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Analysis of US Food and Drug Administration Breast Implant Postapproval Studies Finding an Increased Risk of Diseases and Cancer

Why the Conclusions Are Unreliable

Eric Swanson, MD

In a recent publication in *Annals of Surgery*, Coroneos et al[1] analyze postapproval study data (available online)[2,3] from 2 implant manufacturers, Allergan plc (Dublin, Ireland) and Mentor (Irvine, Calif). The authors compare the incidence of systemic diseases with values obtained from the literature and conclude that there is a significant association between breast implants and serious illnesses, including cancer.[1]

The authors recognize that a major limitation of their study is that women treated with Mentor implants self-reported their diagnoses. Allergan patients required a physician diagnosis, and data were adjusted for covariates. A referenced study found that only 22.7% of self-reported diagnoses of connective tissue diseases could be confirmed by medical records.[4] After correction for this discrepancy, any significant association between breast implants and poly/dermatomyositis, scleroderma, and Sjögren syndrome disappeared.[1]

The authors acknowledge the major attrition among study patients. Only 20% of Mentor patients were followed for 7 years.[3] The benchmark inclusion rate for evidence-based studies to ensure reliability is 80%.[5] The minority of patients who completed questionnaires may not be representative of the whole patient population.[1] Patients with no concerns may be less motivated to complete surveys.

Comparing treatment data with external control data derived from completely different populations (eg, geography, time frame, diagnoses, comorbidities) is seldom reliable.[5] There are simply too many confounders. Another consideration is the denominator. The authors used 10,000 person-years. In epidemiological studies, it is necessary to know the time frame of the observation, which is facilitated by objective hospital and insurance company databases. How is this information obtained from patient questionnaires? Are patients likely to confine their self-reporting of diseases, which may be exaggerated by a factor of 4.5 already,[4] to a certain time frame? No information is available regarding the accuracy of the person-year formulation, which was used by Mentor to calculate incidence rates.[3]

The difference in rates of serious diseases comparing Mentor and Allergan implants is striking, and the conclusions always favor Allergan implants.[1] For example, patients with Allergan implants had a 6-fold decrease in the risk of rheumatoid arthritis ($P < 0.001$); the risk in women with Mentor implants was increased 6-fold ($P < 0.001$). Patients with Allergan implants had a significant reduction in the risk of systemic lupus erythematosus ($P < 0.001$); women with Mentor implants did not. Allergan implants were associated with a reduced risk of cancer and neurological disorders ($P < 0.001$); Mentor implants were associated with an increased risk ($P < 0.001$).

The authors offer no explanation for these profound differences in risks. Do the authors truly believe that intrinsic differences in the breast implants, which are very similar in composition, except for surface texturing methods,[6] account for the widely disparate risk profiles? The authors report, uniquely, a link between breast implants and melanoma, multiple sclerosis, and neurological disorders, but a lower risk of lung cancer and birth defects.[1] Again, no physiological basis is offered for these unexpected findings.[1]

Coroneos et al[1] report 1 case of breast implant–associated anaplastic large-cell lymphoma, in a patient with Mentor implants, and an overall incidence of 1:58,140 for all breast implants. There is no mention of the well-known increased breast implant–associated anaplastic large-cell lymphoma risk associated with Allergan Biocell macrotextured (salt-loss) implants compared with breast implants made by other manufacturers, including Mentor.[6]

Importantly, the authors report no financial conflicts.[1] *Annals of Surgery* conforms to the disclosure policy published by the International Committee of Medical Journal Editors,[7] instructing authors to "report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of

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From the Swanson CenterLeawood, KS.
E.S. is a plastic surgeon in private practice in Leawood, KS.
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Reprints: Eric Swanson, MD, Swanson Center, Leawood, KS. E-mail: eswanson@swansoncenter.com.

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the work."[8] According to the Propublica online database, Dr Clemens received $64,013 from Allergan in 2016 for promoting its Natrelle and Seri products. In 2015, he received $134,782 from Allergan.[9] Awareness of possible bias is essential for proper evaluation of study conclusions.[10]

Questions regarding systemic harm from breast implants came to the forefront after the 1992 silicone breast implant crisis. Evidence from large reputable studies, including a study conducted by Mayo Clinic in 1994,[11] a large study of nurses reported in the *New England Journal of Medicine* in 1995,[12] a review by the Institute of Medicine in 1999,[13] and meta-analyses of 20 major studies also published in the *New England Journal of Medicine* in 2000,[14] showed no increased risk of autoimmune diseases, including connective tissue diseases, or breast cancer in women treated with breast implants.

Unfortunately, the conclusions of this study are likely to cause unnecessary alarm to women considering breast augmentation. This article is also highly prejudicial against Mentor implants. Its limitations are actually something more. They are flaws that produce conclusions that are clearly spurious.

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