Topics in plastic surgery of the breast
Lapid, O.

Citation for published version (APA):
Lapid, O. (2014). Topics in plastic surgery of the breast

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
BREAST IMPLANTS AND THE RISK OF BREAST CANCER: A META-ANALYSIS ON COHORT STUDIES
ABSTRACT

BACKGROUND: Breast augmentation is a common cosmetic procedure, it may be hypothesized that patients with breast implants have an increased incidence of breast cancer.

OBJECTIVE: to perform a meta-analysis of the current literature available on the risk of breast cancer in women with cosmetic breast implants.

METHOD: Meta-analysis of observational studies. A systematic search of the English literature published by August 28th 2013 using PubMed and EMBASE for studies reporting either the relative risk (RR) or the standardized incidence ratio (SIR) of breast cancer in patients that had previously underwent cosmetic breast augmentation.

RESULTS: 17 studies were selected, representing 7 cohorts, some of the studies were follow ups on previous publications. Summary SIR and RR rates and the corresponding 95% CI were calculated, using either a random-effects (SIR) or a fixed-effects (RR) model. The overall SIR, based on 16 studies, was 0.67 (95% CI 0.60-0.76); the overall RR, based on 5 studies, was 0.63 (95% CI 0.57-0.70). Additional sensitivity analysis was performed using only the most recent updates of individual cohorts, showing a significant overall SIR estimate of 0.69 (95% CI 0.56-0.85), meaning the main findings were not affected when selecting only the most recent updates.

CONCLUSION: This meta-analysis suggests that women that underwent cosmetic breast augmentation using implants are not at increased risk of subsequently developing breast cancer.

Eline C. Noels, Oren Lapid, Jan H.N. Lindeman, Esther Bastiaannet

Submitted
INTRODUCTION
Breast augmentation is the most common cosmetic surgical procedure worldwide [1, 2]. While breast augmentation procedure rates continue to grow, so do breast cancer rates among women. In 2010, 1,643,000 cases of breast cancer were diagnosed worldwide, with an annual rate of increase of 3.1% between 1980 and 2010 [3].

It may be hypothesized that breast implants may contribute to the development of breast cancer. Such a notion is not supported by the available literature; which, in fact, suggests a lower risk of breast cancer in patients with breast implants [4]. Yet, interpretation of the available studies is hampered by potential biases and confounders [5]. However, pooling the results could show a stronger association. Meta-analysis is the use of statistical methods to combine results of individual studies. By statistically combining the results of similar studies, precision of estimates can be improved. All kind of studies can be pooled, as long as their design and outcome measure are similar [6]. Therefore, we performed a meta-analysis using state-of-the-art data analysis techniques.

METHODS
A meta-analysis was performed in accordance with the PRISMA statement for reporting systematic reviews and meta-analyses [7].

PUBLICATION SEARCH
A literature search was performed in PubMed and EMBASE on August 28th 2013 for English language articles published in all years. Articles not yet indexed for Medline were included. The search strategy for both databases consisted of terms of exposure (breast implant, breast prosthesis, breast augmentation) and terms of outcome (breast cancer, breast neoplasm, mammary carcinoma and mammary neoplasm) [appendix]. The outcome of this search included epidemiologic studies, case reports, literature reviews and letters. The references of relevant literature were checked for additional relevant articles. A reference librarian reviewed the search strategy. The titles and abstracts of the publications were retrieved.

INCLUSION CRITERIA
Screening of the titles and abstracts was performed by two of the authors (ECN, OL). Articles raising concern were discussed with a third author (EB). During the screening process, the selected reports had to meet the following criteria: (1) cohort design, (2) the exposure of interest was breast implants, (3) the outcome of interest was breast cancer, and (4) studies provided a standardized incidence ratio or relative risk with their 95% confidence intervals. No restrictions were imposed on age or length of follow-up. We included update publications for similar study populations. Cohort studies on patients receiving breast implants for reconstructive purposes were excluded.
The relative risk (RR) indicates the increased or decreased risk of disease associated with exposure to the factor of interest. A relative risk of 1 indicates that the risk is similar for the exposed and unexposed groups. A relative risk greater than 1 indicates that the exposed group has an increased risk compared to the unexposed group; whereas a relative risk of less than 1 indicates that the exposed group has a reduction in the risk of disease. The standardized incidence ratio (SIR) is the ratio of the observed number of cases to the expected number of cases. For both risk estimates, 95% confidence intervals (CI) were calculated; p values were two-sided.

**Data extraction**

Data was individually extracted (ECN) from the studies. The following information was extracted from the studies: first author’s name, publication year, study geographic location, data resources used, mean follow-up, sample size, average age of the cohort, percentage of patients with silicone implants, and estimated effects with their 95% confidence interval. We also noted exclusion criteria of each study and adjustment factors. During data abstraction additional information was extracted concerning setting of the cohort (private plastic surgery practice or public hospital) and if an induction period was applied.

**Statistical methods**

Meta-analyses were performed separately for studies that reported an SIR and studies that reported an RR. Summary SIR and RR rates for breast cancer following breast augmentation mammoplasty using breast implants and the corresponding 95% CI were calculated using STATA/SE version 12.0 (Stata Corp, College Station, Texas, USA). We used data as reported in the studies. Pooled SIR and RR and their 95% CI were calculated, using either a random-effects (SIR) or a fixed-effects (RR) model, depending on the number of included studies and the amount of heterogeneity observed. Some of the authors presented an update of other studies or an update of their previous analyses. In addition to the meta-analysis including all studies, a meta-analysis was performed including only the most recent results of those studies (sensitivity analysis). Cochran’s Q and $I^2$ were used a measure of heterogeneity. Cochran’s Q is calculated as the weighted sum of the squared differences between individual studies and the pooled effect across studies, with the weights being those used in the pooling method. $I^2$ describes the percentage of total variation across studies, which is due to heterogeneity rather than chance. A funnel plot was used to assess publication bias.

**RESULTS**

**Literature search**

The full search strategy is listed in appendix 1. Using terms of exposure and terms of outcome, we identified 2063 titles. Subsequently, 1062 articles were excluded base on the exclusion criteria. An additional 126 articles were excluded using the additional
Reports identified in PubMed, n=709

Reports identified in Embase, n=1354

Total references retrieved from databases, n=2063

Reports excluded, n=1303:
- Because of publication type (review, case report), n=1062
- Because of language other than English, n=126
- Duplicates, n=115

Reports first screened based on title and abstract, n=760

Reports excluded, n=743

- Pooled analyses, n=1
- Re-analyzed report, n=1
- Different outcome measure, n=1

Full text reports reviewed for eligibility, n=17

Cohort studies included in meta-analysis, n=17, consisting of 7 study populations

Full-text reports included after checking references of eligible articles, n=3

Figure 1. Flow diagram of the search strategy

filter ‘English’ for ‘Languages’ (Figure 1 – Flow Diagram). After duplicates were removed, the remaining 760 articles were included for primary screening. Seventeen full text reports were selected; three studies were excluded after reaching consensus with a third author. One because it contained a pooled analysis of two previous studies [8], the second because it was re-analyzed and republished because possible errors were noted shortly after its publication [9], and the third article was excluded because of a different outcome measure [10]. Three more articles were added after reviewing the references of eligible articles [11-13].

Study characteristics

Seventeen cohort studies were selected for the review, and 7 studies were selected for the meta-analysis. The mean follow-up ranged from 6.0 to 23.7 years. The calendar year of surgery ranged from 1953 to 1995; the latest follow-up was in 2007. Seven cohorts were performed in the US, 3 in Canada, and 7 in Europe. Four cohorts applied an induction period; this assumes that breast cancer developing during this period may rather be the result of a process present prior to surgery, than the result of exposure. Induction periods of 1 year were applied to 3 cohorts [14-17]; one cohort applied an induction period of 30 days [12, 18, 19]. The included studies encompassed a total of 62,092 patients, with cohort sizes ranging from 680 up to 24,558 patients.
Three cohorts imposed age restrictions; a lower threshold of 18 [15, 17], and an upper threshold of 55 [11, 13, 20, 21] and one study was limited to women aged between 20 and 64 years [16]. A wide variation was seen in the types of implants used [22]. The characteristics of the 17 cohort studies can be seen in Tables 1 and 2.

### Table 1. Characteristics cohort studies SIR. The last report of a cohort is highlighted

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Implantation period</th>
<th>End of follow-up</th>
<th>Patients (n=)</th>
<th>External rate (n=)</th>
<th>Risk estimate SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brinton 2000</td>
<td>USA</td>
<td>1962-1988</td>
<td>1996</td>
<td>13488</td>
<td>152,2</td>
<td>0.89</td>
<td>0.80-1.10</td>
</tr>
<tr>
<td>Brisson 2006</td>
<td>Canada</td>
<td>1974-1989</td>
<td>1997</td>
<td>24558</td>
<td>331,6</td>
<td>0.57</td>
<td>0.49-0.65</td>
</tr>
<tr>
<td>Bryant 1995</td>
<td>Canada</td>
<td>1973-1986</td>
<td>1991</td>
<td>10835</td>
<td>^^</td>
<td>0.76</td>
<td>0.55-1.02</td>
</tr>
<tr>
<td>Deapen 1986</td>
<td>USA</td>
<td>1953-1980</td>
<td>1981</td>
<td>3112</td>
<td>15,7</td>
<td>0.57</td>
<td>0.26-1.09</td>
</tr>
<tr>
<td>Deapen 1992</td>
<td>USA</td>
<td>1986</td>
<td>3112</td>
<td>31,7</td>
<td>0.66</td>
<td>0.41-1.01</td>
<td></td>
</tr>
<tr>
<td>Deapen 1997</td>
<td>USA</td>
<td>1991</td>
<td>3182</td>
<td>49,2</td>
<td>0.63</td>
<td>0.43-0.90</td>
<td></td>
</tr>
<tr>
<td>Deapen 2007</td>
<td>USA</td>
<td>1994</td>
<td>3139</td>
<td>62,6</td>
<td>0.69</td>
<td>0.50-0.93</td>
<td></td>
</tr>
<tr>
<td>Deapen 2012</td>
<td>USA</td>
<td>2006</td>
<td>3139</td>
<td>99</td>
<td>0.60</td>
<td>0.45-0.77</td>
<td></td>
</tr>
<tr>
<td>Friis 1997</td>
<td>Denmark</td>
<td>1977-1992</td>
<td>1993</td>
<td>1135</td>
<td>7,8</td>
<td>1.00</td>
<td>0.40-2.00</td>
</tr>
<tr>
<td>Friis 2006</td>
<td>Denmark</td>
<td>1973-1995</td>
<td>2002</td>
<td>2767</td>
<td>43,8</td>
<td>0.70</td>
<td>0.50-1.00</td>
</tr>
<tr>
<td>McLaughlin 1994</td>
<td>Denmark</td>
<td>1977-1989</td>
<td>1989</td>
<td>824</td>
<td>4,2</td>
<td>0.24</td>
<td>0.00-1.31</td>
</tr>
<tr>
<td>McLaughlin 1995</td>
<td>Sweden</td>
<td>1965-1983</td>
<td>1989</td>
<td>1756</td>
<td>11,2</td>
<td>0.63</td>
<td>0.30-1.30</td>
</tr>
<tr>
<td>McLaughlin 1998</td>
<td>Sweden</td>
<td>1965-1993</td>
<td>1993</td>
<td>3473</td>
<td>25</td>
<td>0.70</td>
<td>0.40-1.10</td>
</tr>
<tr>
<td>McLaughlin 2006</td>
<td>Sweden</td>
<td>1965-1993</td>
<td>2002</td>
<td>3486</td>
<td>71,9</td>
<td>0.70</td>
<td>0.60-1.00</td>
</tr>
<tr>
<td>Mellemkjaer 2000</td>
<td>Denmark</td>
<td>1973-1995</td>
<td>1995</td>
<td>2767</td>
<td>17,3</td>
<td>0.90</td>
<td>0.50-1.50</td>
</tr>
<tr>
<td>Pan 2012</td>
<td>Canada</td>
<td>1974-1989</td>
<td>2007</td>
<td>24558</td>
<td>^^^</td>
<td>0.54</td>
<td>0.49-0.59</td>
</tr>
</tbody>
</table>

^^ For induction period of 0 years
^^^ Not provided by authors

### Table 2. Characteristics cohort studies RR

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Implantation period</th>
<th>End of follow-up</th>
<th>Patients (n=)</th>
<th>Controls (n=)</th>
<th>Risk estimate RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan 2012</td>
<td>Canada</td>
<td>1974-1989</td>
<td>2006, 2007</td>
<td>24558</td>
<td>15893</td>
<td>0.60</td>
<td>0.53-0.69</td>
</tr>
<tr>
<td>Brisson 2006</td>
<td>Canada</td>
<td>1974-1989</td>
<td>1997</td>
<td>24558</td>
<td>15893</td>
<td>0.64</td>
<td>0.53-0.79</td>
</tr>
<tr>
<td>Friis 2006</td>
<td>Denmark</td>
<td>1973-1995</td>
<td>2002</td>
<td>1630 *</td>
<td>1708 *</td>
<td>0.70</td>
<td>0.40-1.30</td>
</tr>
<tr>
<td>Brinton 2000</td>
<td>USA</td>
<td>1962-1988</td>
<td>1996</td>
<td>13488</td>
<td>3936</td>
<td>0.79</td>
<td>0.60-1.10</td>
</tr>
<tr>
<td>Kern 1997</td>
<td>USA</td>
<td>1980-1993</td>
<td>1993</td>
<td>680</td>
<td>1022</td>
<td>0.67</td>
<td>0.20-2.17</td>
</tr>
</tbody>
</table>

* Private clinic cohort, women without cancer diagnosis prior to entry date
Deapen and colleagues published updates of the same cohort [23-27]. They identified Caucasian augmentation mammoplasty patients operated between 1953 and 1980 from medical records in the private practices of 35 plastic surgeons in Los Angeles County. Record linkage was used to identify breast cancer cases among these patients. The observed breast cancer cases were compared with age and social-economic-status-specific breast cancer incidence rates extracted from a population based cancer registry (Los Angeles County Surveillance Program). Based on these numbers, the observed cases of breast cancer among women with breast implants were (significantly) lower. The latest update published in March 2012 reported 59 cases observed compared to 99.0 expected, resulting in a SIR of 0.60 (95% CI 0.45-0.77) with a median follow-up of 17.7 years [25]. Since the study cohort was generally younger than the breast cancer cases, an additional analysis was performed for those implanted after the age of 40. This resulted in the observation of 14 cases, versus 18.8 expected cases (SIR=0.75; 95% CI 0.41-1.25). Furthermore, an estimate risk by years of exposure was performed in which no significant increase was found [23].

The largest breast implant cohort study to date was conducted by Brisson et al.[15]. Their implant cohort (n=24,558) comprised women 18 years or older, residing in Ontario or Quebec, with a bilateral cosmetic augmentation mammoplasty performed in the years 1974-1989. For internal comparison, there was a control cohort (n=15,893) consisting of similarly aged women who underwent other types of cosmetic surgery, matched by year of entry and by surgeon. Excluded from both cohorts were women with any previous major breast surgery (i.e. reduction mammoplasty, breast lift and breast cancer surgery), women with a male genotype, women with a history of cancer at any site prior to breast implant surgery, and women receiving different types of implants for the left and right breasts. The breast cancer incidence rates for both cohorts were obtained through record linkage using national and provincial mortality databases and subsequently cancer registries. Internal comparison (adjusted for age, province of residence and calendar period) revealed reduced incidence rates of breast cancer among the implant cohort (RR=0.64; 95% CI 0.53-0.79). Comparison of breast cancer incidence rates with the general population using provincial cancer registry, showed 331.6 cases expected, while 188 cases of breast cancers were identified among women in the implant cohort (SIR=0.57; 95% CI 0.49-0.65). No significant differences were found in additional analyses for type of implant, site of implant or fill volume.

In 2012 Pan and colleagues provided an update on this Canadian cohort, with 10 more years of follow-up to 2006 for Quebec and 2007 for Ontario [17]. They observed a total of 414 incidents of breast cancer, while 767 should have been expected in the implant cohort (SIR=0.54; 95% CI 0.49-0.59). The internal comparison showed significantly reduced rates for breast cancer as well (Incidence Rate Ratio=0.60; 95% CI 0.53-0.69). Dissimilar to the observations of Brisson in 2006 [15], breast cancer incidence for separate implant sites differed significantly. Fewer cases were observed
for sub glandular implants (Incidence Rate Ratio=0.78; 95% CI 0.63-0.96). Again, no significant difference was detected for type of implant and fill volume.

Several cohort studies conducted in Scandinavia show similar results. In Sweden, McLaughlin et al. performed a cohort study among 1756 women with cosmetic breast augmentation between 1965 and 1983 [12]. Seven cases of breast cancer were observed (SIR=0.63; 95% CI 0.30-1.30). However, they were not able to adjust for risk factors for breast cancer. Three years later, they published an update with a considerable increase in sample size and extended follow-up time [19]. They now included women who had augmentation mammoplasty from 1965 to 1993. A nationwide linked registry was used. Women with cancer diagnosed prior to implant surgery, or women who died or emigrated prior to follow-up were excluded. The mean follow-up was 10.3 years. Breast cancer occurred less than expected (SIR=0.70; 95% CI 0.4-1.1) based on the general female population of Sweden. A second extension of this nationwide cohort study in Sweden included an additional 9 years of follow-up [18]. Again, the incidence of breast cancer was below expectation, based on 53 cases observed and 71.9 cases expected (SIR=0.70; 95% CI 0.60-1.00). SIRs of breast cancer stratified by time since breast implantation did not show a significant increase or decrease.

McLaughlin et al. identified a Danish implant cohort of 824 women that received implants between 1977 and 1989, by linking hospital discharge data to the national cancer registry [13, 28]. Only one case of breast cancer was identified (SIR=0.24; 95% CI 0.00-1.31). Friis and colleagues expanded this Danish cohort to 1135 women with an additional 3 years of patient accumulation and 4 more years of follow-up [11]. In distinction to what McLaughlin presented previously, the standardized incidence ratio was 1 (8 cases observed, 7.8 expected).

The Danish cohort was further extended, though excluding women aged 55 years or older [21]. The group provided by Friis of 1135 women receiving cosmetic breast implants in public hospitals was further assessed for eligibility. This resulted in the inclusion of 1114 women in the implant cohort. Furthermore, 1653 women who had received breast implants in private plastic surgery clinics during 1973-1995 were identified from medical records from 8 out of 27 private clinics. Follow-up was carried out till 1995. Risk estimates were adjusted for geographic area of residence providing a combined standardized incidence ratio of 0.9 (95% CI 0.50-1.50) based on 16 cases observed and 17.3 cases expected.

To our knowledge, the latest update on this Danish cohort appeared in 2006 [20], providing 7 years of additional follow-up. Beside the general analysis, an additional primary cancer analysis was performed on the private clinic cohort (n=1630) compared to a control cohort (n=1708). The control cohort was obtained from medical records from the same private plastic surgery clinics, and matched for age (±3 years) and calendar year (±18 months). Though, women in the control cohort were slightly older. The internal analysis comparing women with breast augmentation surgery with
women who received other types of cosmetic surgery, showed a non-significant RR of 0.7 (95% CI 0.4-1.3). An SIR of 0.7 (95% CI 0.5-1.0) was found when the group was compared to the general population. Furthermore, stratification by age at implantation, calendar year at implantation, follow-up, and attained age showed no statistically significant ratios.

Brinton and colleagues [14] gained access to medical records of 18 plastic surgery practices, in six geographic areas of the U.S., chosen for having performed large numbers of cosmetic breast implant surgeries prior to 1989. They included 13,488 eligible patients that underwent surgery during the period 1962-1988. A control cohort matched for age, consisted of 3936 patients, who had other type of plastic surgery during the same time period. The calculated risk estimates were adjusted for age at risk, calendar year of follow-up, and race. An external analysis using breast cancer incidence rates of the National Cancer Institute revealed an SIR of 0.89 (95% CI 0.8-1.1) for the implant group. No statistical significant difference was observed for distinction by duration of follow-up, age, calendar year, or type of implant. The additional internal analyses showed a significantly reduced risk of breast cancer among implant patients, who received them after 1984 (RR=0.36; 95% CI 0.20-0.80).

A state-wide cohort study in Connecticut, U.S., compared women who received breast implants during the period 1980-1993 to women that underwent routine sterilization with similar entry and screening criteria [22]. Women with previous breast and non-breast cancers were excluded. The implant group consisted of 680 women, the control group of 1022 women. No statistical significant difference in breast cancer rate was found (RR=0.67; 95% CI 0.20-2.17).

Berkel et al. published a cohort study concerning all women in Alberta, Canada, who underwent cosmetic breast augmentation from 1973 through 1986. However, shortly thereafter, problems involving study methods were identified [9]. Bryant and Brasher therefore performed a re-analysis on this cohort [16]. Included were women aged between 20-64 years, with their first (bilateral) implantation between 1973 and 1986. SIRs were calculated for induction periods of 0, 1, 5, and 10 years. No significant differences were found.

**META-ANALYSIS**

We performed a meta-analysis to obtain the pooled risk. The overall standardized incidence ratio and its 95% confidence interval showed a statistically significant inverse association between breast implants and breast cancer. For studies using standardized incidence rates, the summary SIR was 0.69 (95% CI 0.56-0.85) (Figure 2 – Forest plot SIR); for studies reporting relative risks, the summary RR was 0.63 (95% CI 0.57-0.70) (Figure 3 – Forest plot RR).

All individual studies, with the exception of the 1997 study by Friis and colleagues [11], reported SIRs of less than 1, indicating women with breast implants have a lower
risk of subsequent breast cancer compared to the general population. However, this was statistically significant only in the Canadian and Los Angeles cohorts [17, 25]. All five studies reporting an RR showed it to be less than 1, indicating women with breast implants have a lower risk of subsequent development of breast cancer. This was significant only in the Canadian cohort reported by Brisson [15] and Pan [17].
RISK OF BIAS
The main risk of bias within these cohort studies would be the result of confounding by indication and loss of follow-up, particularly because of migration, since most studies used record linkage at a local level. Potential confounders include the exclusion of women with a history of cancer at sites other than breast, like in the study of Brisson et al. [15], and the setting in which the cohort took place. This is due to differences in factors such as socioeconomic status, reproductive factors, lifestyle, and past history. Although some studies corrected for these factors by matching of control cohorts, a residual bias may remain.

No significant heterogeneity was detected in the meta-analysis of the studies with RR estimates (p=0.6). However, significant heterogeneity was observed in the meta-analysis of studies with SIR estimates (p<0.05). The funnel plots showed considerable asymmetry (Figures 4 and 5).

DISCUSSION
In this review we examine the association of breast cancer with previous breast implant surgery, by performing a meta-analysis of 17 cohort studies. There has never been a paper reporting a significantly increased risk of breast cancer in patients that received breast implants. However some previous studies suffer from heterogeneity in that often also include non-augmentation indications for breast implants. As opposed to previous studies we included exclusively augmentation patients, reconstruction indications for the use of implants were excluded. The overall results show no increased risk of breast cancer associated with previous implant breast augmentation, and even

![Funnel plot SIR (Standardized Incidence Ratio)](image-url)
suggest that the incidence is lower than expected. This meta-analysis confirms the results of previous reviews [5, 29, 30]; furthermore, no significant increased risk was observed for attained age [14, 20, 25, 26], years of exposure [15, 18, 20, 25, 26] and type of implant [14, 15]. However Pan et al. reported a 7 fold increase of breast cancer in the first five years after the use of polyurethane coated implants, but this IRR decreased progressively over time [17]. From the available data it was not possible to know the histological type of breast cancer.

This meta-analysis was considered timely because of raising concern about the safety of breast implants, and the need to focus on the aesthetic use of these implants. In contrast to earlier reviews by Hoshaw [5] and Deapen [30], we omitted some of the studies [31-34]. Either because the full text was not available, or, most importantly, because the publications included women that received breast implants for reconstructive purposes, thus women with a potentially higher risk of local recurrence or developing cancer in the opposite breast [35]. We did not perform quantitative analysis on case control studies, since this had been previously done by Hoshaw et al. [5]. We found no new case control studies. An interesting issue in the cohorts published by Deapen is the inclusion of patients starting in 1953 [23-27]. Silicone implant were first introduced in 1962, thus we assume the implants used were of other sorts, this could have an had an influence on the results [36].

A possible confounder in the study conducted by Deapen et al., was the inability to adjust risk estimates for some known breast cancer risk factors, since they weren’t authorized to contact patients to obtain additional information [27].

The results may also be influenced by more generic factors, such as record-linkage design, therefore missing patients migrating or travelling from distant locations for

---

**Figure 5.** Funnel plot RR (Relative Risk)
surgery. It should also be taken in account that, there was a large variation in sample size, ranging from 680 patients in the smallest group up to 24,558 patients in the largest cohort.

In this meta-analysis, studies measuring risk ratios showed a more pronounced inverse association compared to studies measuring standardized incidence ratios. Such an effect may be explained by the fact that the general population may differ from patients seeking cosmetic augmentation mammoplasty regarding to risk factors for breast cancer. These factors may include demographics, lifestyle, reproductive and medical characteristics [37]. However, these differences are also applicable for women with breast implants compared to women who have had other cosmetic surgery as was done in the study of Brinton et al. [14], Brisson et al. [15], Friis et al. [20], Mellemkjaer et al. [21], and Pan et al. [17]. In addition the general cohorts used were also biased as they supposedly represented the unexposed cohort, but inevitably also included an unknown, albeit small, percentage of women with breast implants.

Another potential confounder could be BMI and breast size. As usually skinnier women with smaller breasts opt for breast augmentation one could claim that they have a smaller risk of breast cancer since they have less breast tissue. However, this is not the case, since it has been shown that BMI and breast size do not differ significantly between women with breast cancer and women in the general population [38].

An issue not mentioned in the studies is the possibility that patients that were included in the cohorts had their implants removed. In the design of the studies this cannot be assessed. We therefore refer to the original exposure of implantation, although we may assume that the majority of the patients kept their implants.

Additional biases include the applied language restriction and publication bias. However, by reviewing the references of obtained eligible articles, no additional articles in a language different from English were found. Therefore, we believe this bias is limited. Publication bias might explain some of the risk we observed, as suggested by the shape of the funnel plot being considerably asymmetric. However, the overall RR estimate of studies measuring RRs was homogenous. Therefore, we consider it can still be stated that women that underwent breast augmentation have a lower risk of subsequent breast cancer compared to women undergoing other types of surgery. This may indicate breast implants hold a protective effect of developing breast cancer.

**CONCLUSION**

Our review focused exclusively on patients with cosmetic breast augmentation, patients with breast reconstructions were excluded. The overall results show no increased risk of breast cancer associated with previous implant breast augmentation, and even suggest that the incidence is lower than expected. Future research should focus on possible explanations for these phenomena.
REFERENCES


APPENDIX 1

SEARCH STRATEGY: PubMed

“Breast Implants/adverse effects”[Majr]
“Breast Implants/statistics and numerical data”[Majr]
“Breast Implants”[TIAB]
“Breast Implant”[TIAB]
“Breast Prosthesis”[TIAB]
“Breast Prostheses”[TIAB]
“Breast Implantation/adverse effects”[Majr]
“Breast Implantation/statistics and numerical data”[Majr]
“Breast Implantation”[TIAB]
“Breast Implantations”[TIAB]
“Breast Augmentation”[All fields]
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
“Breast Neoplasms”[MESH]
“Breast Neoplasms”[all fields]
“Breast Neoplasm”[all fields]
“Breast Tumor”[all fields]
“Breast Tumors”[all fields]
“Breast Tumor”[all fields]
“Breast Tumors”[all fields]
“Mammary Carcinoma”[all fields]
“Mammary Carcinomas”[all fields]
“Mammary Neoplasm”[all fields]
“Mammary Neoplasms”[all fields]
“Breast Cancer”[all fields]
“Cancer of Breast “[all fields]
“Cancer of the Breast”[all fields]
13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
12 and 27
“Review”[Publication Type]
“review”[TI]
“Case Reports”[Publication Type]
“case report”[TI]
29 or 30 or 31 or 32
28 not 33
34 and filters: English, full text available