

Breast Implants and Lymphoma Risk: A Review of the Epidemiologic Evidence through 2008

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Background: In the past, concerns about lymphoma among women with breast implants have been raised by anecdotal observations. A recent report of a case-control study from The Netherlands reported an association of breast implants with anaplastic large T-cell lymphoma, but limitations inherent in the study design and the restriction of the association to saline implants preclude any causal evaluation.

Methods: To determine whether lymphoma risk is in fact elevated in women with breast implants, the authors have reviewed the evidence from five long-term follow-up studies comprising over 43,000 women with cosmetic breast implants followed for up to 37 years, which reported results specifically regarding the incidence of non-Hodgkin's lymphoma, among other cancers.

Results: Overall, there were 48 observed incident cases of non-Hodgkin's lymphoma compared with 53.9 cases expected, yielding a summary standardized incidence ratio of 0.89 (95 percent confidence interval, 0.67 to 1.18). None of the epidemiologic cohort studies reported a primary lymphoma originating in the breast.

Conclusions: To date, there is no credible evidence of an increase of non-Hodgkin's lymphoma regardless of site or specifically originating in the breast among women with cosmetic breast implants. (*Plast. Reconstr. Surg.* 123: 790, 2009.)

Primary breast lymphoma is a rare malignancy, and the vast majority of these lymphomas are of B-cell origin. Concerns about lymphoma among women with breast implants have been raised by a few anecdotal reports of lymphomas in or near the breast among women with breast implants.¹⁻⁵ However, these anecdotal observations have not been supported by evidence from epidemiologic studies of women with breast implants.⁶ Recently, a report of a case-control study from The Netherlands suggested an association of breast implants with anaplastic large T-cell lymphoma.⁷

For the purposes of this review, we performed a systematic search of the literature through PubMed, using the search terms "breast implant," "cancer OR lymphoma," and "epidemiology." Findings of individual studies were evaluated, and reference lists were checked to identify additional relevant stud-

ies. In this article, we review the evidence from all epidemiologic cohort studies of cancer incidence among women with cosmetic breast implants that include results on the incidence of non-Hodgkin's lymphoma, with specific attention to lymphomas arising in the breast.

To date, five long-term cohort studies⁸⁻¹² have evaluated the incidence of non-Hodgkin's lymphoma following cosmetic breast augmentation surgery (Table 1). In a pooled analysis of two large nationwide cohort studies with virtually complete follow-up and cancer ascertainment,⁸ 3486 Swedish and 2736 Danish women who received cosmetic breast implants between 1965 and 1993 were followed for up to 37 years (103,565 total person-years of follow-up), with more than half of the women followed for 15 years or more. At a minimum, 80 percent or more of implants in this study were silicone gel filled. The standardized incidence ratio for non-Hodgkin's lymphoma overall

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Table 1. Summary of Epidemiologic Cohort Studies of Women with Cosmetic Breast Implants Reporting Results on Non-Hodgkin's Lymphoma

Reference	Location	Study Period	Study Population	Mean Follow-Up (range) (yr)	Estimated Relative Risk (95% CI)	Observed Cases
Lipworth et al., 2008 ⁸	Denmark, Sweden	1965–2002	Pooled analysis of 3486 Swedish and 2736 Danish women with breast implants from 1965–1993; Swedish and Danish reference populations	16.6 (0.1–37.8)	SIR, 1.22 (0.56–2.32); none of the 9 cases had primary origin in or near breast	9
Deapen et al., 2007 ⁹	Los Angeles	1953–1994	3139 women with breast implants from 1953–1980; general population rates	15.5 (0.04–23.0)	SIR, 1.29 (0.42–3.01)	5
Brisson et al., 2006 ¹⁰	Canada	1974–1997	24,358 women with breast implants; 15,893 women with other cosmetic procedures at same practices; general population rates	15.4 Quebec, 13.8, Ontario (up to 24)	Implant patients: SIR, 0.75 (0.49–1.11); comparison group: SIR, 0.78 (0.48–1.20); RR,* 0.97 (0.53–1.76)	25; 20
Pukkala et al., 2002 ¹¹	Finland	1970–1999	2171 women with breast implants from 1970–1999; Finnish reference population	8.3 (up to 29)	SIR, 3.7 (0.8–10.7)	3
Brinton et al., 2001 ¹²	Georgia, Alabama, North Carolina, Florida, Washington, D.C.	1960–1996	7447 women with breast implants before 1989, identified at 18 plastic surgery practices; 2203 other plastic surgery patients identified at same practices	12.9	Implant patients: SIR, 0.72 (0.26–1.57); comparison group: SIR, 0.90 (0.25–2.30); RR,* 0.55 (NS†)	6; 4
Combined SIR					0.89 (95% CI, 0.67–1.18)	48

CI, confidence interval; SIR, standardized incidence ratio; RR, relative risk; NS, not stated.

*Relative risk estimated from internal comparison with other cosmetic procedure patients.

†Confidence interval not presented in article but upper bound stated to include 1.0 (Brinton LA, Lubin JH, Burich MC, et al. Cancer risk at sites other than the breast following augmentation mammoplasty. *Ann Epidemiol.* 2001;11:248–256).

was 1.22 (95 percent confidence interval, 0.56 to 2.32), based on nine observed cases (versus 7.36 expected). None of the nine cases was a lymphoma of the breast or near the breast. Information on cell type was not available.

Deapen et al.⁹ conducted a cohort study of 3139 women (from the practices of 35 plastic surgeons) who received cosmetic silicone breast implants between 1953 and 1980 and were prospectively followed for cancer incidence through 1994 by record linkage with the population-based Los Angeles County Cancer Surveillance Program. It is unlikely that a substantial number of incident cancers would have been missed, because all available subject identifiers were obtained from medical records and used for record linkage. With a median follow-up of 15.5 years (range, 0.04 to 20 years), five cases of non-Hodgkin's lymphoma overall were observed among women with implants, compared with 3.9 expected in the general population, yielding a standardized incidence ratio of 1.29 (95 percent confidence interval, 0.42 to 3.01). None was reported to originate in the breast. Information on cell type was unavailable.

A large cohort of 24,558 women in Ontario and Quebec who underwent cosmetic breast implantation between 1974 and 1989 was followed for cancer incidence for up to 24 years, with over 11,500 women followed for more than 15 years.¹⁰ Approximately 80 percent of women received implants that were filled with silicone. Cancer incidence was ascertained through linkage to the population-based Canadian Cancer Registry and to provincial cancer registries. Because of the large size of the cohort and the fact that over 96 percent of cancers were diagnosed in the same province in which the implant surgery took place, any bias attributable to diagnosis of cancer among women with implants while living outside Canada is likely to be minimal. With over 366,000 person-years of follow-up, the overall incidence of non-Hodgkin's lymphoma among women with implants was reduced compared with the general population (standardized incidence ratio, 0.75, 95 percent confidence interval, 0.49 to 1.11; based on 25 observed cases versus 33.5 expected); and when compared with women undergoing other forms of plastic surgery, the ratio of observed to expected number of non-Hodgkin's lymphomas was similar. None of the non-Hodgkin's lymphomas was reported to have originated in the breast; information on cell type was unavailable.

Pukkala et al.¹¹ conducted a cohort study of 2171 Finnish women who received cosmetic breast implants between 1970 and 1999 at 11 of 13 hos-

pitals and private clinics where implant operations were performed during that period. Overall, 99.2 percent of operations with documentation as to type of implant involved silicone gel implants. The women were followed for cancer incidence through the nationwide Finnish Cancer Registry, with a mean follow-up of 8.3 years. Compared with general population rates, there was a non-statistically significant increase in the incidence of non-Hodgkin's lymphoma overall among women with breast implants, with a standardized incidence ratio of 3.7 (95 percent confidence interval, 0.8 to 10.7) based on three observed cases. Again, none was reported to have originated in the breast. Information on cell type was not presented.

Brinton et al.¹² conducted a retrospective cohort analysis of the incidence of cancers of various types among 7447 women with breast implants [83.8 percent silicone gel-filled or silicone/saline (double-lumen)] compared with 2203 women who had other types of plastic surgery and with women in the general population. Overall, six cases of non-Hodgkin's lymphoma were observed among women with implants, after a mean follow-up of 12.9 years since implantation. There was no excess of non-Hodgkin's lymphoma among women with implants when compared with either women in the general population (standardized incidence ratio, 0.72; 95 percent confidence interval, 0.26 to 1.57) or with other plastic surgery patients (relative risk, 0.55). None was reported to have originated in the breast, and information on cell type was not presented.

A summary analysis of total non-Hodgkin's lymphoma incidence in these five follow-up studies of women after cosmetic breast implantation in Denmark, Sweden, the United States, Canada, and Finland (Table 1) gives a standardized incidence ratio of 0.89 (95 percent confidence interval, 0.67 to 1.18), based on 48 observed non-Hodgkin's lymphoma cases. None of the studies reported a primary lymphoma of the breast. Thus, the epidemiologic evidence, drawn from large surveillance studies with long-term follow-up of 43,537 women with breast implants, provides no evidence of an increased risk of non-Hodgkin's lymphoma at any site among women with cosmetic breast implants. In fact, there is the suggestion of an inverse association between breast implants and overall non-Hodgkin's lymphoma incidence when all the published evidence is taken into account (Table 1).

Recently, de Jong et al.⁷ reported results from a case-control study in The Netherlands and concluded that there may be an association between

silicone breast implants and anaplastic large T-cell lymphoma of the breast. The cases in this study were reported to comprise all patients with anaplastic large T-cell lymphoma of the breast identified in The Netherlands between 1990 and 2006, whereas the controls all had lymphomas of the breast but of cell types other than anaplastic large T-cell lymphoma diagnosed during the same time period. Thus, the elevated odds ratio presented in the article does not demonstrate an increased risk of anaplastic large T-cell lymphoma of the breast among women with breast implants per se. In fact, no valid conclusion at all can be drawn regarding whether there is an excess of lymphoma overall, or of anaplastic large T-cell lymphoma in particular, among women with breast implants compared with women without implants, because control patient selection purposefully included only patients with breast lymphomas other than anaplastic large T-cell lymphoma. Of interest, all five of the women with anaplastic large T-cell lymphoma and breast implants had bilateral "saline-filled" implants (see de Jong et al.,⁷ p 2032, column 2), which are used infrequently in Northern Europe, where silicone breast implants have not been taken off the market as they were in North America. Thus, the only valid conclusion that can be drawn from this study is that among women with breast lymphomas in The Netherlands, those whose lymphoma is of the anaplastic, large cell type may be more likely to have received saline implants. In other words, the 18-fold odds ratio is uninterpretable regarding breast lymphoma risk among women with implants because of the unusual nature of the study design and control selection. Furthermore, the remarkably short latency period (<5 years) between placement of the implants and anaplastic large T-cell lymphoma diagnosis reported in the Dutch study for three of the five anaplastic large T-cell lymphomas diagnosed in women with implants weakens the plausibility that any observed association with saline implants is causal in nature. Finally, the putative association is confined to saline-filled implants and does not involve silicone-filled implants, a fact unremarked on by the Dutch investigators and editorial writers.

CONCLUSIONS

The association between cosmetic silicone breast implants and non-Hodgkin's lymphoma has been examined in a number of long-term cohort and surveillance studies, based on large numbers of women with virtually complete follow-up substantially longer than the 17-year study period presented in the Dutch case-control study. In the

only cancer incidence study to include women followed for at least 25 years after implantation,⁸ including 3336 women followed for 15 years or more and 827 followed for at least 25 years, no significant excess of non-Hodgkin's lymphoma was observed overall and not one primary lymphoma of the breast was observed. Moreover, the largest study to date,¹⁰ with cancer surveillance up to 24 years, actually reported a reduced incidence of total non-Hodgkin's lymphoma among almost 25,000 Canadian women with cosmetic breast implants. Based on the epidemiologic studies published to date, there is no evidence of an excess of non-Hodgkin's lymphoma incidence overall among women with cosmetic silicone-filled breast implants.

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