

Chapter III: Epidemiological Analysis of Silicone Breast Implants and Connective Tissue Disease

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Table of Contents

I. Introduction	III-1
II. Descriptive Epidemiology and Diagnostic Criteria for Specific Connective Tissue Diseases	III-2
Rheumatoid Arthritis	III-2
Systemic Lupus Erythematosus	III-3
Scleroderma or Systemic Sclerosis	III-4
Sjögren's Syndrome	III-4
Dermatomyositis/Polymyositis	III-5
III. Meta-analysis of Epidemiological Studies	III-5
Rationale	III-5
Disease Entities Included in the Meta-analyses	III-7
Types of Implants Included in the Analysis	III-8
Sources of Studies	III-9
Inclusion/Exclusion Criteria for Studies	III-10
Statistical Analyses	III-11
Meta-analysis of Unadjusted Effect Estimates	III-11
Meta-analysis of Adjusted Effect Estimates	III-13
Results	III-14
Description of Individual Study Results	III-14
Unadjusted Results from Meta-analyses	III-14
Results Adjusted for Confounding Variables	III-15
Results from Silicone Gel-Filled Implants Only	III-16
Discussion	III-17
Limitations of the Meta-analyses	III-18
Potential Biases in Studies of Silicone Breast Implants and Connective Tissue Diseases	III-19
IV. Power of the Meta-analyses	III-21
V. Population Attributable Fraction	III-23
VI. Summary and Conclusions	III-23

References	III-25
List of Abbreviations	III-33
Tables	III-34
Figures	III-45
Appendix A	III-A-1
Appendix B	III-B-1
Appendix C	III-C-1
Appendix D	III-D-1
Appendix E	III-E-1

Table of Contents

I. Introduction	III-1
II. Descriptive Epidemiology and Diagnostic Criteria for Specific Connective Tissue Diseases	III-2
Rheumatoid Arthritis	III-2
Systemic Lupus Erythematosus	III-3
Scleroderma or Systemic Sclerosis	III-4
Sjögren's Syndrome	III-4
Dermatomyositis/Polymyositis	III-5
III. Meta-analysis of Epidemiological Studies	III-5
Rationale	III-5
Disease Entities Included in the Meta-analyses	III-7
Types of Implants Included in the Analysis	III-8
Sources of Studies	III-9
Inclusion/Exclusion Criteria for Studies	III-10
Statistical Analyses	III-11
Meta-analysis of Unadjusted Effect Estimates	III-11
Meta-analysis of Adjusted Effect Estimates	III-13
Results	III-14
Description of Individual Study Results	III-14
Unadjusted Results from Meta-analyses	III-14
Results Adjusted for Confounding Variables	III-15
Results from Silicone Gel-Filled Implants Only	III-16
Discussion	III-17
Limitations of the Meta-analyses	III-18
Potential Biases in Studies of Silicone Breast Implants and Connective Tissue Diseases	III-19
IV. Power of the Meta-analyses	III-21
V. Population Attributable Fraction	III-23
VI. Summary and Conclusions	III-23

References	III-25
List of Abbreviations	III-33
Tables	III-34
Figures	III-45
Appendix A	III-A-1
Appendix B	III-B-1
Appendix C	III-C-1
Appendix D	III-D-1
Appendix E	III-E-1

Chapter III

Epidemiological Analysis of Silicone Breast Implants and Connective Tissue Diseases

I. Introduction

This chapter is concerned with the analysis and evaluation of the existing epidemiological literature on the postulated association between breast implants and connective tissue diseases (CTDs). For presentation purposes, this chapter is divided into several sections. Section II summarizes the descriptive epidemiology and diagnostic criteria for those selected connective tissue diseases, which are amenable to epidemiological analysis. Section III, a meta-analysis of the epidemiological studies, forms the bulk of the chapter. Several analytic methods for pooling information from multiple studies are described; the results are presented and discussed. Section IV discusses the “power” of the meta-analysis, that is, the ability to detect an adverse effect of breast implants (if there actually is one), given the available data from existing studies. Section V addresses the question of how many cases of the specific CTDs under study might be attributed to breast implants in the population of United States women using the relative risk estimates obtained from the meta-analysis. Last, Section VI provides a summary and conclusions. A list of abbreviations used appears after the references, before the tables.

The chapter is structured to be useful for readers with varying levels of interest and expertise pertinent to the topic of breast implants and CTDs. The summary and conclusions are designed for those who wish to grasp quickly the main findings and their implications. Most readers should find the main body of the narrative, including Tables 1–8 and Figures 1–8, informative. Section III, Meta-analysis of Epidemiological Studies, subheading Statistical Analyses, provides the definitions of epidemiological and statistical terms used in this chapter of the report. Appendix A, containing diagnostic criteria for established CTDs, and Appendix C, which contains a description and critique of each study used in the meta-analyses, provide added detail for the general readership. Appendices B, D, and E are designed for readers oriented to quantitative methods and statistics. The content of the appendices is not essential for understanding the rationale for the methods employed or the findings and their interpretation.

II. Descriptive Epidemiology and Diagnostic Criteria for Specific Connective Tissue Diseases

Numerous CTDs with immunologic alterations and rheumatologic manifestations are described in textbooks on rheumatology (Koopman, *Arthritis and allied conditions: A textbook of rheumatology*, 1997). These diseases are characterized by a multiplicity of signs and symptoms, many of which are nonspecific and overlap across diagnoses. Many of the CTDs exhibit specific genetic predispositions in the human lymphocyte antigen system and are associated with a diversity of immunologic responses, most often in the form of autoantibodies. (These antibodies are produced to combat one's own tissues.) Also, chronic inflammation is a characteristic feature, with the musculoskeletal system and blood vessels being important target organs. For several of the more common CTDs with relatively distinctive immunologic, pathologic or clinical features, diagnostic criteria have been established. These criteria provide standardized case definitions, which are necessary for evaluating therapeutic interventions and disease prognosis, and for research analyses such as discussed in the present report. For most of the established CTDs, life expectancy of those afflicted is reduced when compared to individuals without these illnesses. Although several of the CTDs are associated with specific genetic susceptibilities, the clinical manifestations may be induced or exacerbated by environmental triggers. With rare exceptions, such as drug-induced syndromes, the etiology of the various CTDs is unknown.

Given a diverse set of rheumatologic/autoimmune disorders with overlapping and often nonspecific manifestations, deciding which disease entities should be the focus of analysis was not immediately evident. The decision was ultimately based on practical rather than theoretical considerations. The determining constraints were the availability of studies and the existence of diagnostic criteria for individual diseases. In fact, the former constraint was most important, since we could only report on diseases for which there were epidemiological studies. The diseases cited in the remainder of this section are those included in the subsequent analyses. Less well-defined CTDs and related manifestations are addressed in Sections III and IV of this chapter, and are reviewed in detail in Chapter IV of the report.

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory disease affecting multiple joints; the cause is not known (Felson, 1997). The prevalence of rheumatoid arthritis increases with age in both sexes

(Albani and Carson, 1997; Felson, 1997). The annual incidence is between 27 and 38 per 100,000 women (Table 1) and the prevalence in developed countries varies from 0.5%–1.0% (Albani and Carson, 1997; Felson, 1997). Rates of disease are low in some African, Chinese, and Indonesian communities, and rates are high among some Native American peoples (the Chippewa in Minnesota and the Pima in Arizona). Rheumatoid arthritis is two- to threefold more common in women than in men.

There are few known risk factors for the disease. First-degree relatives of rheumatoid arthritis patients have a two–four times higher risk of disease than unrelated people (Albani and Carson, 1997; Felson, 1997). In certain populations, rheumatoid arthritis is associated with specific haplotypes of the class II major histocompatibility complex (Albani and Carson, 1997; Felson, 1997). Hormonal factors may affect the occurrence or severity of rheumatoid arthritis. Rheumatoid arthritis frequently remits during pregnancy, and exogenous hormones (oral contraceptives and hormone replacement therapy) may protect against severe disease. A positive test for rheumatoid factor is associated with an increased risk for rheumatoid arthritis.

The diagnosis of rheumatoid arthritis is established when the patient has four of the seven criteria put forth by the American College of Rheumatology. The criteria are shown in Appendix A, Table A.1.

Systemic Lupus Erythematosus

Systemic lupus erythematosus is an inflammatory disorder, generally chronic, and characterized by production of autoantibodies (Felson, 1997). Multiple tissues and organ systems are affected. In the United States among Caucasian populations, the reported annual incidence rates vary from 4.5–6.5 per 100,000, with prevalence rates ranging from 12–39 per 100,000. Prevalence and incidence rates are highest in women aged 45 to 64 (Felson, 1997; Wallace and Metzger, 1997). The incidence and prevalence is significantly higher in black compared to white women, and blacks also exhibit an earlier age at onset. The female-to-male incidence ratio for systemic lupus erythematosus is at least 5:1 (Felson, 1997; Wallace and Metzger, 1997).

There is strong evidence for a hereditary component, which is most likely to be polygenic. Nevertheless, concordance among monozygotic twins is no greater than 50%. Various loci and alleles of the major histocompatibility complex are involved (Felson, 1997). The excess of female cases suggests that endogenous or exogenous hormones may play a role (Felson, 1997).

Environmental risk factors are not well defined. A disease similar to idiopathic lupus erythematosus is a rare adverse effect of certain drugs; the two most frequently associated with drug-induced lupus are procainamide and hydralazine, although the syndrome has also been observed with other drugs. Manifestations of drug-induced lupus are similar to those of idiopathic lupus erythematosus, although drug-induced disease tends to be milder and the symptoms resolve rapidly when the drug is withdrawn (Utrecht, 1988).

Established criteria for the diagnosis of lupus erythematosus appear in Appendix A, Table A.2. For classification purposes, four or more of 11 criteria must be present, serially or simultaneously, during any interval of observation (Tan et al., 1982).

Scleroderma or Systemic Sclerosis

Scleroderma is a chronic disorder of connective tissue characterized by inflammation and fibrosis and by degenerative changes in the blood vessels, skin, synovium, skeletal muscle, and certain internal organs, notably the gastrointestinal tract, lung, heart, and kidney (Felson, 1997). There are two distinct clinical variants: diffuse systemic disease and limited cutaneous disease.

Scleroderma may also be part of an “overlap” syndrome with either lupus erythematosus or dermatomyositis/polymyositis. The prevalence of scleroderma ranges from 24.2 to 28.6 per 100,000; the annual incidence is 1.5 to 1.9 per 100,000 with at least a 3:1 female to male incidence ratio (Mayes, 1996).

Race is a risk factor for scleroderma. Black patients have higher age-specific incidence rates and more severe disease than white patients (Mayes, 1996). Genetic markers have been noted to confer susceptibility to disease development (Felson, 1997; Mayes, 1996). Occupational exposures (vinyl chloride, silica dust, organic solvents) and other agents (adulterated rapeseed oil, l-tryptophan, bleomycin) have been associated with scleroderma-like illnesses.

Criteria for the diagnosis of definite scleroderma are shown in Appendix A, Table A.3. One major and several minor criteria are noted.

Sjögren's Syndrome

Sjögren's syndrome occurs in a primary form as a single disease entity. It also occurs in association with almost any of the autoimmune rheumatic diseases, the most frequent being rheumatoid arthritis. The syndrome consists of a chronic autoimmune inflammatory disease

characterized by a progressive lymphocytic and plasma cell infiltration of the salivary and lacrimal glands leading to dry mouth, dry eyes, and salivary gland swelling. Sjögren's syndrome may occur at any age, but primarily affects women during the fourth and fifth decades of life with a female to male incidence ratio of 9:1 (Anaya and Talal, 1997). An age-adjusted incidence rate of 4 per 100,000 is shown in Table 1. Little is known about risk factors other than genetic susceptibility.

Although there is no consensus in the literature on how to define the syndrome, suggested diagnostic criteria are shown in Appendix A, Table A.4. The main criteria are dryness of the eyes and mouth with histologic verification of lymphocytic infiltrates in the salivary glands. Sjögren's syndrome must be distinguished from a number of other disease entities and drug side effects that can cause siccalike symptoms (burning eyes, dry mouth).

Dermatomyositis/Polymyositis

This is a heterogeneous group of diseases characterized by muscle inflammation (Miller, 1997). Limited data, as shown in Table 1, suggest that age-adjusted incidence rates are fewer than 1 per 100,000 white women. Studies based on hospital discharge diagnoses suggest a peak in the 10–14-year-old age group and a second peak in the 45–64-year-old age group (Felson, 1997). The incidence in blacks is about four times greater than in whites (Felson, 1997). There is an increased risk of cancer among middle-aged and older adults with dermatomyositis/polymyositis (Felson, 1997).

Diagnostic criteria for dermatomyositis/polymyositis, shown in Appendix A, Table A.5, delineate three categories of disease (possible, probable, definite), based on a constellation of five symptoms or laboratory tests (Bohan and Peter, 1975)

III. Meta-analysis of Epidemiological Studies

Rationale

Although individual studies of CTDs and silicone breast implants have been conducted, most have included insufficient numbers of women to provide precise estimates of the possible association between implants and disease. In some studies, the total number of women has been large; but, given the rarity of CTDs and silicone breast implants, the frequency of diseased women who also had implants has been small. Because of this, additional analytic procedures are necessary to consolidate the information available from existing studies. We chose to conduct meta-analyses in

which measures of association, usually odds ratios (ORs) or relative risks (RRs), from individual studies are pooled to provide unifying summary effect estimates. *Effect estimate* is a generic term for the measure of association between exposure and disease, obtained either from individual studies or from pooled studies in a meta-analysis. To quote from Blair et al. (1995), “meta-analysis [is] a procedure whereby the results of multiple epidemiological studies are combined, compared, and summarized.” Such analyses can provide an objective, quantitative method for assessing health risks in relation to a specific exposure. One can compare different meta-analytic methods and the impact of individual studies on the strength of the associations obtained.

As used in this report, the term *meta-analysis* refers to a detailed epidemiological and statistical analysis of the results of various sets of studies, each study designed to address the question of whether or not there is evidence of a statistically significant association between breast implants and various CTDs. The goal of our meta-analyses is to identify sources of heterogeneity among studies and to combine the results of homogeneous studies to obtain reasonably precise summary measures of the association between breast implants and various disease outcomes. Homogeneous studies are those that provide effect estimates of roughly the same magnitude.

For several reasons, meta-analysis is a suitable method for evaluating the possible association between silicone breast implants and CTDs. First, it is particularly useful for combining the results of multiple small studies, each with limited statistical power. The pooled summary effect measure is more precise with a narrower confidence interval (CI) than are separate estimates from individual studies; it also reflects the “best estimate” of the underlying association between exposure (silicone breast implants) and disease (CTDs). Second, the methods allow for identifying heterogeneity among individual study effect estimates and for evaluating sources of such heterogeneity. The sources may relate to study design or to idiosyncratic features of an individual study. Last, meta-analysis may help to clarify ambiguity when the results from individual studies are inconsistent or unconvincing.

One notable limitation of meta-analyses should be recognized. Any bias present in the component studies persists in the meta-analysis and the summary effect estimates obtained. Confounding effects or other biases present in individual studies are unlikely to be decreased through meta-analysis. The primary strategy to address this limitation is to evaluate each study individually for possible biases, to consider each study’s weight in the overall analysis, and to suggest the likely direction and magnitude of the bias in the summary effect estimate. If many

studies have the same type and direction of bias, the summary estimate of the exposure/disease association will also be biased in that direction. If the types and directions of bias differ among studies, these biasing factors could be diluted such that the summary effect estimate is not systematically biased in either an upward or a downward direction.

Disease Entities Included in the Meta-analyses

We conducted meta-analyses for each of the following diagnoses:

Rheumatoid arthritis (RA)

Systemic lupus erythematosus (SLE)

Systemic sclerosis/scleroderma (SSC)

Sjögren's syndrome (SS)

Dermatomyositis/Polymyositis (DM/PM)

Definite connective tissue diseases combined (definite CTDs combined)

Other autoimmune/rheumatic conditions (other A/R conditions)

These diagnoses were selected because each is classified as a connective tissue or autoimmune disease, and there are studies that have evaluated one or another of these conditions in relation to breast implants.

The first five diagnoses are established entities with published diagnostic criteria, although these criteria were variably applied within individual studies. Studies also varied on the extent to which the diagnoses were validated by medical records and/or a rheumatologist's evaluation. In general, we accepted the authors' criteria and definitions for each specific diagnosis.

Definite CTDs combined includes the five established diagnoses plus additional diagnostic entities called definite CTDs by individual study authors. The category of definite CTDs combined had to be constructed to use the information as presented in several of the studies. Scientifically, the category of definite CTDs combined has strengths and weaknesses. It allows for the inclusion of diagnoses that have some uncertainty associated with them. Despite the availability of criteria to establish specific diagnoses, the distinctions among the various established CTDs are not definitive and diagnoses are known to fluctuate or change over time. Thus, the combined category allows some justifiable flexibility in CTD diagnosis. On the other hand, this rubric is problematic in that its use as a single disease outcome, in individual studies and in the meta-analyses, implies that any one diagnostic entity is representative of them all. From the perspective of etiology and pathogenesis, this assumption is unlikely to be correct.

Other autoimmune/rheumatic conditions includes a mixture of entities and diagnostic labels: ill-defined rheumatic conditions, undifferentiated connective tissue disease, mixed

connective tissue disease, overlap syndrome, atypical connective tissue disease, autoimmune disease, and other arthritis-related diagnoses and symptoms. Although some of these conditions have published diagnostic criteria, they were not used consistently in the studies. (See Appendix A, Tables A.6 for undifferentiated connective tissue disease and A.7 for mixed connective tissue disease). Some authors provided their own criteria for case definition and others provided little clarification as to the justification for the diagnosis. This grouping is of interest, however, in that it provides a category of illnesses that have signs and symptoms of CTDs without being definite CTDs.

Since our analysis focuses on the postulated role of implants in causing CTDs, implantation should have occurred prior to the onset of the illness. Only cases newly diagnosed after breast implantation (incident cases) should be counted, disregarding cases already present at the time of implant (prevalent cases). When studies provided the numbers separately for prevalent and incident cases, we counted only the incident cases in the analyses. When studies did not distinguish between pre- and postimplant cases, we included all cases as though they were postimplant.

Types of Implants Included in the Analysis

The exposure of interest in this analysis is *silicone breast implants*. This term includes different types of implants, all containing some form of silicone, but it excludes injections of any free material that is not physically bound within a containing wall. Thus, when authors identified study subjects with some type of injectable material (as opposed to an implant) in the breast, these subjects were excluded from our analyses. Some authors provided information on type of implant, e.g., silicone gel-filled, saline-filled, or polyurethane-coated, but others did not. Because of this diversity in the detail of information provided, we focused our primary analysis on “any breast implant” as the exposure of interest. There are additional reasons for choosing this approach. Many studies obtained implant data by questionnaires or interviews of women, not from medical records. Although validation studies (Garbers, 1998; Sanchez-Guerrero, 1995) have shown that women accurately report whether or not they have had a breast implant, their reporting accuracy for type of implant is lower. Furthermore, although the potential for “bleed” may be greatest with silicone gel-filled implants, since the mid-1960s almost all implants have contained silicone at least in the elastomer envelope, allowing for potential silicone exposure.

However, so as not to neglect our charge to focus on the effects of silicone gel-filled implants, we conducted an additional meta-analysis, including only those studies that provided information separately for silicone gel-filled implants. Although this approach greatly reduced the

number of eligible studies and the precision of summary effect measures, it provided the most relevant measurement of exposure.

Sources of Studies

Legal submissions covering all aspects of research on breast implants and CTDs were provided to us through the auspices of the Kobayashi law firm. These materials included published and unpublished articles, abstracts, letters, and proceedings from meetings and related documents. We reviewed all submissions to identify those studies that met our inclusion criteria (see below) for the meta-analyses. Studies referenced in other meta-analyses and reviews (Hochberg et al., 1996b; Lewin and Miller, 1997; Perkins et al., 1995; Wong, 1996) of silicone breast implants and CTDs were also obtained. To assure completeness of the potential study pool, we conducted a literature search similar to that outlined by Perkins et al. (1995). Sources for the study search included: Medline (National Library of Medicine, Bethesda, MD) from 1966 through May 1998; TOXLINE (National Library of Medicine, Bethesda, MD) from 1985 through May 1998; Current Contents Search® (Institute for Scientific Information, Philadelphia, PA) from July 1, 1997, through May 1998; and Dissertation Abstracts Online (University Microfilms International [UMI], Ann Arbor, MI) from 1992 through May 1998.

Search criteria for Medline, TOXLINE, and Current Contents Search® were based on a combination of key words for breast implants and CTDs. Key words for breast implant included *breast implant, breast augmentation, breast reconstruction, mammoplasty* or *mammaplasty*, with all possible suffixes allowed, e.g., *implantation, implants*. Key words for CTDs included *rheumatic diseases, connective tissue disease, autoimmune disease, systemic sclerosis, scleroderma, lupus, dermatomyositis, sarcoidosis, rheumatoid arthritis, fibromyalgia, Sjögren, polymyositis*. Dissertation Abstracts Online was searched with a combination of key words for *breast implant (breast implant, breast augment, breast reconstruct, mammoplasty or mammaplasty)* and *connective tissue disease (autoimmune, systemic sclerosis, scleroderma, lupus, fibromyalgia, Sjögren, polymyositis, dermatomyositis, sarcoidosis, rheumatoid arthritis)*.

The search of each of the four databases extended through May 1998 and was limited to the English language and to human subjects; the searches yielded 756 citations. We were unable to obtain one abstract (Teich-Alasia et al., 1993) which appeared in 1993 and was referenced in two publications (Lewin and Miller, 1997; Wong, 1996). Our search gave no record of subsequent publications related to the abstract in the years following its initial citation.

We made no attempt to identify additional unpublished studies. Our contacts with authors of available studies were few and communications were limited to clarifications on specific aspects

of the methods or data as presented in a particular study. We did not attempt to obtain additional data or analyses, which the authors might have, but which were not available in the existing literature.

Inclusion/Exclusion Criteria for Studies

- English language studies only were included.
- The study had to have an internal comparison group: a nonimplanted group in cohort studies or a nondiseased group in case-control studies.
- Numbers were available in the report for the creation of two by two tables. That is, we could identify the numbers of implanted women with and without disease, and the numbers of nonimplanted women with and without disease.
- The “exposure variable” was defined in the study as the presence or absence of breast implants. Studies were included even if the distinction between types of implants, e.g., silicone gel-filled versus other, was not made by the authors.
- The “disease(s) variable” was the presence or absence of some type of CTD as defined by the authors. Studies were included even though published classification criteria for specific CTDs were not met.
- When more than one publication existed from the same population or patient source, the most recent article was selected for analysis.
- Studies that only included symptom information and the frequency with which each symptom was reported could not be included. The effect estimates obtained from each study and used in the meta-analysis were based on individual women (not individual symptoms) as the unit of analysis.

Application of the above-noted criteria resulted in the exclusion of several published studies, although publication per se was not an inclusion/exclusion criterion. Three studies (Peters et al., 1994; Weisman et al., 1988; and Williams et al., 1997) were excluded for lack of an internal comparison group, although they have appeared in other meta-analyses (Wong, 1996) and have been cited frequently. Additionally, in a case-control study of risk factors for chronic fatigue syndrome, MacDonald et al. (1996) noted a silicone breast implant in one case and two controls. This study was not included in our analysis since chronic fatigue syndrome was not one of the designated diagnoses, although the symptoms may overlap with those experienced by CTD patients.

Published abstracts and letters were included as independent research studies and accorded the same status in our analysis as full-length journal articles. Information available on methods and results from these abbreviated documents was limited. Furthermore, studies presented in these forms have not undergone the peer review required of journal articles. Despite these limitations, each of these brief reports added a distinctive study population with its own data. Without them, a significant body of literature on breast implants and CTDs would have been lost.

Statistical Analyses

In our meta-analyses, we used unadjusted effect estimates (crude estimates that are not corrected for the effects of confounding factors), and adjusted estimates that have been corrected for such confounding effects. The term *effect estimate* is used to describe the magnitude of the association between exposure and disease and is usually expressed as a relative risk (RR) or an odds ratio (OR). The OR, obtained from case-control or cross-sectional studies, often approximates the RR, which is obtained directly from cohort studies. For adjusted estimates, we have added the subscript *a*—OR_a and RR_a. An RR of 1.0 indicates no observed association between exposure (breast implants) and disease (a CTD); a number appreciably larger than 1.0 indicates a likely increase in disease risk associated with the exposure, whereas a number appreciably smaller than 1.0 indicates a likely risk reduction. The decision that a particular RR value is “appreciably” larger or smaller than 1.0 is generally based on whether the lower boundary of the 95% confidence interval exceeds 1.0 for increased risks or the upper boundary is less than 1.0 for decreased risks. A *confidence interval* (CI) defines the range within which the true value for the association between exposure and disease is most likely to be found. The results from the meta-analyses are expressed as summary RRs or ORs, which are pooled effect estimates from all the constituent studies. Also, 95% CIs associated with these summary risks are provided.

Meta-analysis of Unadjusted Effect Estimates

Our analysis of unadjusted effect estimates involves the use of “exact” statistical methods and approximate large-sample statistical methods. The basic data for these unadjusted analyses consist of various series of two by two tables formed by considering two dichotomous variables: the exposure variable is the presence or absence of a (silicone) breast implant and the disease variable is the presence or absence of the disease (CTD) of interest. We abstracted the numbers for the two by two tables directly from the numbers provided by the authors of the individual studies. Because the prevalence of breast implants is very low and because the disease outcomes of

interest are very rare, the number of diseased subjects with a breast implant—the number of exposed cases—can be quite small. Since the individual study is the unit of analysis in these meta-analyses, each study provides a two by two table for each specific CTD reported in the study.

The Exact statistical program (Martin and Austin, 1991) is particularly suitable for meta-analyses containing studies with small sample sizes. The program provides a study-specific Conditional Maximum Likelihood OR with Fisher exact confidence limits. By combining the estimates from a set of studies, a summary OR, representing the overall best estimate of the association between exposure and disease, and a 95% CI are obtained for each disease. The ORs obtained are unadjusted for confounders.

In producing an overall summary effect estimate, it is assumed that the individual studies used to construct that summary estimate are homogeneous with respect to the effect being estimated. Homogeneity indicates consistency of results across studies. The Exact program provides the Zelen exact p-value, and the Breslow-Day chi-square statistic and p-value as tests of homogeneity. These tests indicate the extent to which a group of studies reporting on a specific disease is homogeneous with respect to their individual ORs or RRs. In applying these tests, we chose a p-value of 0.10 as a value below which heterogeneity among studies might exist.

If heterogeneity among studies was identified, we used a process of stratification followed by influence analysis to evaluate the source of heterogeneity and, if possible, eliminate it. Stratification variables vary across studies but not within an individual study. The choice of stratification variables is based on knowledge of the studies and the particular topic under investigation. Furthermore, the information must be available so that each study can be classified on the variable of interest. The stratification variables in our analysis included study design (cohort versus other), medical record validation of disease (yes or no), and date of data collection on disease diagnosis (<1992 or \geq 1992). Other potential stratification variables, which did not prove to be feasible to use, included: subject source (population versus clinic-based), average follow-up duration (<5 versus \geq 5 years), age (<50 versus \geq 50 years), and indication (cosmetic versus reconstruction).

If homogeneity could not be achieved through stratification, we resorted to visual inspection of individual studies in search of outliers. Studies were removed individually or in pairs to achieve homogeneity among the remaining studies (influence analysis). The final set of studies was selected to achieve homogeneity and to retain the largest number of studies and subjects in the analysis.

Tables D.1–D.7 in Appendix D contain the numbers, statistics, and stratification variables

from each study used in these analyses. Table D.8 shows the results from three different analytic approaches to the calculation of summary unadjusted ORs and 95% CIs for each of the seven disease entities. Despite the concern about sparse data, the two large sample methods (Mantel-Haenzel and unconditional Maximum Likelihood Estimate) produced ORs and 95% CIs almost identical to the Exact analysis (conditional Maximum Likelihood Estimate), indicating that the approximate methods performed well.

Possible heterogeneity among individual study OR estimates is suggested by the p-values (≤ 0.10) from one or both tests of homogeneity for definite CTDs combined, scleroderma, and other autoimmune/rheumatic conditions (Appendix D, Table D.8). Stratified analyses, using the variables previously defined, followed by influence analyses excluding individual studies, are shown in Appendix D, Tables D9–D11.

Meta-analysis of Adjusted Effect Estimates

In reviewing the results from individual studies, the adjusted RR estimates were noted to be higher than the unadjusted estimates for many of the diseases. Since the Exact program calculates unadjusted estimates only, we produced an alternative large-sample meta-analysis using adjusted ORs or RRs obtained from the individual studies. Only studies that provided an adjusted estimate, either through analytic methods at the analysis stage or matching at the design phase, could be incorporated in this meta-analysis.

The primary confounders in the adjusted analysis were age, with controls frequently being older than cases, and secular time, because implant frequency and implant type varied by calendar time period. Additionally, length of follow-up sometimes varied between implanted and nonimplanted women within individual studies.

The basic data needed from each study for a meta-analysis of adjusted effects consists of an adjusted effect estimate (an adjusted odds, risk, or rate ratio which we denote as RR_a) and an estimate of its standard error, often obtained indirectly from the confidence interval reported in the study. The adjusted estimates were those reported by the authors. Appendix B, Section B.1, contains a description of the approximate large-sample statistical methods that we used for our meta-analyses.

Appendix E, Tables E.1–E.7, shows the statistics abstracted from each study and the weight of each study in the summary RR_a . For each disease entity, two or more studies had to be excluded because adjusted RRs were not provided by the authors. In some studies, an adjusted RR could not be calculated because there were no subjects in one of the four disease by exposure

categories.

Although our primary meta-analysis of adjusted RRs was based on *any breast implant* as reported by the authors, we produced an additional meta-analysis, using the same analytic methods as noted above, but based on silicone gel-filled implants only. This approach restricted the number of eligible studies to those that had separate analyses for silicone gel-filled implants or silicone breast implants as opposed to the more generic term *breast implants*. In addition, implant data had to be obtained from medical records rather than self-report. Appendix E, Table E.8 contains the studies and related statistics used in this analysis.

Results

Description of Individual Study Results

Review of existing studies and application of the inclusion/exclusion criteria noted previously yielded 20 studies (11 case-control or cross-sectional and nine cohort) that were acceptable for inclusion in our meta-analyses. Table 2 summarizes characteristics of the case-control and cross-sectional studies; Table 3 shows the cohort studies. Most cohort and two cross-sectional studies (Goldman et al., 1995 and Hennekens et al., 1996) evaluated multiple outcomes. Diseases included by the authors under definite CTDs combined and other rheumatic conditions (or other CTDs) are listed in the footnotes to the tables. Adjusted effect estimates are shown, when provided by the authors. For each of the 20 studies, narrative descriptions emphasizing strengths and weaknesses appear in Appendix C.

Unadjusted Results from Meta-analyses

Table 4 gives our best estimates of the summary unadjusted ORs, 95% CIs, and homogeneity p-values for each of the conditions under study. Excluding particular studies had little effect on the magnitude of the summary ORs but substantially improved the homogeneity p-values. Exclusion of Friis et al. (1997) for definite CTDs combined, scleroderma, and other autoimmune/rheumatic conditions, as well as Sanchez-Guerrero et al. (1995) for other autoimmune/rheumatic conditions, provided homogeneous summary ORs, while retaining the largest number of studies. In these unadjusted analyses, the summary ORs were all less than one, with the exception of Sjögren's syndrome: summary OR 1.10 (95% CI 0.74, 1.58). For each of the conditions analyzed, the findings are consistent with a lack of association between breast implants and connective tissue diseases. For several of the conditions, the upper boundary of the 95% CI actually lies below one, which, if interpreted literally, would imply that breast implants protect against these conditions.

Results Adjusted for Confounding Variables

Table 5 shows two summary adjusted RRs and homogeneity p-values for each condition; the first row of values includes, and the second row excludes, the Hennekens et al. study. The next to last column shows the “weight” that the Hennekens study contributed to each summary RR_a. The large size of the Hennekens study relative to all others accounts for its disproportionate weight, which in turn creates a summary that is largely a reflection of the Hennekens’ RR_a. Since the meta-analysis should contribute information beyond that provided by any single study, two sets of summary adjusted RRs were calculated, one with and one without Hennekens.

The summary RR_a for each condition is higher when the Hennekens et al. study is included than when it is excluded. When including Hennekens, the summary adjusted RRs are slightly elevated for definite CTDs combined (1.14), rheumatoid arthritis (1.15), scleroderma (1.30), Sjögren’s (1.47) and other autoimmune/rheumatic conditions (1.15). The 95% CIs include one, except for definite CTDs combined (1.01, 1.28) and Sjögren’s syndrome (1.01, 2.14). When Hennekens is excluded, all summary adjusted RRs approximate one with 95% CIs that overlap one. The summary RR_a for Sjögren’s remains elevated (1.42), but the 95% CI (0.65, 3.11) clearly straddles one. The summary RR_a for dermatomyositis/polymyositis is the Hennekens estimate since other authors either provided no data on dermatomyositis/polymyositis or included it under other autoimmune/rheumatic conditions. (See diseases and conditions included under other autoimmune/rheumatic conditions in footnotes to Tables 2 and 3.)

There was no evidence of heterogeneity among study results. In Table 5, the homogeneity p-values are greater than 0.10 for each of the disease entities.

The p-values shown in the last column of Table 5 assess whether the RR estimate from the Hennekens study was significantly different from the summary estimate obtained from the other studies. For definite CTDs combined, the p value for the comparison was 0.003. For other autoimmune/rheumatic conditions, a difference between the Hennekens estimate and the summary RR_a from the other studies is also suggested by the p-value of 0.08. These differences further support our decision to perform separate meta-analyses with and without Hennekens. They do not, however, inform us as to which of the RR_a estimates is most likely to represent the true association between exposure and disease. An evaluation of the inherent biases in the different studies can help with this interpretation. (See Appendix C for a detailed commentary on each study.)

Figures 1–6 provide graphic presentations of the study-specific adjusted RR estimates with 95% CIs and the summary RR_a for each of the six designated disease entities. (The summary adjusted RRs duplicate those shown in Table 5.) In each figure, the black dots show the RR_a

estimates for individual studies, case-control or cross-sectional studies combined, cohort studies combined, and all studies combined including and excluding the Hennekens study. The horizontal lines extending to the right and left of the black dots show the widths of the 95% CI. A few of the upper boundaries of the 95% CIs extend beyond 8.0 and these are noted by extending the solid line with a dotted line. The variation in the widths of the CIs is, for the most part, a function of the different sample sizes.

Table 6 shows summary adjusted (with and without Hennekens) and unadjusted RRs obtained from the different meta-analyses. There is a continuum in the size of the RRs: the lowest being the unadjusted, the middle being the adjusted without Hennekens, and the highest including Hennekens. In general, the adjusted estimates should be more valid than the unadjusted. However, a number of studies had to be excluded from the adjusted analyses. These range in number from two (definite CTDs combined and rheumatoid arthritis) to seven for scleroderma. A major reason for exclusion was a lack of exposed cases and thus an inability to calculate a study-specific RR_a . Scleroderma provides an important example; seven of the 12 eligible studies could not be included in the adjusted analysis. Six (Edworthy et al. [1998], Gabriel et al. [1994], Goldman et al. [1995], Nyren et al. [1998], Sanchez-Guerrero et al. [1995], and Teel [1987]) of the seven had no implanted cases, suggesting that studies with lower RR estimates may have been selectively excluded from the adjusted analysis. Such exclusions could bias upward the summary RR_a calculated from the remaining studies.

Results from Silicone Gel-Filled Implants Only

The results from the analysis, exclusive to silicone gel-filled implants, appear in Table 7. Several points are evident. All the summary adjusted RRs are lower in the analysis of silicone gel-filled implants than in the analysis of all breast implants (Table 5). The adjusted RRs are less than 1.0 for each of the conditions, when the analysis is limited to silicone gel-filled implants. The summary adjusted RRs shown in Table 7 provide assurance that a significant adverse effect of silicone gel-filled implants has not been obscured in our analyses of *all breast implants*.

Discussion

We have used several meta-analytic approaches in evaluating the existing studies of breast implants and CTDs. These included both exact methods for small sample sizes and approximate large-sample methods. The exact method used the actual number of subjects from each study to calculate study-specific and pooled OR estimates. Factors that might distort the association between breast implants and CTDs (confounding variables) were not accounted for in these

unadjusted analyses. The large-sample method calculated summary adjusted RR estimates using the adjusted RRs taken directly from the individual studies. Fewer studies could be incorporated in the second analysis since some studies did not provide adjusted estimates. Most commonly, adjustments were made for subject age, calendar year, and length of follow-up. Although women with implants differ on many personal and lifestyle characteristics from other women (Cook et al., 1997), these factors would not distort the measure of association between implants and disease unless these characteristics were also risk factors for the disease. Most of the specific CTDs do not have strong, established risk factors, other than gender, age, and race. Specific genetic susceptibility markers are recognized for some of the CTDs, but no information was available in the epidemiological studies to evaluate them.

The findings from these analyses are as follows: summary unadjusted RRs were consistently lower than the summary adjusted RRs. The summary unadjusted RRs were less than one for every CTD except Sjögren's syndrome (1.10, 95% CI 0.74, 1.58). The summary adjusted RR estimates including Hennekens et al. were the highest: definite CTDs combined (1.14, 95% CI 1.01, 1.28) and Sjögren's (1.47, 95% CI 1.01, 2.14). The lower boundaries of the 95% CIs were below one for the remaining conditions. The lack of consensus in the literature on the definition of Sjögren's syndrome creates uncertainty as to the accuracy of the diagnosis and, therefore, the interpretation of the small elevation in the RR_a estimate (see Appendix A, Table A.4; Fox, 1997). Without Hennekens in the meta-analysis, all the summary adjusted RRs were lower and none was elevated to a statistically significant level.

Because of the disproportionately large size of the Hennekens et al. study, it weighed heavily in the results of the meta-analyses. This was particularly evident in the adjusted meta-analyses when several studies lacking an adjusted RR estimate could not be included. The Hennekens study also was subject to various methodologic problems, which could have affected its results. The most serious of these is the probable over-reporting of illness by women with implants during a time period of intensive media publicity about the postulated adverse health effects of breast implants. To the extent that publicity increased awareness of symptoms among women with implants, the results of the Hennekens study could be affected, biasing the effect estimates upward. Bias and validity issues pertaining to the Hennekens study are discussed in Appendix C.

The meta-analysis, which focused solely on silicone gel-filled implants, produced lower summary RR_a estimates for all the diseases than did the analyses based on "any breast implant." In the meta-analyses exclusive to silicone gel-filled implants, there was no suggestion of an association between silicone gel-filled implants and any of the specific connective tissue diseases

or other autoimmune/ rheumatic conditions.

Three meta-analyses, addressing the topic of silicone breast implants and connective tissue diseases, have been published previously (Hochberg et al. 1996a; Perkins et al, 1995; Wong, 1996). None included the Hennekens et al. study, and only Perkins applied formal statistical tests of heterogeneity and conducted an influence analysis. Wong and Hochberg et al. used adjusted effect estimates in their analyses, whereas the Perkins et al. meta-analysis was based on study-specific unadjusted effects, since they noted no difference in the magnitude of adjusted and unadjusted effect estimates. None of the groups evaluated the *power* of their meta-analyses or the *population attributable fraction*. We address these topics in sections IV and V of this report. Despite these differences in the meta-analyses conducted to date, none identified a significant association between implants and connective tissue diseases.

The various approaches to conducting meta-analyses described in the current report lead to the same general conclusion. A true association between breast implants (or silicone gel-filled implants) and any definite CTD or other autoimmune/rheumatic condition is unlikely to exist.

Limitations of the Meta-analyses

If the latency interval (time from implant to manifestations of CTD) were ten to 20 years or more, we would not be able to detect a true association even if it did exist. Only Hennekens et al. had sufficient data to analyze CTDs that occurred ten or more years after implantation. In their study, statistical tests for trend by categories of duration of implantation for each specific CTD, all CTDs combined, and other CTDs (including mixed), were not statistically significant. These results suggest that the duration of time after implantation did not affect the risk of CTDs. Person-years or categories of follow-up duration were not evaluated in our meta-analyses, since most studies did not report those data. Thus, it is not known if adverse effects of breast implants become manifest only long after implantation. However, little in the biological sphere supports such a prolonged latency period. The rare drug toxicities that have produced CTD-type syndromes have done so promptly.

The meta-analyses did not address the effect of implant rupture or bleed on the propensity to develop CTDs. The epidemiological studies did not gather or present data that could be used to address this issue. Similarly, data were not available in the epidemiological studies on the genetic susceptibility loci that have been related to various CTDs.

The most serious limitation of any meta-analysis is the quality and validity of the studies on which the meta-analysis is based. That some of the studies were never published in refereed journals, but were only available as abstracts from meeting proceedings or as letters to an editor,

is bothersome. If a study has useful information and the methods and analysis are adequate, it ought to be suitable for a full-length publication. The information available in abstracts and letters on methods and results is scanty, which inevitably leads to questions about the quality of the research. Whatever biases are present in the original studies are further perpetuated in the meta-analysis. If the biases differed from study to study and functioned to increase the RR estimate artificially in some studies and to reduce it in others, then there could be some dilution of the individual study biases in the meta-analysis. However, if most studies had systematic biases that either consistently increased or decreased their RR estimates, these would persist in the meta-analysis. For this reason, we elaborate on the types of potential biases likely to be present in some of the individual studies in the next section of this chapter. For reference to specific studies, see the narrative comments provided in Appendix C.

Potential Biases in Studies of Silicone Breast Implants and Connective Tissue Diseases

Reporting bias is likely to have occurred when designation of disease status was based on questionnaire or interview of study subjects during or following the extensive media publicity surrounding silicone breast implants and various systemic diseases. Although Connie Chung's television program on breast implants on CBS's "Face to Face" occurred December 10, 1990, the major publicity occurred in the winter and spring of 1992 when the U.S. Food and Drug Administration had hearings and made rulings limiting the use of silicone breast implants. The media publicity is likely to have sensitized implanted women to their symptoms and resulted in over-reporting of disease for implanted women relative to nonimplanted women. Reporting bias would cause an artificial increase in the estimates of risk for CTDs. In the United States, extensive publicity and litigation may pose threats to internal and external validity of silicone breast implant studies.

Unlike disease status, studies have shown that women accurately report their implant status. However, reporting on the type of implant and date of implant is less accurate. Since these are important variables in the analysis, medical record validation should be conducted to corroborate the information. In the absence of medical record data, some misclassification of implant type and date is likely to occur. Implant date is important for determining whether the implant occurred before or after the CTD diagnosis and for estimating the time to event—the latent period between implant and disease onset or diagnosis. Implant type is important given that bleed or rupture of silicone gel-filled implants will produce greater exposure to silicone than similar experiences with saline implants. Thus, knowledge of implant date and type contributes to the interpretation of the

plausibility of the postulated association between exposure and disease.

Internal and external validity of population-based studies can be evaluated in several ways. Two of these involve comparisons of study rates to the population at large. For case-control studies, the implant frequency in controls should be similar to that reported in the reference population, e.g., women of the same age, race, and geographic region. In cohort studies, disease frequency in nonimplanted women should be comparable to reported disease rates in the reference population, which for CTDs would be the age, race, and country-specific incidence rates. Notable elevations or reductions in either of the rates (implants in controls in case-control studies and disease rates in nonimplanted women in cohort studies) will bias the RR estimates.

Comparisons of implant and disease rates to a reference population are less meaningful for clinic-based studies, since the nature of the clinic and its referral sources is likely to determine the specific rates and also the internal validity of the study.

Low response rates in case-control studies and low follow-up rates in cohort studies are other sources of potential bias. In case-control studies, response rates of 80–85% have been achievable until the past decade when these rates began dropping. The problem is that nonrespondents often differ from respondents on characteristics related to the exposure and the disease; these differences can bias study results based on respondents only. Differences in response rates for cases and controls, or follow-up rates among implanted and nonimplanted women, may adversely affect validity of the results.

Many studies ignored the indication for implant in their design and analysis. Whether the implants were performed for cosmetic reasons or for reconstruction after breast cancer surgery could significantly alter the results. The indication for implants, e.g., breast cancer, may affect the signs and symptoms subsequently experienced. Similarly, the therapies employed to treat cancer may induce manifestations of autoimmune disease, e.g., bleomycin causes Raynaud's phenomenon and interstitial pulmonary disease (Felson, 1997). Cohort studies should have dual comparison groups for implanted women with and without breast cancer. Ideally, women with and without breast cancer should be analyzed separately, but the rarity of outcome events (disease occurrence) was an inducement for authors to perform a combined analysis.

Data on potential confounders of the association between breast implants and CTDs were missing from many studies. This lack of information could bias the results. However, when potential confounders other than age, race, and calendar time were evaluated, they had little effect on the RR_a estimates from individual studies. At present, the role of confounders is uncertain, because of the lack of data in many studies and the lack of scientific knowledge as to which factors may be important.

Publication bias is frequently cited as a reason for lack of validity in meta-analyses. Publication bias could occur if studies finding no association between exposure and disease were less likely to be submitted and accepted for publication than those showing a positive association. With respect to silicone breast implants and CTDs, publication bias is unlikely to be an important issue, because negative studies are just as important to the various scientific, public, and legal audiences as are positive studies. Thus, study results, positive or negative, should not influence submission propensity or publication policy. In fact, the majority of studies included in our meta-analyses were negative, as stated by the authors.

IV. Power of the Meta-analyses

Despite the essentially negative results from our meta-analyses, suppose for the moment that there is a true positive association between breast implants and one or more CTDs. Given this relationship in the population at large, how likely is it that our meta-analyses could identify the association? From a practical standpoint, we are asking the question of whether the set of studies on which we conducted the meta-analyses is sufficiently “powerful” to detect this true underlying association. In this context, we define *power* to be the probability that the lower limit of the 95% CI for the true summary RR exceeds one in value, given that the true underlying exposure-disease association is positive.

A number of factors affect power. In general, power increases with increasing sample size (increasing numbers of studies in the meta-analysis) and with the strength of the true underlying exposure–disease relationship in the population under study. The strength of this association is reflected in the size of the observed summary RR. Power decreases as variability in the RR estimates increases. (The larger the standard error of any RR estimate, the greater is its variability.) Power may also be affected by the choice of statistical analytic methods.

Power calculations are usually conducted at the design stage of a study to help researchers choose the sample size necessary to provide sufficiently high power to detect a positive or negative (protective) association that has been suggested to exist from other studies or ancillary information. In contrast, in our meta-analysis situation, we necessarily had to concern ourselves with analysis-stage power considerations. In any one of our meta-analyses, the sample size (the number of studies) was completely predetermined, as were the values of the study-specific RR estimates and their standard errors. However, we used these standard errors from the studies as “givens” and computed power values for a range of true population relative risk values. An

important assumption is made in these calculations, namely, that the underlying population relative risk being estimated exceeds one in value. Given the results from the individual studies and our summary RR estimates, we cannot be sure that this assumption is valid. However, if it were a valid assumption, the elevation in the true relative risk for any CTD is likely to be small. Thus, we have computed power values to detect small increases in the population relative risk ranging from 1.1 to 2.0. A brief discussion of the statistical methods for these calculations appears in Appendix B, Section B.2.

Figure 7 graphs the results of these computations. This figure shows that for definite CTDs combined the power is nearly 90% to detect a population summary RR_a of 1.2 or greater. For rheumatoid arthritis and other autoimmune/rheumatic conditions, we have > 80% power to detect summary adjusted RRs of 1.3 or greater. For systemic lupus erythematosus, Sjögren's syndrome, and scleroderma, the smallest population summary RRs detectable with 80% power are about 1.5, 1.7, and 1.8, respectively. In most situations, the ability to detect true summary relative risk values of 1.5–2.0 with 80–90% power would be considered adequate.

Figure 8 is based on the same calculations as Figure 7 but excludes the Hennekens et al. study from the analysis. Without this large study, the power to detect small increases in the population summary RRs is lower. Specifically, for definite CTDs combined and other autoimmune/rheumatic conditions, the power to detect a summary RR of 1.4 or greater is nearly 80%. For rheumatoid arthritis, there is about 80 % power to detect a relative risk of at least 1.7, whereas for scleroderma, lupus erythematosus, and Sjögren's syndrome, the power to detect an RR of 2.0 is 70%, 60%, and 40%, respectively. One would like to have greater power to detect smaller true relative risk values than was available for this analysis.

V. Population Attributable Fraction

Our meta-analyses and the studies on which the analyses were based produced “relative risk” estimates—that is, the risk of developing a particular CTD among women with breast implants compared to those without implants. Another concept, the population attributable fraction, is useful in thinking about the impact of an exposure, e.g., breast implants, on disease incidence in a population. In our situation, the population attributable fraction is the proportion of the disease

burden in a population that may be caused by the implants. The population attributable fraction can also be used to estimate how much of the disease burden in a population would be eliminated if the suspect exposure (breast implants) were eliminated.

Standard formulas are available for the calculation of population attributable fraction as noted in the footnote to Table 8 (Northridge 1995; Rockhill et al., 1998). To calculate the number of cases attributable to implants, we used the summary adjusted RRs obtained from our meta-analysis (including Hennekens et al. [1996]) and assumed the frequency of breast implants in the United States to be 1%, which is a fairly high estimate. To obtain the number of women who developed CTDs as the result of breast implants, the annual incidence rate of disease (an average of those shown in Table 1) was multiplied by the population attributable fraction.

The last column of Table 8 shows that, among ten million U.S. women, 4.3 of 3,303 new cases of rheumatoid arthritis and fewer than one case each of lupus erythematosus, scleroderma, and dermatomyositis/polymyositis may be attributed to breast implants annually. From a public health perspective, breast implants appear to have a minimal impact on the number of women developing CTDs and elimination of implants would not be important in reducing the incidence of CTDs.

VI. Summary and Conclusions

Analyses in this chapter of the report were designed to assess whether or not there is an association between breast implants and several definite connective tissue diseases or other less well-defined connective tissue, autoimmune, or rheumatic conditions (other autoimmune/rheumatic conditions).

To summarize the findings from 20 epidemiological studies, we conducted several meta-analyses, using different analytic approaches. All analyses had the same goal of combining results across studies to produce summary relative risks that would be better estimates of the true underlying association between exposure and disease than could be obtained from any one study. (Summary relative risk estimates greater than one are consistent with a positive association; values less than one may suggest protective effects; and one indicates no association). We provided summary relative risk estimates (unadjusted and adjusted for confounding variables) with 95% confidence intervals for definite connective tissue diseases combined, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis/scleroderma, Sjögren's syndrome,

dermatomyositis/polymyositis, and other autoimmune/rheumatic conditions. Separate analyses were conducted, including and excluding the Hennekens et al. study, which heavily affected the analyses because of its large size. An additional analysis was conducted based on silicone gel-filled implants exclusively, rather than the more inclusive group designated *breast implants*.

The *unadjusted meta-analysis* included all eligible studies but took no account of potential confounding factors. All summary relative risk estimates were less than or close to one.

The *adjusted meta-analysis* was based on the subset of studies that reported relative risk estimates adjusted for confounding variables. When Hennekens et al. was excluded from these analyses, the summary adjusted relative risks approximated one for all diseases and conditions except for Sjögren's syndrome. For the latter, the summary adjusted relative risk was 1.42 (95% confidence interval 0.65, 3.11). When including Hennekens in the meta-analyses, the summary adjusted relative risks for definite connective tissue diseases combined and for Sjögren's syndrome were elevated with the lower boundary of the 95% confidence interval exceeding one: 1.14 (1.01, 1.28) and 1.47 (1.01, 2.14), respectively.

The *meta-analysis of silicone gel-filled breast implants* provided summary adjusted relative risks of one or lower for each of the diseases or conditions. The small elevations in some of the summary adjusted relative risk estimates, noted in the analysis of all breast implants, was not supported in the analysis of silicone gel-filled implants only.

In all these analyses, many of the summary relative risk estimates for different diseases were lower than one, and some were significantly lower such that the upper boundary of the 95% confidence interval did not include one. In the paragraphs above, we have noted only those few summary relative risk estimates that were greater than one. Yet, most of the 95% confidence intervals bounding these estimates overlapped one. The most likely conclusion from these several analyses is that there is no meaningful or consistent association between breast implants or silicone gel-filled implants and any of the conditions studied.

If an association between implants and connective tissue diseases had been found, a discussion of the possible causal versus noncausal mechanisms for the association would be required. Since there was no consistent or meaningful association, a discussion of possible biologic mechanisms has little value.

An analysis of the *power* to detect an adverse effect, assuming such an effect actually existed, was conducted, based on the available studies. Including Hennekens et al., the ability of

our analyses to detect a small increase in the summary adjusted relative risk (1.2–1.8 for different conditions) was good. Excluding Hennekens, we could not be confident of detecting a true underlying relative risk of two or less for several of the disease outcomes.

Finally, we evaluated the possible public health impact of breast implants on the various connective tissue diseases. The *population attributable fraction* estimates the proportion of all cases of a specific disease in a population that might be caused by breast implants, or conversely, that might be prevented if implants were no longer used. Our best estimates of the number of women affected annually in the United States because of implants was 4.3 (rheumatoid arthritis), 1.3 (Sjögren's syndrome), and less than one (lupus erythematosus, scleroderma, and dermatomyositis/polymyositis) per ten million women.

References

- Alarcon GS, Williams GV, Singer JZ, Steen VD, Clegg DO, Paulus HE, Billingsley LM, Luggen, ME, Polisson RP, Willkens RF, Yarboro C, Ma K-N, Egger MJ, Williams HJ, Ward JR. Early undifferentiated connective tissue disease. 1. Early Clinical manifestation in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of well established connective tissue disease. *J Rheumatol* 18:1332–39, 1991.
- Alarcon-Segovia D, Cardiel MH. Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients. *J Rheumatol* 16:328–34, 1989.
- Albani S and Carson DA. Etiology and pathogenesis of rheumatoid arthritis. In *Arthritis and allied conditions: A textbook of rheumatology*, WJ Koopman, ed. 13th ed. Williams & Wilkins, Baltimore, vol. 1, pp. 979–92, 1997.
- Anaya J-M and Talal N. Sjogren's syndrome and connective tissue diseases associated with other immunologic disorders. In *Arthritis and allied conditions: A textbook of rheumatology*, WJ Koopman, ed. 13th ed. Williams & Wilkins, Baltimore, pp. 1561–80, 1997.
- ARA Scleroderma Criteria Cooperative Study: preliminary clinical criteria for systemic sclerosis. *Arthritis Rheum* 23:381–90, 1980.
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 31:315–24, 1988.
- Benbassat J, Geffel D, Zlotnick A. Epidemiology of polymyositis-dermatomyositis in Israel, 1960-

76. *Isr J Med Sci* 16:197–200, 1980.
- Bennett, RM, O’Connell DJ. Mixed connective tissue disease: A clinicopathologic study of 20 cases. *Sem Arthritis Rheum* 10:25–51, 1980.
- Blair A, Burg J, Foran J, Gibb H, Greenland S, Morris R, Raabe G, Savitz D, Teta J, Wartenberg D et al. Guidelines for application of meta-analysis in environmental epidemiology. *Regul Toxicol Pharmacol* 22:189-97, 1995.
- Bohan A, Peter JB. Polymyositis and dermatomyositis (First of two parts). *N Engl J Med* 292:344–47, 1975.
- Burns CJ, Laing TJ, Gillespie BW, Heeringa SG, Alcsér KH, Mayes MD, Wasko MCM, Cooper BC, Garabrant DH, Schottenfeld D. The epidemiology of scleroderma among women: Assessment of risk from exposure to silicone and silica. *J Rheum* 23:1904–11, 1996.
- Cook LS, Daling JR, Voigt LF, deHart MP, Malone KE, Stanford JL, Weiss NS, Brinton LA, Gammon MD, Brogan D. Characteristics of women with and without breast augmentation. *JAMA* 277:1612–17, 1997.
- Cook RR, DeLongchamp RR, Woodbury M, Perkins LL, Harrison MC. The prevalence of women with breast implants in the United States—1989. *J Clin Epidemiol* 48:519–25, 1995.
- Dugowson CE, Koepsell TD, Voigt LF, Bley L, Nelson JL, Daling JR. Rheumatoid arthritis in women. Incidence rates in group health cooperative. Seattle, Washington, 1987–1989. *Arthritis Rheum* 34:1502–07, 1991.
- Dugowson CE, Daling J, Koepsell TD, Voigt L, Nelson L. Silicone breast implants and risk for rheumatoid arthritis. [American College of Rheumatology, presented at the American College of Rheumatology, annual meeting, Atlanta, October 11-15, 1992.] *Arthritis Rheum* 35(9):S66, abstract 192, 1992.
- Edworthy SM, Martin L, Barr SG, Birdsell DC, Brant RF, Fritzler MJ. A clinical study of the relationship between silicone breast implants and connective tissue disease. *J Rheum* 25:254–60, 1998.
- Englert H, Morris D, March L. Scleroderma and silicone gel breast prostheses—the Sydney study revisited. *Aust NZ J Med* 26:349–55, 1996.
- Felson DT. Epidemiology of the rheumatic diseases. In *Arthritis and allied conditions: A textbook of rheumatology*, WJ Koopman, ed. 13th ed. Williams & Wilkins, Baltimore, vol. 1, pp. 3-34, 1997.

- Fessel WJ. Systemic lupus erythematosus in the community. Incidence, prevalence, outcome and first symptoms; the high prevalence in black women. *Arch Intern Med* 134:1027–35, 1974.
- Fox, RI. Sjögren's syndrome. Controversies and progress. *Clin Lab Med* 17:431-44, 1997.
- Fox RI, Robinson C, Curd J, Michelson P, Bone R, Howell FV. First international symposium on Sjögren's syndrome: suggested criteria for classification. *Scand J Rheumatol Suppl.* 61:28–30, 1986.
- Friis S, Mellekjaer L, McLaughlin JK, Breiting V, Kjaer SK, Blot W, Olsen JH. Connective tissue disease and other rheumatic conditions following breast implants in Denmark. *Ann Plast Surg* 39:1–8, 1997.
- Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE, Melton LJ 3rd. Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 330:1697–1702, 1994.
- Garbers S, Terry MB, Toniolo P. Accuracy of self-report of breast implants. *Plast Reconstr Surg* 101:695–98, 1998.
- Giltay EJ, Bernelot Moens HJ, Riley AH, Tan RG. Silicone breast prostheses and rheumatic symptoms: A retrospective follow up study. *Ann Rheum Dis* 53:194–96, 1994.
- Goldman JA, Greenblatt J, Joines R, White L, Aylward B, Lamm SH. Breast implants, rheumatoid arthritis and connective tissue diseases in a clinical practice. *J Clin Epidemiol* 48:571–82, 1995.
- Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 9:1–30, 1987.
- Greenland S, Ackerman DL. Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. *Fertil Steril* 64:936–41, 1995.
- Gudmundsson S, Steinsson K. Systemic lupus erythematosus in Iceland 1975–1984. A nationwide epidemiological study in an unselected population. *J Rheum* 17:1162–67, 1990.
- Hennekens CH, Lee I-M, Cook NR, Hebert PR, Karlson EW, LaMotte F, Manson JE, Buring JE. Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. *JAMA* 275:616–21, 1996.
- Hochberg MC. The incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970-1977. *Arthritis Rheum* 28:80–86, 1985.

- Hochberg MC, Perlmutter DL. The association of augmentation mammoplasty with connective tissue disease, including systematic sclerosis (scleroderma): a meta-analysis. *Curr Top Microbiol Immunol* 210:411–17, 1996a.
- Hochberg MC, Perlmutter DL, Medsger TA Jr, Nguyen K, Steen V, Weisman MH, White B, Wigley FM. Lack of Association between augmentation mammoplasty and systemic sclerosis (scleroderma). *Arthritis Rheum* 39:1125–31, 1996b.
- Hook EB, Regal RR. Effect of variation in probability of ascertainment by source (“variable catchability”) upon “capture-recapture” estimates of prevalence. *Am J Epidemiol* 137:1148–66, 1993.
- Hopkinson ND, Doherty M, Powell RJ. The prevalence and incidence of systemic lupus erythematosus in Nottingham, UK, 1989–90. *Br J Rheum* 32:110–15, 1993.
- Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England: a relationship to ethnicity and country of birth. *Arthritis Rheum* 38:551–58, 1995.
- Jonsson H, Nived O, Sturfelt G, Silman A. Estimating the incidence of systemic lupus erythematosus in a defined population using multiple sources of retrieval. *Br J Rheum* 29:185–88, 1990.
- Kasukawa R, Tojo T, Miyawaki S, Yoshida H, Tanimoto K, Nobunaga M., Suzuki T, Takasaki Y, Tamua T. Preliminary diagnostic criteria for classification of mixed connective tissue disease. In *Mixed Connective Tissue Diseases and Anti-Nuclear Antibodies: Proceedings of the International Symposium on Mixed Connective Tissue Disease and Anti-nuclear Antibodies, Tokyo, 29–30 August 1986*, R Kasukawa and GC Sharp, eds. International Congress Series no. 719. Excerpta Medica, Amsterdam, pp. 41–47, 1986.
- Koopman, WJ, ed. *Arthritis and allied conditions: A textbook of rheumatology*, 2 vols.. 13th ed. Williams & Wilkins, Baltimore, 1997.
- Lacey JV, Laing TJ, Gillsepie EW, Schottenfeld C. Letter to the Editor [reply to Koeger A-C, Nguyen J-M, Fleurette F, Epidemiology of scleroderma among women: Assessment of risk from exposure to silicone and silica]. *J Rheum* 24:1854–55, 1997.
- Laing TJ, Gillespie BW, Lacey JV Jr, Garabrant DH, Cooper BC, Heerings SG, Alcer KH, Cho S, Mayes MD, Schottenfeld D. The association between silicone exposure and undifferentiated connective tissue disease among women in Michigan and Ohio. [American

- College of Rheumatology, 60th National Scientific Meeting, October 18–22, 1996, Orlando FL.]. *Arthritis Rheum* 39(9):S150, abstract 740, 1996.
- Lewin SL, Miller TA. A review of epidemiologic studies analyzing the relationship between breast implants and connective tissue diseases. *Plast Reconstr Surg* 100:1309–13, 1997.
- MacDonald KL, Osterholm MT, LeDell KL, White KE, Schenck CH, Chao CC, Persing DH, Johnson RC, Barker JM, Peterson PK. A case-control study to assess possible triggers and cofactors in chronic fatigue syndrome. *Am J Med* 100:548–54, 1996.
- Martin D, Austin H. An efficient program for computing conditional maximum likelihood estimates and exact confidence limits for a common odds ratio. *Epidemiology* 2:359–62, 1991.
- Mayes MD. Scleroderma epidemiology. *Rheum Dis Clin North Am* 22:751–64, 1996.
- Medsgers TA. Systemic sclerosis (scleroderma): clinical aspects. In *Arthritis and allied conditions: A textbook of rheumatology*, WJ Koopman, ed. 13th ed. Williams & Wilkins, Baltimore, pp. 1433–64, 1997.
- Medsgers TA Jr, Dawson WN Jr, Masi AT. The epidemiology of polymyositis. *Am J Med* 48:715–23, 1970.
- Michet CJ Jr, McKenna CH, Elveback LR, Kaslow RA, Kurland LT. Epidemiology of systemic lupus erythematosus and other connective tissue diseases in Rochester, Minnesota, 1950 through 1979. *Mayo Clin Proc* 60:105–13, 1985.
- Miller FW. Inflammatory myopathies: polymyositis, dermatomyositis, and related conditions. In *Arthritis and allied conditions: A textbook of rheumatology*, WJ Koopman, ed. 13th ed. Williams & Wilkins, Baltimore, pp. 1407–31, 1997.
- Northridge ME. Public health methods—attributable risk as a link between causality and public health action. *Am J Public Health* 85:1202–4, 1995.
- Nossen J. Systemic lupus erythematosus on the Caribbean island of Curacao: an epidemiologic investigation. *Ann Rheum Dis* 51:1197–1201, 1992.
- Nyren O, Yin L, Josefsson S, McLaughlin JK, Blot WJ, Engqvist M, Hakelius L, Boice JD Jr, Adami H-Ol. Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. *BMJ* 316:417–22, 1998.
- Oddis CV, Conte CG, Steen VD, Medsgers TA Jr. Incidence of polymyositis-dermatomyositis: A 20-year study of hospital diagnosed cases in Allegheny County, PA 1963–1982. *J Rheum*

- 17:1329–34, 1990.
- Park JP, Black RJ, Sarhadi NS, Chetty U, Watson ACH. Silicone gel-filled breast implants and connective tissue diseases. *Plast Reconstr Surg* 101:261–68, 1998.
- Perkins LL, Clark BD, Klein PJ, Cook RR. A meta-analysis of breast implants and connective tissue disease. *Ann Plast Surg* 35:561–70, 1995.
- Peters W, Keystone E, Snow K, Rubin L, Smith D. Is there a relationship between autoantibodies and silicone-gel implants? *Ann Plast Surg* 32:1–7, 1994.
- Reichlin M. Undifferentiated connective tissue diseases, overlap syndromes, and mixed connective tissue diseases. In *Arthritis and allied conditions: A textbook of rheumatology*, WJ Koopman, ed. 13th ed. Williams & Wilkins, Baltimore, vol. 2, pp. 1309–18, 1997.
- Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 88:15–19, 1998.
- Sanchez-Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, Liang MH. Silicone breast implants and the risk of connective-tissue diseases and symptoms. *N Engl J Med* 332:1666–70, 1995.
- SAS Companion for the Microsoft Windows Environment*, version 6, SAS Institute. Inc., Cary, NC, 1993.
- Schusterman MA, Kroll SS, Reece GP, Miller MJ, Ainslie N, Halabi S, Balch CM. Incidence of autoimmune disease in patients after breast reconstruction with silicone gel implants versus autogenous tissue: A preliminary report. *Ann Plast Surg* 31:1–6, 1993.
- Sharp GC. Diagnostic criteria for classification of MCTD. In *Mixed Connective Tissue Diseases and Anti-Nuclear Antibodies: Proceedings of the International Symposium on Mixed Connective Tissue Disease and Anti-nuclear Antibodies, Tokyo, 29–30 August 1986*, R Kasukawa and GC Sharp, eds. International Congress Series no. 719. Excerpta Medica, Amsterdam, pp. 23–32, 1986.
- Star VL, Scott J, Sherwin R, Hochberg MC, Lane N, Nevitt M. Validity of self-reported physician-diagnosed rheumatoid arthritis for use in epidemiologic studies. *Arthritis Rheum* 36:S100, abstract A15, 1993.
- Steen VD, Oddis CV, Conte CG, Janoski J, Casterline GZ, Medsger TA Jr. Incidence of systemic sclerosis in Allegheny County, Pennsylvania. A twenty-year study of hospital-diagnosed cases, 1963–1982. *Arthritis Rheum* 40:441–45, 1997.

- Strom BL, Reidenberg MM, Freundlich B, Schinnar R. Breast silicone implants and risk of systemic lupus erythematosus. *J Clin Epidemiol* 47:1211–14, 1994.
- Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 23:581–90, 1980.
- Symmons DPM, Barrett EM, Chakravorry K, Scott DGI, Silman AJ. The incidence of rheumatoid arthritis in Norfolk, England. *Arthritis Rheum* 35:S126, abstract B59, 1992.
- Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Shaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25:1271–77, 1982.
- Tan EM, Feltkamp TEW, Smolen JS, Butcher B, Dawkins R, Dawkins R, Fritzler MJ, Gordon T, Hardin JA, Kalden JR, Lahita RG. Range of antinuclear antibodies in “healthy” individuals. *Arthritis Rheum* 40:1601–11, 1997.
- Teel WB. A population-based case-control study of risk factors for connective tissue disease (lupus erythematosus, sjogren's syndrome, breast implants, sclerosis, silicone, crest syndrome, polymyositis, dermatomyositis). Ph.D dissertation, University of Washington, 1997.
- Teich-Alasia S, Ambroggio GP, DiVittoria S, Sismondi P, Strani GF, Blandamura R. Autoimmune connective tissue disease and silicone implants. International Confederation for Plastic Reconstructive Surgery, 7th Congress Berlin, Germany, June 2–6, 1993.
- Utrecht JP. Mechanism of drug induced lupus. *Chemical Research Toxicol* 1:133–43, 1988.
- Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, Bjerrum KB, Braga S, Coll J, de Vita S. et al. Preliminary criteria for the classification of Sjogren’s syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 36:340–47, 1993.
- Wallace DJ and Metzger AL, Systemic lupus erythematosus: clinical aspects and treatment. In *Arthritis and allied conditions: A textbook of rheumatology*, WJ Koopman, ed. 13th ed. Williams & Wilkins, Baltimore, pp. 1319–45, 1997.
- Weisman MH, Vecchione TR, Albert D, Moore LT, Mueller MR. Connective-tissue disease following breast augmentation: A preliminary test of the human adjuvant disease hypothesis. *Plast Reconstr Surg* 82:626–30, 1988.

- Wells KE, Cruse CW, Baker JL Jr, Daniels SM, Stern RA, Newman C, Seleznick MJ, Vasey FB, Brozena S, Albers SE, Fenske N. The health status of women following cosmetic surgery. *Plastic Reconstr Surg* 93:907–12, 1994.
- Williams HJ, Weisman MH, Berry CC. Breast implants in patients with differentiated and undifferentiated connective tissue disease. *Arthritis Rheum* 40:437–40, 1997.
- Wolfe P. Silicone breast implants and the risk of fibromyalgia and rheumatoid arthritis. [American College of Rheumatology, 59th National Science Meeting, San Francisco, October 21–26, 1995.] *Arthritis Rheum* 38:S265, abstract 671, 1995.
- Wong O. A critical assessment of the relationship between silicone breast implants and connective tissue diseases. *Regul Toxicol Pharmacol* 23(1 part 1):74–85, 1996.

List of Abbreviations

ACA = American College of Rheumatology

A/R = autoimmune / rheumatic

ARA = American Rheumatism Association

Bca = breast cancer

B-D = Breslow-Day

CI = confidence interval

CREST = a form of scleroderma with prominent calcinosis, Raynaud's phenomenon, esophageal dysfunction, limited involvement of the skin, and telangiectasia

CTD = connective tissue disease

DM/PM = dermatomyositis /polymyositis

Dx = diagnosis

EUCTD = early undifferentiated connective tissue disease

Hx = medical history

ICD = International Classification of Diseases

lab = laboratory studies

MCTD = mixed connective tissue disease

MD = physician

OR = odds ratio

OR_a = adjusted odds ratio

PAF = population attributable fraction

Px = physical examination

Q = questionnaire

RA = rheumatoid arthritis

RBG = Robins-Breslow-Greenland

RP = Raynaud's phenomenon

RR = relative risk

RR_a = adjusted relative risk

SBI = silicone breast implant

SLE = systemic lupus erythematosus

SS = Sjögren's syndrome

S/Ss = signs and symptoms

SSc = scleroderma / systemic sclerosis

UCTD = undifferentiated connective tissue disease

Table 1. Age-Adjusted Incidence Rates of Selected Connective Tissue Diseases in Women

Disease/Study by First Author	Study Period	Incidence (per 100,000)
Rheumatoid arthritis		
Dugowson, 1991	1987–1989	27.9
Sanchez-Guerrero, 1995	1972–1990	33.2*
Symmons, 1992	1990–1991	38.0*
Systemic Lupus Erythematosus		
Michet, 1985	1950–1979	2.5
Hochberg, 1985 (white)	1970–1977	3.9
Johnson, 1995	1991	4.5
Jonsson, 1990	1981–1986	5.4
Teel, 1997	1983–1991	5.4
Gudmundsson, 1990	1975–1984	5.8
Hopkinson, 1993	1989–1990	6.5
Nossen, 1992 (black)	1980–1990	7.9
Sanchez-Guerrero, 1995	1972–1990	8.1*
Hochberg, 1985 (black)	1970–1977	11.4
Scleroderma		
Sanchez-Guerrero, 1995	1972–1990	1.2*
Teel, 1997	1983–1991	1.5
Michet, 1985	1959–1970	1.6
Mayes, 1996	1989–1991	1.9
Steen, 1997	1963–1982	2.0
Sjögren's syndrome		
Teel, 1997	1983–1991	4.0
Dermatomyositis/Polymyositis		
Benbassett, 1980	1960–1976	0.3
Medsker, 1970	1947–1968	0.3
Teel, 1997	1983–1991	0.5
Oddis, 1990	1863–1982	0.6
Sanchez-Guerrero, 1995	1972–1990	1.0*

*Not adjusted for age.

Note: Incidence rates (per 100,000) from Hennekens et al. (1996): RA 61.8; SLE 15.1; SSc 3.1; Sjögren's 7.3; DM/PM 7.1

Table 2. Epidemiologic Studies of Breast Implants and Connective Tissue Diseases (CTDs): Characteristics of Case-Control/Cross-Sectional Studies

First Author, Year, Place	Data Sources: Implants	Data Sources: Disease	Diseases	No. of Cases (No. with implants)	No. of Controls (No. with implants)	OR (95% CI)	Matched or Adjusted for
Burns, 1996 Michigan	telephone Q	medical records	SSc	274 (2)	1184 (14)	0.95 (0.21, 4.36)	age, birth year, race
Dugowson, 1992 King County, WA	cases: mailed Q controls: in-person interview	MD Dx: Hx, Px & lab	RA	300 (1)	1456 (12)	0.41(0.05, 3.13)	age
Englert, 1996 Sydney	medical records	medical records	SSc	286 (3)	253 (4)	1.00 (0.16, 6.16)	SES, age, ethnicity
Goldman, ¹ 1995 Atlanta	medical records	medical records	RA & CTDs RA SLE SSc Sjögren's DM/PM MCTD	721 (12) 392 (9) 180 (1) 64 (0) 49 (2) 36 (0) 49 (0)	3508 (138)	0.52 (0.29, 0.92) 0.84 (0.41, 1.62) 0.14 (0.02, 1.23) - 1.46 (0.36, 6.39) - -	age at 1st visit to practice, income, time period of 1st visit
Hennekens, ² 1996 USA & Puerto Rico	mailed Q	mailed Q	any CTD RA SLE SSc Sjögren's DM/PM Other CTD	11805 (231) 6429 (107) 1593 (32) 324 (10) 774 (22) 747 (20) 3354 (83)	395543 (10830)	1.24 (1.08, 1.41) 1.18 (0.97, 1.43) 1.15 (0.81, 1.63) 1.84 (0.98, 3.46) 1.49 (0.97, 2.28) 1.52 (0.97, 2.37) 1.30 (1.05, 1.62)	age, birth year
Hochberg, 1996 Baltimore, San Diego, Pittsburgh	cases: mailed Q controls: telephone Q	MD Dx: Hx, Px & lab	SSc	837 (11)	2507 (31)	1.07 (0.53, 2.13)	age, race, geographic site
Lacey, 1997 Ohio	telephone Q	medical records	SSc	189 (1)	1043 (10)	1.01 (0.13, 8.15)	age, birth year

Table 2. (Continued) Epidemiologic Studies of Breast Implants and Connective Tissue Diseases (CTDs): Characteristics of Case-Control/Cross-Sectional Studies

First Author, Year, Place	Data Sources: Implants	Data Sources: Disease	Diseases	No. of Cases (No. with implants)	No. of Controls (No. with implants)	OR (95% CI)	Matched or Adjusted for
Laing, ³ 1996 Michigan & Ohio	telephone Q	medical records	UCTD	205 (3)	2220 (27)	2.27 (0.67, 7.71)	age, birth year
Strom, 1994 Philadelphia	telephone Q	medical records	SLE	133 (1)	100 (0)	-	age
Teel, ⁴ 1997 Seattle	mailed Q	medical records	All CTDs SLE SSc Sjögren's DM/PM MCTD	427 (6) 191 (2) 55 (0) 161 (4) 17 (0) 3 (0)	1577 (24)	0.9 (0.4, 2.3) 0.8 (0.2, 3.4) 1.6 (0.5, 4.7)	age, reference year, race
Wolfe, 1995 Wichita KS	cases: mailed Q controls: telephone Q	medical records	RA	637 (3)	1134 (4)	1.35 (0.30, 6.06)	age

¹Mixed connective tissue disease (MCTD) (ICD9 code 710.9, 711); 6 of 12 CTDs diagnosed prior to the implant.

²Other connective tissue disease, including mixed; "any CTD" includes definite CTDs and "other CTDs."

³Undifferentiated connective tissue disease (UCTD) (ICD9 code 710.9). The diagnosis was assigned if: (1) referring physician's diagnosis or the HCIA discharge code was UCTD, or (2) patient had been given the diagnosis of scleroderma, but did not meet ACR criteria; and (3) patient did not meet diagnostic criteria for another CTD, and (4) a minimum of two signs, symptoms, or laboratory values suggestive of a CTD were documented.

⁴Criteria for MCTD were from the literature.

Table 3. Epidemiologic Studies of Breast Implants and Connective Tissue Diseases (CTDs): Characteristics of Cohort Studies

First Author, Year, Place	Data Sources		No. of Women		Diseases	No. of Cases		RR (95% CI)	Matched or Adjusted for
	Implants	Disease	Implanted	Not Implanted		Implanted	Not Implanted		
Edworthy, ¹ 1998 Alberta Canada	medical record	MD Dx: Hx, Px, lab	1576	727	Def. CTDs comb.	19	16	1.00 (0.45, 2.22)	age, exposure time
					RA	11	6	1.44 (0.50, 4.15)	
					SLE	3	3	0.94 (0.17, 5.23)	
					SSc	0	3	-	
					Sjögren's	5	4	0.99 (0.17, 5.94)	
Friis, ² 1997 Denmark	medical record	medical record	2570	11023	Def. CTDs comb.	10	25	not provided	age, calendar year
					RA	7	16	not provided	
					SLE	1	5	not provided	
					SSc	1	1	not provided	
					Sjögren's	1	1	not provided	
					DM/PM	0	2	-	
Gabriel, ³ 1994 Olmstead Co. MN	medical record	medical record	749	1498	any CTD	5	10	1.10 (0.37, 3.23)	age, index year
Giltay, ⁴ 1994 Amsterdam	medical record	mailed Q	235	210	joint swelling	14	10	1.27 (0.55, 2.92)	age
Nyren, ⁵ 1998 Sweden	medical record	medical record	7442	3353	Def. CTDs comb.	16	11	0.8 (0.5, 1.4)	age, follow-up time
					RA	11	5	1.3 (0.7, 2.5)	
					SLE	3	3	0.7 (0.3, 1.6)	
					SSc	0	3	-	
					Sjögren's	1	0	-	
					DM	1	0	-	
					Other CTDs	20	8	not provided	

Table 3. (Continued) Epidemiologic Studies of Breast Implants and Connective Tissue Diseases (CTDs): Characteristics of Cohort Studies

First Author, Year, Place	Data Sources		No. of Women		Diseases	No. of Cases		RR (95% CI)	Matched or Adjusted for
	Implants	Not Implanted	Implanted	Not Implanted		Implanted	Not Implanted		
Park, ⁶ 1998 S. E. Scotland	medical records	MD Dx: Hx, Px & lab	317	216	RA	1	1	0.42 (0.01, 15.63)	BCa pts: age, stage of disease, surgery date
Sanchez- Guerrero, ⁷ 1995 USA-11 geographic areas	mailed Q	medical record	1183	86318	Def CTDs comb.	3	513	0.6 (0.2, 2.0)	age
					RA	3	389	0.9 (0.3, 2.6)	
					SLE	0	96	-	
					SSc	0	14	-	
					Sjögren's	0	2	-	
					DM/PM	0	12	-	
other rheum. cond.	29	4541	not provided						
Schusterman, ⁸ 1993 Houston TX	medical record	medical record	250	353	rheumatic disease	1	1	1.08 (0.10, 17.20)	indication
Wells, ⁹ 1994 Tampa FL	medical record	mailed Q	220	80	arthritis	11	2	1.16 (0.15, 9.04)	age, year of surgery

¹"Other rheumatic diseases" or musculoskeletal conditions includes discoid lupus, Raynaud's phenomenon, CREST, psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, fibromyalgia, osteoarthritis, hypothyroidism, multiple sclerosis, DM/PM, Crohn's disease. A certainty score for diagnosis was assigned and any subject with a greater than 50% certainty of any possible condition was included in the analysis for atypical autoimmune diseases.

²"Other and ill-defined rheumatic conditions" includes: polymyalgia rheumatica and temporal arteritis (ICD8 code 446.30-39); muscular rheumatism, fibrositis, and myalgia (ICD8 code 717.9, 717.99); arthritis not further specified (ICD8 code 715.99); rheumatism not further specified (ICD8 code 718.99); and CTD not further specified (ICD8 code 734.91, 734.99). Friis did not provide relative risk estimates. He calculated observed to expected ratios for each condition in his implanted and unimplanted cohorts.

³"Definite CTDs" includes RA, SLE, Sjögren's syndrome, DM/PM, SSc, ankylosing spondylitis, psoriatic arthritis, polymyalgia rheumatica, vasculitis, arthritis associated with inflammatory bowel disease, polychondritis. "Any CTD" includes 17 different diagnoses. "Any arthritis" includes swelling of the wrist, swelling of 3 or more joints, symmetric

joint swelling, or any other documented arthritis or synovitis.

⁴"Joint swelling" includes any swelling of joints for at least 1 week.

⁵"Nondefinite CTD" includes polymyositis (ICD8 code 716.10; ICD9 code 710E), polymyalgia rheumatica (ICD8 code 446.38; ICD9 code 725), polyarteritis nodosa, temporal arteritis (ICD8 code 446.30; ICD9 code 446F), other specified CTD (ICD8 code 734.98; ICD9 code 710W), CTD or collagenosis without further specification (ICD8 code 734.91, 734.99.10; ICD9 code 710X), sarcoidosis (ICD8 code 135; ICD9 code 135), localized lupus (ICD8 code 695.40; ICD9 code 695E), ankylosing spondylitis (ICD8 code 712.40; ICD9 code 720A), fibromyalgia (ICD8 code 712.50, 717.98, 718.99; ICD9 code 729A), psoriatic arthritis (ICD8 code 696.00; ICD9 code 696A, 713D).

⁶Three of 4 groups are retrospective cohorts. One group is cross-sectional.

⁷Includes patient reports of any rheumatic, musculoskeletal, CTD, not further specified, or any other arthritis.

⁸Mild autoimmune syndrome, requiring therapy, without convincing laboratory findings for an absolute diagnosis of an autoimmune disease.

⁹Physician diagnosis of arthritis as reported on a questionnaire.

Table 4. Meta-analysis Showing Summary Unadjusted Odds Ratios for the Association between Breast Implants and Connective Tissue Diseases (CTDs)

Studies Included	No. of Studies	Summary OR ¹	95% CI ²	Homogeneity p-value ³
Definite CTDs combined	16	0.69	0.62, 0.78	0.10
all studies, excluding Friis	15	0.68	0.60, 0.77	0.31
Rheumatoid arthritis	10	0.62	0.52, 0.73	0.17
Systemic Lupus Erythematosus	8	0.63	0.44, 0.86	0.24
Scleroderma	12	0.73	0.46, 1.10	0.10
all studies, excluding Friis	11	0.70	0.44, 1.08	0.14
Sjögren's syndrome	8	1.10	0.74, 1.58	0.56
Dermatomyositis/polymyositis	6	0.90	0.55, 1.39	0.88
Other autoimmune/rheumatic conditions	12	0.91	0.79, 1.04	<0.001
all studies, excluding Friis and Sanchez-Guerrero	10	0.92	0.77, 1.10	0.52

¹Obtained with Exact statistical software; conditional maximum likelihood estimates presented except for categories of definite CTDs combined and rheumatoid arthritis where Mantel-Haenszel estimate is shown.

²Exact limits presented, except for categories of definite CTDs combined and rheumatoid arthritis where Robins-Breslow-Greenland limits are shown.

³Zelen exact p-value presented, except for categories of definite CTDs combined, rheumatoid arthritis, and other autoimmune/rheumatic conditions where the p-value for the Breslow-Day χ^2 statistic is shown.

Table 5. Meta-analysis Showing Summary Adjusted Relative Risk Estimates¹ for the Association between Breast Implants and Connective Tissue Diseases (CTDs)

Studies Included	No. of Studies	Summary RR _a	95% CI	Homogeneity p-value	Hennekens' weight in summary RR _a	p-value*
Definite CTDs combined	14	1.14	1.01, 1.28	0.34	0.80	
excluding Hennekens	13	0.80	0.62, 1.04	0.92	-	0.003
Rheumatoid arthritis	8	1.15	0.97, 1.36	0.90	0.79	
excluding Hennekens	7	1.04	0.72, 1.51	0.87	-	0.56
Systemic Lupus Erythematosus	5	1.01	0.74, 1.37	0.33	0.77	
excluding Hennekens	4	0.65	0.35, 1.23	0.53	-	0.12
Scleroderma	5	1.30	0.86, 1.96	0.55	0.42	
excluding Hennekens	4	1.01	0.59, 1.73	0.80	-	0.16
Sjögren's syndrome	4	1.47	1.01, 2.14	0.98	0.77	
excluding Hennekens	3	1.42	0.65, 3.11	0.90	-	0.92
Dermatomyositis/Polymyositis	1	1.52	0.97, 2.37	-	1.00	
excluding Hennekens	-	-	-	-	-	-
Other A/R conditions	7	1.15	0.97, 1.36	0.11	0.59	
excluding Hennekens	6	0.96	0.74, 1.25	0.19	-	0.08

*p-value for the grouped χ^2 ; this tests whether the RR_a estimate from the Hennekens study is significantly different from the pooled RR_a estimate obtained from the other studies.

¹Obtained with SAS statistical software

Table 6. Comparison of Summary RR Estimates Obtained from the Unadjusted and Adjusted Meta-analyses

Disease	No. of Studies		Studies Excluded ¹	RR (95% CI)		
	Unadjusted	Adjusted	No. (%)	Unadjusted	Adjusted ²	Adjusted ³
Definite CTDs combined	16	14	2 (13)	0.69 (0.62, 0.78)	0.80 (0.62, 1.04)	1.14 (1.01, 1.28)
RA	10	8	2 (20)	0.62 (0.52, 0.73)	1.04 (0.72, 1.51)	1.15 (0.97, 1.36)
SLE	8	5	3 (38)	0.63 (0.44, 0.86)	0.65 (0.35, 1.23)	1.01 (0.74, 1.37)
SSc	12	5	7 (58)	0.73 (0.46, 1.10)	1.01 (0.59, 1.73)	1.30 (0.86, 1.96)
Sjögren's	8	4	4 (50)	1.10 (0.74, 1.58)	1.42 (0.65, 3.11)	1.47 (1.01, 2.14)
DM/PM	6	1	5 (83)	0.90 (0.55, 1.39)	-	1.52 (0.97, 2.37)
Other A/R conditions	12	7	5 (42)	0.91 (0.79, 1.04)	0.96 (0.74, 1.25)	1.15 (0.97, 1.36)

¹No. (%) of studies excluded from the adjusted analysis.

²excludes Hennekens et al.

³ includes Hennekens et al

Table 7. Meta-analysis Showing Summary Adjusted Relative Risk Estimates for the Association between Silicone Gel-Filled Breast Implants and Connective Tissue Diseases (CTDs)

Studies Included (First Author)	No. of Studies	Summary RR_a¹	95% CI	Homogeneity p-value
Definite CTDs Combined (Burns, Edworthy, Englert, Lacey, Park, Sanchez-Guerrero)	6	0.82	0.46, 1.46	0.82
Rheumatoid Arthritis (Edworthy, Park, Sanchez- Guerrero)	3	0.98	0.40, 2.37	0.43
Systemic Lupus Erythematosus (Edworthy)	1	0.94	0.17, 5.23	-
Scleroderma (Burns, Englert, Lacey)	3	0.85	0.32, 2.25	0.70
Sjögren's syndrome (Edworthy)	1	0.99	0.17, 5.94	-
Other A/R conditions (Giltay, Sanchez-Guerrero, Schusterman, Wells)	4	0.71	0.50, 1.01	0.41

¹Obtained with SAS statistical software.

Table 8. Number of Cases of Connective Tissue Diseases Attributable to Breast Implants Occurring in the United States Annually

Disease	RR _a ¹	PAF ²	No. of Cases per 10 Million Women	No. of Cases "Due to" Breast Implants per 10 Million Women ³
Rheumatoid Arthritis	1.15	0.0013	3,303	4.29
Systemic Lupus Erythematosus	1.01	0.0001	526	0.05
Scleroderma/Systemic Sclerosis	1.30	0.0023	164	0.38
Sjogren's Syndrome	1.47	0.0032	400	1.28
Dermatomyositis/Polymyositis	1.52	0.0034	54	0.18

¹The adjusted summary RR_a includes Hennekens.

²The population attributable fraction = $\left(\frac{RR_a - 1}{RR_a} \right) pr(E)$

pr(E) = the proportion (prevalence) of implants in the population and assumes that pr(E) = pr(E|D), the prevalence of implants among diseased persons. pr(E) is estimated at 0.01.

³Cases attributable to implants = incidence × population attributable fraction. Incidence rates for white women are obtained from Table 1.

Figure 1. Adjusted Relative Risk Estimates for Definite CTDs Combined

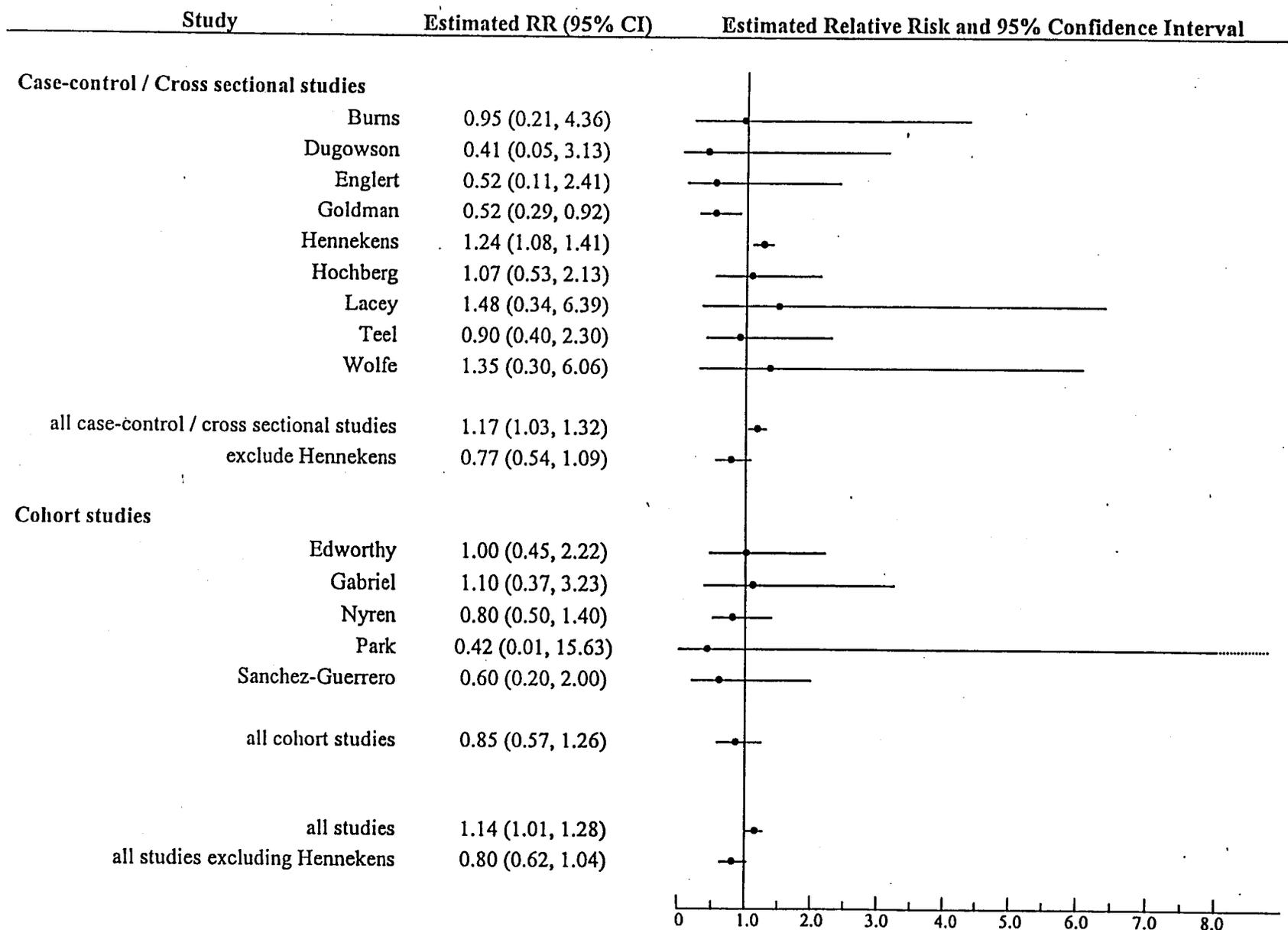


Figure 2. Adjusted Relative Risk Estimates for Rheumatoid Arthritis

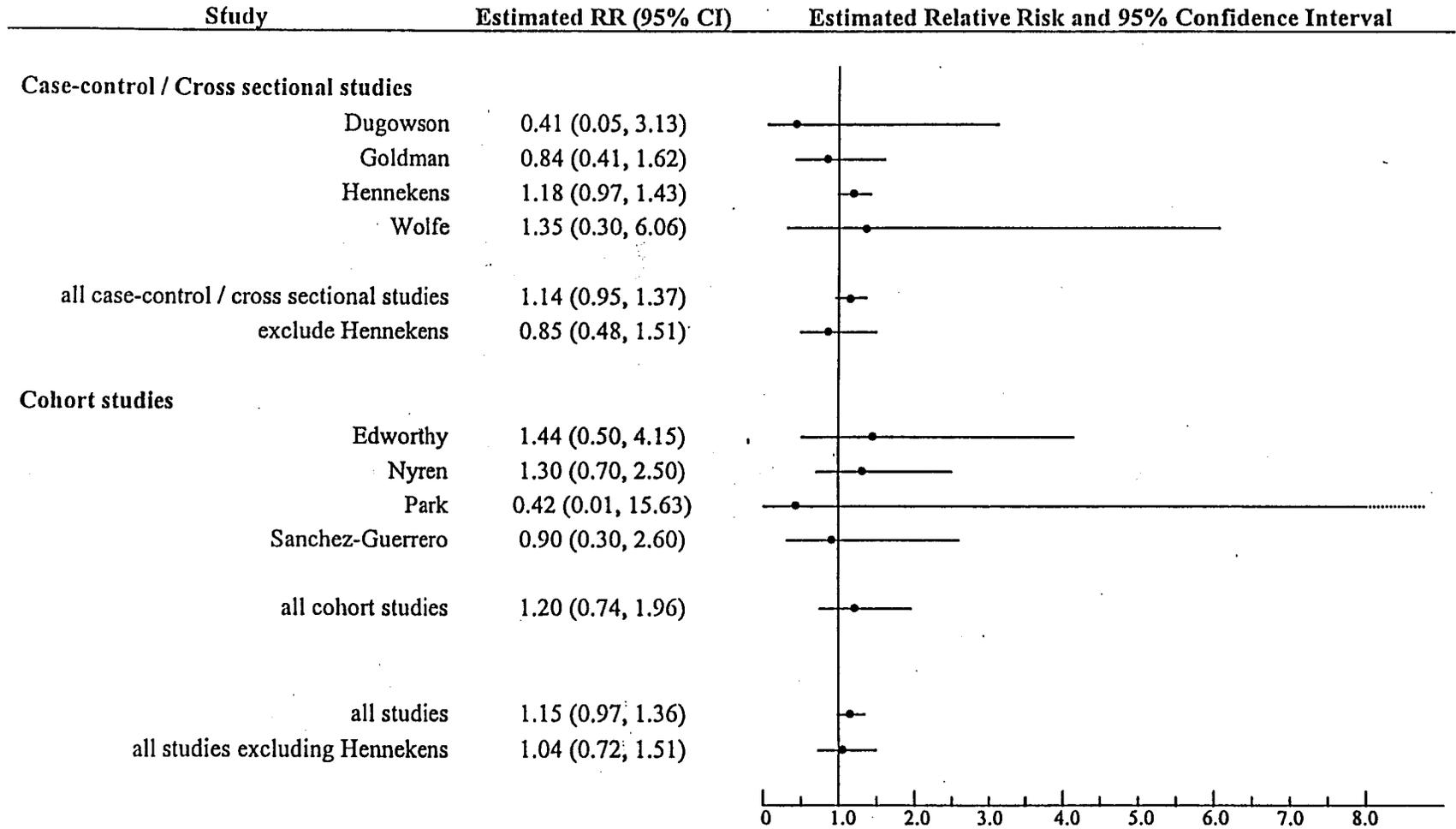


Figure 3. Adjusted Relative Risk Estimates for Systemic Lupus Erythematosus

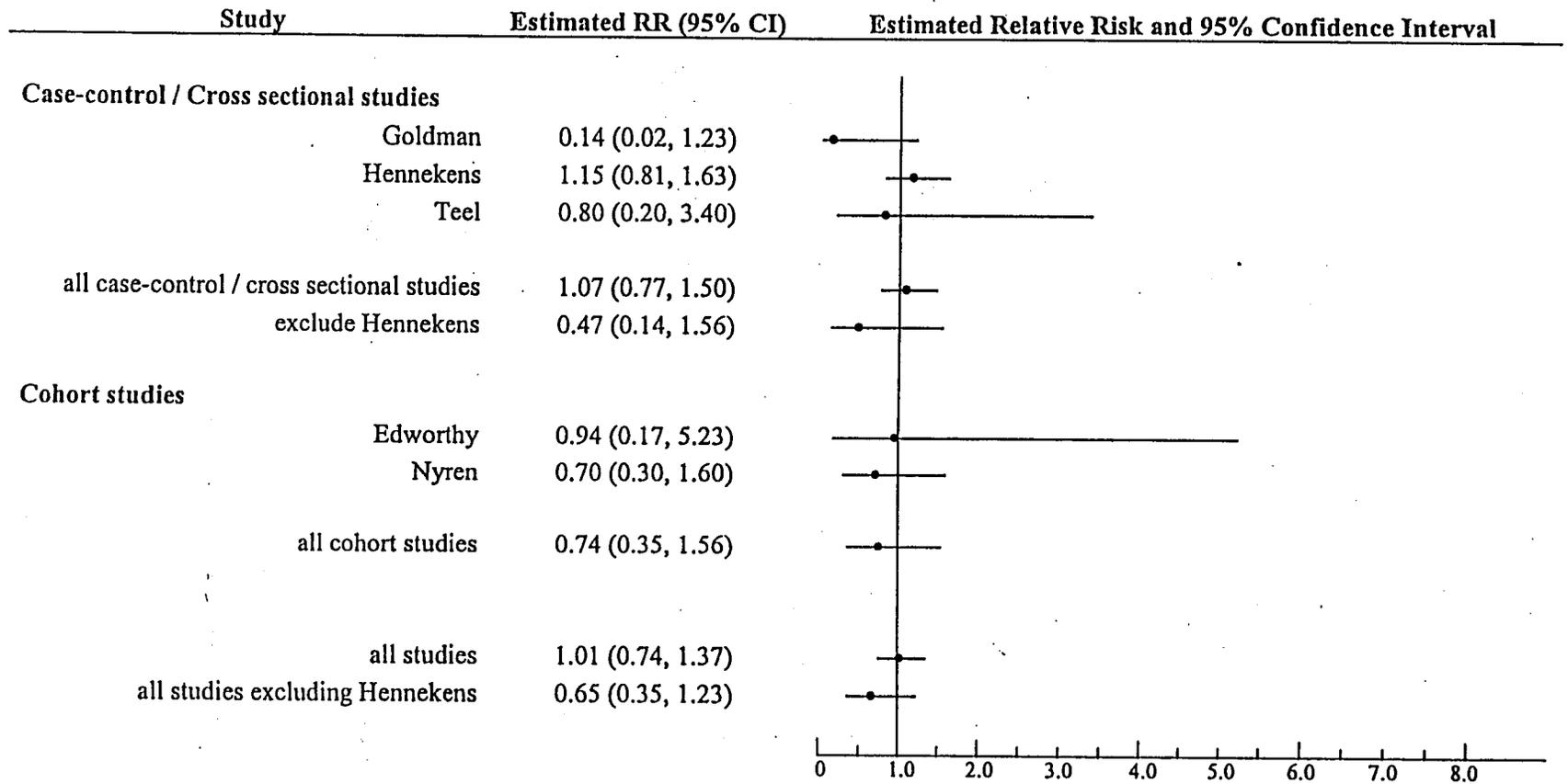


Figure 4. Adjusted Relative Risk Estimates for Systemic Sclerosis

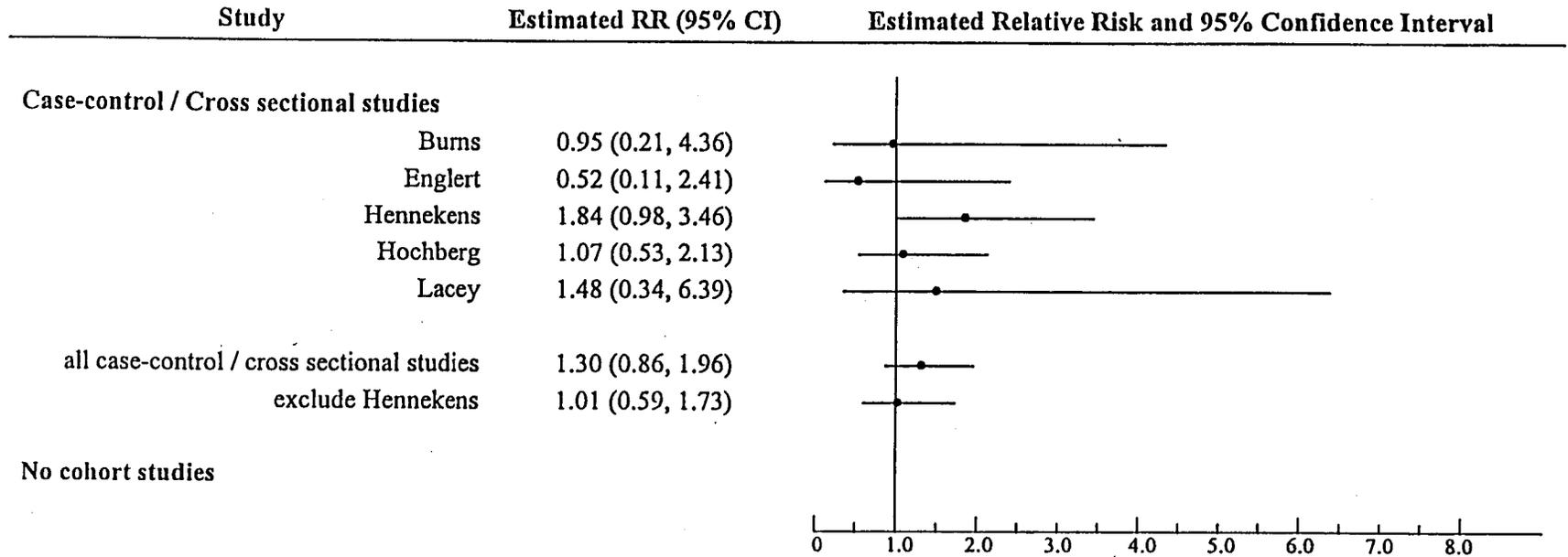


Figure 5. Adjusted Relative Risk Estimates for Sjögren's Syndrome

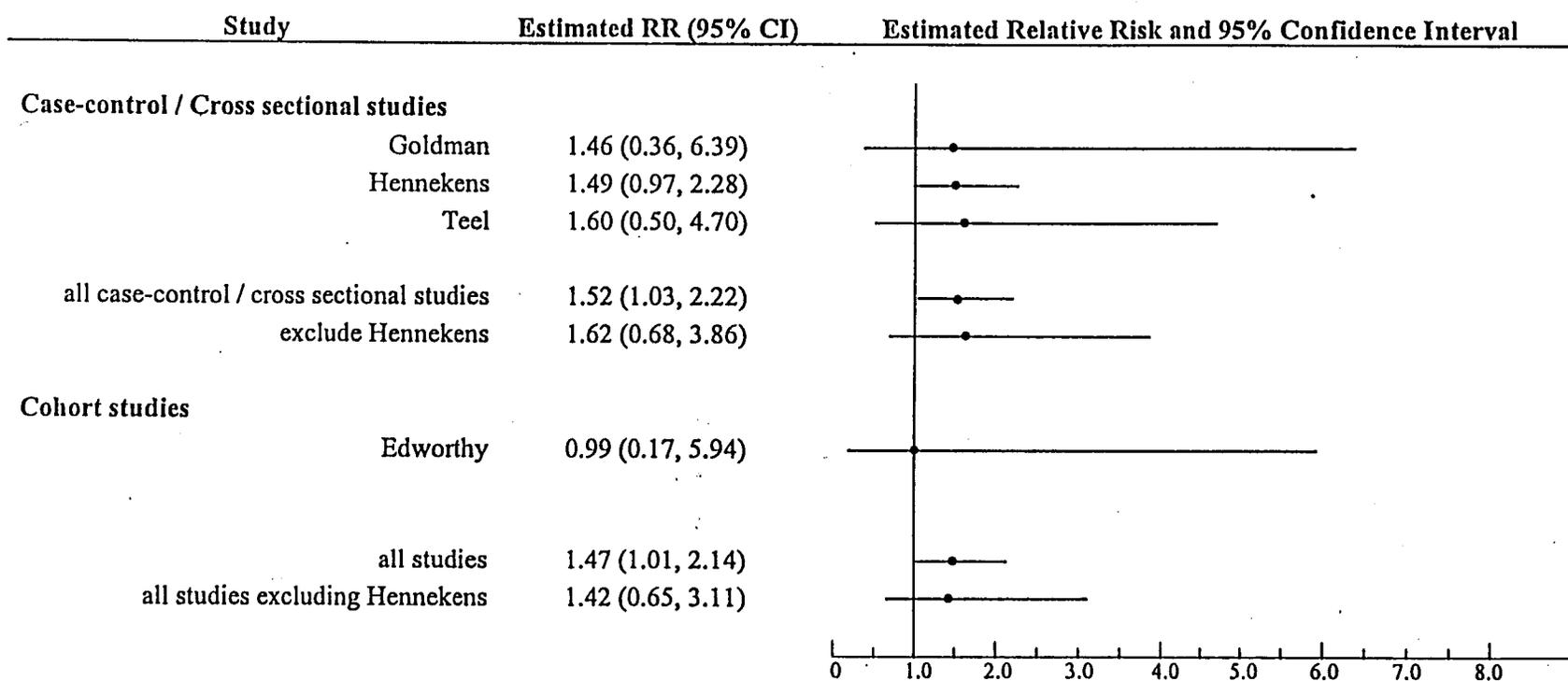


Figure 6. Adjusted Relative Risk Estimates for Other Autoimmune/Rheumatic Conditions

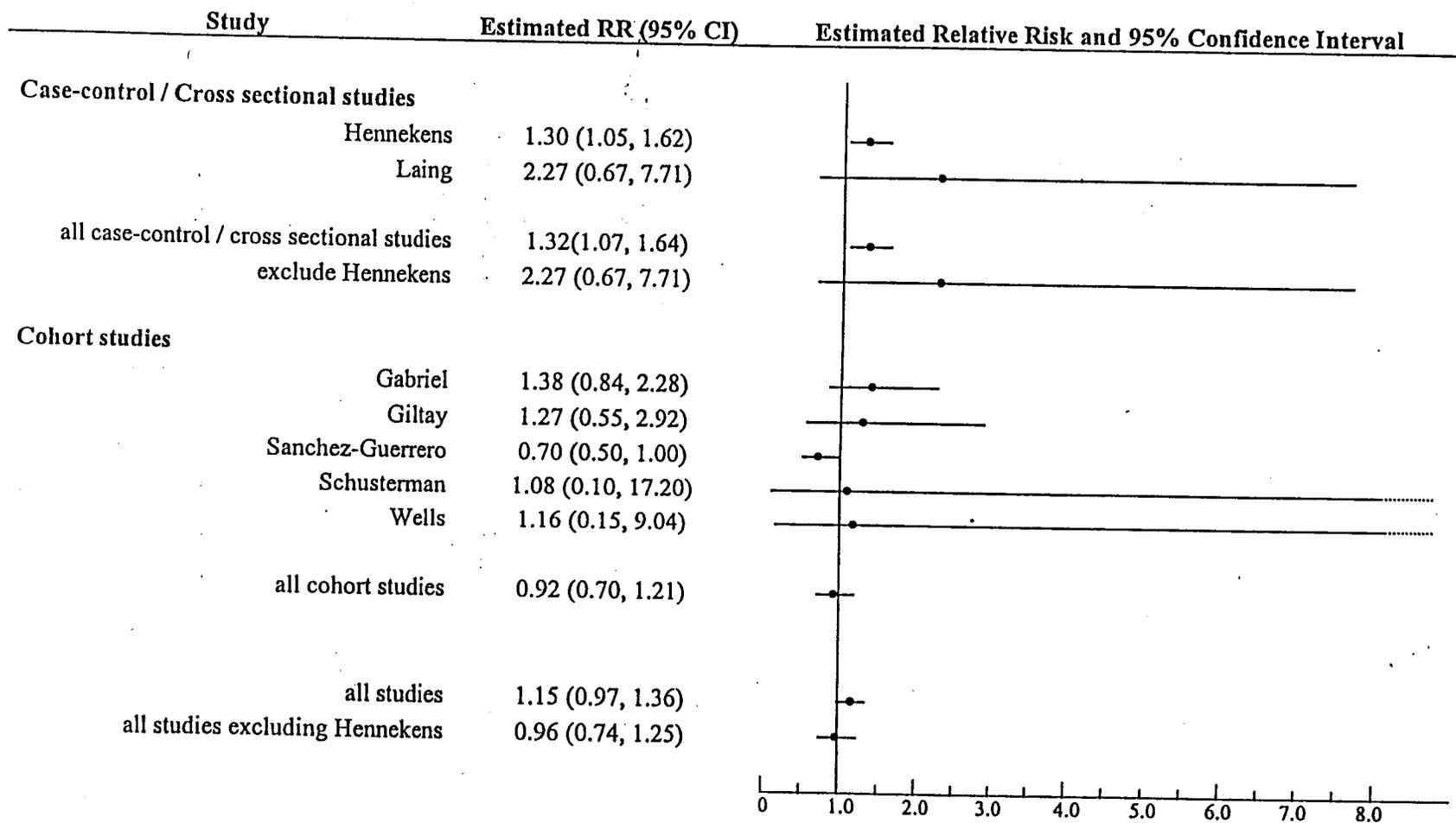


Figure 7. Power Versus True Underlying Effect Measure
Including Hennekens

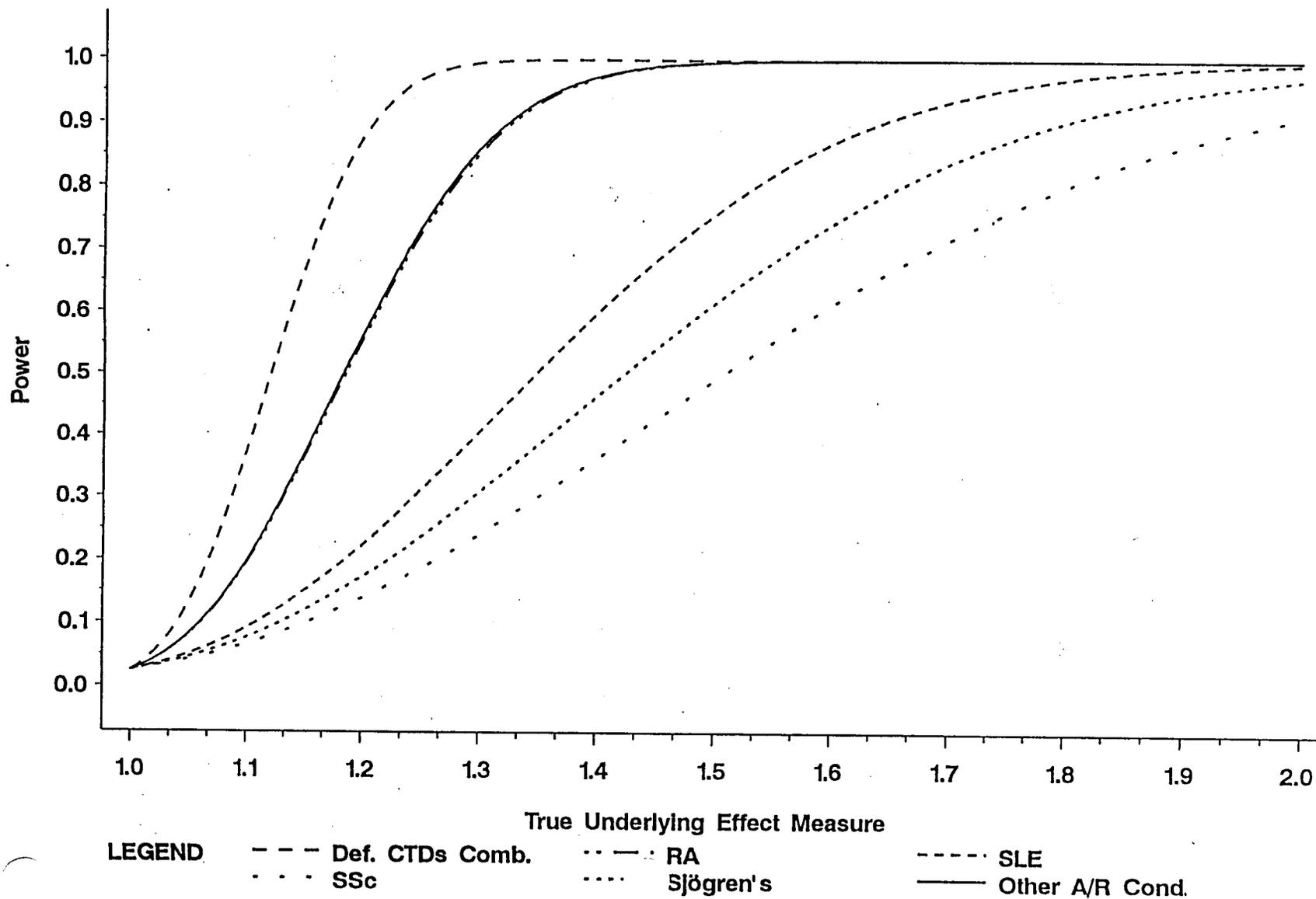
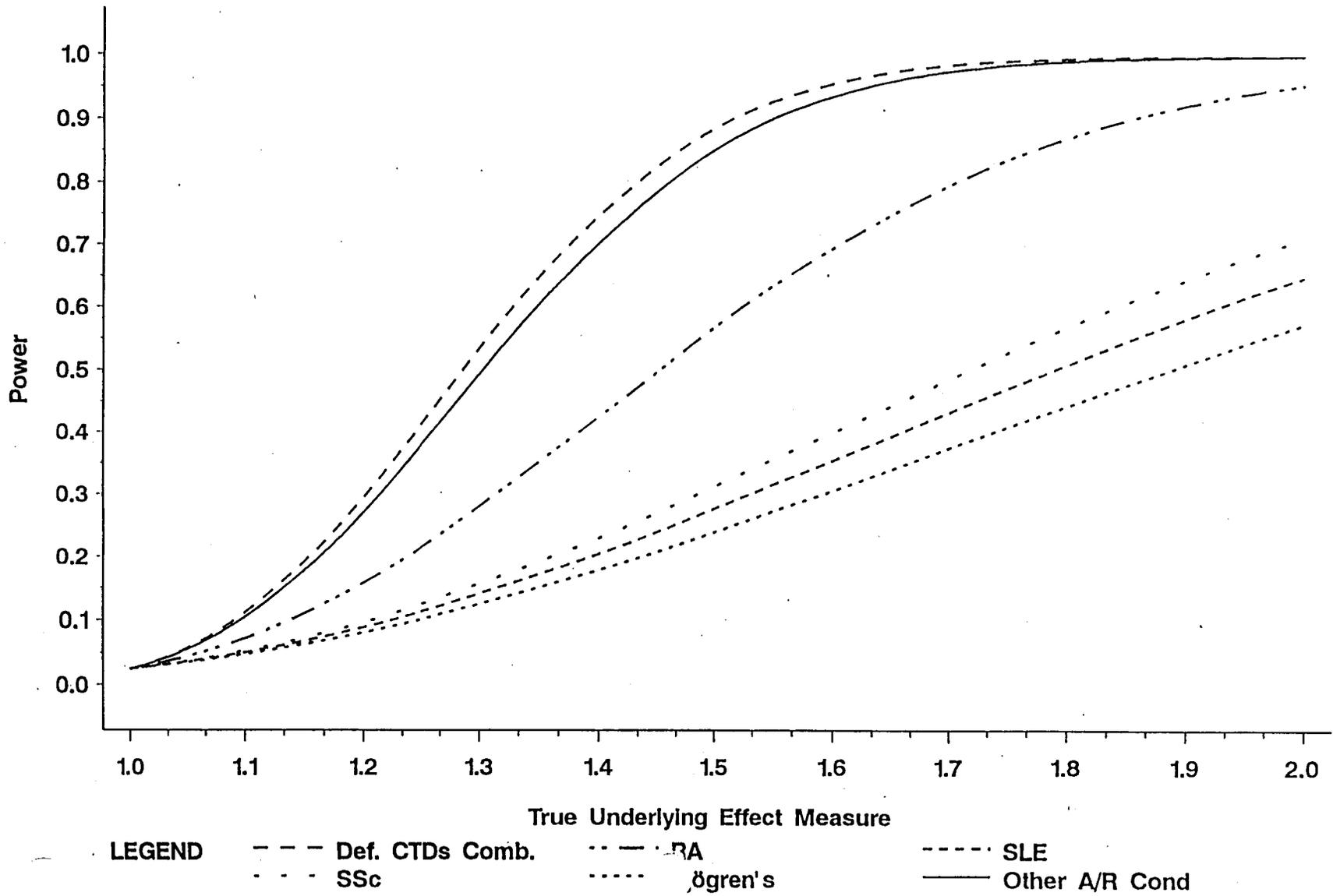


Figure 8. Power Versus True Underlying Effect Measure
Excluding Hennekens



Appendix A.
Diagnostic Criteria

Appendix A. Diagnostic Criteria

Table A.1 Diagnostic Criteria for Rheumatoid Arthritis

-
1. Morning stiffness
 2. Arthritis of three or more joint areas
 3. Arthritis of hand joints
 4. Symmetric arthritis
 5. Rheumatoid nodules
 6. Serum rheumatoid factor
 7. Radiographic changes
-

For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Criteria 1–4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. (Arnett FC et al. ARA revised criteria for the classification of rheumatoid arthritis, *Arthritis Rheum* 31:315–323, 1988).

Table A.2 Diagnostic Criteria for Systemic Lupus Erythematosus

1. Malar rash
 2. Discoid rash
 3. Photosensitivity
 4. Oral ulcers
 5. Arthritis (nonerosive)
 6. Serositis (pleuritis or pericarditis)
 7. Renal disorder (proteinuria or cellular casts)
 8. Neurologic disorder (seizures or psychosis)
 9. Hematologic disorder (hemolytic anemia or leukopenia or lymphopenia or thrombocytopenia)
 10. Immunologic disorder (Positive LE prep or anti-DNA or anti-Sm or false positive STS)
 11. Antinuclear antibody
-

For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any 4 or more of the 11 criteria are present serially or simultaneously, during any interval of observation. (Tan EM et al., The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25:1271-77, 1982.)

Table A.3 Diagnostic Criteria for Scleroderma (Systemic Sclerosis)

1. Proximal scleroderma is the single major criterion; sensitivity was 91% and specificity was over 99%
 2. Sclerodactaly, digital pitting, scars of fingertips or loss of substance of the distal finger pad, and bibasilar pulmonary fibrosis contributed further as minor criteria in the absence of proximal scleroderma
 3. One major or two or more minor criteria were found in 97% of definite systemic sclerosis patients, but only in 2% of the comparison patients with systemic lupus erythematosus, polymyositis/dermatomyositis, or Raynaud's phenomenon).
-

This excludes localized scleroderma and pseudosclerodermatous disorders (Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis [scleroderma]. *Arthritis Rheum* 23:581-90, 1980).

Table A.4 Diagnostic Criteria for Sjögren's Syndrome

1. Keratoconjunctivitis sicca
 - a. Decreased tear flow rate using Schirmer's test (<9mm/5 min) and
 - b. Increased staining from Rose Bengal or fluorescein dye
 2. Xerostomia
 - a. Symptomatic xerostomia and
 - b. Decreased basal and stimulated salivary flow rate
 3. Extensive lymphocytic infiltrate on minor salivary gland biopsy (focus score of at least two per 4 mm² on the Greenspan scale) obtained through normal buccal mucosa
 4. Laboratory evidence of a systemic autoimmune disease
 - a. Positive RF factor (titer \geq 1:160) or
 - b. Positive ANA (titer \geq 1:160) or
 - c. Positive SS-A or SS-B
 5. Exclusions: pre-existent lymphoma, graft versus host disease, acquired immune deficiency disease (AIDS), sarcoidosis
-

Fox RI, et al . First International Symposium on Sjögren's syndrome: suggested criteria for classification. *Scand J Rheumatol* 61(suppl):28-30, 1986.

Table A.5 Diagnostic Criteria for Dermatomyositis/Polymyositis

1. Typical skin rash of dermatomyositis
2. Symmetric proximal muscle weakness by history and physical examination
3. Elevation of one or more serum muscle enzymes
4. Myopathic changes on electromyogram
5. Typical polymyositis on muscle biopsy

Category of disease	Dermatomyositis criteria	Polymyositis criteria
definite	1+ any three of 2, 3, 4, or 5	all four of 2, 3, 4, and 5
probable	1+ any two of 2, 3, 4, or 5	any three of 2, 3, 4, or 5
possible	1+ any one of 2, 3, 4, or 5	any two of 2, 3, 4, or 5

Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 292:344–347, 1975.

Table A.6 Diagnostic Criteria for Early Undifferentiated Connective Tissue Disease

One of the three criteria listed below:

1. Raynaud's phenomenon
 2. Isolated keratoconjunctivitis sicca
 3. Unexplained polyarthritis, including possible and probable rheumatoid arthritis
and
 4. At least three other criteria that could not be attributed to other disease processes:
Raynaud's phenomenon
myalgias
rash
keratoconjunctivitis sicca
pleuritis
pericarditis
central nervous system symptoms
pulmonary symptoms
peripheral neuropathy
elevated erythrocyte sedimentation rate
false positive serologic test for syphilis
mixed connective tissue disease
anti-ribonucleoprotein antibodies
-

Alarcon GS, Williams GV, Singer JZ, Steen VD, Clegg DO, Paulus HE, Billingsley LM, Luggen, ME, Polisson RP, Willkens RF, Yarboro C, Ma K-N, Egger MJ, Williams HJ, Ward JR. Early undifferentiated connective tissue disease. 1. Early Clinical manifestation in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of well established connective tissue disease. *J Rheumatol* 18:1332-39, 1991.

Table A.7 Diagnostic Criteria for MCTD (Mixed Connective Tissue Disease)

I. Bennett and O'Connell, 1980 (*Sem Arthritis Rheum*, 10:25–51)

1. High titer of soluble ribonucleoprotein antibodies
2. Lack of antibody to double-stranded DNA and Sm, a glycoprotein moiety in saline extractable nuclear antigen

II. Alarcon-Segovia and Cardiel, 1989 (*J Rheumatol*, 16:328–34)

1. Serological: positive anti-ribonucleoprotein antibody at a hemagglutination titer of 1:1600 or higher
2. Clinical: edema of the hands
synovitis
myositis
Raynaud's phenomenon
acrosclerosis

Diagnosis is based on:

1. Serology
 2. At least three of the five clinical criteria
 3. The association of edema of the hands, Raynaud's phenomenon, and acrosclerosis requires at least one of the other two clinical criteria.
-

Two other sets of criteria are discussed: Sharp and Kasukawa et al., both chapters in: Kasukawa R, Sharp GC, eds. *Mixed Connective Tissue Diseases and Anti-Nuclear Antibodies*. Elsevier, Amsterdam, pp. 23–32, 41–47, 1987.

APPENDIX B: APPROXIMATE LARGE-SAMPLE META-ANALYSIS METHODS

The purpose of this appendix is to discuss approximate large-sample meta-analysis methods and to describe how they are applied in this chapter. These approximate methods are generally used when considering estimated adjusted effects and their standard errors, and they can also be used when considering unadjusted effects estimated from simple two-by-two tables. This appendix has two sections: Section B.1 contains discussions on a homogeneity chi-squared test and confidence interval estimation; Section B.2 contains a discussion on power calculations.

B.1: Homogeneity Chi-Squared Test and Confidence Interval Estimation

For purposes of discussion, we will assume that we wish to conduct a meta-analysis involving k separate studies, where RR_{ai} denotes the estimated adjusted relative risk for the i -th study and where σ_i denotes the standard error of $\ln(RR_{ai})$, $i = 1, 2, \dots, k$. Here, the term *adjusted relative risk* is used generically in the sense that RR_{ai} can be an adjusted odds, risk, or rate ratio estimated via regression analysis methods. Further, RR_{ai} is assumed to be a valid estimator of the true underlying (adjusted for confounding) association between a dichotomous “exposure variable” [namely, the presence or absence of a (silicone) breast implant] and a dichotomous “health outcome variable” of interest (namely, the presence or absence of some particular disease). Also, the k standard errors $\sigma_1, \sigma_2, \dots, \sigma_k$ will often be treated statistically as being essentially nonstochastic (i.e., they will be considered to be known values). In most instances, the literature only provides the numerical value of the estimated adjusted relative risk RR_{ai} and an associated 95% confidence interval (CI) with lower limit L_i and upper limit U_i . The typical assumption leading to these limits is that, for large samples, the quantity $\ln(RR_{ai})$ is approximately normally distributed with standard error σ_i . Given this 95% confidence interval, it is easy to compute σ_i indirectly using the formula

$$\sigma_i = [\ln(U_i/RR_{ai})]/1.96.$$

So, given that the available data for a particular meta-analysis consist of the k pairs $\{RR_{ai}, \sigma_i\}$, $i = 1, 2, \dots, k$, the first step is to decide whether or not these k estimated adjusted relative risks are estimating the same underlying association. To make such a decision, we conduct a chi-squared homogeneity test (Greenland, 1987). The chi-squared homogeneity test statistic takes the form

$$\chi_h^2 = \sum_{i=1}^k [\ln(RR_{ai}) - \ln(SRR_a)]^2 / \sigma_i^2, \quad (1)$$

where

$$\ln(\text{SRR}_a) = \frac{\sum_{i=1}^k \sigma_i^{-2} \ln(\text{RR}_{ai})}{\sum_{i=1}^k \sigma_i^{-2}} \quad (2)$$

is the natural logarithm of the *summary relative risk* SRR_a and is an inverse-variance-based weighted average of the individual $\ln(\text{RR}_{ai})$ values [so that studies with smaller standard errors (or, essentially equivalently, studies with larger numbers of subjects) get more weight than studies with larger standard errors].

Under the null hypothesis that the k estimated adjusted relative risks are estimating the same underlying association (i.e., the null hypothesis of homogeneity), the statistic χ_h^2 given by expression (1) has a chi-squared distribution with $(k - 1)$ degrees of freedom (df). If this null hypothesis of homogeneity is not rejected, then it is probably reasonable to make the conclusion that it is permissible to combine these k estimated adjusted relative risks via expression (2) to obtain an adjusted summary relative risk SRR_a , with 95% confidence interval given by the expression

$$(\text{SRR}_a) e^{\pm 1.96 \sqrt{V[\ln(\text{SRR}_a)]}}, \quad (3)$$

where the variance of the estimator $\ln(\text{SRR}_a)$ is

$$V[\ln(\text{SRR}_a)] = 1 / \sum_{i=1}^k \sigma_i^{-2}. \quad (4)$$

If the null hypothesis of homogeneity is rejected, then it is necessary to determine the sources of this heterogeneity among the k estimated adjusted relative risks. One valid way to make this determination is via the use of stratification methods, whereby subgroups of studies are defined by levels of certain variables (e.g., type of study design) and by the elimination of particular studies (so-called influence analysis). Such stratification is used to define subgroups of studies for which the subgroup-specific chi-squared homogeneity test statistics are not statistically significant. Within each homogeneous subgroup so determined, an estimated summary adjusted relative risk estimate and associated confidence interval can then be validly computed as described above.

Once an estimated summary adjusted relative risk estimate (2) and an associated 95% confidence interval (3) have been computed based on a set of studies determined to be homogeneous via (1), it is important to decide whether such summary information provides evidence of a statistically significant exposure-disease association. Clearly, one standard method for making such a decision is to see whether the 95% confidence interval (3) contains the null value of 1; if the computed 95% confidence interval does not

include the value 1, then it is standard practice to say that the data provide evidence of a statistically significant exposure-disease association and to say that the values included in the 95% confidence interval represent a set of possibly plausible parameter values for the true underlying association.

B.2.: Power Calculations

In our context, the “power” attendant with our statistical meta-analysis of a set of k studies refers to the chance (or, more formally, the probability) of detecting the presence of a true underlying nonnull association between a dichotomous “exposure” variable [namely, the presence or absence of a (silicone) breast implant] and some dichotomous “disease” variable [namely, the presence or absence of some specific disease]. By the phrase *true underlying nonnull association*, we mean that the common population adjusted exposure-disease relative risk (say, ψ) has a value greater than 1 in the underlying populations from which the various data sets arose. More specifically, we define the meta-analysis power θ_m to be the probability that the lower limit of a 95% confidence interval of the form (3) exceeds the value 1 given that the true underlying common population relative risk ψ is actually greater than 1 in value.

Given the set of standard errors $\sigma_1, \sigma_2, \dots, \sigma_k$ for the k studies under consideration, it can be shown that an approximate expression for the meta-analysis power θ_m is

$$\theta_m \doteq \text{pr}\{Z > 1.96 - \ln(\psi) / \sqrt{V[\ln(\text{SRR}_a)]} \mid \psi > 1\}, \quad (5)$$

where Z is a standard normal random variable, where $V[\ln(\text{SRR}_a)]$ is given by expression (4), and where ψ has some specified value greater than 1. Given the set of $\{\sigma_i\}$ values, power curves can be constructed by plotting values of θ_m as a function of values of ψ .

Appendix C.
Summaries of Studies
in Meta-Analysis

Appendix C: Summaries of Studies in Meta-analysis

Burns et al., *J Rheum* 1996

Burns et al. reported on a population-based case-control study of scleroderma in Michigan. Cases recruited from hospitals, rheumatologists' offices, and the United Scleroderma Foundation were verified by medical record abstraction and rheumatologist review of the abstracts, employing several classification criteria including those of the American College of Rheumatology. Controls were identified through random digit dialing methods and of those selected, 80% participated. Cases and controls were administered telephone questionnaires to obtain information on breast implants and other possible medical, occupational, and avocational exposures to silicone and silica. The analysis was based on 272 cases (two with silicone breast implants) and 1170 controls (14 implants, of which 12 were silicones). The odds ratio (OR) adjusted for age, race, and date of birth was 1.30 (95% CI 0.27, 6.23) considering silicone gel breast implants only. The OR was 1.39 (95% CI 0.29, 6.68) in an analysis of white women only. (No black cases had had implants.) The analysis of other possible sources of silicone exposure did not have an appreciable impact on the interpretation of the breast implant data.

The study had several strengths. A "capture-recapture" analysis (Hook and Regal, 1993) estimated that 81% of incident cases diagnosed in Michigan in 1985 through 1991 were identified for the study. This high rate of case ascertainment and good response rate in cases and controls reduced the likelihood of bias because of case selection or nonresponse. The authors conducted a separate validation study to estimate the error in implant reporting. There was 94% concordance between questionnaires and medical records on presence of implants; agreement levels were similar among those with and without rheumatic symptoms, suggesting that differential accuracy in reporting of implants by cases and controls was unlikely to bias the results. An unresolvable problem, however, was the rarity of implants; the study had low power to detect effects despite the large number of scleroderma cases. The authors estimated that they would have 80% power to detect a relative risk of four among white women. ($\alpha = 0.05$, prevalence of implants 10/1000).

Dugowson et al., *Arthritis Rheum* 1992

An abstract for a case-control study of rheumatoid arthritis was presented at the American

College of Rheumatology meeting in Atlanta, GA, in October 1992. The study was based on 300 cases of rheumatoid arthritis diagnosed between 1986 and 1991 in King County, WA. The cases were mailed a questionnaire asking about breast surgery, and specifically silicone breast implants, prior to the diagnosis of rheumatoid arthritis. The 1456 controls were obtained from the same population as the cases through random digit dialing and by sampling members of the Group Health Cooperative of Puget Sound. Controls had been identified previously, as members of the control group for another study, and interviewed about their implant history. With one case and 12 controls having had breast implants, the age-adjusted OR was 0.41 (95% CI 0.05, 3.13). This result suggests that silicone breast implants do not increase risk for rheumatoid arthritis, but the wide confidence interval indicates a very imprecise estimate.

Edworthy et al., *J Rheum* 1998

Women in this study were identified as having had a breast implant or other cosmetic surgery through the Alberta Health Registry between 1978 and 1986. Of 16,600 women identified, fewer than 20% could be contacted, were willing to participate, and fulfilled eligibility criteria. Women who had had implants for breast cancer reconstruction were excluded. Included were 1576 women with implants (1112 silicone-gel filled) and 727 who had had other cosmetic procedures. Participants had blood samples collected and completed an extensive questionnaire. Those who responded positively to questions related to specific symptoms, diagnoses, or medications were invited to receive an examination by a nurse clinician and a rheumatologist, the latter of whom was unaware of the implant status of the woman. Based on physical examination, symptoms and laboratory test results the rheumatologist determined whether or not the woman had any one of 16 CTDs or musculoskeletal conditions.

Several symptoms (thought problems, numbness in extremities, muscle pain, headache, and hand pain) were more common in the implanted women. The incidence of specific CTDs (rheumatoid arthritis, lupus erythematosus, scleroderma, Sjögren's syndrome), all definite CTDs combined, and atypical autoimmune diseases did not differ between the two groups. The relative risk for all CTDs combined was 1.0.

Because of the large nonresponse rate, nonparticipating women were compared with participants. Physician utilization rates were higher in participants than nonparticipants, and for implanted women with rheumatoid arthritis or lupus erythematosus than for women with other

cosmetic surgery having the same conditions. In theory, this differential frequency of medical attention could result in misclassification of disease and bias the risk ratios upward. However, the determination of disease diagnosis by physician evaluation should ameliorate this potential problem.

Englert et al., *Aust NZ J Med* 1996

In 1994 and 1996, Englert et al. reported on a case-control study of scleroderma and silicone breast implants in Sydney, Australia. The second report amplified on the earlier one by adding medical record validation on the existence, type, and timing of breast implants and by obtaining more complete information on deceased cases and those previously not located. Cases diagnosed before 1989 were identified from death certificates, hospital records, and physicians' office records. Specified criteria including a residency requirement determined case eligibility. Controls were obtained from 29 randomly selected general practitioners in Sydney and were required to have visited that practitioner since 1990. Subject ascertainment and data collection for the first study was largely completed by 1991. The number of cases and controls was 532 and 289, respectively, but the number available for analysis varied. Subjects with interviews included 287 cases and 252 controls. Only medical record data were available for deceased cases. Information on implants was obtained from telephone interviews and correlated highly with medical records ($\kappa = .86$ to 1.0 for different subject groups). Three cases and four controls had silicone breast implants prior to diagnosis or proxy date for the controls. No association was found between implants and case status irrespective of which case-control set was analyzed. For interviewed subjects with data on age, social economic status, and ethnicity, the OR_a was 1.00 (95% CI 0.16, 6.16). Without adjustment the OR was 1.33 (95% CI 0.26, 6.71).

The rationale for the choice of controls is not fully clarified. Controls were selected from any of 29 practitioners' offices in Sydney and most were living at the time of interview (unlike the large proportion of deceased cases). The choice of controls could influence the prevalence of implants and thus influence the odds ratio. The observed prevalence of 1.7% is somewhat high but not inconsistent with estimates provided from the United States. Power was inadequate to detect relative risks lower than about four.

Friis et al., *Ann Plastic Surg* 1997

This study covers the entire Danish female population between 1977 and 1992. All women hospitalized and receiving implants in that time frame were identified in the Danish Central Hospital Discharge Register. Implanted cohorts were separated by indication: cosmetic (N = 1135) and reconstruction (N = 1435). Three nonimplanted cohorts were established based on breast reduction surgery (N = 7071), mammoplasty correction surgery (N = 472), and breast cancer without implant (N = 3952). All cohorts were followed through record linkage for five definite CTDs and a number of "other and ill-defined rheumatic conditions." For each CTD identified, medical records were obtained for verification of the CTD and implant status. CTD classification was determined by experienced rheumatologists.

Observed to expected numbers of cases were presented for each of the four larger cohorts. The expected numbers of each CTD and other rheumatic conditions were calculated by multiplying the number of person-years of follow-up in the cohorts by the sex-specific national hospital discharge rates for each five-year age group and calendar period of observation. For the definite CTDs combined or rheumatoid arthritis alone, the observed/expected ratio approximated one in each cohort, with or without implants. The only exception was the nonimplanted breast cancer cohort, which exhibited a deficit of rheumatoid arthritis cases relative to expectation. A total of 235 cases of "muscular rheumatism" were observed; the number was in excess for each of the four cohorts, irrespective of implant status.

This retrospective cohort study based on medical record linkage for an entire country provides significant numbers of cases of rheumatoid arthritis and all CTDs combined. However, because of the rarity of specific CTDs, the power is still low to identify an effect, if such existed. Also, only hospitalized cases were ascertained omitting those treated only in an ambulatory setting. These omissions should not bias the results if they were nondifferentially distributed between implanted and nonimplanted cohorts. That all four cohorts exhibited an excess of "muscular rheumatism" relative to expectation, suggests that some aspect of breast surgery per se, or a covariate highly correlated with it, is associated with less well-defined rheumatologic conditions.

Gabriel et al., *N Engl J Med* 1994

Gabriel and colleagues published a retrospective cohort study using linked medical records

within the Mayo Clinic and affiliated hospitals in Ulmsted County, MN. Female county residents, who had had a breast implant between January 1964 and December 1991, were identified. The 749 such women were divided into three groups based on indication for implant: reconstruction after breast cancer surgery, reconstruction after prophylactic mastectomy, and implants for cosmetic reasons. Two women without implants were matched on age, date of medical visit, and Mayo Clinic registration number to each implanted woman. Two additional comparison women who had had breast cancer but no implant were selected for each implanted breast cancer patient. The medical records were abstracted for evidence of definite CTDs, rheumatic symptoms, and four laboratory tests characteristic of different CTDs.

Follow-up for women with implants averaged 7.8 years with 36% followed for ten years. Five implanted women and ten comparison women developed any one of 12 conditions classified a priori by the authors as CTDs. The hazard ratio for any CTD was 1.10 (95% CI 0.37, 3.23). Among the ten signs and symptoms, only morning stiffness exhibited a statistically significant elevation in the hazard ratio for implanted women. However, the incidence rates for this complaint were similar for breast cancer patients with and without implants, suggesting that morning stiffness was more likely to be associated with the indication for the implant than with the implant itself. The risk of developing an abnormal laboratory test (antinuclear antibody, rheumatoid factor, thyroid-stimulating hormone, antimicrosomal antibody) was the same for implanted and nonimplanted women.

The study methods were strong: a retrospective cohort based on record linkage in the Mayo medical system and excellent follow-up in a defined population. On the other hand, given the modest size of the cohort, the power to detect an effect for rare diseases was low.

Giltay et al., *Ann Rheum Dis* 1994

Giltay et al. reported on the frequency of nine rheumatic signs and symptoms, antirheumatic drug use, and medical consultations for rheumatic symptoms among surgical patients from the Department of Plastic Surgery in the Free University Hospital in Amsterdam. Study subjects included 374 women who had silicone-gel filled implants and 374 age-matched comparison women who had cosmetic breast surgery between January 1978 and December 1990. Because 174 women were lost to follow-up or not eligible, questionnaires were mailed to 574 women (287 in each group) in June 1992. The response rate was higher from implanted (82%) than

nonimplanted (73%) women. Overall, 37% of implanted women versus 21% of nonimplanted women responded that they had experienced one or more of the nine signs and symptoms since their surgery. The excess was concentrated in the categories of painful joints, burning eyes, and skin abnormalities aggravated by sunlight. No statistically significant excess was reported by either group in response to questions on use of antirheumatic drugs or medical consultations regarding rheumatic symptoms. A rheumatologist's assessment of additional data collected on selected study subjects provided no evidence for the existence of any definite CTDs.

Methodologic problems inherent to this study include the potential for selection bias, given that 37% of eligible implanted women and 44% of comparison women either could not be followed or did not respond to the questionnaire. Women who did respond may have been aware of the issues surrounding implants, since the questionnaire was mailed at a time when media publicity was prominent. Reporting bias could result, if women with implants were sensitized to the presence of symptoms and their possible import. Approximately a third of the implanted women had breast cancer, whereas women with this diagnosis were not included in the comparison group.

Goldman et al., *J Clin Epidemiol* 1995

Goldman et al. conducted a cross-sectional study of breast implants and CTDs in his referral rheumatology practice in Atlanta, GA, for the decade 1982 to 1992. From 1986 to 1992, medical records were computer accessible, assuring complete ascertainment for all diagnoses. A total of 4229 female patients with adequate data were identified among whom 150 (3.5%) had implants. Diagnosis of 721 cases of definite CTDs (including rheumatoid arthritis) was confirmed by medical record review, applying criteria established by various rheumatologic organizations. Of 12 implanted cases, the diagnosis preceded the implant in six. Multiple logistic regression analysis focused on three endpoints: rheumatoid arthritis, CTDs (one lupus erythematosus and two Sjögren's syndrome among implanted women), and rheumatoid arthritis/CTDs combined. Age, income, and time period of first clinic visit were included as covariates in the model. All adjusted (and crude) odds ratios were less than one. For CTDs, and rheumatoid arthritis/CTDs combined, the upper bound of the 95% CI was less than one.

Study strengths include the time period for case diagnosis (almost all before 1992) and the use of established diagnostic criteria in determining case status. However, including women in

the analysis whose implants occurred after the CTD diagnosis make the findings uninterpretable with respect to causal inference. Referral biases could affect the patient population in a single rheumatology practice, since the types of patients referred may be influenced by the specialty interests and expertise of the practicing physicians.

Hennekens et al. *JAMA* 1996

Hennekens et al. is the largest published study of breast implants and CTDs. A questionnaire was mailed to 1.75 million women health professionals in the U.S. and Puerto Rico between September 1992 and May 1995. Among other health-relevant items, there were questions on prior breast implants and diagnosis of five definite CTDs and “other CTDs including mixed.” The response rate was 24%. After exclusions, a study population of 395,543 women remained. Among these, 10,830 (2.8%) reported having had a breast implant between 1962 and 1991. Risk estimates (hazard ratios) were presented for “any CTD,” rheumatoid arthritis, lupus erythematosus, Sjögren’s syndrome, dermatomyositis/polymyositis, scleroderma, and “other CTDs including mixed.” Hazard ratios were obtained using Cox proportional hazard models with time-varying exposure. Small but statistically insignificant elevations in risk were noted for each definite CTD. Only for “other CTDs” and “any CTD” were the risk estimates elevated, 1.30 and 1.24 respectively, such that the 95% CIs did not overlap one. The “any CTD” category included women who had any of the five definite CTDs or an “other CTD.”

Several features of this study could bias the results. All data were self-reported through mailed questionnaire, collected between September 1992 and May 1995. During this time period, publicity concerning silicone breast implants and their possible adverse effects, particularly for CTD-like syndromes, was intense in the scientific and public media. This high media visibility could be conducive to reporting bias, i.e., women with implants and perceived illness would be more likely to respond to the questionnaire than would unaffected women.

The prevalence of implants in the Hennekens et al. study was more than twice as high as that in the population at large, indicating that women with implants were more likely to respond to the questionnaire than nonimplanted women. For women aged 45–54, the implant prevalence was 35.7/1000 as compared to population estimates of 11–16.3/1000 (Cook et al., 1995). In the total study group, implant prevalence was 2.8% versus less than 1% in the U.S. population more than 18 years of age (Cook et al., 1995).

The CTD incidence rates reported in the Women's Health Cohort substantially exceeded those reported by others, as shown in Table 1. Several studies have shown low concordance between self-reported CTDs and medical record validation. In one study, only 21% of self-reported rheumatoid arthritis cases were validated in medical records. (Star et al., 1993) About 10% of self-reported definite CTDs could be validated by medical records in the Nurses Health Study (Sanchez-Guerrero et al., 1995). Thus, self-report on a mailed questionnaire was likely to over-report definite and other CTDs.

Other problems with the study have been frequently cited. The 76% nonresponse rate to the mailed questionnaire could bias the results; this occurred if respondents and nonrespondents differed significantly on characteristics that influenced their implant and disease status. The high-observed prevalence of implants and of definite CTDs is likely to reflect selection bias in the study population. Missing data on dates of diagnosis of the CTDs and on surgery for implants was common. Neither the type of implant nor the indication for its placement was known. Validation studies have shown excellent concordance (90% agreement) between self-reported implants and medical record documentation, indicating that self-report is an acceptable method for obtaining implant status (Sanchez-Guerrero et al., 1995). However, the type of implant and date of implantation are less accurately obtained from self-report (Garbers et al., 1998; Sanchez Guerrero et al., 1995).

These data problems are likely to produce over-reporting of disease, incomplete information on exposure, and uncertainty as to the ordering of disease diagnosis and implant placement. The high implant prevalence among participants suggests that women with implants were more likely to respond to the questionnaire. Study participants also reported an unusually high frequency of CTDs. If women with implants were also more likely to report various signs and symptoms as CTDs, the RR estimates would be biased upward. Selection and reporting biases could readily result from the widespread publicity in the media and the over-reporting of ill-defined diseases.

Hochberg et al., *Arthritis Rheum* 1996

Hochberg et al. conducted a case-control study of scleroderma including 837 cases and 2507 controls in the analysis data set. The cases were those being followed and managed at several tertiary care medical centers in three geographic areas: Baltimore/Washington, San Diego, and

Pittsburgh. Data were collected from cases on breast surgery and implants by mailed questionnaire during 1990 and 1991, except for 18 women on whom additional information was obtained in 1993. All cases included in the study were diagnosed before 1992. Controls were age and race matched to local women who were obtained by random digit dialing methods; the questionnaire was administered to them by telephone. The response rate for cases was 73% and for controls 59%. If one considers only eligible controls in the denominator, the response rate was better, 90.6%. The authors conducted a validation study to assess accuracy of implant self-report on a 5% random sample of controls. Agreement on presence or absence of an implant was 96.7%.

Odds ratios adjusted for age, race, and geographic site were calculated from unconditional multiple logistic regression models. The adjusted OR was 1.07 (95% CI 0.53, 2.13) or 1.08 (0.53, 2.17) after excluding 35 cases diagnosed before 1963 with no opportunity for exposure to silicone breast implants. The lack of association between implants and scleroderma is notable, since a study of this size had 80% power to detect an OR of 1.8 or greater.

Problems with the study were several. Data were collected by mail for cases and telephone for controls. The differential nonresponse rates between cases and controls could bias the results if the characteristics of participants differed from those of nonparticipants. No classification criteria to assure uniformity of case definition were provided. Cases were selected from tertiary care centers and arose from "prevalence cohorts" for whom the average disease duration at time of study recruitment was ten years. If one postulated that silicone breast implants caused a particularly virulent form of scleroderma, women who had received implants would be less likely to have survived to take part in the study than women who had not received implants. Although there are no data to support this theory, the effect of such a survival difference would be to reduce artificially the size of the OR.

Lacey et al., *J Rheum* 1997

The Michigan study of scleroderma (Burns et al., 1996) was replicated in Ohio and reported in a letter. Using the same study protocol as in Michigan, 189 incident cases of scleroderma were compared to 1043 randomly selected controls from Ohio. The OR adjusted for age and year of birth was 1.01 (95% CI 0.13, 8.15). Only one case and ten controls had had a silicone breast implant.

Laing et al., *Arthritis Rheum* 1996

In an abstract for the American College of Rheumatology, Laing et al. took advantage of the data collection system that had been developed for scleroderma in Michigan and Ohio (Burns, 1996) to study undifferentiated connective tissue disease. Disease definition was based on physician diagnosis, absence of a definite CTD or at least two signs, symptoms, or laboratory values suggestive of a CTD. Thus, cases did not meet published definitions of undifferentiated connective tissue disease (Alarcon et al., 1991) but they did exhibit rheumatologic signs and symptoms. With 205 cases (three with silicone breast implants) and 2220 controls diagnosed between 1980 and 1992, the crude OR was 1.21 (95% CI 0.36, 4.01); the OR adjusted for age and year of birth was 2.27 (95% CI 0.67, 7.71). This study also evaluated other implanted devices and found increased risks of rheumatologic symptoms for several implant types, with and without silicone content.

Nyren et al., *BMJ* 1998

In a retrospective cohort study, women with breast implants and breast reduction surgery during 1964–93 were identified from the Swedish National Inpatient Registry, which was subsequently linked with registries of the total Swedish population, migrations, and deaths. Women discharged from hospital between 1972 and 1993 with any definite or possible CTD were also identified from the inpatient registry. Medical record review for all registry-identified cases was used to validate the diagnoses. Analyses were of two types: standardized hospitalization ratios based on observed to expected numbers and risk ratios comparing disease rates in implanted women to those without implants. In the standardized hospitalization ratios analyses, national rates of first hospitalizations by age, sex, and calendar year for each specific diagnosis and all definite CTDs combined were multiplied by the person-years of observation to provide the expected number of cases. No correction for pre-existing or misclassified diagnoses was made, since the entire population of women in the inpatient registry could not be validated against medical records. In the second analysis, relative risks adjusted for age and follow-up time were calculated, comparing the implanted with the nonimplanted cohorts. All erroneous diagnoses were corrected and cases pre-existing prior to breast surgery were excluded.

The number of women available for analysis was 7442 (implantation cohorts) and 3353 (breast reduction cohort) with an average of 8.0 and 9.9 years of follow-up, respectively. For the

analysis using standardized hospitalization ratios, there were 29 and 14 cases of all definite CTDs combined in the implanted and nonimplanted cohorts, respectively. The standardized hospitalization ratios, were 1.6 (cosmetic implants), 0.8 (reconstruction implants), and 1.3 (breast reduction). All had 95% CI which bounded unity. No remarkable risk elevations were noted for any of the five definite CTDs nor the 11 nondefinite CTDs for any cohort. In the analyses with direct comparisons between implanted and nonimplanted cohorts the age and length of follow-up adjusted RR for all definite CTDs was 0.8, 95% CI 0.5, 1.4. The RR for rheumatoid arthritis was 1.3 and for lupus erythematosus 0.7.

The strengths of the study include; the large population base (all women in Sweden), the availability of multiple population-based registries, the cohort design with record linkage, and medical record validation of case status. Only women who were hospitalized for diagnosis or treatment were included, which does not bias the study, but does reduce the scope to women with relatively serious illnesses.

Park et al., *Plast Reconstr Surg* 1998

Subjects were assembled from two hospitals in Southeast Scotland for a retrospective cohort/cross-sectional study of silicone breast implants and CTDs or selected symptoms. Patients having undergone implants for augmentation between 1982 and 1991 were compared with an undefined sample of outpatients at a plastic surgery department. A subset of breast cancer patients having received implants for reconstruction during the same decade was matched on age, stage, and time period of operation to breast cancer patients without implants. All study subjects attended clinic for history, physical, and laboratory tests. For both surgical indications, a higher proportion of implanted patients participated than nonimplanted patients. Analyses using ORs, CIs, and chi-square statistics were conducted separately for the augmentation and the reconstruction patients.

In total, 317 implanted women and 216 comparison women were available for analysis. The only CTD identified was rheumatoid arthritis with one case each among the implanted and the comparison women. Groups were compared on the frequency of positive responses to each of 19 signs, symptoms, and laboratory tests. There were no statistically significant differences for any of the 19 items between implanted and nonimplanted women with either surgical indication or when only the matched subset of breast cancer patients was analyzed. The most commonly

reported symptoms among implanted and nonimplanted women were joint pain, muscle pain and fatigue.

Sanchez-Guerrero et al., *N Engl J Med* 1995

The Nurses Health Study provides an excellent opportunity to evaluate the relation between breast implants and CTDs. This study has been in progress since 1976 when over 120 thousand nurses in 11 geographic regions of the United States and Canada were enrolled in a cohort, which has been followed prospectively for 30 years with biennial questionnaires. Nurses were identified for the implant/CTD study on the basis of their being alive and participating in the 1992 biennial questionnaire. On several of the prior biennial questionnaires, questions had been asked about physician-diagnosed definite CTDs, rheumatic conditions, and "CTDs not further specified." Case ascertainment was based on positive responses to these questions from June 1976 to May 1990. In the 1992 biennial questionnaire, questions were asked about breast implant surgery or injections. Women who responded positively to these questions were mailed a supplemental questionnaire requesting specific information about their implants. The response rate was 97% but exclusions were numerous because of incomplete information or lack of eligibility. Information on indication and type of implant, laterality of surgery, and number of operations was available for 1183 women with implants and 86,318 women without implants.

"Disease" was categorized in four different ways. In response to the biennial mailings, 5086 women reported a diagnosis of a rheumatic condition or CTD. These women received a supplemental questionnaire that included questions about 30 signs and symptoms known to be associated with definite CTDs as defined by the American College of Rheumatology. The criteria used to establish "case" status from the supplemental questionnaire were as follows: a positive response to any three or more of the signs and symptoms or an indication of two or more swollen joints of at least six weeks duration. Using these criteria, 1294 women were classified as "cases." The remaining two approaches to disease status were based on medical record review. Medical records were abstracted for the women who were cases as defined by the self-reported signs and symptoms. Two rheumatologists independently abstracted 41 signs, symptoms, and laboratory tests by using medical records from which data on implants had been removed. Positive information in the medical record on any one of the 41 signs, symptoms, or laboratory tests was a third approach to classifying a woman as a case, resulting in 904 "case" designations. Last, the

rheumatologists used standard American College of Rheumatology criteria to establish a diagnosis of a definite CTD based on the abstracted list of signs, symptoms, and laboratory tests. The number of women with definite CTDs was 516.

The age-adjusted relative risk (age-adjusted incidence rate of CTD in women with implants divided by the age-adjusted incidence rate in women without implants) was in no instance statistically greater than unity, irrespective of case definition or type of implant (silicone only or all types). For definite CTDs, defined by rheumatologists from medical record abstraction, the RR was 0.3 (0.0, 1.9) for silicone gel implants and 0.6 (0.2, 2.0) for all implants.

The strengths of this study are several: most important, is the method and timing of case ascertainment, including only those women who reported a CTD before June 1990. Furthermore, this cohort was followed for 14 years with a mean duration between implant and disease diagnosis of almost ten years, providing a reasonably long latency period, if such is required for adverse effects to occur. Additional refinements included a validation study of the accuracy of self-report of implants compared to medical records (99% agreement was found with respect to the presence of an implant). Disease status from medical records was determined blindly with information on implant status having been removed.

This study has been criticized for not querying all women in the cohort (88,153) about signs and symptoms rather than just the 5086 who had previously responded positively to a diagnosis of a CTD. With the approach taken, nonspecific, transient complaints were not captured. On the other hand, rheumatologic complaints, resulting in a physician visit and at least a tentative diagnosis, were included. The incidence rates reported for each of the definite CTDs, identified through medical records, was in the range of other published rates, suggesting that under-reporting was not a major problem.

Schusterman et al., *Ann Plastic Surg* 1993

Schusterman et al. reported on a cohort of breast cancer patients who underwent breast reconstruction between 1986 and 1992. Two hundred fifty had silicone-gel implants and 353 had autogenous tissues used for reconstruction. All were followed through medical records and questionnaires for the development of medically identified and treated "rheumatic disease." Two such cases occurred within nine months of reconstruction surgery (one from each group) and both were successfully treated with corticosteroids. Neither case was a definite CTD. Person-

years of follow-up were 616 for the implanted women and 663 for the autogenous tissue group. The rate ratio for a rheumatic condition was 1.08 (95% CI 0.1, 17.2).

A strength of this study is the elimination of potential confounding by indication for implant. Since all women had breast cancer, any effect of the disease in producing rheumatic complaints should be equally evident in both the implanted and nonimplanted cohort. Study weaknesses are small cohort size and short follow-up.

Strom et al., *J Clin Epid* 1994

Strom et al. reported on a case-control study of incident lupus erythematosus cases and friend controls. Cases, who conformed to the revised American Rheumatism Association criteria for lupus erythematosus (Tan et al., 1982), were identified from 22 rheumatologists' offices and the Lupus Foundation in Philadelphia during 1985–1987. The 1994 report was based on a 1992 attempt to recontact cases and controls from the prior study to obtain information by telephone on surgical events, emphasizing breast implants and injections, prior to the lupus erythematosus diagnosis for cases and comparable index date for controls. The response rate for the re-contact effort was 76% (cases) and 77% (controls). Female subjects available for analysis were 133 cases, one of whom had had an implant, and 100 controls with no implants. Because of the absence of exposed controls, the authors used the controls from the Cancer and Steroid Hormone study conducted in 1980–1982 to calculate an odds ratio and 90% exact CI. The resulting odds ratio was 4.5 and 90% CI of 0.2, 27.3.

The use of external controls from different geographic locales than the cases was not an optimal design feature. Furthermore, it is difficult to interpret the odds ratio of 4.5 when the 90% CI spans a range of values more than five times greater or five times lower than the point estimate.

Teel, Dissertation, University of Washington 1997

A population based case-control study of CTDs and breast implants was conducted among King County, WA, residents. Cases diagnosed between 1983 and 1991 who met published diagnostic criteria were identified from medical records in rheumatologists' offices. Two sets of control women were considered: those interviewed in person between 1986 and 1991 and used as controls in other studies, and “new” controls selected through random digit dialing and frequency

matched on age and reference year to the cases. All new controls and cases were mailed questionnaires in 1994–1996 to obtain information on implant status and potential covariates. Because of comparability in data collection methods and ability to match on covariates, the primary analysis was based on these subjects. Logistic regression analyses were conducted adjusting for age, reference year, and race.

The results were as follows: among 55 scleroderma patients, 17 dermatomyositis/polymyositis patients, and three mixed connective tissue disease patients, none had had implants, so these women could only be included in the analysis of all CTDs combined. With four implanted Sjögren's syndrome and two implanted lupus erythematosus women, the ORs and 95% CIs were 1.6 (0.6, 4.7) and 0.8 (0.2, 3.4), respectively. For all CTDs combined the comparable numbers were 0.9 (0.4, 2.3). The findings from these authors do not support a significantly increased risk for these well-defined CTDs in relation to breast implants.

Wells et al., *Plast Reconst Surg* 1994

Wells et al. reported on a retrospective cohort of women who received silicone breast implants (cosmetic or reconstructive) or other cosmetic surgery from a single plastic surgeon's practice in Tampa, FL. In 1990–1991, women who had had these procedures between 1970 and 1990 were mailed questionnaires asking about 23 signs and symptoms and four diagnoses experienced either before or after the relevant surgery. After telephone follow-up on a sample of nonrespondents, the response rate was 59% in the silicone breast implant cohort and 46% in the other surgery cohort. This provided 222 women with silicone breast implants and 80 women with other cosmetic surgery for the analysis. The analysis was based only on newly presenting signs and symptoms or diagnosed CTDs that occurred after the relevant surgery. Analytic methods included Mantel-Haenzel ORs with 95% CIs and logistic regression with age and year of surgery as covariates. The silicone breast implant group was younger and had had a higher frequency of procedures in the 1970s than the other surgery group. After applying the Bonferroni correction for multiple endpoints, only three of 27 possible outcomes differed between the two groups of women. These were swollen and tender axillary glands, both more common in silicone breast implant women, and change in skin color, which was more common in the other surgery group. Information was not provided as to how long after surgery the signs and symptoms arose or whether they were temporary postoperative complications. The silicone breast implant group

included some women undergoing reconstruction after breast cancer surgery, which itself could have accounted for swollen and tender axillary nodes. In response to the questions on medically diagnosed CTDs, one Raynaud's phenomenon and several arthritis cases were reported with no statistically significant differences between groups.

Wolfe, *Arthritis Rheum* 1995

An abstract featuring rheumatoid arthritis and silicone breast implants appeared in the proceedings from the American College of Rheumatology meeting in October 1995. Subjects were categorized in four groups: cases of rheumatoid arthritis and fibromyalgia, and controls consisting of osteoarthritis patients and "randomly selected women in the general population." Information was collected from patients by mailed questionnaire and from the population controls by telephone interview. No information was provided on the source population or method of subject ascertainment for any case or control group. (The author was from the University of Kansas in Wichita, which suggests an area of residence for study subjects as well.) Three of 637 rheumatoid arthritis patients had silicone breast implants prior to diagnosis compared to two of 653 community controls. The age-adjusted OR was 0.97 (95% CI 0.15, 6.20) for cases compared to community controls, 1.76 (95% CI 0.28, 11.04) with osteoarthritis controls and 1.35 (95% CI 0.30, 6.06) with the two control groups combined.

Appendix D.
Unadjusted Analysis

Table D.1 Sum of "Definite CTDs" (RA, SLE, SSs, Sjögren's Syndrome, DM/PM, and Those So Designated by Author) by Study

Study by First Author	Implant ¹		No Implant		Crude OR ^{3,4} (95% CI)	ln(OR)	SE[ln(OR)]	Cond MLE ⁴ (Fisher 95% CI)	Adj OR ⁵ (95% CI)	Dsn ⁶	Dx ⁷	Yr ⁸
	D ²	Ḑ	D	Ḑ								
Burns	2	14	272	1170	0.61 (0.14, 2.72)	-0.4869	0.7589	0.61 (0.07, 2.70)	0.95 (0.21, 4.36)	0	1	1
Dugowson, 1992	1	12	299	1444	0.40 (0.05, 3.11)	-0.9101	1.0428	0.40 (0.01, 2.74)	0.41 (0.05, 3.13)	0	1	1
Edworthy	19	1093	16	711	0.77 (0.39, 1.51)	-0.2581	0.3427	0.77 (0.37, 1.62)	1.00 (0.45, 2.22)	1	1	0
Englert	4	4	527	249	0.47 (0.12, 1.90)	-0.7497	0.7113	0.47 (0.09, 2.56)	-	0	1	1
Friis	10	2560	25	10998	1.72 (0.82, 3.58)	0.5414	0.3748	1.72 (0.74, 3.71)	-	1	1	1
Gabriel	5	744	10	1488	1.00 (0.34, 2.94)	0.0000	0.5496	1.00 (0.27, 3.22)	1.10 (0.37, 3.23)	1	1	1
Goldman	6	144	709	3370	0.20 (0.09, 0.45)	-1.6195	0.4187	0.20 (0.07, 0.44)	-	0	1	1
Hennekens	231	10599	11574	373139	0.70 (0.62, 0.80)	-0.3530	0.0672	-	1.24 (1.08, 1.41)	0	0	0
Hochberg, 1996b	11	31	826	2476	1.06 (0.53, 2.13)	0.0618	0.3532	1.06 (0.48, 2.19)	1.07 (0.53, 2.13)	0	1	1
Lacey	2	13	187	1030	0.85 (0.19, 3.79)	-0.1656	0.7637	0.85 (0.09, 3.79)	1.48 (0.34, 6.39)	0	1	1

Nyren	16	7426	11	3342	0.65 (0.30, 1.41)	-0.4237	0.3922	0.65 (0.29, 1.56)	0.80 (0.50, 1.40)	1	1	1
Park	1	316	1	215	0.68 (0.04, 10.94)	-0.3851	1.4170	0.68 (0.01, 53.65)	-	1	1	0
Sanchez-Guerrero	3	1180	513	85805	0.43 (0.14, 1.32)	-0.8552	0.5798	0.43 (0.09, 1.25)	0.60 (0.02, 2.00)	1	1	1
Strom	1	0	132	100	-	-	-	(0.02, ∞)	-	0	1	1
Teel	6	24	421	1553	0.92 (0.37, 2.27)	-0.0810	0.4597	0.92 (0.31, 2.34)	0.90 (0.40, 2.30)	0	1	1
Wolfe	3	4	634	1130	1.34 (0.30, 5.99)	0.2903	0.7654	1.34 (0.20, 7.93)	1.35 (0.30, 6.06)	0	?	?

¹All types of implants were included.

²Only cases in which disease followed implant were included when that information was available.

³Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) confidence limits.

⁴Obtained with the Exact statistical program.

⁵Reported by author.

⁶1 if cohort, 0 if not.

⁷1 if by medical record validation, 0 if not.

⁸1 if data on disease diagnosis collected <1992 in at least 90% of the cases, 0 if not.

Table D.2 Cases of Rheumatoid Arthritis (RA) by Study

Study by First Author	Implant ¹		No Implant		Crude OR ^{3,4} (95% CI)	ln(OR)	SE[ln(OR)]	Cond MLE ⁴ (Fisher 95% CI)	Adj OR ⁵ (95% CI)	Dsn ⁶	Dx ⁷	Yr ⁸
	D ²	D	D	D								
Dugowson	1	12	299	1444	0.40 (0.05, 3.11)	-0.9101	1.0428	0.40 (0.01, 2.74)	0.41 (0.05, 3.13)	0	1	1
Edworthy	11	1101	6	721	1.20 (0.44, 3.26)	0.1828	0.5098	1.20 (0.40, 3.97)	1.44 (0.50, 4.15)	1	1	0
Gabriel	0	749	2	1496	-	-	-	(0.00, 10.65)	-	1	1	1
Friis	7	2563	16	11007	1.88 (0.77, 4.57)	0.6307	0.4537	1.88 (0.65, 4.83)	-	1	1	1
Goldman	5	141	383	3696	0.34 (0.14, 0.84)	-1.0724	0.4582	0.34 (0.11, 0.83)	-	0	1	1
Hennekens	107	10723	6322	378391	0.60 (0.49, 0.72)	-0.5155	0.0980	-	1.18 (0.97, 1.43)	0	0	0
Nyren	11	7431	5	3348	0.99 (0.34, 2.86)	-0.0088	0.5398	0.99 (0.32, 3.64)	1.3 (0.70, 2.5)	1	1	1
Park	1	206	1	87	0.42 (0.03, 6.83)	-0.8620	1.4200	0.42 (0.01, 33.53)	0.42 (0.01, 15.63)	1	1	0
Sanchez-Guerrero	3	1180	389	85929	0.56 (0.18, 1.75)	-0.5770	0.5803	0.56 (0.12, 1.66)	0.90 (0.30, 2.60)	1	1	1
Wolfe	3	4	634	1130	1.34 (0.30, 5.99)	0.2903	0.7654	1.34 (0.20, 7.93)	1.35 (0.30, 6.06)	0	?	?

¹All types of implants were included.

²Only cases in which disease followed implant were included when that information was available.

³Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) confidence limits.

⁴Obtained with the Exact statistical program.

⁵Reported by author.

⁶1 if cohort, 0 if not.

⁷1 if by medical record validation, 0 if not.

⁸1 if data on disease diagnosis collected <1992 in at least 90% of the cases, 0 if not.

Table D.3 Cases of Systemic Lupus Erythematosus (SLE) by Study

Study by First Author	Implant ¹		No implant		Crude OR ^{3,4} (95% CI)	ln(OR)	SE[ln(OR)]	Cond MLE ⁴ (Fisher 95% CI)	Adj OR ⁵ (95% CI)	Dsn ⁶	Dx ⁷	Yr ⁸
	D ²	D̄	D	D̄								
Edworthy	3	1109	3	724	0.65 (0.13, 3.24)	-0.4265	0.8179	0.65 (0.09, 4.89)	0.94 (0.17, 5.23)	1	1	0
Friis	1	2569	5	11018	0.86 (0.10, 7.35)	-0.1534	1.0957	0.86 (0.02, 7.67)	-	1	1	1
Goldman	0	149	179	3900	-	-	-	(0.00, 0.55)	-	0	1	1
Hennekens	32	10798	1561	383152	0.73 (0.51, 1.03)	-0.3183	0.1788	0.73 (0.50, 1.03)	1.15 (0.81, 1.63)	0	0	0
Nyren	3	7439	3	3350	0.45 (0.09, 2.23)	-0.7978	0.8168	0.45 (0.06, 3.36)	0.70 (0.30, 1.6)	1	1	1
Sanchez- Guerrero	0	1183	96	86222	-	-	-	(0.00, 2.86)	-	1	1	1
Strom	1	0	132	100	-	-	-	(0.02, ∞)	-	0	1	1
Teel	2	24	189	1553	0.68 (0.16, 2.92)	-0.3788	0.7400	0.68 (0.08, 2.80)	0.80 (0.20, 3.40)	0	1	1

¹All types of implants were included.

²Only cases in which disease followed implant were included when that information was available.

³Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) confidence limits.

⁴Obtained with the Exact statistical program.

⁵Reported by author.

⁶1 if cohort, 0 if not.

⁷1 if by medical record validation, 0 if not.

⁸1 if data on disease diagnosis collected <1992 in at least 90% of the cases, 0 if not.

Table D.4 Cases of Systemic Sclerosis/Scleroderma (SSc) by Study

Study by First Author	Implant ¹		No implant		Crude OR ^{3,4} (95% CI)	ln(OR)	SE[ln(OR)]	Cond MLE ⁴ (Fisher 95% CI)	Adj OR ⁵ (95% CI)	Dsn ⁶	Dx ⁷	Yr ⁸
	D ²	Ḑ	D	Ḑ								
Burns	2	14	272	1170	0.61 (0.14, 2.72)	-0.4869	0.7589	0.61 (0.07, 2.70)	0.95 (0.21, 4.36)	0	1	1
Edworthy	0	1112	3	724	-	-	-	(0.00, 1.58)	-	1	1	0
Englert	4	4	527	249	0.47 (0.12, 1.90)	-0.7497	0.7113	0.47 (0.09, 2.56)	-	0	1	1
Friis	1	2569	1	11022	4.29 (0.27, 68.62)	1.4564	1.4144	4.29 (0.05, 336.81)	-	1	1	1
Gabriel	0	749	1	1497	-	-	-	(0.00, 78.00)	-	1	1	1
Goldman	0	150	64	4015	-	-	-	(0.00, 1.61)	-	0	1	1
Hennekens	10	10820	314	384399	1.13 (0.60, 2.12)	0.1235	0.3214	1.13 (0.54, 2.11)	1.84 (0.98, 3.46)	0	0	0
Hochberg, 1996b	11	31	826	2476	1.06 (0.53, 2.13)	0.0618	0.3532	1.06 (0.48, 2.19)	1.07 (0.53, 2.13)	0	1	1
Lacey	2	13	187	1030	0.85 (0.19, 3.79)	-0.1656	0.7637	0.85 (0.09, 3.79)	1.48 (0.34, 6.39)	0	1	1
Nyren	0	7442	3	3350	-	-	-	(0.00, 1.09)	-	1	1	1

Sanchez-Guerrero	0	1183	14	86304	-	-	-	(0.00, 22.02)	-	1	1	1
Teel	0	24	55	1553	-	-	-	(0.00, 4.84)	-	0	1	1

¹All types of implants were included.

²Only cases in which disease followed implant were included when that information was available.

³Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) confidence limits.

⁴Obtained with the Exact statistical program.

⁵Reported by author.

⁶1 if cohort, 0 if not.

⁷1 if by medical record validation, 0 if not.

⁸1 if data on disease diagnosis collected <1992 in at least 90% of the cases, 0 if not.

Table D.5 Cases of Sjögren's Syndrome by Study

Study by First Author	Implant ¹		No implant		Crude OR ^{3,4} (95% CI)	ln(OR)	SE[ln(OR)]	Cond MLE ⁴ (Fisher 95% CI)	Adj OR ⁵ (95% CI)	Dsn ⁶	Dx ⁷	Yr ⁸
	D ²	Ḑ	D	Ḑ								
Edworthy	5	1107	4	723	0.82 (0.22, 3.05)	-0.2029	0.6725	0.82 (0.18, 4.13)	0.99 (0.17, 5.94)	1	1	0
Friis	1	2569	1	11022	4.29 (0.27, 68.62)	1.4564	1.4144	4.29 (0.05, 336.81)	-	1	1	1
Gabriel	1	748	0	1498	-	-	-	(0.05, ∞)	-	1	1	1
Goldman	1	148	47	4032	0.58 (0.08, 4.23)	-0.5454	1.0140	0.58 (0.01, 3.44)	-	0	1	1
Hennekens	22	10808	752	383961	1.04 (0.68, 1.59)	0.0385	0.2165	1.04 (0.65, 1.59)	1.49 (0.97, 2.28)	0	0	0
Nyren	1	7441	0	3353	-	-	-	(0.01, ∞)	-	1	1	1
Sanchez- Guerrero	0	1183	2	86316	-	-	-	(0.00, 388.64)	-	1	1	1
Teel	4	24	157	1553	1.65 (0.56, 4.81)	0.4999	0.5465	1.65 (0.41, 4.88)	1.60 (0.50, 4.70)	0	1	1

¹All types of implants were included.

²Only cases in which disease followed implant were included when that information was available.

³Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) confidence limits.

⁴Obtained with the Exact statistical program.

⁵Reported by author.

⁶1 if cohort, 0 if not.

⁷1 if by medical record validation, 0 if not.

⁸1 if data on disease diagnosis collected <1992 in at least 90% of the cases, 0 if not.

Table D.6 Cases of Dermatomyositis/Polymyositis (DM/PM) by Study

Study by First Author	Implant ¹		No implant		Crude OR ^{3,4} (95% CI)	ln(OR)	SE[ln(OR)]	Cond MLE ⁴ (Fisher 95% CI)	Adj OR ⁵ (95% CI)	Dsn ⁶	Dx ⁷	Yr ⁸
	D ²	\bar{D}	D	\bar{D}								
Friis	0	2570	2	11021	-	-	-	(0.00, 22.84)	-	1	1	1
Goldman	0	150	36	4043	-	-	-	(0.00, 2.94)	-	0	1	1
Hennekens	20	10810	727	383986	0.98 (0.63, 1.52)	-0.0231	0.2269	0.98 (0.59, 1.52)	1.52 (0.97, 2.37)	0	0	0
Nyren	1	7441	0	3353	-	-	-	(0.01, ∞)	-	1	1	1
Sanchez- Guerreo	0	1183	12	86306	-	-	-	(0.00, 26.29)	-	1	1	1
Teel	0	24	17	1553	-	-	-	(0.00, 16.79)	-	0	1	1

¹All types of implants were included.

²Only cases in which disease followed implant were included when that information was available.

³Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) confidence limits.

⁴Obtained with the Exact statistical program.

⁵Reported by author.

⁶1 if cohort, 0 if not.

⁷1 if by medical record validation, 0 if not.

⁸1 if data on disease diagnosis collected <1992 in at least 90% of the cases, 0 if not.

Table D.7 Cases of Other Autoimmune/rheumatic Conditions (Including UCTD, MCTD) by Study

Study by First Author	Implant ¹		No Implant		Crude OR ^{3,4} (95% CI)	ln(OR)	SE[ln(OR)]	Cond MLE ⁴ (Fisher 95% CI)	Adj OR ⁵ (95% CI)	Dsn ⁶	Dx ⁷	Yr ⁸
	D ²	\bar{D}	D	\bar{D}								
Edworthy	36	1076	36	691	0.64 (0.40, 1.03)	-0.4429	0.2407	0.64 (0.39, 1.06)	-	1	1	0
Friis	73	2497	195	10828	1.62 (1.24, 2.13)	0.4845	0.1390	1.62 (1.22, 2.14)	-	1	1	1
Gabriel	25	724	39	1459	1.29 (0.78, 2.15)	0.2560	0.2602	1.29 (0.74, 2.21)	1.38 (0.84, 2.28)	1	1	1
Giltay	14	221	10	200	1.27 (0.55, 2.92)	0.2367	0.4254	1.27 (0.51, 3.26)	1.27 (0.55, 2.92)	1	0	0
Goldman	0	150	49	3321	-	-	-	(0.00, 1.75)	-	0	1	1
Hennekens	83	10747	3271	381442	0.90 (0.72, 1.12)	-0.1047	0.1116	0.90 (0.71, 1.12)	1.30 (1.05, 1.62)	0	0	0
Laing	3	27	202	2193	1.21 (0.36, 4.01)	0.1876	0.6130	1.21 (0.23, 3.97)	2.27 (0.67, 7.71)	0	1	1
Nyren	20	7406	8	3334	1.13 (0.50, 2.56)	0.1181	0.4188	1.13 (0.47, 2.96)	-	1	1	1
Sanchez- Guerrero*	29	1151	4541	81264	0.45 (0.31, 0.65)	-0.7965	0.1886	0.45 (0.30, 0.65)	-	1	0	1

Schusterman	1	249	1	352	1.41 (0.09, 22.71)	0.3462	1.4166	1.41 (0.02, 111.28)	1.08 (0.10, 17.20)	1	1	1
Teel	0	24	3	1553	-	-	-	(0.00, 161.57)	-	0	1	1
Wells	11	198	2	70	1.94 (0.42, 8.99)	0.6650	0.7812	1.94 (0.41, 18.45)	1.16 (0.15, 9.04)	1	0	1

*These numbers exclude the 516 women diagnosed with definite CTD: by medical record review.

¹All types of implants were included.

²Only cases in which disease followed implant were included when that information was available.

³Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) confidence limits.

⁴Obtained with the Exact statistical program.

⁵Reported by author.

⁶1 if cohort, 0 if not.

⁷1 if by medical record validation, 0 if not.

⁸1 if data on disease diagnosis collected <1992 in at least 90% of the cases, 0 if not.

Table D.8 Summary Unadjusted Odds Ratios and Tests of Homogeneity for All CTDs Combined, Specific CTDs, and Other Autoimmune/Rheumatic (A/R) Conditions

Disease (No. of Studies)	Summary Odds Ratio Estimates ¹			Tests of Homogeneity ²	
	Mantel- Haenszel (95% CI) ³	Conditional MLE (95% CI) ⁴	Unconditional MLE (95% CI) ⁵	B-D χ^2 (df), p	Zelen's exact p
Definite CTDs combined (16)	0.69 (0.62, 0.78)	-	0.69 (0.62, 0.78)	22.19 ₍₁₅₎ , p = 0.10	-
RA (10)	0.62 (0.52, 0.73)	-	0.62 (0.53, 0.74)	12.92 ₍₉₎ , p = 0.17	-
SLE (8)	0.63 (0.45, 0.86)	0.63 (0.44, 0.86)	0.63 (0.45, 0.86)	7.28 ₍₇₎ , p = 0.40	0.24
SSc (12)	0.74 (0.50, 1.11)	0.73 (0.46, 1.10)	0.73 (0.48, 1.10)	16.65 ₍₁₁₎ , p = 0.12	0.10
Sjögren's syndrome (8)	1.10 (0.77, 1.58)	1.10 (0.74, 1.58)	1.10 (0.77, 1.57)	4.58 ₍₇₎ , p = 0.71	0.56
DM / PM (6)	0.90 (0.58, 1.40)	0.90 (0.55, 1.39)	0.90 (0.58, 1.39)	2.64 ₍₅₎ , p = 0.76	0.88
Other A/R conditions(12)	0.91 (0.80, 1.04)	0.91 (0.79, 1.04)	0.91 (0.80, 1.04)	40.42 ₍₁₁₎ , p <0.001	-

¹Obtained with Exact statistical software.

²Obtained with Exact statistical software; B-D = Breslow-Day χ^2 homogeneity test. The χ^2 values were calculated using moments from the unconditional model for definite CTDs combined and RA. The other χ^2 values were calculated using moments from the exact (conditional) model.

³Robins-Breslow-Greenland (RBG) limits.

⁴Maximum likelihood estimate (MLE), Fisher exact limits.

⁵Cornfield-type limits.

Table D.9 Analysis of Sources of Heterogeneity among Studies of Definite CTDs Combined

Studies Included (No.)	Unadjusted Summary OR ² (95% CI)	Cond MLE ¹ (Fisher 95% CI)	Tests of homogeneity ¹	
			B-D p-value	Zelen's exact p
All studies (16)	0.69 (0.62, 0.78)	-	0.10	-
Cohort studies (6)	0.83 (0.58, 1.19)	0.83 (0.56, 1.21)	0.32	0.30
Noncohort studies (10) (case-control & cross-sectional)	0.68 (0.60, 0.77)	-	0.10	-
Medical record validation ³ (14)	0.64 (0.49, 0.83)	0.65 (0.49, 0.84)	0.05	-
Self-report (1)	0.70 (0.62, 0.80)	-	-	-
Information on diagnosis <1992 (12)	0.62 (0.47, 0.83)	0.63 (0.46, 0.83)	0.02	-
Information on diagnosis ≥1992 ³ (3)	0.70 (0.62, 0.80)	-	0.96	-
All studies, excluding Friis (15)	0.68 (0.60, 0.77)	-	0.31	-

¹Obtained with Exact statistical software; B-D = Breslow-Day χ^2 homogeneity test statistic.

²Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) limits, obtained with Exact statistical software.

³Information on validation and year of data collection for disease diagnosis is missing for 1 study.

Table D.10 Analysis of Sources of Heterogeneity among Studies of Systemic Sclerosis

Studies Included (No.)	Unadjusted Summary OR ² (95% CI)	Cond MLE ¹ (Fisher 95% CI)	Tests of homogeneity ¹	
			B-D p-value	Zelen's exact p
All studies (12)	0.74 (0.50,1.11)	0.73 (0.46, 1.10)	0.12	0.10
Cohort studies (5)	0.16 (0.03,0.98)	0.09 (0.00, 0.67)	<0.001	0.04
Noncohort studies (7) (case-control & cross-sectional)	0.84 (0.56, 1.27)	0.84 (0.53, 1.27)	0.56	0.64
Medical record validation (11)	0.60 (0.36, 0.98)	0.58 (0.32, 0.98)	0.13	0.11
Self-report (1)	1.13 (0.60, 2.12)	1.13 (0.54, 2.11)	-	-
Information on diagnosis <1992 (10)	0.65 (0.39, 1.08)	0.64 (0.36, 1.08)	0.23	0.21
Information on diagnosis ≥1992 (2)	0.93 (0.50,1.75)	0.93 (0.42, 1.79)	0.03	0.06
All studies, excluding Friis (11)	0.72 (0.48, 1.08)	0.70 (0.44,1.08)	0.14	0.14

¹Obtained with Exact statistical software; B-D = Breslow-Day χ^2 homogeneity test statistic.

²Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) limits, obtained with Exact statistical software.

Table D.11 Analysis of Sources of Heterogeneity among Studies of Other Autoimmune/ Rheumatic Conditions

Studies Included (No.)	Unadjusted Summary OR ² (95% CI)	Cond MLE ¹ (Fisher 95% CI)	Tests of homogeneity ¹	
			B-D p-value	Zelen's exact p
All studies (12)	0.91 (0.80, 1.04)	0.91 (0.79, 1.04)	<0.001	-
Cohort studies (8)	0.92 (0.78, 1.09)	0.92 (0.78, 1.09)	<0.001	-
Noncohort studies (4) (case-control & cross-sectional)	0.89 (0.72, 1.10)	0.89 (0.71, 1.10)	0.52	0.35
Medical record validation (8)	1.22 (0.99, 1.50)	1.23 (0.99, 1.53)	0.04	0.03
Self-report (4)	0.75 (0.62, 0.90)	0.75 (0.62, 0.90)	0.004	0.003
Information on diagnosis <1992 (9)	0.95 (0.79, 1.14)	0.95 (0.79, 1.14)	<0.001	-
Information on diagnosis ≥1992 (3)	0.87 (0.72, 1.06)	0.87 (0.71, 1.06)	0.29	0.29
All studies, excluding Friis & Sanchez-Guerrero (10)	0.92 (0.78, 1.09)	0.92 (0.77, 1.10)	0.52	-

¹Obtained with Exact statistical software; B-D = Breslow-Day χ^2 homogeneity test statistic.

²Mantel-Haenszel estimate with Robins-Breslow-Greenland (RBG) limits, obtained with Exact statistical software.

Appendix E.
Adjusted Analysis

Table E.1 Adjusted Relative Risk Estimates for Definite CTDs Combined—All Types of Implants

Study by First Author	Estimated RR (95% CI)	SE(ln[RR])	Study Weight	Study Weight¹
Burns	0.95 (0.21, 4.36)	0.7774	0.01	0.03
Dugowson	0.41 (0.05, 3.13)	1.0371	0.00	0.02
Edworthy	1.00 (0.45, 2.22)	0.4069	0.02	0.11
Englert	0.52 (0.11, 2.41)	0.7824	0.01	0.03
Friis	-	-	-	-
Gabriel	1.10 (0.37, 3.23)	0.5496	0.01	0.06
Goldman	0.52 (0.29, 0.92)	0.2911	0.04	0.21
Hennekens	1.24 (1.08, 1.41)	0.0656	0.80	-
Hochberg	1.07 (0.53, 2.13)	0.3513	0.03	0.14
Lacey	1.48 (0.34, 6.39)	0.7463	0.01	0.03
Nyren	0.80 (0.50, 1.40)	0.2855	0.04	0.22
Park	0.42 (0.01, 15.63)	1.8453	0.00	0.01
Sanchez-Guerrero	0.60 (0.20, 2.00)	0.6143	0.01	0.05
Strom	-	-	-	-
Teel	0.90 (0.40, 2.30)	0.4787	0.02	0.08
Wolfe	1.35 (0.30, 6.06)	0.7661	0.01	0.03

¹Excluding Hennekens.

Table E.2 Adjusted Relative Risk Estimates for Rheumatoid Arthritis—All Types of Implants

Study by First Author	Estimated RR (95% CI)	SE(ln[RR])	Study Weight	Study Weight¹
Dugowson	0.41 (0.05, 3.13)	1.0371	0.01	0.03
Edworthy	1.44 (0.50, 4.15)	0.5400	0.03	0.12
Friis	-	-	-	-
Gabriel	-	-	-	-
Goldman	0.84 (0.41, 1.62)	0.3351	0.07	0.32
Hennekens	1.18 (0.97, 1.43)	0.0980	0.79	-
Nyren	1.30 (0.70, 2.50)	0.3336	0.07	0.32
Park	0.42 (0.01, 15.63)	1.8453	0.00	0.01
Sanchez-Guerrero	0.90 (0.30, 2.60)	0.5413	0.03	0.12
Wolfe	1.35 (0.30, 6.06)	0.7661	0.01	0.06

¹Excluding Hennekens.

Table E.3 Adjusted Relative Risk Estimates for Systemic Lupus Erythematosus—All Types of Implants

Study by First Author	Estimated RR (95% CI)	SE (ln[RR])	Study Weight	Study Weight¹
Edworthy	0.94 (0.17, 5.23)	0.8757	0.03	0.14
Friis	-	-	-	-
Goldman	0.14 (0.02, 1.23)	1.1087	0.02	0.09
Hennekens	1.15 (0.81, 1.63)	0.1780	0.77	-
Nyren	0.70 (0.30, 1.60)	0.4218	0.14	0.59
Sanchez-Guerrero	-	-	-	-
Strom	-	-	-	-
Teel	0.80 (0.20, 3.40)	0.7382	0.04	0.19

¹Excluding Hennekens.

Table E.4 Adjusted Relative Risk Estimates for Systemic Sclerosis—All Types of Implants

Study by First Author	Estimated RR (95% CI)	SE (ln[RR])	Study Weight	Study Weight¹
Burns	0.95 (0.21, 4.36)	0.7774	0.07	0.13
Edworthy	-	-	-	-
Englert	0.52 (0.11, 2.41)	0.7824	0.07	0.12
Friis	-	-	-	-
Gabriel	-	-	-	-
Goldman	-	-	-	-
Hennekens	1.84 (0.98, 3.46)	0.3222	0.42	-
Hochberg	1.07 (0.53, 2.13)	0.3513	0.36	0.61
Lacey	1.48 (0.34, 6.39)	0.7463	0.08	0.14
Nyren	-	-	-	-
Sanchez- Guerrero	-	-	-	-
Teel	-	-	-	-

¹Excluding Hennekens.

Table E.5 Adjusted Relative Risk Estimates for Sjögren's Syndrome—All Types of Implants

Study by First Author	Estimated RR (95% CI)	SE (ln[RR])	Study Weight	Study Weight ¹
Edworthy	0.99 (0.17, 5.94)	0.9142	0.04	0.19
Friis	-	-	-	-
Gabriel	-	-	-	-
Goldman	1.46 (0.36, 6.39)	0.7532	0.06	0.28
Hennekens	1.49 (0.97, 2.28)	0.2170	0.77	-
Nyren	-	-	-	-
Sanchez- Guerrero	-	-	-	-
Teel	1.60 (0.50, 4.70)	0.5498	0.12	0.53

¹Excluding Hennekens.

Table E.6 Adjusted Relative Risk Estimates for Dermatomyositis/Polymyositis—All Types of Implants

Study by First Author	Estimated RR (95% CI)	SE (ln[RR])	Study Weight	Study Weight ¹
Friis	-	-	-	-
Goldman	-	-	-	-
Hennekens	1.52 (0.97, 2.37)	0.2266	1.0	-
Nyren	-	-	-	-
Sanchez-Guerrero	-	-	-	-
Teel	-	-	-	-

¹Excluding Hennekens.

**Table E.7 Adjusted Relative Risk Estimates for Other Autoimmune/Rheumatic Conditions—
All Types of Implants**

Study by First Author	Estimated RR (95% CI)	SE (ln[RR])	Study Weight	Study Weight¹
Edworthy	-	-	-	-
Friis	-	-	-	-
Gabriel	1.38 (0.84, 2.28)	0.2562	0.11	0.28
Giltay	1.27 (0.55, 2.92)	0.4248	0.04	0.10
Goldman	-	-	-	-
Hennekens	1.30 (1.05, 1.62)	0.1123	0.59	-
Laing	2.27 (0.67, 7.71)	0.6238	0.02	0.05
Nyren	-	-	-	-
Sanchez- Guerrero	0.70 (0.50, 1.00)	0.1820	0.22	0.55
Schusterman	1.08 (0.10, 17.20)	1.4122	0.00	0.01
Teel	-	-	-	-
Wells	1.16 (0.15, 9.04)	1.0476	0.01	0.02

¹Excluding Hennekens.

Table E.8 Adjusted Relative Risk Estimates for Connective Tissue Diseases in Women with Silicone Gel-Filled Breast Implants

Disease/Study by First Author	Estimated RR, (95% CI)	SE(In[RR])	Study Weight
Definite CTD Combined			
Burns	1.30 (0.27, 6.23)	0.7995	0.14
Edworthy	1.00 (0.45, 2.22)	0.4069	0.52
Englert	0.52 (0.11, 2.41)	0.7824	0.14
Lacey	1.01 (0.13, 8.15)	1.0653	0.08
Park	0.42 (0.01, 15.63)	1.8453	0.03
Sanchez-Guerrero	0.30 (0.00, 1.90)	0.9417	0.10
Rheumatoid Arthritis			
Edworthy	1.44 (0.50, 4.15)	0.5400	0.70
Park	0.42 (0.01, 15.63)	1.8453	0.06
Sanchez-Guerrero	0.40 (0.10, 2.40)	0.9142	0.24
Systemic Lupus Erythematosus			
Edworthy	0.94 (0.17, 5.23)	0.8757	1.0
Scleroderma			
Burns	1.30 (0.27, 6.23)	0.7995	0.38
Englert	0.52 (0.11, 2.41)	0.7824	0.40
Lacey	1.01 (0.13, 8.15)	1.0653	0.22
Sjögren's Syndrome			
Edworthy	0.99 (0.17, 5.94)	0.9142	1.0
Other A/R Conditions			
Giltay	1.27 (0.55, 2.92)	0.4248	0.18
Sanchez-Guerrero	0.60 (0.40, 0.90)	0.2069	0.77
Schusterman	1.08 (0.10, 17.20)	1.4122	0.02
Wells	1.16 (0.15, 9.04)	1.0476	0.03