

## BREAST IMPLANTS AND CANCER RISK IN DENMARK

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**Although millions of women worldwide have received breast implants for cosmetic or medical reasons, possible late effects (in particular cancer) have not been well studied. To provide quantitative information on cancer occurrence among women undergoing breast implant surgery, 1,135 women treated for cosmetic reasons in Denmark were evaluated. Patients were identified using the nationwide Hospital Discharge Registry with linkage to the nationwide Danish Cancer Registry to determine subsequent cancer incidence. The average age of the women at implant surgery was 31 years, and the average follow-up was 8.4 years, up to a maximum of 17 years. Overall, 27 cancers developed after implant surgery compared with 24.7 expected based on incidence rates from the general population (standardized incidence ratio [SIR] = 1.1; 95% CI: 0.7–1.6). Eight breast cancers were observed vs. 7.8 expected (SIR = 1.0; 95% CI: 0.4–2.0). No evidence was found to link breast implants with increased cancer risk in the decade after surgery. While the results are encouraging, longer follow-up into later life will be necessary to assess fully any possible adverse effects. Int. J. Cancer 71:956–958, 1997.**

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The carcinogenic potential of silicone has been questioned since the 1950s when sarcomas at the site of implantation of silicone and other foreign materials were reported in rodents (Oppenheimer *et al.*, 1955), although it is unclear whether a similar mechanism of foreign body carcinogenesis occurs in humans (Brand, 1994). Moreover, some silicone breast implants are coated with polyurethane, which may dissolve and produce toluene diamine, a known carcinogen in rats and mice (Sontag, 1981). Concern over this degradation product led to the removal of polyurethane-coated implants from the U.S. and other markets in 1991 (Ersek *et al.*, 1993). Silicone gel has also been reported to induce plasmacytomas in genetically predisposed mice (Potter *et al.*, 1994). Case reports of breast cancer, multiple myeloma and lymphomas following breast implants have appeared (Gottlieb *et al.*, 1984; Cook *et al.*, 1995; Duvic *et al.*, 1995; Silverman *et al.*, 1996). However, since chance cannot be ruled out as an explanation, such clinical observations cannot provide convincing evidence of a cause-effect relationship.

To date, epidemiologic studies have not suggested that implants pose a carcinogenic risk. Four retrospective cohort studies (Deapen and Brody, 1992; McLaughlin *et al.*, 1994, 1995a; Bryant and Brasher, 1995) and 2 case-control studies (Malone *et al.*, 1992; Brinton *et al.*, 1996) actually found a lowered incidence of breast cancer among women with cosmetic breast implants. In the 2 largest cohort studies (Deapen and Brody, 1992; Bryant and Brasher, 1995), the standardized incidence ratios (SIR) for breast cancer were 0.66 (95% confidence intervals [CI]: 0.41–1.01) and 0.76 (95% CI: 0.55–1.02) when compared with the general population. In the population-based case-control studies of breast cancer (Malone *et al.*, 1992; Brinton *et al.*, 1996), the risks were reduced, with odds ratios (OR) of 0.2 (95% CI: 0.1–1.3) and 0.6 (95% CI: 0.4–1.0). The findings in the case-control studies, however, were based on a small number of women with breast implants and relied on self-reports of prior surgery. In a case-control study of women with silicone gel implants for reconstruction purposes after breast cancer, no increased or decreased risk was seen for second primary breast cancer (Petit *et al.*, 1994). For

other cancer sites, no significantly altered risks have been found other than elevations in lung and vulvar cancer in one study (Deapen and Brody, 1992). In a recent update of this study (Deapen and Brody, 1995), no cases of multiple myeloma or other plasma cell tumors were observed vs. 0.6 expected.

To provide further information on the risk of cancer following breast implants in Denmark, we expanded our earlier nationwide registry-based study (McLaughlin *et al.*, 1994) with an additional 3 years of patient accrual and 4 more years of follow-up.

### MATERIAL AND METHODS

The Danish Hospital Discharge Register (HDR) was used to identify 1,135 women who underwent breast implant surgery for cosmetic reasons (*i.e.*, excluding reconstruction following mastectomy) between 1977 and 1992. Information on vital status, migration, and cancer occurrence was obtained through linkages with the Danish Central Population Register and the Danish Cancer Registry by use of the personal identification number obtained from the HDR. Information on reproductive variables was obtained from linkage with the Population Registry for the exposed cohort and from census data for the general population (Ewertz and Jensen, 1984; Statistics Denmark, 1977–1993). Person-years of observation were calculated from the date of the implant operation until the date of death, date of emigration or December 31, 1993, whichever occurred first. Expected numbers of cancers were calculated by multiplying the age and calendar year-specific person-years of observation by the corresponding cancer incidence rates for Danish women. SIRs and 95% CIs were computed, assuming a Poisson distribution of the observed cancers.

### RESULTS

The average age of the 1,135 women at the time of implant was 31 years (range, 13–64), and the average follow-up was 8.4 years (maximum: 17 years). Overall, 27 cancers were observed vs. 24.7 expected based on Danish national cancer incidence rates (SIR = 1.1; 95% CI: 0.7–1.6) (Table I). Breast cancer was the most common cancer, with 8 observed (all adenocarcinomas) vs. 7.8 expected (SIR = 1.0; 95% CI: 0.4–2.0). No statistically significant increased or decreased risk was seen for any cancer site. One patient developed sarcoma (chondrosarcoma of the lower leg) vs. 0.4 expected, while one had non-Hodgkin's lymphoma vs. 0.5 expected. There were no cases of multiple myeloma (0.1 expected).

Four cases of breast cancer developed 10 or more years after breast implant surgery (SIR = 1.7; 95% CI: 0.4–4.2) (Table II). However, no cases arose 15 or more years after surgery vs. 0.3 expected. No clear differences in risk according to age at surgery were observed (Table II). Four of 8 breast cancers were localized at diagnosis, while 4 were regional. Nationally, 50% of breast cancers are localized, 37% regional and 13% either distant or unknown at

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Received 3 December 1996; accepted 24 February 1997

TABLE I—STANDARDIZED INCIDENCE RATIOS FOR SELECTED CANCERS AMONG 1,135 WOMEN WHO RECEIVED BREAST IMPLANTS FOR COSMETIC REASONS DURING 1977–1992 IN DENMARK<sup>1</sup>

Cancer site (ICD7 <sup>2</sup> )	Obs	Exp	SIR	95% CI
All malignant neoplasms (140–205)	27	24.7	1.1	0.7–1.6
Lung (162)	2	1.4	1.5	0.2–5.3
Breast (170)	8	7.8	1.0	0.4–2.0
Ovary (175)	3	1.2	2.5	0.5–7.3
Malignant melanoma (190)	1	1.5	0.7	0.0–3.7
Non-melanoma skin cancer (191)	5	3.1	1.6	0.5–3.7
Non-Hodgkin's lymphoma (200, 202)	1	0.5	2.2	0.0–12.0
Sarcomas	1 <sup>3</sup>	0.4	2.7	0.0–14.9
Other sites <sup>4</sup>	6	8.7	0.7	0.3–1.5

<sup>1</sup>Obs, observed; Exp, expected; SIR, ratio of observed-to-expected; CI, confidence interval. <sup>2</sup>Modified version of the 7th revision of the International Classification of Diseases. <sup>3</sup>Chondrosarcoma of lower leg. <sup>4</sup>Includes colon (1), cervix uteri (1), corpus uteri (1), kidney (1), brain and nervous system (1) and unspecified metastatic tumor (1).

TABLE II—STANDARDIZED INCIDENCE RATIOS FOR BREAST CANCER AMONG 1,135 WOMEN WITH BREAST IMPLANTS, ACCORDING TO AGE AND TIME SINCE IMPLANT<sup>1</sup>

	Obs	Exp	SIR	95% CI
Age at implant (yr)				
13–29	0	1.1	0.0	0.0–3.5
30–39	5	3.9	1.3	0.4–3.0
40–49	2	2.1	1.0	0.1–3.5
≥50	1	0.8	1.3	0.0–7.3
Time since implant (yr)				
0–4	2	2.6	0.8	0.1–2.7
5–9	2	2.8	0.7	0.1–2.6
≥10	4	2.4	1.7	0.4–4.2
Total	8	7.8	1.0	0.4–2.0

<sup>1</sup>Obs, observed; Exp, expected; SIR, ratio of observed-to-expected; CI, confidence interval.

diagnosis among women of similar ages as those with implants (Storm *et al.*, 1996).

Reproductive histories of the women with implants were generally similar to those of the general population for average age at first birth (22.2 vs. 24.1 years), average number of live births (1.8 vs. 1.7) and proportion of nulliparous women (18% vs. 20%) (Ewertz and Jensen, 1984; Statistics Denmark, 1977–1993).

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## DISCUSSION

This analysis of women with cosmetic breast implants throughout Denmark expands and extends our earlier preliminary report (McLaughlin *et al.*, 1994), increasing the number of women in the cohort and tripling the number of cancers observed. The study population was well defined, and the follow-up was virtually complete, since the Central Population Register and the Cancer Registry cover the entire Danish population. The systematic national approach also ensured that cancer ascertainment was unbiased. Nonetheless, certain limitations of the study should be mentioned. First, we could not obtain information on potentially confounding factors other than age and reproductive status. It has been claimed, for example, that women who receive breast implants for cosmetic reasons may be at low risk of breast cancer because relatively small breasts have less glandular tissue (Trichopoulos and Lipman, 1992). However, the relationship between breast size and breast cancer risk is complex (MacMahon, 1994), and small breast size has been linked to increased cancer risk in other Scandinavian populations (Thurfjell *et al.*, 1996). Second, the period of observation in our study may not be sufficient to reveal excess risks for tumors with long latency or low incidence, *e.g.*, plasma cell or lymphoproliferative disorders (Deapen and Brody, 1995). Finally, we were unable to study cancer rates associated with the various types of breast implants, although at least 85% were likely silicone gel-filled prostheses (McLaughlin *et al.*, 1995b). To the best of our knowledge, polyurethane-coated implants were not marketed in Denmark during the study period.

Although based on only 8 cases, we found little difference in the stage of diagnosis of breast cancer when compared with Danish women as a whole (Storm *et al.*, 1996). The percentage of localized tumors among women with implants was as expected. This is of note because of concern that implants may hinder mammographic detection of early stage breast cancer (Council Report, 1993).

In summary, breast implants were not related to an excess risk of breast or other cancers in our population-based cohort study. However, we found no evidence of a reduced risk of breast cancer, as suggested in previous epidemiologic studies. Future investigations should include larger numbers of women with implants, longer follow-up, information on implant types and a comprehensive accounting of known cancer risk factors.

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