Commentary on: Breast Implants and the Risk of Breast Cancer: A Meta-Analysis on Cohort Studies

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A meta-analysis is an accepted statistical method for pooling published comparative information and an attempt to understand a disease pathway. In this study, a very small selection of peer-reviewed studies, found by key wording in the literature, are pooled and analyzed. The intention of this publication is to summate separate published cohorts using meta-analysis to discover if there is a statistical connection between breast cancer and use of the generation of breast implants utilized mostly before 1989. Unfortunately, this type of study is often far from persuasive and not an exact science. It very much depends on the quality of the review, the comparability between each cohort included in the study, and the quality of initial peer review of papers included within the study. In this case, there are serious flaws, but the general conclusion is that breast implants, however manufactured, do not cause breast cancer, and this is an important take-home message that the authors seek to emphasize.

It does not take a genius to discover this because there has never been a publication of a cohort that can show that breast implants cause breast cancer in women. The Oppenheimer effect that can occur in the genetically predisposed rodent is not a human phenomenon. There is, however, an increasing awareness that anaplastic large-cell lymphoma (ALCL) may, extremely rarely, have an association with any silicone implant, especially textured silicone implants, particularly those textured using salt extraction technology. At reporting, Reisman identified 8% of a responding cohort of plastic surgeons in the United States that had personally treated ALCL and emphasized the importance of early reporting and, perhaps, centralization of care. This, however, was not known at the time of publishing the few, historical studies included within this meta-analysis, which, incidentally, appears to have analyzed data only in the generation of patients having now-extinct, high-bleed, nontextured implants. Even so, the numbers of reported ALCL are so tiny that there would be little impact. Hart et al reported 2 cases of ALCL and identified a further total of 63 reported ALCL cases in the literature. Malignant cells presenting in seroma and noninvasively within the capsule appear to fare better than when presenting with a palpable lump. There have been only 4 deaths from ALCL, but this represents an 8% mortality and highlights the need for a strict management protocol.

I have personal access to a series of patients with more than 1000 polyurethane implants used in breast augmentation, both primary and secondary, and in breast reconstruction since 2005, and I have not seen a Baker 3 or 4 capsular contracture at follow-up, but more specifically, I have not seen a breast malignancy, ALCL, or any other malignancy in these women. In the past 20 years, I am aware of only 3 cases of malignancy in the many cosmetic and reconstructive patients under my care who had silicone textured implants prior to 2006. I believe this is far lower than the incidence in the general matched population. If the Anglia Ruskin, MCh Aesthetic Surgery Training Programme and the subsequent trained surgeon data are included, there are many more polyurethane augmentation cases to add, but this follow-up is only at 4 years. I have been reviewing my polyurethane-implanted patients annually since the introduction of the conical polyurethane in the United Kingdom in 2009, but it will take a further 5 years to get solid meaningful data, and until then, I can only watch carefully. If there is an increased risk in the first 5 years after polyurethane implants are inserted, then I am not seeing it. I believe this is a common finding among all...
international surgeons who regularly use polyurethane implants, especially for primary augmentation.

Another difficulty that a large body of international plastic surgeons has is explaining the benefits of polyurethane breast implants to regulators when alarmist articles appear from authors, who may not be plastic surgeons, publishing from nonusing polyurethane countries such as the United States or Canada, stating that 2,4 TDA (2,4 Toluene Diamine, a chemical produced by the hydrolysis of polyurethane) causes breast cancer, specifically in the first 5 years after augmentation when, after 44 years of continuous usage, numbering millions of women, there has never been a reported clinical case or clinical series suggesting such a causation, let alone an association. There is no foundation, other than speculation, and this is harming women wanting augmentation or reconstruction by denying them the informed opportunity to have implants with a 17-fold reduced risk of the commonest problem (capsular contracture) and with the inevitable associated risks of more difficult repeat surgery thereafter. This meta-analysis, quite rightly, does not specifically address this issue, other than to generically state that all women with breast implants have a reduced incidence of breast cancer compared with controls, and for that there must be credit.

The fundamental flaws in this meta-analysis fall down to shortcomings in data collection at the time of the original studies, the very small numbers of articles included in the meta-analysis, the generation of silicone and shell technology being analyzed (most were before the Food and Drug Administration [FDA] moratorium, and we all know that silicone technology has changed considerably since 1992), and the actual statistical methodology. As an example of accuracy in reporting in the largest series of patients included in this meta-analysis, Pan et al in 2012, utilizing the same data, reached a different conclusion from that of Brisson et al in 2006. These 2 studies largely included the same group of authors, bizarrely contradicting each other by suggesting after statistical manipulation that polyurethane implants may increase the relative risk of breast cancer within 5 years of implantation. This was both alarmist and fundamentally flawed in a letter that that journal’s editor subsequently refused to publish. That letter is available from Dr Daniel Fleming in Australia. Fleming has also published other meaningful supportive data on the use of polyurethane implants. The study by Brisson et al, in my view, did interpret the data correctly and concluded there were too many confounders and too much error within the data for interpretation to be safe. This and subsequent publications and presentations online confirm that all their data must be treated with caution. In strict definitions of meta-analysis, therefore, perhaps this study should be itself excluded. Looking in more detail at how the original data appear to have been collected shows how error can creep in and be repeated thereafter. For example, when looking for women who have implants and subsequently develop breast cancer, no record of those with a family history (ie, genetic predisposition) of breast cancer was made, and therefore it may have significantly influenced the end result, particularly if only small numbers of incident cases are actually found in any one group. In this example, there was a likely false low level of cancers found in a large silicone-implanted group and a tiny but likely false high number in a very small group of women who chose to have polyurethane implants. More important, there were a large number of patients in whom the implant shell type used was not recorded and, in all likelihood, would have been silicone implants, thus leaving a fairly large number of incident cancers unaccounted (Table 1). This was down to the field researchers who surely could/should have made more effort to be specific and identify the actual implants used.

The polyurethane implants used in the Canadian studies between 1970 and 1989 were presumably all first-generation Natural-Y® implants but, when eventually published in the 2006 Canadian cohort, a discrepancy appears in that these implants were apparently used by only 2 surgeons, from only 1 of the 2 Canadian provinces from which all data were collected. It also appears that the study actually identified that these implants were used in only Canadian women in the 4 years between 1995 and 1989, with the cancer incidence being measured in 1997. This sharply contrasts with the evidence on implant safety produced with Canadian data by Kerrigan in 1989. There is no doubt that the statistical methodology within this meta-analysis is sound, but this can only work meaningfully with accurate and complete data collection from researchers, and in this epidemiological study, there are questions. My interpretation using their published data is as shown in Table 2, and this clearly demonstrates that all women with breast implants, whether silicone or polyurethane, have a reduced incidence of breast cancer compared with controls for at least up to 20 years. Of course, this does not account for statistical confounders and errors. There is an international move among mathematicians and statisticians to insist that authors make all raw data available to scrutiny, especially at the time of peer review.

Little, therefore, has actually happened since Caroline Kerrigan produced her 19-year review of the risk of breast cancer in patients with silicone implants, previously published in the Aesthetic Surgery Journal. **Table 1. Outer Shell Coverings of Implants Used in Primary Breast Augmentation as Demonstrated by Brisson et al and Pan et al**

<table>
<thead>
<tr>
<th>Implant Shell</th>
<th>Total Cases</th>
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<tbody>
<tr>
<td>Silicone</td>
<td>15,896</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>2,569</td>
</tr>
<tr>
<td>Unknown</td>
<td>6,093</td>
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developing breast cancer in breast-implanted Canadian women in 1989, stating that there was no evidence that breast implants, especially polyurethane breast implants, cause cancer. It is interesting that the data within Kerrigan’s review state that polyurethane implants were used in Canada since 1970 (shown in a nice table within that commissioned review explaining the implants and naming the now historical manufacturers of silicone implants at that time), yet the Canadian epidemiology group, contributing the most patient data to this meta-analysis, could only find polyurethanes used between 1984 and 1989 in Canada. Pre-1989 silicone implants were used by the few cohorts included in this meta-analysis study, and clearly they are of a past generation of prostheses.

Whether by design, error, or obfuscation, the published FDA core and extended studies have also failed to directly compare the performance of implants manufactured by the 3 US-approved silicone implant manufacturers’ products, especially with regard to comparative safety. No causation or association of cancer to breast implants was found. Although it is all that we have, is that data better than nothing, or is it misleading information? Clearly, there has always been a need for an accurate, detailed, comparative long-term study on breast implant safety, and I wish that I had realized it when I started plastic surgery in 1984. Perhaps all of the current international discussions about a common implant registry may bear fruit eventually, but as my late mother used to say about a fruit tree growing from a seed, “pears are for heirs,” and it is likely our successors will discover the answers.

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REFERENCES