

Monoclonal Gammopathy of Undetermined Significance and Exposure to Breast Implants

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Background: Animal studies and uncontrolled case series in humans have suggested a possible association between breast implant exposure and monoclonal gammopathy.

Objective: To assess whether there is an increased risk of monoclonal gammopathy in women with silicone breast implants, we conducted a retrospective study of women exposed to breast implants and matched nonexposed women nested within a prospective cohort study (the Nurses' Health Study).

Methods: We used serum protein electrophoresis and immunoglobulin subtype by immunofixation to test 288 women exposed to breast implants and 288 age-matched, nonexposed women who previously had provided a blood sample (1989-1990) for monoclonal proteins.

Results: Among the women exposed to breast implants, 5 had monoclonal gammopathy of undetermined significance (MGUS) compared with 4 women among those not exposed (odds ratio, 1.25; 95% confidence interval, 0.27-6.39). The distribution of isotypes was similar across exposure groups. The exposed women with MGUS tended to be older than the nonexposed women (mean age, 60.4 years vs 52.5 years, respectively; $P=.03$). None of the 9 women with MGUS had reported multiple myeloma or other hematologic malignancies up through 1996.

Conclusions: We find little evidence to support a substantial increased risk of MGUS in women exposed to breast implants. Larger studies are needed to determine if a more modest relationship exists.

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IN 1962, Potter and Boyce¹ demonstrated that adjuvants (such as mineral oil) injected into mice caused chronic inflammation and in some strains, plasmacytomas. Since then, plasmacytomas have been induced in mice by intraperitoneal introduction of paraffin oils, pure alkanes, and solid lucite.² Recently, Potter et al³ injected silicone gel as found in silicone breast implants into the peritoneal cavity of genetically susceptible strains of mice and caused plasmacytomas. In addition, cases of multiple myeloma developing at unusually young ages have occurred in women with silicone breast implants.⁴⁻⁶ These observations suggested a possible association between exposure to silicone gel and multiple myeloma and prompted the National Cancer Institute (Bethesda, Md) to establish a registry of patients with silicone implants and either multiple myeloma or monoclonal gammopathy⁷ and to call for further epidemiologic investigations.⁸

Twenty-four percent of patients with monoclonal gammopathy of unde-

termined significance (MGUS) eventually develop multiple myeloma, macroglobulinemia, amyloidosis, or related diseases.⁹ We investigated the possible association of MGUS and breast implants using archived plasma from 32 826 women enrolled in the Nurses' Health Study.

RESULTS

At the time of the original blood collection, the mean age was 52.0 years for the exposed and 51.7 years for the nonexposed women. Mean \pm SD and median duration of implant exposure was 11.72 \pm 6 years and 12.13 years, respectively.

Among the exposed women with any type of breast implant, 5 (1.7%) of 288 women had MGUS compared with 4 (1.4%) of 288 women among the nonexposed (odds ratio, 1.25; 95% CI, 0.27-6.39; $P>.99$) (**Table 1**). The age-adjusted odds ratio was 1.23 (95% CI, 0.32-4.66; $P=.76$). Among women with

PARTICIPANTS AND METHODS

STUDY POPULATION

The Nurses' Health Study (made up of 121 700 female nurses aged 30 through 55 years at enrollment in 1976) is a prospective study of dietary, hormonal, lifestyle, and other risk factors for cancer, cardiovascular disease, and other chronic diseases. Participants receive biennial questionnaires to update exposure and disease status; the response rate as of 1996 remained at 90%. In 1988, all participants were asked to provide 30 mL of blood to be stored for future studies, and 32 826 blood samples were collected. This project was approved by the institutional review board of the Brigham and Women's Hospital, Boston, Mass.

STUDY DESIGN

The study is a retrospective cohort nested within the ongoing prospective cohort study (the Nurses' Health Study). The subjects were selected on the basis of their breast implant exposure status, and then their blood was tested for immunologic abnormalities to determine disease status.

SELECTION OF EXPOSED WOMEN

On the 1992 biennial questionnaire, 1890 women reported having undergone breast implant surgery and 1480 (78%) responded to a supplemental questionnaire regarding the date of surgery and complications since surgery. Of 1183 women who underwent breast implant surgery before the time of the blood collection (who provided information regarding date of implant) 76% reported having silicone gel-filled implants. We studied subjects with any type of breast implant and performed analyses by type of implant. We selected only women who reported having implants for cosmetic or prophylactic purposes. We excluded subjects without a blood sample ($n=670$), and subjects who reported any condition potentially associated with hypergammaglobulinemia or monoclonal gammopathy, such as breast cancer, multiple myeloma, or other cancer ($n=460$); connective tissue disease ($n=33$); and breast implant surgery after breast cancer surgery ($n=386$) before the time of the blood collection (exclusions not mutually exclusive). This left 288 exposed women who had blood collected after breast implant surgery; 235 (82%) with silicone gel-filled implants; and 53 (18%) with saline-filled, unknown, or other type of implant. The duration of exposure was calculated as the time from the breast implant surgery to the date the blood sample was collected.

SELECTION OF NONEXPOSED WOMEN

Using identical exclusion criteria, 26 258 women without breast implants were potential controls. Of these, 288 were

randomly selected and matched to the exposed group by year of birth and the date the blood sample was returned to form the nonexposed group.

PROCESSING OF BLOOD SAMPLES

From 1989 to 1990, blood samples were delivered overnight to our laboratory where they were centrifuged into aliquot components of plasma, red blood cells, and white blood cells and then archived in liquid nitrogen freezers. Monoclonal proteins are known to be stable for up to 50 years if samples are frozen (Robert A. Kyle, personal communication, 1999).

SERUM PROTEIN STUDIES

Monoclonal gammopathy was detected by immunofixation using the Titan Agarose Gel Immunofixation Electrophoresis (Helena Laboratories, Beaumont, Tex). Immunofixations were interpreted independently by 2 blinded reviewers (M.T., P.H.S.). The heavy chain and light chain isotypes were determined. Monoclonal band size (tiny, small, moderate, and large) was assessed qualitatively by inspecting the gel. After the initial review of samples, interrater agreement was 97%. The 2 reviewers reached consensus on the remaining 3%.

BLINDING AND QUALITY CONTROL PROCEDURES

Plasma samples were labeled only with an identification number, and laboratory personnel were blinded to the group identity of the samples. Prior to the study, the reproducibility of the laboratory assay and interrater agreement was assessed by testing split samples of known positive and known negative controls. Ninety-eight percent of positive and negative controls were correctly identified. Included in every batch of study samples were random negative and positive controls. Of these, 100% of 48 positive controls and 100% of 52 negative controls were correctly identified with qualitative estimates of monoclonal band size (intensity) identical in 62% and off by only 1 size category in the remaining 38%.

STATISTICAL METHODS

We performed analyses according to the type of implant (silicone gel-filled, saline-filled, or other type) as well as any type of breast implant. We tested the association of MGUS and breast implant exposure using the Fisher exact test and computed exact univariate confidence intervals (CIs). An age-adjusted analysis was performed using multivariate logistic regression controlling for age as a continuous variable. Mean age according to exposure to breast implants and mean duration of exposure between women with MGUS and women without MGUS were compared by the *t* tests. All *P* values are 2-tailed.

silicone gel-filled implants, 3 (1.3%) of 235 had MGUS (odds ratio, 0.92; 95% CI, 0.13-5.49).

The distribution of MGUS isotypes and qualitative estimates of band size were similar across exposure groups (data not shown). The 5 exposed women with MGUS

tended to be older than the 4 nonexposed women (mean age, 60.9 years vs 53 years, respectively; $P=.04$). There was no significant difference in the duration of exposure to breast implants between those women with and without MGUS (11.07 vs 11.73 years; $P=.81$). None of

the 9 women with MGUS had reported multiple myeloma or other hematologic malignancies on biennial questionnaires through 1996 (**Table 2**).

COMMENT

Monoclonal gammopathy is a benign condition that occurs at a younger age than multiple myeloma occurs and is a precursor to multiple myeloma, macroglobulinemia, amyloidosis, or related diseases in up to 24% of cases.⁹ We found little evidence for an increased frequency of MGUS in women exposed to breast implants. The 5 women with breast implants who had MGUS were significantly older than the 4 women without silicone breast implants who had MGUS, suggesting that exposure to breast implants does not cause monoclonal gammopathy at younger than expected ages.

Our results stand in contrast to 3 case series and the National Cancer Institute's registry,^{4,7} whose findings might be due to referral, ascertainment, and/or detection bias. Five women with silicone breast implants and multiple myeloma referred to a cancer center were described: 2 women had MGUS prior to breast implant surgery, and 3 women were aged 45 years or younger, suggesting a higher than expected rate of multiple myeloma in the age range of 35 to 45 years.⁴ Among 324 patients with newly diagnosed

multiple myeloma from another cancer center, 9 had silicone breast implants. The mean age at diagnosis was similar to controls without breast implant exposure.⁵ Of 34 female patients with multiple myeloma at a university medical center, 3 patients had silicone gel breast implants.⁶ Among 284 women with silicone gel-filled breast implants who were referred for rheumatic symptoms, 1.7% had MGUS.⁶ The National Cancer Institute's registry includes 18 women with multiple myeloma and silicone breast implants (including the above cases).⁷ The mean and median duration of exposure was 12 and 14 years, respectively, with a range of 2 to 25 years. Thus, the duration of exposures observed in our study falls within the range reported in the registry, and we demonstrated no significant association between exposure and MGUS and found no evidence for MGUS occurring at younger ages in women exposed to breast implants.

In contrast, 5 studies have failed to demonstrate an increased risk of monoclonal gammopathy or multiple myeloma in women with breast implants.¹⁰⁻¹⁴ No cases of multiple myeloma were found in 1135 women with cosmetic implants from a Denmark study,^{10,11} in 1756 Swedish women with cosmetic implants,¹² or in 3182 US women¹³ (type of implant not specified). A Mayo Clinic study of 749 women who received breast implants (82% silicone gel-filled implants) found no cases of MGUS, multiple myeloma, macroglobulinemia, primary amyloidosis, or lymphoproliferative disorder compared with 1 case of multiple myeloma and 4 cases of MGUS among 1498 controls.¹⁴

The present study is the first cohort study of the possible association between breast implants and MGUS using stored blood samples rather than medical records to identify outcomes, and the selection of subjects was unbiased by symptoms or diseases. Some limitations require discussion. Monoclonal gammopathy of undetermined significance occurs so infrequently that even this large cohort study had limited power to detect anything but large increases in relative risk. Although we studied all available plasma samples from women who had breast implants done for cosmetic purposes (n=288), the upper bound of the CI (6.39) suggested that we could not rule out a relative risk of 6.39 (or less) for the risk of mono-

Table 1. Cases of MGUS Among Women With and Without Breast Implants, Nurses' Health Study*

MGUS Isotype	Cases of MGUS		P†
	With Breast Implant (n = 288)	Without Breast Implant (n = 288)	
Any isotype	5	4	>.99‡
IgG κ	3	3	>.99
IgG λ	0	1	>.99
IgM κ	1	0	>.99
IgM λ	1	0	>.99

*MGUS indicates monoclonal gammopathy of undetermined significance.

†Fisher exact test, 2-tailed P value.

‡Odds ratio, 1.25 (95% confidence interval, 0.27-6.39).

Table 2. Description of 5 Breast Implant-Exposed Women With MGUS*

Characteristic	Patient No.				
	1	2	3	4	5
Age at MGUS assessment, y	61.1	55.4	57.2	63.4	66.8
Duration of implant exposure, y	15.3	8.6	17.8	9.4	4.3
Isotype used in test	IgG κ	IgM κ	IgG κ	IgM λ	IgG κ
Qualitative estimate of band size†	Small	Moderate	Moderate	Moderate	Moderate
Implant type	Silicone gel filled	Silicone gel filled	Unknown	Saline filled	Silicone gel filled
Implant rupture	No	No	No	No	No
Implant contracture	Yes	No	Missing	No	Missing
Subsequent condition(s) reported	Colon polyp	Multiple sclerosis	No report	Hip fracture	Macular degeneration; glaucoma; colon polyp; interstitial cystitis

*MGUS indicates monoclonal gammopathy of undetermined significance.

†Band sizes in the 4 women not exposed to breast implants were tiny, small, small-moderate, and moderate.

clonal gammopathy associated with breast implants. Finally, although unlikely, there may have been bias introduced by selecting women who were willing and able to give blood rather than women who were not. However, to result in a biased relative risk participation would need to vary by both breast implant status and MGUS status. In conclusion, we find little evidence for a substantial increased risk of MGUS in women with breast implants compared with women without implants.

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