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RESEARCH

Breast cancer detection and survival among women with cosmetic breast implants: systematic review and meta-analysis of observational studies


OPEN ACCESS

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Abstract

Objectives To evaluate whether the stage distribution among women diagnosed as having breast cancer differs between those who have received breast implants for cosmetic purposes and those with no implants and to evaluate whether cosmetic breast augmentation before the detection of breast cancer is a predictor of post-diagnosis survival.

Design Systematic review of observational studies with two meta-analyses.

Data sources Systematic search of the literature published before September 2012 conducted in Medline, Embase, Global health, CINAHL, IPAB, and PsycINFO.

Study selection Eligible publications were those that included women diagnosed as having breast cancer and who had had augmentation mammaplasty for cosmetic purposes.

Results The overall odds ratio of the first meta-analysis based on 12 studies was 1.26 (95% confidence interval 0.99 to 1.60; P=0.058; I^2=35.6%) for a non-localized stage of breast cancer at diagnosis comparing women with implants who had breast cancer and women without implants who had breast cancer. The second meta-analysis, based on five studies, evaluated the relation between cosmetic breast implantation and survival. This meta-analysis showed reduced survival after breast cancer among women who had implants compared with those who did not (overall hazard ratio for breast cancer specific mortality 1.38, 95% confidence interval 1.08 to 1.75).

Conclusions The research published to date suggests that cosmetic breast augmentation adversely affects the survival of women who are subsequently diagnosed as having breast cancer. These findings should be interpreted with caution, as some studies included in the meta-analysis on survival did not adjust for potential confounders. Further investigations are warranted regarding diagnosis and prognosis of breast cancer among women with breast implants.

Introduction

Cosmetic breast augmentation has become increasingly popular.[1] In the United States, for example, cosmetic breast augmentation was the most commonly performed cosmetic surgical procedure in 2011; 307 000 surgeries were performed,[2] an increase of approximately 800% compared with the early 1990s. Although breast augmentation is popular, controversies about the long term health effects of breast implants remain.

The weight of evidence from epidemiological studies indicates that cosmetic breast implants are not associated with increased risk of breast cancer.[3-26] Concern remains, however, that implants may impair the ability to identify breast cancer at an early stage by mammography because cosmetic breast implants are radio-opaque, impairing the visualization of breast tissue with mammography and making detection of breast cancer at an early stage more difficult.[4 27-29] Specialized radiographic techniques have been developed for women with breast implants to improve visualization, which involve displacing the implant posteriorly against the chest wall and pulling breast tissue over and in front of the implant.[29-31] However, one third of the breast is still not adequately visualized despite such techniques, leading to an increase in false negative mammograms.[28] An estimated one in eight US women will be diagnosed as having breast cancer at some time in their lives.[32] Therefore, some women with breast implants will eventually develop breast cancer, which raises

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concerns about the possible effects of implants on detection of breast cancer.

Most studies that have evaluated the detection of breast cancer among women with cosmetic breast implants compared the stage distribution of breast cancer at diagnosis between women with and without implants. The findings from these studies have been inconsistent. For instance, some studies reported that women with breast augmentation may be more likely to be diagnosed as having advanced cancers,[18 27 33 34] whereas others have reported no such difference.[8 10 13 15 17 19-21 25 35-43] These conflicting results may be explained by methodological problems within studies, as well as the small number of cases of incident breast cancer in these studies which limits statistical power to obtain significant results. In addition to the question of stage of breast cancer at diagnosis, no study to date has been able to establish that women with breast implants, although they may receive a diagnosis at a more advanced stage, have a poorer survival following diagnosis of breast cancer compared with women without implants, but these studies were also impaired by relatively low statistical power.[8 10 18 34 39-41] Better understanding of the detection of breast cancer and survival patterns following diagnosis of breast cancer among women with implants will aid in giving clear information on the consequences of breast augmentation surgery to these women and their physicians. The fact that implants may interfere with the early detection of breast cancer is particularly relevant and carries with it important clinical and public health implications.

Most recent reviews that summarized the evidence of the long term effects of cosmetic breast implants concluded that they were not associated with advanced breast cancers and nor was survival affected.[9 44 45] Although these papers provided a timely synthesis of the scientific literature on this question, they were not presented as systematic reviews and did not provide a quantitative meta-analysis of published studies. Through a systematic literature search, we have identified additional papers published in the past decades that were not captured by previous reviews, as well as three more recent publications,[8 18 34] providing suitable data for a quantitative meta-analysis on the diagnosis and prognosis of breast cancer among augmented women.

Specifically, our objectives were to verify the stage distribution of breast cancer and post-diagnosis survival among women with cosmetic breast implants compared with women without implants by means of a systematic review and two meta-analyses in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) reporting guidelines.[46] We also sought to identify sources of heterogeneity in risk estimates in the existing literature and to identify gaps in the current state of knowledge. This investigation is important to consolidate the existing knowledge on the long term effects of cosmetic breast implants.

Methods

Search strategy

To identify eligible studies published before September 2012, we applied a systematic literature search strategy to the following electronic databases: Medline, Embase, Global health, CINAHL, IPAB, and PsycINFO. We also searched the Cochrane Library's Database of Systematic Reviews. We used the following keywords and subject headings in combination to identify relevant articles in electronic databases: breast neoplasms AND (breast implants OR breast augmentation OR mammaplasty OR mammoplasty OR breast implantation OR breast prosthesis) AND (women without implants OR non augmented women) AND (delayed diagnosis OR prognosis OR survival OR delayed detection OR staging). We manually examined reference lists from retrieved articles[8 10 13 15 17-21 25 27 34-43 47] and published reviews[9 16 23 44] to identify additional manuscripts. Eligible articles were original, peer reviewed, published studies. We reviewed abstracts from identified articles to assess eligibility. Additionally, as direct contact with experts has been shown to be an effective method of retrieving relevant articles, we surveyed international experts who published papers on detection of breast cancer among women with cosmetic breast implants and associated survival rate patterns to request any relevant published or unpublished scientific articles.[48] The search was limited to French and English articles.

Study eligibility

Eligible publications (that is, case-control studies, cohort studies, or cross sectional studies) were those that included women diagnosed as having breast cancer and who had had antecedent augmentation mammaplasty for cosmetic purposes. The comparison group consisted of women diagnosed as having breast cancer who had had other common elective cosmetic surgeries or who were from the general female population.

Eligible publications for the evaluation of the association of breast implants with the stage distribution of breast cancer had to include the number of women with breast implants diagnosed as having breast cancer (exposed group) and women without implants diagnosed as having breast cancer (unexposed group) per stage of breast cancer at diagnosis or per status of nodal involvement, metastases, or both. We used measures of association describing the odds of having non-localized breast tumors (nodal involvement positivity, metastases to distant sites, or both) comparing the exposed breast cancer cases with the unexposed cases if they were provided in the paper. Otherwise, we calculated the crude odds ratios, their respective standard errors, and 95% confidence intervals from the contingency tables.

Publications eligible for the evaluation of breast implants and survival following diagnosis of breast cancer provided either hazard ratios comparing the mortality rate due to breast cancer after diagnosis between the exposed and unexposed group or provided Kaplan-Meier breast cancer specific survival curves graphically for women with breast cancer with and without implants. For these last studies, we estimated hazard ratios by using the spreadsheet provided by Tierney et al,[49] based on published statistics provided in the manuscripts, and by extracting data directly from Kaplan-Meier survival curves by using recommended techniques for time to event meta-analysis.[50 51]

When several publications were available for the same study group, we retained the most recent one for analysis. We excluded publications without a comparison group for the women with implants. We also excluded those that did not provide measures of association and did not provide crude numbers in contingency tables allowing calculation of measures of association regarding stage of breast cancer at diagnosis.

A certified librarian did the search, and two authors (EL and SYP) independently excluded studies at the first stage of evaluation for eligibility. The two authors discussed studies identified for a more detailed assessment on the basis of the abstract and title.

Data abstraction

Two authors (EL and SYP) independently extracted characteristics of studies and resolved any uncertainty through

discussion. The characteristics extracted were source of data on implant, source of data on breast cancer diagnosis, source of data on mortality, assessment of stage of breast cancer, nodal involvement, type of comparison group, number of women with implants with breast cancer, number of women without implants with breast cancer, mean length of follow-up, average age at diagnosis of breast cancer, whether statistical adjustment for potential confounders was done (for example, adjusting for age at diagnosis, period of diagnosis) and results (cell counts, odds ratios, hazard ratios, and 95% confidence intervals). Adjusted estimates were always selected over unadjusted estimates when provided in the paper. We created a dichotomous variable for the exposure variable (presence of breast implants with breast cancer versus no implants with breast cancer) and for the outcome (stage distribution of breast cancer). Staging of breast cancer among the studies included principally the American Joint Committee on Cancer's tumor node metastasis (TNM) classification,[52 53] without limiting the edition of the classification that was used, and the US National Cancer Institute's surveillance epidemiology and end results (SEER) summary stage system.[54] For the purpose of consistency in the analyses, we excluded, when possible, ductal carcinoma in situ, lobular carcinoma in situ, and all other non-invasive breast cancers. We did this because several publications included in our meta-analyses excluded these cases on the basis of problems with data quality related to the reporting of in situ cancers. Therefore, we considered only invasive breast cancers. Given the considerable variability across studies for the classification used for stage distribution of breast cancer, especially between the TNM classification and the SEER summary stage system, we dichotomized the response variable as non-localized breast cancer (regional or distant) versus localized breast cancer. We firstly chose this cut-off for clinical relevancy because localized breast tumors are potentially more curable than non-localized tumors and are associated with better survival rates.[55] Additionally, we chose this cut-off for purposes of compatibility between the two cancer staging systems. Irrespective of the classification system, breast tumors that did not spread to regional lymph nodes or distant sites were considered to be localized tumors. Therefore, non-localized breast tumors were considered to be advanced or later stage breast cancers.

Statistical analyses

The statistical analyses, forest plots, and sensitivity, meta-regression, and publication bias analyses were produced with Stata software, release 12. Studies had to provide sufficient data for calculation of an effect size measure to be included in the quantitative analysis. We used a Dersimonian-Laird random effects model to derive a pooled effect across studies for the association between cosmetic breast implants and stage distribution of breast cancer.[56] We used the random effects model because it accounts for variations between studies in addition to sampling error within studies.[57] All analyses were conducted on the natural log scale. We calculated the summary odds ratio with 95% confidence interval from study specific adjusted odds ratios taken directly from the study or estimated as crude odds ratios from cell counts. We also took study specific confidence intervals directly from the study if reported or calculated them by using the corresponding standard error. We used a random effects model to calculate the summary hazard ratio for the association between cosmetic breast implants and survival. We calculated the pooled effect from study specific hazard ratios that were obtained directly from the study or calculated from survival curves. To quantify the degree of heterogeneity across studies, we used Cochrane's Q test and the Higgins I^2 statistic with 95% confidence intervals.[58 59] This last statistic indicates the proportion of the variance attributable to between study variability.[59]

We also did sensitivity analyses to identify studies contributing disproportionately to the observed heterogeneity. We did this by omitting each study one by one to analyze the influence of individual studies on the summary estimate,[60] and also by comparing the studies for which in situ breast cancers could not be excluded with those studies for which we excluded in situ breast cancers. We also made a visual inspection by using the Galbraith plot to detect possible outlier studies that have an excessive influence on the overall estimate.[61 62] To identify potential sources of heterogeneity, we examined only the association between cosmetic breast implants and stage distribution of breast cancer, as we had too few studies to examine sources of heterogeneity for the association between cosmetic breast implants and survival. We did this by calculating a summary odds ratio across strata of factors selected a priori as potentially related to quality of study and that were present enough across studies to allow stratification. These factors included source of comparison group (other cosmetic surgery controls versus population based controls), source of exposure data (plastic surgeons' records versus medical records), breast cancer staging system (TNM staging versus SEER staging), and statistical adjustment of the odds ratio for potential confounders (adjusted versus unadjusted). We also evaluated the effect of these factors on heterogeneity by using random effects meta-regression models. This investigates how a categorical or continuous characteristic at the study level is associated with the effect estimate in the meta-analysis.[60] The outcome variable in the meta-regression models in this study is the odds ratio and the explanatory variables, also called potential effect modifiers, are the factors selected a priori as potentially related to study quality. We also evaluated the year of publication of each study as a potential source of heterogeneity as a continuous variable in a meta-regression model. We assessed publication bias for the association between cosmetic breast implants and stage distribution of breast cancer by using a funnel plot and Egger's test.[63] We did not have enough studies to examine heterogeneity and publication bias for the association between cosmetic breast implants and survival.

Results

We identified 282 unique papers after searching Medline, Embase, Global health, CINAHL, IPAB, and PsycINFO. Of these, 22 publications (n=28 924 women) met eligibility for the evaluation of stage distribution of breast cancer and breast implants, and seven publications (n=18 026 women) met eligibility criteria for the evaluation of survival following breast cancer diagnosis and breast implants (fig 1⇓). No papers were identified after searching the Cochrane Library's Database of Systematic Reviews, through further investigation of previous reviews, or through manual examination of references or querying of the experts. No unpublished scientific articles were identified through expert consultations. A quality assessment scale also showed that publications that met eligibility were of acceptable quality to be included in these meta-analyses (supplemental file in web appendix).[64]

Breast implants and stage distribution of breast cancer

Twelve studies, all cross sectional in their design, provided sufficient data to be included in a meta-analysis to evaluate the association between cosmetic breast implants and stage

distribution of breast cancer. Table 1⇓ shows characteristics of the 12 studies meeting the inclusion criteria and selected for the quantitative analysis. Most of these were published after 2000 and were conducted in the United States. The remainder were conducted in northern Europe or Canada. The other 10 papers were all excluded because they overlapped with more recent publications with an extended follow-up of the same study group.

Figure 2⇓ shows the results of the meta-analysis. The size of each box indicates the relative weight of each publication in the meta-analysis, and the bars show the 95% confidence intervals. Based on the 12 studies, the summary odds ratio with the random effects model was 1.26 (95% confidence interval 0.99 to 1.60; P=0.058) for a non-localized stage of breast cancer at diagnosis comparing women with breast cancer who had implants with women with breast cancer who did not have implants. Moderate heterogeneity was present (Q=17.07, P= 0.11, I^2=35.6%).

Sensitivity analysis and publication bias

Sensitivity analyses showed that one publication, Clark et al,[38] accounted for all the observed heterogeneity. When we included all 12 studies in the analysis, I^2 was 35.6 %. I^2 was 0% when this paper was removed, suggesting that it had an important influence on the overall estimate.[60] Additionally, the Galbraith plot showed that this study contributed disproportionately to the observed heterogeneity (data not shown). The summary odds ratio using the random effects model when that study was excluded was 1.42 (1.19 to 1.68). The omission of all other studies separately resulted in random variation around the overall estimate for the remaining 11 studies. Moreover, sensitivity analyses showed that the omission of five studies for which in situ breast cancers could not be excluded resulted in an overall estimate similar to the one mentioned above (odds ratio 1.40, 1.10 to 1.78).[8 17 38 40 43] The Egger's test did not indicate the presence of publication bias (P=0.16). Additionally, a visual inspection of the funnel plot did not suggest publication bias as the studies were distributed symmetrically about the combined effect size (data not shown).

Meta-regression analysis

Table 2⇓ shows results with stratification by variables potentially related to quality of study. Overall odds ratios stratified by these variables did not produce meaningful differences, except for the studies that provided adjusted estimates for relevant covariates such as age at diagnosis of breast cancer and calendar period of diagnosis (odds ratio 1.51, 1.18 to 1.92). In comparison, studies that did not provide adjusted estimates yielded an overall odds ratio of 1.07 (0.74 to 1.55). In addition, the summary effect for the three studies that compared women with cosmetic breast implants with women who received other elective cosmetic surgery was 1.53 (0.89 to 2.64) and the odds ratio when comparing women with implants and the general female population was 1.16 (0.88 to 1.53). Table 2⇓ also shows the statistical significance of meta-regression models. Inclusion of these variables one at a time in a random effects meta-regression model did not reach statistical significance.

Breast implants and survival

Table 3⇓ shows a description of the five publications, all with a cohort design, included in the meta-analysis for the association between cosmetic breast implants and breast cancer specific survival following diagnosis of breast cancer. The two papers that were excluded overlapped with a more recent publication.

Figure 3⇓ shows the results of the meta-analysis of cosmetic breast implants and breast cancer specific survival. The overall hazard ratio comparing the breast cancer specific mortality after diagnosis between women with breast cancer who had implants and women with breast cancer who did not have implants was 1.38 (1.08 to 1.75), with no heterogeneity observed (Q=3.35, P=0.50, I^2=0.0 %). The Egger's test did not indicate the presence of publication bias (P=0.84). Omission of the publication that assessed overall mortality resulted in random variation around the overall estimate of the four remaining studies. We did not have enough studies to do a meta-regression.

Discussion

This systematic review suggests that women with cosmetic breast implants have later stage tumors at diagnosis of breast cancer. In our second meta-analysis, the results show a higher risk of breast cancer specific mortality among women with breast cancer who have implants compared with women with breast cancer without implants. Nevertheless, the overall estimate should still be interpreted with caution because this meta-analysis included a relatively small number of studies. Of concern, three of five studies had unadjusted hazard ratios (not adjusted for age at diagnosis, or period of diagnosis) and all five studies were unadjusted for other potential confounding factors such as body mass index, which could translate into a biased estimate of the summary hazard ratio. A lack of adjustment for body mass index has previously been shown to lead to underestimation of the association between cosmetic breast implants and breast cancer mortality.[18] Moreover, one study included in this meta-analysis assessed overall mortality rather than breast cancer specific mortality,[39] which could have biased our summary estimate towards the null. The small number of studies and insufficient amount of follow-up time in these studies are suspected to limit statistical power to clearly evaluate survival rate patterns among augmented women. Given the limited evidence, no conclusion regarding breast cancer specific survival can be drawn and continued follow-up to further evaluate this question is particularly relevant.

Possible explanations for findings

The finding of later stage tumors at diagnosis of breast cancer in women with implants can be explained by multiple mechanisms, the first being that both silicone and saline implants create radio-opaque shadows on mammograms, which impair the visualization of breast tissue.[65] The amount of parenchymal breast tissue obscured at mammography by the implant is known to be between 22% and 83%.[66] Insufficient compression of the breast to visualize the parenchyma and the production of implant related artifacts on the film can also make interpretation of mammographic examinations difficult in women with augmented breasts.[28 29] Additionally, capsular contracture, which develops in about 15-20% of women with implants, has been shown to reduce mammographic sensitivity by 30-50%.[65] Furthermore, specific characteristics of breast implants might affect the detection of breast cancer.[67] Specifically, implants placed under the breast glands (subglandular placement), because of their proximity with breast tissue, are suspected to obstruct mammographic visualization of the breast more than those with submuscular placement.[4 33] However, to date, only one study has been able to evaluate the stage distribution of breast cancer according to implant placement.[18 34] Results from this study were inconclusive.

Despite the fact that implant displacement techniques are widely used with mammography, studies suggest that breast tissue is

still not adequately visualized.[8 65] Recent reports suggest that magnetic resonance imaging of the breast may be a helpful diagnostic tool for women with breast implants; it allows examination of all breast tissue surrounding the implant,[68 69] and so has greater sensitivity than mammography.[70] However, insufficient evidence exists to support the use of magnetic resonance imaging in the diagnosis and prognosis of breast cancer, which warrants further research.

Stratification and meta-regression models showed that no potential factors seem to unduly affect the results of the study. When we calculated a summary effect for the three studies that used women who had received other elective cosmetic surgery (chemical peel or dermabrasion, coronal brow lift, otoplasty, rhinoplasty, rhytidectomy, or blepharoplasty) as the comparison group, we observed a stronger association than the one obtained when the general female population was used as the comparison group. Women with other cosmetic surgery are recognized in the scientific literature as being a more appropriate comparison group when studying the health effects associated with cosmetic breast implants, because they tend to be more similar in terms of sociodemographic and lifestyle factors as well as health consciousness than are women in the general population.[71 72] A previous study conducted in the United States showed no significant differences with respect to family income between women with cosmetic breast implants and women with other cosmetic surgery, which supports the notion that both groups are of similar socioeconomic status.[71] For example, women seeking cosmetic surgeries could have better screening and self examination practices than women in the general female population, which would translate into higher chances of a breast tumor being diagnosed after screening mammography if one is present. This suggests that using other women with cosmetic surgery would be more adequate in terms of controlling for potential confounders. Moreover, studies with adjustment for confounding factors such as the age of breast cancer at diagnosis yielded statistically significant effects that were stronger than those without adjustment. One study showed that a lack of adjustment for the age at which breast cancer was diagnosed underestimates the measure of association.[34] This outlines the importance of providing adjusted estimates. In meta-regression models, we were not able to detect the modifying effect of the type of comparison group and the adjustment for cofactors, but a lack of statistical power due to the small number of studies may explain why the above differences in odds ratios are not statistically significant.

The long term presence of cosmetic breast implants has been hypothesized to cause atrophy, thinning, and compression of the breast parenchyma, which may facilitate the detection of palpable breast tumors on physical examination.[8 10 17 20] The breast implants could serve as a base against which the mass may be more likely to be differentiated.[73] This suggests that tumors of equal size may be more easily palpated in patients with implants, especially for implants placed in the subglandular position,[66] and this may compensate somewhat for the potential impairment of mammography. However, very few studies have evaluated this question, providing no conclusive results.[10 17 20] Furthermore, the fact that women with implants present more often with palpable tumors could also be because of the smaller native breast volumes making tumors more pronounced with palpation.[38]

Limitations of study

Our study has several limitations specific to our analysis and to the different methods used across studies. For instance, certain studies used in both meta-analyses included cases of in situ breast cancer because we were not able to exclude them on the basis of the limited information available in the papers.[8 17 38 40 43] This could have resulted in a non-differential misclassification bias of the outcome variable. One study, by Clark et al,[38] was responsible for all observed heterogeneity in the analysis of stage distribution of breast cancer at diagnosis. We believe that the results of this publication may be affected by a selection bias, which is supported by the quality assessment scale (supplemental file in web appendix). Moreover, a previous publication also raised the concern that the results of the study by Clark et al may have been influenced by a selection bias.[39] Pooling results from several observational studies has the advantage of increasing statistical power but does not increase internal validity. Misclassification bias, selection bias, and assessment of confounding affecting individual studies will also affect the meta-analyses. Misclassification biases within each study could also be a factor affecting study specific measures of association and consequently our pooled effect. For example, the identification of deaths from breast cancer could be affected by data quality problems such as a misclassification of the cause of death. This could result in biased estimates of breast cancer specific survival, resulting in an underestimation of our pooled effect. Although we have evaluated the quality of the studies with an assessment scale,[64] no threshold scores were available to distinguish between "good" and "poor" quality studies, which could limit our results as we may have included studies of poorer quality in our analyses. Another limitation of our study could be related to the methods used to pool the hazard ratios from available data in each study, which may have underestimated the variance of the estimates.

Conclusions and implications

Our results should be interpreted with caution, considering the current gaps and limitations in the available literature. The accumulating evidence suggests that women with cosmetic breast implants who develop breast cancer have an increased risk of being diagnosed as having non-localized breast tumors more frequently than do women with breast cancer who do not have implants. Moreover, current evidence also suggests that cosmetic breast implants adversely affect breast cancer specific survival following the diagnosis of such disease. Further investigations are warranted into the long term effects of cosmetic breast implants on the detection and prognosis of breast cancer, adjusting for potential confounders.

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Contributors: EL, JB, and EJH were responsible for study concept and design and supervised the study. EL and SYP acquired the data, which was analyzed and interpreted by EL, JB, EJH, SYP, PJV, KCJ, DAF, and HM. EL drafted the manuscript, which was critically revised for important intellectual content by EL, JB, EJH, SYP, PJV, KCJ, DAF, and HM. EL did the statistical analysis with supervision from JB, EJH, and DAF. EL is the guarantor.

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What is already known on this topic

Cosmetic breast implants have become increasingly popular in recent decades

Breast implants are radio-opaque at mammography, impairing the visualization of breast tissue

Studies have raised the concern that breast implants may impair the ability to identify breast cancer at an early stage when survival is generally more favorable

What this study adds

On the basis of studies published to date, cosmetic breast augmentation seems to adversely affect the survival experience of women who are subsequently diagnosed as having breast cancer

Ethical approval: Not required.

Data sharing: No additional data available.

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Tables

Table 1| Characteristics of 12 studies selected for quantitative analysis to evaluate association between cosmetic breast implants and stage distribution of breast cancer at diagnosis

First author, country, year	Source of data on implants	Source of data on breast cancer	Assessment of stage of breast cancer	Comparison group	Women with breast implants with breast cancer	Women without breast implants with breast cancer	Mean length of follow-up (years)*	Average age at breast cancer diagnosis (years)†	Adjustment
Lavigne, Canada, 2012‡[18]	Plastic surgeons' records, hospital discharge data	Canadian Cancer Registry, medical records	AJCC TNM	Women with other cosmetic surgery diagnosed as having breast cancer	409 women: localized 195; non-localized 162; unknown 52	444 women: localized 266; non-localized 132; unknown 46	16.1 (range 1-32)	52.3 (range 25-85)	Adjusted for age at diagnosis, period of diagnosis, and province of residence
Handel, United States, 2007§[8]	Medical records	Medical records	AJCC TNM	Women treated for breast cancer at same clinics as implant patients	128 women: localized 69; non-localized 59	3795 women: localized 2467; non-localized 1328	Unknown	46.8 (range 29-71)	None
Tuli, United States, 2006‡[13]	Medical records	Medical records	AJCC TNM	Women diagnosed as having breast cancer at same hospital as implant patients	12 women: in situ 2; localized 5; non-localized 4; unknown 1	3565 women: in situ 809; localized 401; non-localized 202; unknown 2153	12.6 (range 1-31)	49.2 (range 31-63)	Adjusted for age at diagnosis
Friis, Denmark, 2005§[15]	Plastic surgeons' records, hospital records	Hospital records, Danish cancer registry	SEER EOD	Women with other cosmetic surgery diagnosed as having breast cancer	31 women: localized 17; non-localized 14	30 women: localized 13; non-localized 15; unknown 2	Range 0-30	Unknown	None
Miglioretti, United States, 2004[42]	Mammography registries	State cancer registries	AJCC TNM	Women diagnosed as having breast cancer in same mammography registry as implant patients	137 women: in situ 21; localized 78; non-localized 36; unknown 2	685 women: in situ 122; localized 388; non-localized 152; unknown 23	Unknown	Unknown	Matched (5:1) by age at diagnosis, ethnicity, mammography examination within 2 years of diagnosis (yes/no), first or subsequent mammogram, and mammography registry
Jakub, United States, 2004§[17]	Medical records	Medical records	NSABP	Women treated for breast cancer at same hospital as implant patients	76 women: localized 45; non-localized 28; unknown 3	4186 women: localized 2758; non-localized 1352; unknown 76	14	49.5	None
Pukkala, Finland, 2002[19]	Medical records	Finnish cancer registry	SEER EOD	General female population with breast cancer	7 women: localized 4; non-localized 2; unknown 1	Estimates¶: localized 6.8; non-localized 4.8; unknown 0.9	8.3	Unknown	Standardized for age at diagnosis, calendar period of diagnosis
Deapen, United States, 2000[41]	Plastic surgeons' records	Cancer registry	SEER EOD	General female population with breast cancer	37 women: in situ 5; localized 19; non-localized 13	External rate¶: in situ 3.8; localized 18.5; non-localized 14.6	12.2	50.3	Standardized for age; restricted to white women
Brinton, United States, 2000§[21]	Plastic surgeons' records, self administered questionnaire	Medical records, death certificates	SEER EOD	Women with other cosmetic surgery with breast cancer	78 women: in situ 12; localized 32; non-localized 27; unknown 7	36 women: in situ 10; localized 19; non-localized 6; unknown 1	12.9	48	None
Cahan, United States, 1995§[43]	Medical records	Medical records	—	Women treated for breast cancer at same institution as implant patients	22 women: localized 13; non-localized 7; unknown 2	611 women: localized 473; non-localized 138	10	—	None

Table 1 (continued)

First author, country, year	Source of data on implants	Source of data on breast cancer	Assessment of stage of breast cancer	Comparison group	Women with breast implants with breast cancer	Women without breast implants with breast cancer	Mean length of follow-up (years)*	Average age at breast cancer diagnosis (years)†	Adjustment
Clark, United States, 1993§[38]	Medical records	Medical records	AJCC TNM	Women diagnosed as having breast cancer and identified in same breast cancer registry as implant patients	33 women: localized 25; non-localized 6; unknown 2	1735 women: localized 1024; non-localized 711	—	43	None
Birdsell, Canada, 1993§[40]	Health insurance claims, medical records	Alberta cancer registry	AJCC TNM, 4th edition	General female population with breast cancer	41 women: localized 25; non-localized 13; unknown 3	13 246 women: localized 2172; non-localized 1084; unknown 9990	7.5	45.7 (range 30-68)	None

AJCC TNM=American Joint Committee on Cancer, tumor node metastasis classification; NSABP=National Surgical Adjuvant Bowel Project; SEER EOD=surveillance epidemiology and end results summary stage system.

*Mean length of follow-up between date of breast implantation and earliest of diagnosis of breast or any other cancer, date of death, or end of follow-up period.

†Average age at diagnosis of breast cancer among women with breast implants.

‡Adjusted odds ratio obtained by corresponding author of this paper.

§Crude odds ratio calculated using data in paper.

¶ Expected cases estimated on basis of information in paper.

Table 2| Random effects overall odds ratio for association between cosmetic breast implants and stage distribution of breast cancer at diagnosis stratified by variables potentially related to study quality

Stratification variable	No of studies	Overall effect—odds ratio (95% CI)	Meta-regression (P value)*
Source of comparison group:			
Other non-augmented controls	9	1.16 (0.88 to 1.53)	0.33
Other cosmetic surgery controls	3	1.53 (0.89 to 2.64)	
Breast cancer staging system†:			
SEER EOD	4	1.11 (0.58 to 2.13)	0.87
AJCC TNM	6	1.21 (0.86 to 1.71)	
Adjustment for potential confounders:			
Adjusted	5	1.51 (1.18 to 1.92)	0.27
Unadjusted	7	1.07 (0.74 to 1.55)	
Source of exposure data:			
Medical records	8	1.18 (0.88 to 1.59)	0.53
Plastic surgeons' records	4	1.39 (0.86 to 2.23)	
Year of publication	12	0.03‡ (0.00 to 0.07)	0.06

AJCC TNM=American Joint Committee on Cancer, tumor node metastasis classification; SEER EOD=surveillance epidemiology and end results summary stage system.

*Statistical significance for meta-regression model.

†Two studies were not included in this analysis.

‡Slope for model including year of publication as continuous variable.

Table 3| Characteristics of five studies selected for quantitative analysis to evaluate association between cosmetic breast implants and breast cancer specific survival following breast cancer diagnosis

First author, country, year	Source of data on breast cancer	Source of data on mortality	Reference group	Women with breast implants and breast cancer with survival probability	Women without breast implants with breast cancer with survival probability	Mean follow-up after diagnosis (years)*	Average age at breast cancer diagnosis (years)†	Adjustment
Lavigne, Canada, 2012‡[18]	Canadian cancer registry, medical records	Canadian mortality database	Women with other cosmetic surgery diagnosed as having breast cancer	400 women: 98.0% at 1 year; 86.5% at 5 years; 77.2% at 10 years	434 women: 99.1% at 1 year; 90.7% at 5 years; 83.5% at 10 years	7.7 (range 0.1-31.9)	52.3 (range 25-85)	Adjusted for age at diagnosis, period of diagnosis, and province of residence
Handel, United States, 2007§[8]	Medical records	Medical records	Women treated for breast cancer at same clinics as implant patients	120 women: 99.0% at 1 year; 90.5% at 5 years	3922 women: 99.5% at 1 year; 92.5% at 5 years	10.5 (range 0.5-37.0)	46.8 (range 29-71)	—
Holmich, Denmark, 2003§¶[39]	Danish cancer registry, hospital records	Danish cancer registry	General female population diagnosed as having breast cancer	23 women: 95.5% at 1 year; 86.0% at 5 years	253 women: 97.0% at 1 year; 78.0% at 5 years	6.4 (range 0.3-15.7)	47.2** (range 35-75)	—
Deapen, United States, 2000§[41]	Plastic surgeons' records, cancer registry	Cancer registry, National Center for Health Statistics, death certificates	General female population	37 women: 94.6% at 1 year; 88.5% at 5 years	External rate: 97.9% at 1 year; 84.1% at 5 years	6.6 (range 0.2-17.3)	50.3	Standardized for age at diagnosis, stage at diagnosis, and years of diagnosis
Birdsell, Canada, 1993§[40]	Health insurance claims, Alberta cancer registry, medical records	Alberta cancer registry	General female population	41 women: 94.0% at 1 year; 83.0% at 5 years; 73.0% at 10 years	13 246 women: 96.0% at 1 year; 74.0% at 5 years; 62.0% at 10 years	10.2 (range 1.0-18.0)	45.7 (range 30-68)	—

*Length of interval between date of diagnosis of breast cancer and earliest of date of death from breast cancer or end of the follow-up period among women with breast implants.

†Average age at diagnosis of breast cancer among women with breast implants.

‡Hazard ratio adjusted for age at diagnosis, period of diagnosis, and province provided in paper.

§Hazard ratio calculated using data in paper.

¶Assessed overall mortality.

**Average age at breast cancer diagnosis among both implant patients and comparison group.

Figures

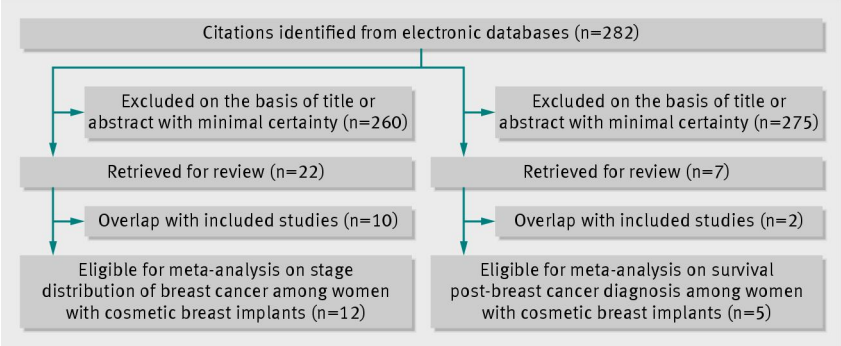

Fig 1 Flow chart of meta-analysis search strategy and process of selecting articles on association between cosmetic breast implants and stage distribution of breast cancer and association between cosmetic breast implants and survival after diagnosis of breast cancer

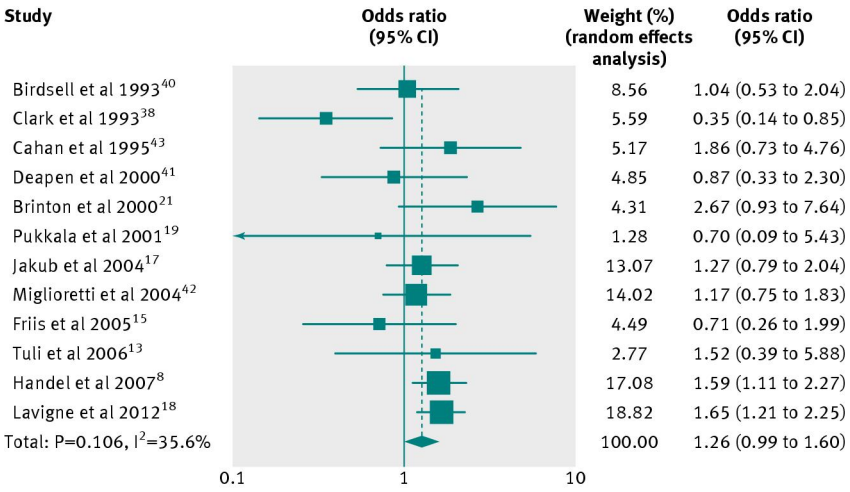

Fig 2 Forest plot with study specific and random effects overall odds ratio for association between cosmetic breast implants and stage distribution of breast cancer at diagnosis (dichotomized as non-localized (regional or distant) versus localized breast cancer)

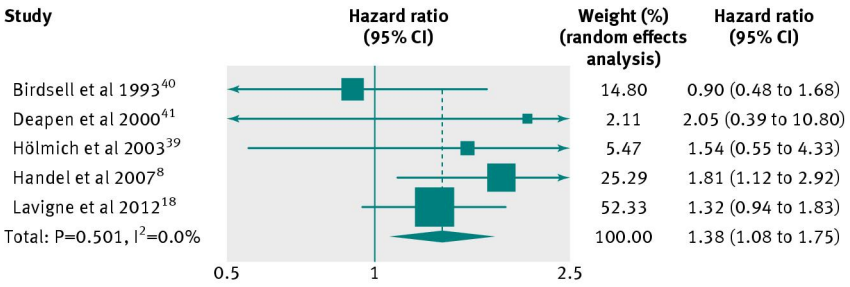

Fig 3 Forest plot with study specific and random effects overall hazard ratio for association between cosmetic breast implants and breast cancer specific survival