

Supplementary File 4. Summary of studies reporting on the association between breast implants and risk of mixed, undifferentiated or combinations of connective tissue diseases

Study (Year)	% in silicone	Implant group, n/N*	Comparator group, n/N*	Measure of effect (95% CI)	Follow-up, y	Adjustments	Notes	NOS	\$
Cohort studies comparing with other cosmetic surgeries and breast reduction surgeries									
Fryzek et al. (2007)	>84%	21/2761	69/8807	HR 1.3 (0.9-1.9) (SSc,Sjö,SLE,RA,DM/PM)	13.4	Age, calendar year, clinic, time since operation	Danish national hospital registry + private clinics	9	NR
Cohort studies comparing with other cosmetic surgeries									
Brinton et al. (2004)	50%	24/7234	4/2138	RR 2.0 (0.7-5.4) (SSc,Sjö,RA) (confirmed)	12.1	Age, race, calendar period	18 plastic surgery practices	9	NR
		310/7234	54/2138	RR 2.2 (1.6-3.0) (self-reported)				8	
Englert et al. (2001)	100%	53/458	72/687	RR 1.10 (0.79-1.54) **	15	Age, clinic, calendar year	16 plastic surgery practices	9	Yes
Cohort studies comparing with breast reduction surgeries									
Nyren et al. (1998)	56%	16/7442	11/3353	RR 0.8 (0.5-1.4) (SSc,Sjö,SLE,RA,DM)	8.0	Age, follow-up	Swedish national inpatient registry	8	Yes
Breiting et al. (2004)	100%	9/190	11/186	OR 0.8 (0.3-1.9) (SSc,Sjö,SLE,RA,DM,PM) (self-reported)	19	Age	2 hospital/private plastic surgery practices	5	Yes
Cohort studies comparing with women from the community without breast implants									
Watad et al. (2018)	100%	6510/24651	22634/98604	OR 1.22 (1.18-1.26) (prevalence)**	9.7	Age, SES, smoking, breast cancer	Israeli healthcare database	8	No
		193/1797	569/7109	HR 1.45 (1.21-1.73) (incidence)**				9	
Gabriel et al. (1994)	85%	5/749	10/1498	RR 1.10 (0.37-3.23)**	7.8	Age, calendar	Tertiary care and affiliated centers	8	No
Barbosa et al. (2021)	NR	14/452 (0% C)	21/452	OR 0.66 (0.33-1.31) (RA, SLE)	NR	Age, social, health care use, follow-up, comorbidities, medication use	Military healthcare system; prevalent not excluded?	7	No
		10/452 (0% C)	13/452	OR 0.76 (0.33-1.76) (RA, SLE)	≥ 5 visits			8	
Breiting et al. (2004)	100%	9/190	5/149	OR 1.4 (0.5-4.3) (self-reported SSc,Sjö,SLE,RA,DM,PM)	19	Age	2 plastic surgery practices	5	Yes
Cohort studies comparing with female health professionals without breast implants									
Sanchez-Guerrero et al. (1995)	74%	3/1183	513/86318	RR 0.6 (0.2-2.0) (SSc,Sjö,SLE, RA,DM,PM,MCTD)	9.9	Age	Nurses' Health Study	7	Yes
		0/1183	0/86318	RR not calculable (MCTD)					
Hennekens et al. (1996)	NR	231/10830	11574/384713	HR 1.24 (1.08-1.41) (self-reported SSc,Sjö,SLE,RA,DM, PM,other CTD)	<4≥10	Age, calendar year, cancer, implant duration	Women's Health Study	6	Yes
		83/10830	3271/384713	HR 1.30 (1.05-1.62) (self-reported other CTD, MCTD)					
Lee et al. (2011)	70%	21/3950	74/19897	HR 1.21 (0.68-2.15) (SSc,Sjö, SLE, RA,DM,PM,MCTD,other)	3.6	Age, body mass index, smoking, hormone, cancer	Women's Health Study	5	Yes
		7/3950	30/19897	HR 1.46 (0.62-3.45) (MCTD, other)					
Cohort study comparing with post-mastectomy reconstructive surgery without implants									
Greenland et al. (2000)	NR	19/31820 person-y	NR	RR 4.11 (2.44-6.91) (UCTD)	Limited	Age, sex, time since surgery	Medicare (age ≥ 65); prevalent?	4	Yes
Cohort studies comparing with national rates									
Fryzek et al. (2007)	>84%	26/2761 (4 not confirmed)	NR	SIR 1.4 (0.9-2.0) (SSc,Sjö,SLE,RA,DM/PM)	13.4	Age, sex, calendar period	Danish national hospital registry + private clinics	9	NR
		5/2761		SIR 1.8 (0.6-4.1) (CTD not otherwise specified)					
Nyren et al. (1998)	56%	29/7442 (12 prevalent, 2 misclassified)	NR	SHR 1.1 (0.8-1.6) (SSc,Sjö,SLE,RA,DM) (includes prevalent and misclassified)	8.0	Age, sex, calendar year	Swedish national inpatient registry	7	Yes
Case-control studies									
Laing et al. (2001)	100%	3/205	26/2,095	OR 2.22 (0.65-7.57) (UCTD)	NR	Age, birth year	Community controls	8	Yes
Goldman et al. (1995)	85%	3/334 (2 prevalent)	138/3508	OR 0.25 (0.09-0.79) (SSc,Sjö,SLE,DM/PM,MCTD)	8.3 (cases)	Age, income, period	Rheumatology practice controls, no CTD or RA	6	Yes
Williams et al. (1999)	100%	2/323	8.08/1,000 women	Prevalence OR: 1.15 (0.23-3.41) (early CTD)	NR	Age, sex, race, geography	National rates (United States)	5	No

*For case-control studies: Case group (n breast implants/N); Control group (n breast implants/N); **Englert et al. (2001): Any CTD or CTD-related outcome measure, including positive ANA, abnormal nailfold capillaroscopy, self-reported digital vasospasm, sicca and/or validated RA, SLE or SSc with onset after index surgery. Watad et al. (2018): any autoimmune/rheumatic disorder, including ankylosing spondylitis, fibromyalgia/chronic fatigue syndrome, hypothyroidism, hyperthyroidism, multiple sclerosis, psoriasis, psoriatic arthritis, RA, sarcoidosis, Sjö, SLE, SSc and vasculitis. Gabriel et al. (1994): any rheumatic disease, including SSc, Sjö, SLE, RA, DM/PM, systemic vasculitis, polymyalgia rheumatica, polychondritis, ankylosing spondylitis and inflammatory bowel disease-related arthritis. CI: confidence interval; CTD: connective tissue disease; DM: dermatomyositis; HR: hazard ratio; MCTD: mixed connective tissue disease; N/A: not applicable; NOS: Newcastle-Ottawa scale; NR: not reported; OR: odds ratio; PM: polymyositis; RA: rheumatoid arthritis; RR: relative risk; SES: socioeconomic status; SHR: standardized hospitalization ratio; SIR: standardized incidence ratio; Sjö: Sjögren's syndrome; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; UCTD: undifferentiated CTD; y: years; \$: potential financial or other conflict of interest.