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REVIEW

Breast size and breast cancer: A systematic review

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KEYWORDS
Breast size;
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Summary *Background:* There are many known breast cancer risk factors, but traditionally the list has not included breast size. The aim of this study was to synthesize the literature on breast size as a risk factor for breast carcinoma by examining studies addressing this question both directly and indirectly.
Methods: A systematic review was performed searching MEDLINE from 1950 to November 2010, and updated again in February 2014. Literature was sought to assess the relationship between the following variables and breast cancer: 1) breast size; 2) breast reduction; 3) breast augmentation; and 4) prophylactic subcutaneous mastectomy. Findings were summarized and the levels of evidence were assessed.
Results: 50 papers were included in the systematic review. Increasing breast size appears to be a risk factor for breast cancer, but studies are limited by their retrospective nature, imperfect size measurement techniques and confounding variables. The evidence is stronger for risk reduction with breast reduction, including prophylactic subcutaneous mastectomy at the extreme. Generally the breast augmentation population has a lower risk of breast cancer than the general population, but it is unclear whether or not this is related to the bias of small breasts in this patient population and the presence of other confounders.
Conclusions: There is direct and indirect evidence that breast size is an important factor in the risk of developing breast cancer. Plastic surgeons are in a unique position to observe this effect. Well-designed prospective studies are required to further assess this risk factor.
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Introduction

Breast cancer accounts for over 10% of all cancers among women worldwide, making it the most common non-skin cancer among females.[1] There are many known breast cancer risk factors, including age, personal and family history and high breast density.[2] Traditionally, breast size has not been considered to be an independent risk factor. While several studies have been published examining the relationship between breast size and breast cancer, a true consensus on the issue has yet to be reached.

The aim of this study was to synthesize the literature on breast size as a risk factor for breast carcinoma. Although a possible link may be gleaned from studies that assess this issue directly, it is also useful to examine the effect of interventions that alter breast size. Plastic surgeons are in a unique position to analyze this link by due to their knowledge of patients undergoing breast reductions, breast augmentations and prophylactic mastectomies.

A systematic review was performed across four areas considered to be relevant. The literature was searched for articles examining the relationship between the following variables and breast cancer by assessing the risk of breast cancer compared to the general female population: 1) breast size; 2) breast reduction; 3) breast augmentation; and 4) prophylactic subcutaneous mastectomy.

Patients and methods

A systematic review was conducted in December 2010 using MEDLINE from 1950 to November 2010. The search was updated in February 2014 by checking for any new citations from previously identified articles. Four searches were conducted corresponding to the areas examined: breast size, breast reduction, breast augmentation and prophylactic subcutaneous mastectomy. For each search, breast cancer was added using the Boolean operator "AND" (e.g. "breast reduction AND breast cancer"). For the second search, only studies dealing specifically with the incidence of breast cancer following reduction mammoplasty in non-cancer patients were considered relevant. The search strategy protocol was determined in advance and is summarized in Table 1. Studies were limited to human subjects in the English language with female patients, specifically assessing the risk of breast cancer according to the four search areas that were deemed relevant. No specific follow-up period was required. All selected studies were graded based on the University of Oxford Center for Evidence Based Medicine Levels of Evidence[3] (Table 2). The same authors who performed the searches extracted data and summarized them to include PICOS variables (participants, interventions, comparators, outcomes, and study design). These variables, along with the level of evidence, helped assess the risk of bias in individual studies. All key reported summary measures were extracted (e.g. hazard ratio, relative risk or odds ratio). No quantitative methods were employed to perform a meta-analysis. This was an unfunded study.

Table 1 Literature search strategies.

Relationship to breast cancer being investigated	MEDLINE search strategy
#1: Breast size	Terms: "breast", "breast cancer", "breast size", "cancer", "size"
#2: Breast reduction	"breast", "breast cancer", "breast reduction", "cancer", and "reduction"
#3: Breast augmentation	"breast implants", "breast", "implants", "breast cancer", "breast augmentation" and "cancer"
#4: Prophylactic subcutaneous mastectomy	"breast", "breast cancer", "cancer", "mastectomy", "subcutaneous", and "subcutaneous mastectomy"

Results

The literature search results are illustrated in the flow diagram in Figure 1.

Breast size and breast cancer

Breast size is usually not included on exhaustive lists of risk factors for breast cancer.[4] A review of the existing literature that assesses the potential relationship between breast size and breast cancer is shown in Table 3. The overall results from the 20 papers are conflicting.[5–20]

Breast size was generally estimated based on self-reported questionnaires using brassiere size (current or in

Table 2 The University of Oxford Center for Evidence Based Medicine Levels of Evidence.

Level	Description
1A	Systematic review of randomized control trials with homogeneity
1B	Individual RCT
1C	All or none (e.g. all had a particular outcome prior to an intervention and now no such outcomes occur)
2A	Systematic review of cohort studies with homogeneity
2B	Individual cohort study
2C	Ecological studies and "outcomes" research
3A	Systematic review of case-control studies with homogeneity
3B	Individual case-control study
4	Case series or poor quality cohort and case-control studies
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"

RCT = randomized controlled trial.

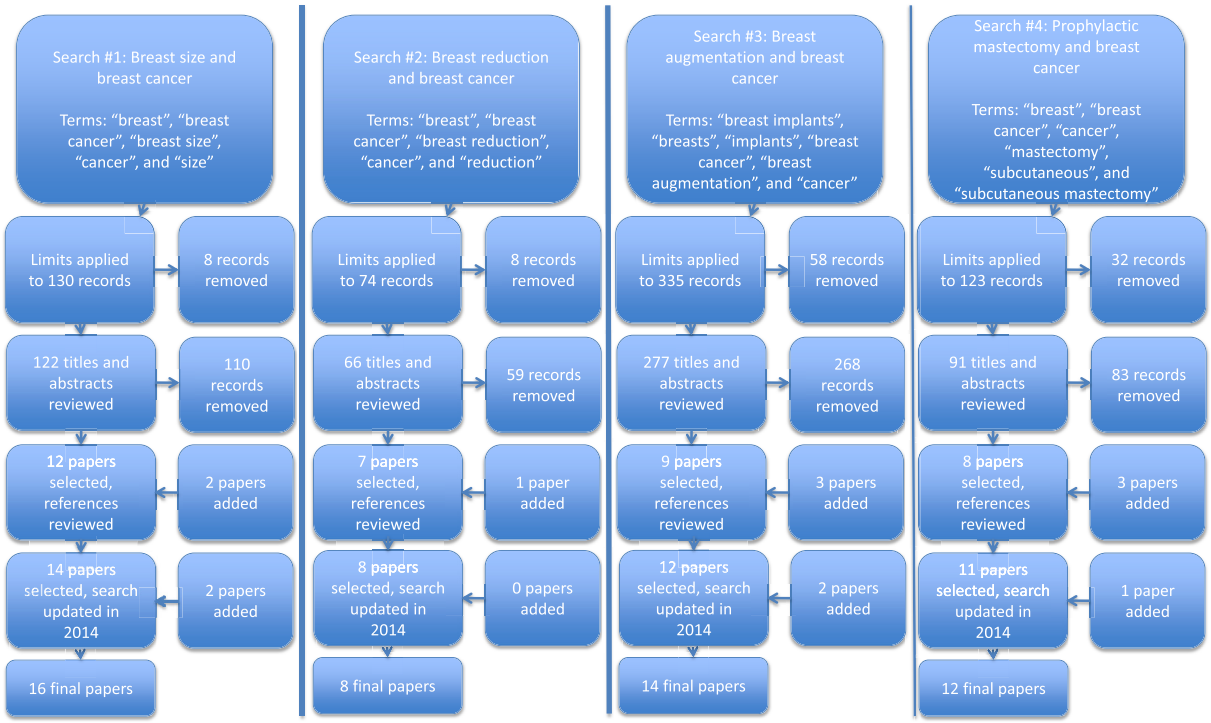

Figure 1 Flow diagram of literature searches.

early adulthood), for example using the classifications "infantile, small, average, or large",[5] or "small, medium or large".[11] One study measured brassiere size based on chest circumference.[8] Other papers calculated breast size based on mammograms, with results validated by comparisons with tissue from mastectomy patients.[6]

Brassiere use was assessed as a risk factor in one paper.[9] The authors found that premenopausal women who did not wear brassieres had half the risk. This relationship was hypothesized to be due to breast size or other factors such as the thermal effects of brassiere use.

In 2013, Williams studied a sample of 79,124 women. Cup size was a strong predictor of breast cancer mortality, even when adjusted for BMI and other covariates.[19] Another recent study by Eriksson and colleagues[20] addressed the ongoing uncertainty regarding the link between breast size and risk of cancer. Noting the heritable nature of breast size, they identified genetic variants that affected both size and risk, using data from a consumer genetics company, supplemented by online questionnaire data on brassiere size. These results are encouraging for helping understand links between breast size and cancer risk, and offer potential additional tools for screening.

Reduction mammoplasty and breast cancer

The literature supports the notion that reduction mammoplasty decreases breast cancer risk, as demonstrated by the 8 studies in Table 4.[21–28] While many plausible mechanisms have been discussed, the elimination of a pool of epithelial cells with the potential to become cancerous[29] and changes in the duct-lobular unit microenvironment through the removal of adipose tissue[21,30] seem to be the prevailing theories.

Many of the studies showing risk reductions were large cohort studies, and the risk reductions appeared to be both statistically and clinically significant.

Breast augmentation and breast cancer

Multiple studies have refuted early concerns over the potential association between silicone breast implants and the development of breast cancer. Rather, several large studies with long term follow-up have revealed a decreased risk associated with breast implants (Table 5).[28,31–44] If the latter is true, it is possible that the presence of the implant somehow decreases the risk of developing breast cancer. More likely, this population may have a lower inherent risk of breast cancer due to confounding variables including small breast size.

Prophylactic subcutaneous mastectomy and breast cancer

Subcutaneous mastectomies are performed for both therapeutic and prophylactic purposes.[45] A subcutaneous mastectomy could be considered to be an aggressive breast reduction, with the goal being a maximal reduction in breast cancer risk.

Table 6 summarizes the literature on the effect of prophylactic mastectomy on the risk of breast cancer.[46–57] There are small case series and reports of women who have developed breast cancer after undergoing the procedure.[46–49] Despite these cases, large studies have shown significant risk reductions. For example, an early large cohort study with an average follow-up of 9 years

Table 3 Summary and levels of evidence for studies examining breast size and breast cancer.

Study	Level of evidence	Design/Findings
Wynder, 1960[5]	3B	• Questionnaire with 748 cases and 748 controls • Breast size categorized as infantile, small, average or large • No significant difference (34% vs. 30%)
Katariya, 1974[6]	3B	• Breast size calculated from mammograms of 42 cases and 42 controls • No significant difference (790.4 mL vs. 790.2 mL, $p > 0.3$)
Scutt, 1997[7]	3B	• Breast size calculated from mammograms of 250 cases and 250 controls • Significantly higher median breast size among cancer group (942 mL vs. 678 mL, $p = 0.0001$)
Kolonel, 1986[8]	3B	• Self-reported interview of 272 cases and 296 controls • Brassiere size (chest circumference) compared • No significant difference (35.1 inches vs. 34.9 inches in Japanese group, 36.2 inches vs. 36.0 inches in Caucasian group)
Hsieh, 1991[9]	3B	• Interviews of 2561 cases and 7682 controls • Assessed association between brassiere-usage and cup size with breast cancer • Increased cancer risk among postmenopausal women with large cup sizes (OR = 1.27, $p = 0.026$) • Breast cancer risk 50% lower among non-brassiere-wearing premenopausal women
Joensuu, 1992[10]	3B	• Questionnaire that included cup size given to 32,557 women who then underwent a screening mammogram, with 204 cancer cases • No significant difference in cup size between group of 204 cancer cases and 612 controls randomly selected from non-cancer patients • Higher risk of breast cancer among women with D cup than A cup (OR = 1.71, 95% CI 0.85–3.41)
Dupont, 1987[11]	2B	• Interviews of 3303 women previously biopsied for benign disease with median follow-up of 17 years • Breasts self-characterized as small, medium or large • No effect of breast size on cancer risk in women without proliferative disease • Increased cancer risk among those with proliferative disease and medium and large size breasts (RR = 1.4, 95% CI 1.1–1.9, $p = 0.012$; RR = 2.1, 95% CI 1.2–3.5, $p = 0.006$)
Senie, 1993[12]	3B	• Based on enrollment in the United States' Breast Cancer Detection and Demonstration Project from 1973 to 1980 • Breast size determined from mammograms and categorized by quartiles • 261 cases compared to 291 controls • No significant difference found even after adjusting for BMI
Kato, 1995[13]	2B	• Prospective cohort of 14,291 women with pre-diagnostic mammograms • Mammographic size of 197 cases compared to 521 controls over 5.5 years • Breast size associated with cancer risk among premenopausal women (OR = 2.8, $p = 0.04$, 95% CI 1.0–7.3 for upper third)
Thurfjell, 1996[14]	2B	• Pre-diagnostic mammographic breast sizes of cohort of women followed for 5 years • 295 cases compared to 589 controls • Inverse association of breast size and breast cancer (OR = 2.09, $p < 0.05$, 95% CI 1.52–2.86)
Tavani, 1996[15]	3B	• Interviews of 2557 cases and 2556 controls • Asked to recall brassiere size at age 30 • Increased risk among women with small breasts (OR = 1.16 (95% CI 0.87–1.54 after adjusting for known risk factors)
Koch, 2004[16]	4	• Questionnaire of 146 cases and 146 controls comparing brassiere size • Based on national lingerie store data • No significant difference found
Kusano, 2006[17]	2B	• Prospective study of cup size and cancer risk among 89,268 premenopausal women over 8-year period • Women with BMI less than 25 with D cup or larger breasts at increased risk compared to A cup breasts (HR = 1.80, $p = 0.01$, 95% CI 1.13–2.88) • No difference seen in group with BMI over 25
Egan, 1999[18]	3B	• Interviews of 2015 women aged 50 to 79 with history of breast cancer and 2556 controls • Brassiere dimensions estimated from a young age compared • RR = 1.34 (95% CI 1.04–1.74) and 1.76 (95% CI 1.04–3.01) for B and C cup among those with chest circumference <34 inches ($p = 0.005$)

Table 3 (*continued*)

Study	Level of evidence	Design/Findings
Williams, 2013[19]	3B	• Sample of 79,124 women • Cup size was a strong predictor of breast cancer mortality, even when adjusted for BMI and other covariates (HR = 1.579, 95% CI 1.268–1.966, $p < 0.0001$)
Eriksson, 2012[20]	4	• Genetics analysis using commercial genetics company data and online questionnaire data on brassiere size • Genetic variants were identified affecting both breast size and cancer risk

BMI = body mass index.
CI = confidence interval.
HR = hazard ratio.
OR = odds ratio.
RR = relative risk.

Table 4 Summary and levels of evidence for studies examining breast reduction surgery and breast cancer.

Study	Level of evidence	Design/Findings
Lund, 1987[21]	2B	• Incidence of breast cancer among 1245 Danish women who had breast reduction over 28 year period from 1943 to 1971 compared to expected matched incidence (follow-up 39 years) • 18 cases vs. 30 expected (RR = 0.59, 95% CI 0.35–0.94, $p < 0.05$)
Baasch, 1996[22]	2B	• Extension of Lund's study[23] with 47 years of follow-up • 32 cases vs. 53 expected (RR = 0.61, 95% CI 0.42–0.86) • Greatest risk reduction among those with >600 g resections (RR = 0.30, 95% CI 0.10–0.69, $p < 0.05$)
Boice, 1997[23]	2B	• Incidence of breast cancer among 7720 breast reduction patients over 25 year period compared to expected rates in population using Danish national cancer registry • 29 cases vs. 54 expected (SIR = 0.50, 95% CI 0.4–0.8, $p < 0.05$) • Risk reduction only for women >40 years of age at time of surgery
Boice, 2000[24]	2B	• Incidence of breast cancer among 31,910 breast reduction patients over 28 year period compared to expected matched incidence • 161 cases vs. 224 expected with mean follow-up of 7.5 years (SIR = 0.72, 95% CI 0.61–0.84, $p < 0.05$) • Risk reduction most pronounced in older women
Brown, 1999[25]	2B	• Incidence of breast cancer among 28,042 Canadian breast reduction patients over 13 year period compared to expected matched incidence • Average follow-up 6.5 years • 101 cases vs. 166 expected with mean follow-up of 6.5 years (SIR = 0.61, 95% CI 0.50–0.74, $p < 0.05$)
Fryzek, 2006[26]	2B	• Further follow-up of Boice, 2000 extended to 16 years • 443 cases vs. 624 expected (SIR = 0.71, 95% CI 0.65–0.78, $p < 0.05$)
Brinton, 2001[27]	3B	• Analysis of volume of tissue resection and risk of cancer using population from Boice's 2000 study[26] • 161 cases compared to 483 controls from same cohort of 31,910 women • Resections above 1600 g had a significantly lower risk of cancer than subjects with resections under 800 g (OR = 0.24, 95% CI 0.1–0.5, $p < 0.05$)
Brinton, 1996[28]	3B	• Questionnaire of 2174 cases of breast cancer and 2009 controls • 10 cases with prior breast reduction vs. 13 controls (RR = 0.70, 95% CI 0.3–1.6)

CI = confidence interval.
RR = relative risk.
SIR = standardized incidence ratio.

Table 5 Summary and levels of evidence for studies examining breast augmentation and breast cancer.

Study	Level of evidence	Design/Findings
Deapen, 1986, 2007, 2012[31–33]	2B	• Incidence of breast cancer among 3111 Caucasian women from Los Angeles augmented over a 27 year period (1953–1980) compared to expected population matched incidence • Published in 1986 and updated in 2007 and 2012 • 43 cases vs. 63 expected with median follow-up of 17.7 years (SIR = 0.60, 95% CI 0.45–0.77, $p < 0.05$)
Berkel, 1992[34]	2B	• Incidence of breast cancer among 11,676 women augmented over a 13 year period from 1973 to 1986 compared to expected matched incidence • 41 cases vs. 86 expected with mean follow-up of 10.2 years (SIR = 0.48, $p < 0.01$)
Bryant, 1995[35]	2B	• Re-analysis of Berkel's 1992 data[33] using deterministic and probabilistic methods, with adjustments to database linking and age rounding • Unlike original study, no significant difference in cancer rates was detected
Brinton, 1996[28]	3B	• Interviews of 2174 younger women with breast cancer and 2009 controls • History of previous augmentation assessed • 36 cases vs. 44 controls with a history of augmentation (RR = 0.60, 95% CI 0.4–1.0)
Brinton, 2000[36]	2B	• Questionnaire of 13,488 augmented women followed for a mean of 12.9 years compared to 3936 women who underwent other procedures followed for mean of 11.6 years • No significant difference in breast cancer incidence
Pukkala, 2002[37]	2B	• Incidence of breast cancer among 2171 augmented women compared to population matched expected incidence • 50% expected number of cases among cohort, but not statistically significant
Kern, 1997[38]	2B	• Incidence of breast cancer among 680 augmented women followed for a mean of 4.6 years compared to 1022 woman control group followed for a mean of 5.4 years • Lower risk of breast cancer among implant group (RR = 0.67, 95% CI 0.20–2.17) but not statistically significant
Brisson, 2006[39] and Pan, 2012[40]	2B	• Incidence of breast cancer among 24,558 augmented women compared to control group of 15,893 women who underwent other cosmetic procedures • Up to 24 year follow-up • RR = 0.64 (95% CI 0.53–0.79) • Updated in 2012 with additional 10 years of follow-up showing RR = 0.54 (95% CI 0.49–0.59)
McLaughlin, 2006[41]	2B	• Incidence of breast cancer among 3486 augmented women compared to expected population matched incidence • SIR = 0.70 (95% CI 0.6–1.0), with mean follow-up of 18.4 years
Friis, 2006[42]	2B	• Comparison of breast cancer incidence among 1653 women augmented at a private facility, 1110 women augmented at public hospitals, and 1763 non-augmented female plastic surgery patients with expected population matched incidence • SIR = 0.70 (95% CI 0.5–1.0) among augmented groups
Lipworth, 2009[43]	2B	• Pooled data from 2006 studies by McLaughlin[41] and Friss[42] • Mean follow-up 16.6 years • Breast cancer risk reduction was statistically significant (SIR = 0.73, 95% CI 0.58–0.90)
Friis, 1997[44]	2B	• Incidence of breast cancer among 1135 augmented Danish women compared to expected population matched incidence • 8 cases vs. 8 expected with mean follow-up of 8.4 years (SIR = 1.0, 95% CI 0.7–1.6)

CI = confidence interval.
RR = relative risk.
SIR = standardized incidence ratio.

found the risk of developing breast cancer following a subcutaneous mastectomy to be only 0.5%.[50,51]

A cochrane review on prophylactic mastectomy for the prevention of breast cancer was published in 2010.[57] It covered 39 observational studies and data on 7384 women with a range of risk factors. Its findings were consistent with those in this review. Although the report noted the efficacy of the procedure for reducing the risk of breast cancer it called for more rigorous prospective studies.

Discussion

Traditional teaching has suggested that there is no relationship between breast size and the risk of developing breast cancer. Studies looking at this relationship may not support this conclusion. Volume reduction provides a clear risk reduction, whether by reduction mammoplasty or subcutaneous mastectomy. Although women with strong genetic risk may develop cancer regardless of the number

Table 6 Summary and levels of evidence for studies examining prophylactic subcutaneous mastectomy and breast cancer.

Study	Level of evidence	Design/Findings
Goodnight, 1984[46]	4	• Case series of 3 patients with breast cancer following subcutaneous mastectomies for benign breast disease
Elder, 1984[47]	4	• Case report of ductal carcinoma 8 years after subcutaneous mastectomies for fibrocystic disease
Jameson, 1997[48]	4	• Case report of metastatic breast cancer 42 years after bilateral subcutaneous mastectomies for non-malignant disease
Willemsen, 1998[49]	4	• Case report of breast carcinoma 6 years after prophylactic subcutaneous mastectomy
Pennisi, 1984[50]	2B	• Prospective cohort study of 1244 women who had prophylactic subcutaneous mastectomies • 0.5% incidence of carcinoma with 7 year mean follow-up
Pennisi, 1989[51]	2B	• Extension of Pennisi, 1984 study[49] with total cohort of 1500 patients • 0.4% incidence of carcinoma with 9 year mean follow-up
Hartmann, 1999[52]	2B	• Comparison of 575 high-risk women following prophylactic subcutaneous mastectomy with 403 sisters without surgery • Significant decrease in incidence of breast cancer in subcutaneous mastectomy group with 14-year median follow-up (7 out of 575, or 1.2% vs. 156 out of 403, or 38.7%)
Hartmann, 2001[53]	2B	• Examination of incidence of breast cancer among the 26 women from previous study cohort later identified to be BRCA1 and BRCA2 carriers • No cases were observed vs. 6—9 expected with 13.4 year median follow-up • Risk reduction 89-5-100% (95% CI 41.4%—100%)
Yiacoumettis, 2005[54]	4	• Retrospective review of 52 women who underwent bilateral prophylactic subcutaneous mastectomies with reconstruction over 9 year period • No cases of cancer with mean follow-up of 7 years
Crowe, 2008[55]	4	• Prospective study of 110 consecutive patients undergoing 149 subcutaneous mastectomies for various indications over 6 year period • No cases of cancer development in subgroup of 13 non-cancer patients who underwent surgery for prophylaxis
Ashikari, 2008[56]	4	• Retrospective review of 67 high-risk women who underwent prophylactic subcutaneous mastectomies with reconstruction • No cases of cancer with mean follow-up of 4.6 years
Lostumbo, 2010[57]	3	• Cochrane review on prophylactic mastectomy for the prevention of breast cancer • 39 observational studies were included • Data on 7384 women with a range of risk factors • Noted procedure is effective for reducing incidence of breast cancer (and associated mortality), but more rigorous prospective studies are required

of target cells, this may not be the case in those women with environmentally induced cancer. It is reasonable to consider that with fewer target cells, there is a lower likelihood for malignant transformation. Studies that show a low risk of breast cancer in the breast augmentation population support this theory as these women generally have smaller breast size than the overall population.

The literature assessing the direct role of breast size in breast cancer development has been highly inconsistent and of variable quality. The concept of breast size itself remains controversial. Breast volume and breast density must be distinguished, and the appropriate measure, whether subjective reporting, cup size, mammographic assessment or three-dimensional imaging, remains unclear. In addition, confounding variables must be controlled, such as BMI and brassiere-usage. Multiple studies have yielded results both supporting and refuting a positive association, but issues such as small sample size, unreliable size measures, and retrospective designs, limit final conclusions. Based on the current data, no clear relationship between breast size and breast cancer can be drawn, but when considering other indirect sources of information, the evidence seems to favor an association. A meta-analysis was not performed in this systematic review due to the high level of heterogeneity between studies. In addition to limitations at the study and outcome level, further biases are present at the review level, due to such reasons as publication bias and failing to identify all relevant studies.

The breast reduction literature indicates that surgery significantly decreases the potential for carcinoma. The mechanism behind this association remains poorly understood. However, given that studies have shown a direct relationship between the size of excision and degree of cancer protection,[27] it seems likely that the epithelial cell pool theory, which proposes cancer risk to be related to stem cell burden, is plausible. If the risk reduction was due

to the impact of the breast incisions, including the induction of a localized inflammatory response, one would expect that breast biopsies for benign disease would result in a reduction in breast cancer risk. The opposite, however, has been found to be true.[61]

The decreased incidence of breast cancer among women with cosmetic breast augmentation has also been fairly well established. While some authors have suggested that the silicone implant itself has an anticarcinogenic effect,[16] this is not well supported. Most papers point to a combination of factors including greater tumor palpability, higher breast self-awareness, and other confounding factors such as body mass index.[62]

The prophylactic subcutaneous mastectomy literature further supports the link between breast size and the risk of breast cancer. The subcutaneous mastectomy, essentially a radical reduction mammoplasty, has been shown in large studies to be an effective method of risk reduction in the prevention of breast cancer. Even among high-risk women with genetic predispositions, removal of large volumes of breast tissue has been shown to significantly lower risk.

Finally, there is biological evidence from both a general oncologic and breast-specific perspective that having a smaller pool of cells from which a carcinoma has the potential to develop can decrease cancer risk.[58,59] As well, there is basic science evidence to support that fat deposits in the breast may contribute to local estrogen levels,[30] and serve as repositories for fat-soluble carcinogens.[60]

Overall, a significant proportion of the literature supports an association between breast size and breast cancer. While studies directly assessing the issue remain inconclusive, the majority of the literature relating to changes in breast size is in keeping with a positive correlation.

Although further information is necessary before drawing any clear conclusions, there is significant evidence to suggest that in some women, altering breast size can affect the risk of breast cancer development. Plastic surgeons are in a unique position to observe this effect through breast reductions and prophylactic mastectomies, and to examine risks in women with a range of different breast sizes. Prospective cohort studies with proven methodology for assessing breast size are needed to provide further evidence.

Conflict of interest

Dr. Brown is a medical consultant with Allergan and a speaker for Lifecell. Dr. Jansen is completing a fellowship in breast reconstruction that is sponsored by Allergan.

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None.

Ethics

No ethics approval was obtained for this study, as it was a systematic review that did not involve human or animal subjects.

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