences with respect to potential cancer risk factors, including the implant patients more often being white, having limited education, having early ages at first birth, being thin, and having had frequent screening for breast disease (26). We, therefore, adjusted cancer risks for these factors, using data derived from either questionnaires or medical records. Adjustment for these as well as various other factors (cigarette smoking, alcohol consumption, income) did not substantially change any of the previously observed RRs. Analyses also considered whether risk estimates differed within subgroups defined by the above mentioned factors, i.e., whether there was any substantial effect modification. Numbers became sparse for these analyses, particularly for cancers where a primary means of ascertainment was a death certificate, in which case questionnaire data were not available. Nonetheless, we did not observe any noteworthy variations according to levels of selected risk factors, including socioeconomic status. Potential effect

TABLE 4. RRs for breast implant patients of selected cancers according to age and calendar year at initial implant, years since implant, and type of implant; Comparison based on other plastic surgery patients

	All cancers	Respiratory	Brain	Leukemia
Age at implant				
<30	1.07 (71)	∞ (2)	∞ (1)	∞ (1)
30–34	0.78 (83)	∞ (3)	∞ (3)	∞ (3)
35–39	0.87 (82)	∞ (5)	∞ (6)	0.00 (0)
40+	1.08 (123)	2.26[a] (27)	1.09 (1)	3.66 (4)
Calendar year at implant				
<1975	0.86 (50)	9.97 (8)	0.00 (0)	∞ (1)
1975–79	1.03 (149)	4.09[a] (18)	∞ (8)	∞ (4)
1980–84	1.19 (113)	1.55 (8)	1.05 (2)	1.37 (2)
1985–88	0.76 (47)	0.80 (3)	∞ (1)	0.25 (1)
Years since implant				
<5	0.92 (64)	1.09 (2)	∞ (3)	0.16 (1)
5–9	0.99 (110)	1.81 (12)	0.00 (0)	∞ (3)
10–14	1.01 (99)	2.02 (6)	1.49 (4)	∞ (1)
15+	0.83 (86)	2.85 (17)	∞ (4)	∞ (3)
Type of implant				
Silicone gel	1.07 (208)	2.60[a] (24)	2.90 (5)	1.66 (3)
Double lumen	0.76 (85)	2.06 (9)	4.99 (5)	0.80 (3)
Saline	1.08 (47)	1.60 (2)	2.43 (1)	2.73 (1)
Other/unspecified	1.11 (19)	3.75 (2)	0.00 (0)	6.70 (1)

Numbers in parentheses represent number of observed cancers.
[a] 95% CI excludes 1.0.

modification of lung cancer risks by cigarette smoking was of interest, but could not be evaluated given that all but one case (in a comparison subject) were smokers.

Death certificates and medical records were reviewed in an attempt to determine additional information regarding the observed brain cancers and leukemias. Since all of the observed brain cancers were defined on the basis of death certificates, special efforts were expended to retrieve medical records to confirm the assigned causes of death. All but one case was confirmed as having the malignancy originate in the brain (one case with brain cancer as an underlying cause and breast cancer as a contributory cause on the death certificate was confirmed as a primary breast cancer). Of the 10 subjects for whom surgery was performed, nine had tumors that were classified as glioblastoma multiforme and one as a malignant mixed glioma. Pathology slides and/or blocks were also obtained for six of these subjects; review by a neurologic pathologist showed no unusual characteristics. The two medically verified leukemias were comprised of an acute myelocytic leukemia and a lymphocytic leukemia. Notations on the death certificates included acute erythroblastic leukemia, acute myelogenous leukemia and chronic lymphatic leukemia.

A total of 107 implant patients died as a result of their malignancies, compared to 138.55 expected based on U.S. mortality rates (SMR = 0.77, 95% CI 0.6–0.9) (Table 5). The risk among the comparison subjects was also reduced (SMR = 0.67, 95% CI 0.5–0.9), reflecting that patients with plastic surgery are generally healthier than their peers. The mortality ratio for implant patients for all malignancies based on rates generated by the comparison group was 1.37 (95% CI 0.9–2.0). Internally derived risks showed a significant elevation for lung cancer (SMR = 2.78, 95% CI 1.2–6.2) and a non-significant increase for brain cancer (SMR = 2.30, 95% CI 0.4–13.4).

DISCUSSION

This large follow-up study offered an opportunity to evaluate the relationship of breast implants to cancer sites other than the breast, an issue that has only been peripherally examined in other studies (17, 19, 23). In all of the studies in which these relationships were evaluated, numbers of observed events were small, limiting the extent to which conclusions could be drawn. Nonetheless, observations regarding excesses of cancers of the lung (17, 23), cervix (17, 23), and vulva (23) were of interest, and deserving of further pursuit in this larger investigation.

In our study, we observed excesses of cervical and vulvar cancers, with a 2- to 3-fold excess risk prevailing when the implant patients were compared with the general population. These excess risks must be cautiously interpreted, since medical documentation was not available for all reported cancers and some of the reports could not be verified by available medical records. To the extent to which this could be evaluated, any potential bias appeared to operate similarly for implant and comparison patients. The fact that the risk

TABLE 5. Standardized mortality ratios (SMR) for deaths due to cancers among breast implant patients: Comparisons based on both U.S. mortality rates, 1970–1995 and the other plastic surgery patients

	Implant patients			Comparison patients			Internal comparison	
	Deaths	SMR	95% CI	Deaths	SMR	95% CI	SMR	95% CI
All malignancies	107	0.77	0.6–0.9	53	0.67	0.5–0.9	1.37	0.9–2.0
Large intestine	6	0.68	0.3–1.5	9	1.50	0.8–2.9	0.45	0.1–1.5
Pancreas	3	0.68	0.2–2.1	3	0.92	0.3–2.8	1.45	0.3–7.5
Respiratory	29	0.98	0.7–1.4	9	0.45	0.2–0.9	3.04	1.4–6.7
Lung	27	0.93	0.6–1.4	9	0.46	0.2–0.9	2.78	1.2–6.2
Breast	23	0.61	0.4–0.9	8	0.45	0.2–0.9	1.15	0.5–2.8
Brain	12	2.52	1.4–4.4	2	0.90	0.2–3.6	2.30	0.4–13.4
Hematopoietic	7	0.62	0.3–1.3	3	0.48	0.2–1.5	1.85	0.4–8.3
Leukemia	4	0.88	0.3–2.3	0	0.00		∞	
Lymphatic	3	0.59	0.2–1.8	1	0.30	0.0–2.1	1.73	0.2–18.4

Only causes of death with three or more observed events among the implant patients are presented.

of cervical cancer decreased to a non-significant excess of 80% when the implant patients were compared with an internal group of other plastic surgery patients may reflect that much of the excess risk of cervical cancer among implant patients is due to women seeking plastic surgery having cancer risks that are different from the general population (27). Thus, our findings suggest that previously observed cervical cancer excesses among implant patients are probably more attributable to reproductive and lifestyle factors common to women undergoing plastic surgery than to the effects of silicone exposure.

Of the other cancer sites that have been suggested as increased among breast implant patients, we had the greatest capability to evaluate respiratory cancers, given the relatively large number of observed cases. Like others (17, 23), we observed some excess risk of lung cancers. However, somewhat surprisingly, the excess incidence as well as mortality of respiratory cancers in our study was more apparent when comparisons were made with the other plastic surgery patients than with the general population, reflecting that our comparison subjects had a relatively low rate of these cancers. Since such a large proportion of the observed respiratory cancers in our study were identified through death certificates (in the absence of questionnaire information), we were unable to account fully for confounding or modifying effects of cigarette smoking. However, we did not find cigarette smoking rates to differ substantially between the implant and comparison patients (26), although our measure of exposure may have been imprecise. Confounding by smoking must be considered as a possible explanation, especially since several smoking-related sites also showed elevated risks (notably cancers of the larynx and pancreas). Alternatively, it is noteworthy that the highest respiratory cancer risks were observed among implant patients with the longest follow-up. Whether our observed excess represents a chance finding, one due to bias or confounding, or a true biologic relationship requires further study.

Brain cancers also occurred in excess among the breast implant patients in our study. Brain cancer has not previously been linked to breast implants, although given its rarity it would have been difficult for the previous smaller investigations to detect effects. The excess that we observed was difficult to interpret given that it was based on relatively small numbers (11 observed events among the implant patients) and that all were noted as causes of death rather than incident cancers. Although brain cancers noted on death certificates often reflect metastases from other sites (28), additional medical record information obtained for our study subjects did not support this notion, with the majority of subjects having been diagnosed with glioblastoma multiforme. We could, however, not identify any distinctive pathologic characteristics which would lead us to conclude that these cases were directly related to silicone exposure. Given that brain cancer was not a site that we had *a priori* hypothesized would be linked with silicone exposure, we have no ready explanation for our observed increase in risk. Further surveillance among breast implant patients will be necessary to determine reasons underlying the observed elevation in risk.

Additional concerns regarding breast implants have been expressed for sarcomas (29, 30), given the possibility of solid state carcinogenesis (31), and a variety of hematopoietic malignancies, given several immunologic alterations linked to silicone exposure (32, 33). We observed four connective tissue cancers among implant patients, which appeared excessive when external analyses were employed, but close to expectation when compared to the other plastic surgery patients. Given the small numbers involved, interpretation of any potential relationship was difficult. Hematopoietic malignancies were more common, with 15 cases observed among the implant patients. Although there have been several reports of lymphomas occurring among women with silicone implants (34–37), we found neither Hodgkin disease nor non-Hodgkin lymphoma to occur excessively

among our implant patients. We did, however, observe some increase in the risk of leukemias, although the variety of histologies as well as the absence of any striking relationships with characteristics of the implants suggests a non-biological relationship. However, it is of interest that McLaughlin and others (17) in a follow-up study of Swedish patients also found an excess risk of leukemias, although their SIR of 2.7 was non-significant and based on only three observed cases.

Multiple myeloma has been an additional cancer site that has been of concern, provoked by laboratory findings of induction of plasma cell tumors in genetically susceptible substrains of BALB/c mice following the injection of silicone gel from mammary implants (38). Several investigations have assembled series of women with multiple myeloma who have had histories of breast implants (39–41). In addition, a registry of breast implant patients with multiple myeloma has been established, with 18 cases from four medical practices identified (42). More analytic studies, including the Los Angeles (43), Swedish (17), and Danish (19) cohorts, however, have not observed any multiple myelomas, a finding not surprising given the limited follow-up in these investigations and the rarity of this cancer. We also did not observe any cases among our implant patients, although one case of multiple myeloma was observed among the comparison patients. However, even with our large sample size, it was difficult to evaluate this cancer site, as evidenced by the expected value based on general population rates of 1.73 among the implant patients.

Our location and questionnaire response rates, which were 80% and 70%, respectively, warrant attention. If nonresponse had been differential by exposure status, this could have introduced some misclassification. However, we have no reason to suspect that this occurred, especially since our location and response rates were identical for the implant and comparison patients. In fact, if reporting bias had occurred, we would have expected to have seen an excess risk of breast cancer among the implant patients, given that this is the cancer that has received the most attention. In addition, we were unable to validate all of the reported cancers, particularly those diagnosed in the distant past, for which many records were no longer available. It was thus reassuring that for most cancer sites there was consistency between the patients reports and documentation in their medical records. For a few sites, in which there were inconsistencies between the two sources of information (e.g., for cervical cancer and melanoma), more caution in interpretation of the findings may be warranted. However, it appears that such inaccuracies similarly affected the implant and the comparison patients, resulting in risk estimates being biased towards the null.

In summary, in comparisons with the general population, this study, like previous investigations (17, 23), found excess risks of cervical, vulvar, and lung cancers among women with previous augmentation mammoplasties. Internal comparison of the implant patients with patients with other types of plastic surgery suggested that the excesses of cervical and vulvar cancers may be related to reproductive or lifestyle characteristics of the implant patients, rather than to an effect of their breast implants. Although the internal analyses suggested similar risks for most cancer sites between the implant and comparison patients, a few differences persisted, including higher risks for respiratory and brain cancers, and leukemia. The latter excess may be a chance finding, given the histologic diversity of the observed cancers. Reasons for the elevations of respiratory and brain cancers were less apparent.

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