

# Breast Cancer Risk in Relation to Amount of Tissue Removed during Breast Reduction Operations in Sweden

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**BACKGROUND.** Women who undergo breast reduction operations have substantially lowered risks of breast cancer, and the reasons remain unclear. The current investigation attempted to assess whether the reduction in breast cancer risk was related directly to the amount of breast tissue removed.

**METHODS.** Medical record retrieval was attempted for 161 breast cancer patients in a Swedish cohort of 31,910 women who had had breast reduction surgery and for 483 women who had not developed breast cancer. Information on amount of breast tissue removed was abstracted along with other factors that influence breast cancer risk. Odds ratios of developing breast cancer were calculated based on amount of breast tissue removed.

**RESULTS.** The amount of tissue removed was a significant predictor of risk, as subjects in the highest quartile of tissue removal had a significantly lower risk than those in the lowest quartile. Considering the total amount of tissue removed (both breasts), subjects with  $\geq 1600$  versus  $< 800$  grams removed had an odds ratio (OR) of 0.24 [95% confidence interval (CI) 0.1–0.5]. This relation persisted after adjustment for other breast cancer risk factors and was apparent within every subgroup examined.

**CONCLUSIONS.** The finding that breast cancer risk was reduced in proportion to the amount of tissue removed should be reassuring to women who are considering breast reduction procedures and to women who are electing to have bilateral total prophylactic mastectomies because of a strong genetic predisposition. *Cancer* 2001;91:478–83. Published 2001 by the American Cancer Society.\*

**KEYWORDS:** breast cancer, breast reduction, risk.

A number of investigations<sup>1-4</sup> have shown that patients who undergo breast reduction operations have a reduced risk of developing breast cancer, especially if their procedures occurred after the age of 40 years. The magnitude of the reduction in risk is substantial, on the order of 30–50%. It has been suggested that the lowered risk is related directly to the amount of breast tissue removed during the procedure. However, this hypothesis has been examined in only one small investigation of 32 breast cancer cases, in which a maximum reduction in risk was achieved for women who had 600 grams or more of tissue removed.<sup>1</sup>

We recently conducted a nationwide record-linkage study in Sweden to assess the relation of breast reduction procedures to subsequent breast cancer risk.<sup>5</sup> Among 31,910 women who underwent breast reduction surgery, there was an overall standardized incidence ratio of 0.72, with risk reductions most pronounced for women whose operations were performed after age 50 years and for those who were followed for more than 5 years. The current study uses information

from medical records to assess the relation between breast cancer risk and the amount of tissue removed during these procedures, taking into account other risk factors. Ages at and interval since the procedure also were evaluated.

## MATERIALS AND METHODS

The subjects in the current study were identified through a previously described record-linkage study<sup>5</sup> involving the Swedish Inpatient Register.<sup>6,7</sup> In brief, this register was used to identify women who had undergone breast reduction surgery (procedures codes 3850–3851) between 1965 and 1993. Using a unique national registration number assigned to each Swedish resident, we performed a linkage of this cohort to the Swedish Register of the Total Population, the Death Register, the Swedish Cancer Register, and the Migration Register to determine information on vital status, cancer incidence, and migration. This linkage identified 161 initial breast cancers among the 31,910 women who had had previous breast reduction operations and who had been identified as eligible for the cohort analyses. The calculation of person-years of observation began at 3 months after the date of breast reduction surgery and ended at the date of death, migration, or December 31, 1993 (whichever occurred first). This calculation method enabled a comparison with expected numbers of cancers according to age and calendar-year-specific person-years of observation, which were derived from cancer incidence rates of the general female Swedish population.

The current investigation attempted to obtain the medical records of the 161 breast reduction patients who subsequently developed breast cancer. Our investigation also required a 3:1 ratio of women randomly selected from the cohort ( $n = 483$ ) who had not developed breast cancer, who had not died prior to the date of diagnosis of the matched case, and who matched the cases by their year of birth and year of hospital admission. Records were retrieved for 137 of the breast cancer patients (85.1%) and for 422 of the control patients (87.4%). This group of 559 patients contained 1 case with no matched control record, 19 controls with no matched case record, and 136 cases with 1–3 matched control records. The retrieved records were reviewed by trained nurse abstractors who were blinded to case or control status. The abstractors recorded the details of surgery and information on breast cancer risk factors onto standardized forms. Surgical information included the date of operation, indication, whether a preoperative mammogram was performed, amount of tissue removed from each breast, postoperative complications, and subsequent operations. Breast cancer risk factors included age at menarche, parity, age at first birth, oral contra-

ceptive use, hormone replacement therapy, gynecologic operations, family history of breast cancer, height, weight, and occupation. Information on breast size before surgery generally was not available in the medical records.

Of primary analytic interest was the relation of breast cancer risk to the amount of breast tissue removed during the breast reduction operations. Although separate information was recorded on amount of tissue removed from the left and right breast, in most instances the amounts removed were comparable between the two breasts, with a divergence of  $\geq 200$  grams for only 11.6% of the subjects. Thus, although analyses focused on the maximum amount of tissue removed from either breast, in most instances this was the amount removed from either breast. In addition, analyses considered the total amount removed from both breasts. Unconditional logistic regression analyses were conducted to assess the relation to breast cancer risk with these variables. Maximum likelihood estimates of odds ratios (ORs) were calculated both before and after adjustment for identified breast cancer risk factors.<sup>8</sup> Tests for trend for categorical variables were calculated by introducing a scored variable (i.e., 1, 2, 3) into the logistic models. Differences between ORs across categories of other factors were assessed through tests of homogeneity. We also conducted selected analyses using conditional logistic regression analysis. However, this approach necessitated eliminating unmatched elements, resulting in a substantial loss of power. Since the selected conditional logistic regression analyses generally confirmed results from the unconditional analyses, we chose the latter for presentation.

## RESULTS

Although the nationwide record-linkage study on which this investigation was based found the median age at breast reduction surgery to be 33 years,<sup>5</sup> breast cancers more commonly occurred in subjects who had their surgeries at older ages. This resulted in an older average age at breast reduction surgery among subjects selected for this study (median age at breast reduction surgery of 47 yrs for both cases and controls). Cases and controls also were found to have comparable median calendar years of surgery (1980 for cases vs. 1981 for controls), which confirmed the effectiveness of matching on this factor. The median age at breast cancer diagnosis among cases was 52 years.

The relation to breast cancer of a variety of identified risk factors is shown in Table 1. Because information often was missing from the medical records on a number of these parameters, ORs also were calculated for an unknown category for each variable. In

**TABLE 1**  
Breast Cancer by Risk Factors

Risk factor	Cases	Controls	OR	95% CI
Height (cm)				
< 160	29	75	1.00	
160–162	18	61	0.76	0.4–1.5
163–165	16	67	0.62	0.3–1.2
≥ 166	40	95	1.09	0.6–1.9
Unknown	34	124	0.71	0.4–1.3
Weight (kg)				
< 60	22	51	1.00 <sup>1</sup>	
60–69	34	108	0.83	0.4–1.6
70–79	23	100	0.88	0.4–1.8
≥ 80	25	70	1.84	0.8–4.1
Unknown	33	93	1.04	0.5–2.0
Body mass index				
< 23	25	58	1.00 <sup>1</sup>	
23–25	28	86	0.76	0.4–1.4
26–28	20	68	0.68	0.3–1.4
≥ 29	23	77	0.69	0.4–1.3
Unknown	41	133	0.72	0.4–1.3
Parity				
Parous	91	272	1.00	
Nulliparous	17	37	1.37	0.7–2.6
Unknown	29	113	0.77	0.5–1.2
Number of Children				
1	22	62	1.00	
2	43	118	1.03	0.6–1.9
3	11	49	0.63	0.3–1.4
≥ 4	11	37	0.84	0.4–1.9
Nulliparous	17	37	1.29	0.6–2.8
Unknown	33	119	0.78	0.4–1.5
Oral contraceptive use				
No	13	39	1.00	
Yes	10	27	1.11	0.4–2.9
Unknown	114	356	0.96	0.5–1.9
Hormone replacement therapy				
No	18	36	1.00	
Yes	10	23	0.87	0.3–2.2
Unknown	109	363	0.60	0.3–1.1

most instances, the proportion of unknowns was similar between the cases and controls. The results were largely consistent with the current understanding of breast cancer risk factors, with cases being heavier and more often nulliparous.<sup>9</sup> No relation with risk was apparent for height or body mass index. Information was incomplete on use of exogenous hormones, although the limited data suggested no relation to oral contraceptives or to hormone replacement therapy. Information on family history of breast cancer and ages at menarche or first birth also was rarely available in the medical records.

Among control subjects, the amount of tissue removed was related strongly to a number of characteristics (Table 2). The mean amount of breast tissue was related directly and significantly to both age and weight at surgery. As expected, weight was the strongest predictor, with the mean amount of total tissue

**TABLE 2**  
Total Amount of Breast Tissue Removed (Sum of Both Breasts) Among Controls by Selected Parameters

Characteristic	Number of controls <sup>a</sup>	Tissue removed (mean)	Standard deviation
Age at breast reduction			
< 40	118	1126.4	643.8
40–49	123	1295.2	649.6
≥ 50	158	1461.0	705.9
Unknown	3	1982.3	1018.8
Weight (kg) at breast reduction			
< 60	44	852.3	852.3
60–69	105	1022.6	508.6
70–79	99	1414.8	427.2
≥ 80	68	1995.5	848.4
Unknown	86	1260.1	645.1
Parity			
Nulliparous	35	1198.0	519.8
Parous	260	1335.5	747.3
Unknown	107	1306.9	573.1

<sup>a</sup> Excludes 20 controls for whom information on the total amount of tissue removed was not available.

removed increasing from 852.3 to 1995.5 grams across 4 weight categories. However, age had an effect independent of weight, with the largest amount of tissue removed being among heavier women (≥ 80 kgs) who had had their operations at older ages (≥ 50 yrs). Parous women also tended to have more tissue removed than nulliparous women.

Breast cancer risk was related inversely to the amount of tissue removed during the breast reduction procedures (Table 3). Adjustment for factors in addition to the matching factors (weight, parity) served to strengthen the reduced risks. Significant inverse trends ( $P < 0.001$ ) were observed for all parameters of tissue removal (left breast, right breast, maximum amount, total amount removed). Generally, subjects in the highest category of amount of tissue removed had a 70–75% lower risk than subjects in the lowest category. Considering the maximum amount of tissue removed from either breast, subjects who had ≥ 800 grams as compared with those who had < 400 grams removed had an OR of 0.24 (95% CI 0.1–0.5). An identical OR was seen when the total amount of tissue removed was considered and when subjects who had ≥ 1600 grams were compared with those who had < 800 grams removed.

We also examined whether the risks associated with amount of tissue removed varied according to a number of parameters, including indication for the operation (mainly discomfort), occurrence of postoperative complications (minority of cases with hemorrhage, infection, or necrosis), age at and interval since the operation, and selected patient characteristics (Table 4). No significant heterogeneity was observed, and

**TABLE 3**  
Breast Cancer Risk by Amount of Breast Tissue Removed

	Cases	Controls	OR <sup>a</sup>	OR <sup>b</sup>	95% CI
Maximum breast tissue (Left or right breast)					
< 400	42	75	1.00	1.00	
400–599	38	93	0.69	0.68	0.4–1.2
600–799	25	104	0.41	0.36	0.2–0.7
≥ 800	26	135	0.31	0.24	0.1–0.5
Unknown <sup>c</sup>	6	15	0.57	0.56	0.2–1.7
Total amount (sum of both breasts)					
< 800	45	79	1.00	1.00	
800–1199	31	112	0.46	0.45	0.3–0.8
1200–1599	26	99	0.43	0.40	0.2–0.7
≥ 1600	22	112	0.32	0.24	0.1–0.5
Unknown	13	20	1.07	0.98	0.4–2.2

<sup>a</sup> Odds ratios adjusted for patient's year of birth and year of surgery.

<sup>b</sup> Odds ratios (and 95% CI) adjusted for above factors, plus weight and parity. All trends were significant ( $P < 0.01$ ).

<sup>c</sup> If unknown amount from one breast, the amount removed from the other breast was considered the maximum. Unknowns therefore consist of subjects with missing information for both breasts.

amounts of tissue removed were related inversely to breast cancer risk across all examined subcategories. Inverse relations were observed across all age categories, including subjects who had had their breast reduction operations before the age of 40 years. Further discrimination of risks found this to be true for most lengths of follow-up, although subjects who had had their operations before the age of 40 years and had had follow-up times of less than 5 years showed a less protective relation to amount of tissue removed than other subjects (data not shown). Moreover, inverse relations were observed among both thin and heavy women. The association was less evident among nulliparous than parous women, although statistical assessment of the former group was limited by the small population of nulliparous women in our study.

To determine the joint influence of several factors, we calculated risks by amount of tissue removed, relating all risks to one common referent group. Although numbers for this analysis became sparse, the risk reduction was most pronounced in subjects who had large amounts of tissue removed and who also had extended follow-up. Thus, compared with subjects with the least amount of tissue removed (< 800 grams) and the shortest interval (< 5 years), the OR of those who had ≥ 1600 grams removed and more than 10 years of follow-up was 0.14 (95% CI 0.0–0.5). A similarly low risk was observed in women who had had breast-reduction surgery at young ages and, generally, had had longer follow-up periods.

**TABLE 4**  
Odds Ratios<sup>a</sup> of Breast Cancer by Total Amount of Tissue Removed According to Indications for Surgery, Postoperative Complications, Timing of Surgery, and Patient Characteristics

	Total amount of tissue removed (grams)			
	< 800	800–1199	1200–1599	≥ 1600
Indication for operation	45	31	26	22
Discomfort	1.00 (27) <sup>b</sup>	0.41 <sup>c</sup> (24)	0.45 <sup>c</sup> (26)	0.27 <sup>c</sup> (20)
Other <sup>c</sup>	1.00 (18)	0.74 (7)	0.00 (0)	0.18 (2)
Postoperative complications				
No	1.00 (42)	0.42 <sup>c</sup> (27)	0.37 <sup>c</sup> (20)	0.23 <sup>c</sup> (18)
Yes <sup>d</sup>	1.00 (3)	0.77 (4)	0.65 (6)	0.44 (4)
Age at operation (yrs)				
< 40	1.00 (19)	0.54 (9)	0.19 (2)	0.26 (3)
40–49	1.00 (12)	0.80 (11)	0.52 (8)	0.41 (7)
≥ 50	1.00 (12)	0.24 <sup>e</sup> (11)	0.32 <sup>e</sup> (16)	0.15 <sup>e</sup> (12)
Interval since operation (yrs)				
< 5	1.00 (15)	0.61 (17)	0.37 (10)	0.33 (9)
5–9	1.00 (13)	0.37 (7)	0.19 <sup>e</sup> (6)	0.18 <sup>e</sup> (9)
≥ 10	1.00 (15)	0.25 <sup>e</sup> (6)	0.49 (10)	0.11 <sup>e</sup> (4)
Weight (kg)				
< 70	1.00 (27)	0.48 (13)	0.85 (11)	0.16 (1)
≥ 70	1.00 (5)	0.32 (9)	0.22 <sup>e</sup> (12)	0.26 (19)
Parity status				
Nulliparous	1.00 (3)	0.78 (5)	0.30 (4)	0.33 (3)
Parous	1.00 (32)	0.46 <sup>e</sup> (21)	0.45 <sup>e</sup> (15)	0.29 <sup>e</sup> (13)

<sup>a</sup> Odds ratios adjusted, where appropriate, for patient's year of birth, year of surgery, weight and parity.

<sup>b</sup> Numbers in parentheses are numbers of cases.

<sup>c</sup> Includes laxity, psychological reasons, asymmetry, and other indications.

<sup>d</sup> Includes hemorrhage, infection, necrosis, and other complications.

<sup>e</sup> 95% CI excludes 1.0.

## DISCUSSION

Although several studies have reported that patients who have undergone breast reduction operations have a reduced risk of subsequent breast cancer,<sup>1–5</sup> the biologic mechanisms are unclear. Breast tumors occasionally are detected preoperatively or at the time of breast reduction procedures,<sup>10</sup> but this occurrence does not explain the continued decreases in risk over time that have been observed in many of the previous cohort studies. In testing the hypothesis that the lowered risk results from a reduced mass of breast tissue, we found a strong inverse relation between the amount of tissue surgically removed and subsequent breast cancer risk. Subjects who had ≥ 800 grams of tissue removed had a 76% decreased risk relative to those who had < 400 grams of tissue removed from either breast. This finding is consistent with a small Danish study<sup>1</sup> of 32 cases of breast cancer that observed a 70% reduction in risk for women who had ≥ 600 grams of breast tissue removed (as compared with those who had < 400 grams removed).

In attempting to determine reasons for our observed relations, we were somewhat limited by not having information on preoperative breast sizes. How-

ever, most studies that have attempted to examine the relation of breast size to breast cancer risk have not found preoperative breast size to be an important predictor of risk.<sup>11-17</sup> Presumably, this is because the breast is structurally heterogeneous, comprising varying proportions of adipose and glandular tissue, so that total breast size is only a crude indicator of glandular mass. Thus, glandular mass has been hypothesized to be a stronger risk factor for breast cancer.<sup>18</sup> Additional support for this hypothesis appears in studies that have related mammographic parenchymal patterns or proportional amounts of breast densities to increased risks of subsequent breast cancer.<sup>19-20</sup> By extension, our finding, which shows that risk can be reduced by removal of large amounts of breast tissue, supports the notion that breast cancer risk can be lowered by reducing the number of potential glandular structures at risk of cancer development.<sup>21-22</sup> However, in the absence of information on breast size, our study does not allow us to determine the relative importance of tissue removal to women with small versus large breasts.

Although breast reduction surgery may lower breast cancer risk by removing epithelial cells that are potentially at risk of malignant change, other factors may be involved. In particular, the removal of adipose and periductal stromal tissue may contribute to the lowered risk by changing the microenvironment of epithelial foci and thus affecting genotoxic activity,<sup>23</sup> aromatase expression,<sup>24</sup> or other carcinogenic mechanisms.

Most studies assessing the relation of breast reduction surgery to breast cancer risk have noted that the lowered risk appears concentrated among women whose operations were performed at 40 years of age or older.<sup>2,5</sup> It is unclear why women with operations at younger ages would not experience a similar reduction in risk, but the finding may be related to comparatively short follow-up, differential effects of breast screening before surgery, chance, or different risk factors for breast hypertrophy and breast cancer among younger and older women. In their most recent analysis, Boice et al.<sup>5</sup> observed a nonsignificant elevation in risk within the first 5 years after surgery among women operated on before age 40, suggesting that risk is related directly to age at surgery and that younger women require longer follow-up to detect any lowered risk.

In the current study, we found a reduced risk associated with greater amounts of breast tissue removed among women of all ages. Our study finding is consistent with a recent Canadian follow-up study of women with breast reduction operations, which also revealed a lowered risk of breast cancer for women of all ages.<sup>4</sup> It is of note that our findings differ from the

cohort study<sup>5</sup> on which this investigation is based. Since weight was found to be a primary determinant of breast reduction surgery, we thought that the detection of reduced risk in the cohort analyses might be obscured by the inherently higher risk of breast cancer among heavier women. However, this would pertain only to postmenopausal women, because weight is related inversely to the risk of premenopausal breast cancer, in contrast to the positive association with postmenopausal disease.<sup>14,16</sup> In general, younger women had smaller amounts of tissue removed, which might contribute to the age-related differences in breast cancer risk previously observed. Although we could not specifically compare the risks of younger versus older women in our study because date of birth was a matching factor, it is noteworthy that women who had greater amounts of tissue removed showed reduced breast cancer risks within each age group examined. Thus, it appears that removal of breast tissue has beneficial effects for women of all ages.

Several reports have suggested that bilateral prophylactic mastectomy may play an important role in reducing the subsequent risk of breast cancer in genetically susceptible women.<sup>25-28</sup> The major evidence stems from a recent Mayo Clinic study in which prophylactic bilateral mastectomy substantially reduced the risk of breast cancer among women with a positive family history.<sup>29</sup> However, concern continues to be expressed about the malignant potential of residual breast tissue following these operations, especially because a study in mastectomized rats showed that the risk of developing mammary tumors after administration of a carcinogen was not affected by the amount of tissue removed.<sup>30</sup> Thus, our finding that the risk of breast cancer is reduced in proportion to the amount of tissue removed should be reassuring to women concerned that breast reduction procedures may increase risk or obscure the detection of early breast cancers, and especially to women who elect prophylactic mastectomy because of a strong familial history and/or germline mutations of BRCA1 or 2. The finding of a "dose-response" relation between the amount of breast tissue removed and the risk of breast cancer substantiates the claim that prophylactic total mastectomy significantly reduces breast cancer risk in women at increased genetic risk.

Total mastectomy can be disfiguring, especially in the absence of breast reconstruction. Thus, one should not view surgical breast reduction as an alternative preventive strategy for women who are genetically prone to breast cancers because the operation leaves substantial amounts of tissue at risk of malignant transformation.<sup>31</sup> Instead, the lowered risk of subsequent cancer may be an added benefit of breast reduction procedures in selected women, who have

sought surgical relief from pain and discomfort.<sup>32</sup> Whether breast reduction surgery will prove useful for certain women with moderate increases in breast cancer risk (e.g., dense mammographic patterns) awaits further evaluation and comparison with the efficacy of other approaches, including intensive screening and chemoprevention.<sup>33,34</sup>

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