

**Supplementary File 8. Summary of cross-sectional studies reporting on the association between biomarkers and risk of rheumatic disease among breast implant users**

**A) CLASSICAL AUTOANTIBODIES**

As expected, antinuclear antibodies were generally more frequent in patients with connective tissue diseases compared to asymptomatic patients, but not more frequent in patients with undefined rheumatic symptoms.

Study (Year) Location, study period	Biomarker	Rheumatic disease, symptom or severity	No. with biomarker / No. with outcome	Measure of effect	Time from implant to testing	Notes	NOS	\$
<b>Claman et al. (1994)</b> United States, NR	ANA ≥1:256	No symptoms (n=19)	19%	Similar	10.0 years (mean)	- Consecutive patients recruited through media (if no symptoms) or referred by plastic surgeons, primary care physicians, rheumatologists, news media or support group - Multiple logistic regression adjusted for age, number / duration / indication / type of BI, possible leak: group status significantly correlated with ANA positivity (OR NR)	6	Yes
		Symptoms (fatigue, arthralgia, myalgia) without definite CTD (n=82)	26%		11.9 years (mean)			
		Autoimmune disease (n=11; 6 scleroderma, 2 SLE, 2 RA, 1 Sjögren)	64%	P = 0.01 compared to other groups combined	15.3 years (mean)			
<b>Bridges et al. (1993)</b> United States, 1990-1992	ANA ≥1:80 / RF	No symptoms (n=12) (controls)	8% / 0%	Reference	9.4 years (mean)	- Consecutive patients referred to rheumatologists for rheumatic symptoms	5	No
		Joint and muscle pain (n=95)	15% / 9%	P > 0.2				
		Joint swelling (n=32)	22% / 9%	P > 0.15				
		Connective tissue disease (n=29; 14 scleroderma, 3 SLE, 1 MCTD, 1 polymyositis, 10 early CTD)	45% / 17%	P > 0.2 for RF				
<b>Zandman-Goddard et al. (1999)</b> Israel, NR	Autoantibodies to histones / SSA / SSB / RNP / Scl-70 / cardiolipin / phosphatidyl-serine / GBM	Asymptomatic (n=86)	4% / 3% / 13% / 1% / 0% / 2% / 3% / 0%	-	8.2 years (mean)	- Asymptomatic: recruited through advocate dealing with BI liabilities - Symptomatic: 1 Sjögren, 1 RA, 1 scleroderma, 1 SLE, 6 autoimmune syndromes, fatigue, arthralgia, myalgia, fibromyalgia, morning stiffness, polyarthritis, Raynaud, memory loss	5	No
		Symptomatic (n=116)	9% / 8% / 26% / 24% / 12% / 19% / 5% / 0%	-	15.0 years (mean)			
		Multiple autoantibodies	Asymptomatic Symptomatic	4% 45%	- -			
<b>De Jong et al. (2004)</b> Netherlands, May-Nov 1998	ANA ≥1:40	Limited symptoms	16/65 (25%)	-	17-20 years (mean)	- Symptomatic SBI recipients from national consumer registry - 62% had explanted SBI - Symptoms include fatigue, arthralgias, myalgias, sicca, morning stiffness and others	4	NR
		Mild symptoms	0/8 (0%)	-				
		Moderate symptoms	2/4 (50%)	-				
		Advanced symptoms	1/7 (14%)	-				
<b>Press et al. (1992)</b> United States, 1989-1992	ANA	Chronic fatigue, arthralgias, myalgias (n=13)	7 ANA+/13 (54%) Low titer (1/80-1/160) in 6/7, no antigen specificities	-	>9.8 years (mean)	- Referred or self-referred to rheumatology clinic for rheumatic symptoms	4	No
		Connective tissue disease (n=11; 6 scleroderma, 2 MCTD, 1 SLE, 2 RA)	10 ANA+/11 (91%) High titer (1/320-1/640) in 9/10, antigen specificities in 7/10	-	>8.8 years (mean)			
<b>Tenenbaum et al. (1997)</b> United States, Apr-Sept 1994	ANA ≥1:40	Limited symptoms	6/34 (18%)	Reference	NR	- 50% of consecutive women with SBI from rheumatology center - Symptoms include fatigue, arthralgias, myalgias, sicca, morning stiffness and others	3	No
		Mild symptoms	5/26 (19%)	NS				
		Moderate symptoms	0/16 (0%)	NS				
		Advanced symptoms	6/19 (32%)	NS				
		SLE, systemic sclerosis or Sjögren's	5/15 (33%)	NS				
<b>Bridges et al. (1996)</b> United States, NR	ANA ≥1:80 / 1:160 / 1:320 / 1:640 / ≥1:1280 / ENA (SSA, SSB, Jo1, Scl-70, RNP, Sm, dsDNA)	Asymptomatic (n=25)	28% / 8% / 8% / 4% / 0% / 0%	-	NR	- Symptomatic: consecutive patients referred to rheumatology and pulmonology for symptoms (not further specified) - Asymptomatic: matched on age	3	No
		Symptomatic (n=500)	30% / 12% / 3% / 3% / 7% / 4.8%	-				
<b>Silverman et al. (1996)</b> United States, 1993-1994	ANA >1:80 / >1:160 / mean titer	No symptoms (n=37)	3% / 0% / -	-	NR	- Consecutive patients from 5 rheumatology practices referred by self or attorneys	3	No
		Rheumatic symptoms (n=3184)	35% / 17.6% / 225					
		Fibromyalgia (n=200)	28% / 12.8% / 114					
<b>Karlson et al. (1999)</b> United States, 1989-1992	Antibodies to ssDNA	No connective tissue disease (n=200)	41%	P = 0.02	11.9 years (mean)	- Women in Nurses' Health Study with SBI and available samples (random selection)	3	Yes
		Connective tissue disease (n=17)	12%		NR			

<b>Brunner et al. (1996)</b> Germany, NR	ANA ≥1:80	Arthralgia, stiffness, joint swelling (n=33/239)	–	NS for symptoms correlation	Majority >5 years	- Patients receiving BI in hospital center, 41% response rate	3	NR
<b>Contant et al. (2000)</b> Netherlands, 1990-1995	ANA (titer NR)	Sjögren's symptoms	5/10 ANA+; 26/53 ANA-	–	15.3 months (median)	- Women with silicone BI reconstruction post-mastectomy - Self-reported symptoms	2	NR
		At least 1 of joint pain, swelling or stiffness or Raynaud's	8/10 ANA+; 32/53 ANA-	–				
		At least 2 of above	3/10 ANA+; 17/53 ANA-	–				

## B) IMMUNOLOGICAL ASSAYS AGAINST SILICONE COMPONENTS

Some studies reported an association between antibodies against silicone components and the presence or severity of rheumatic symptoms, but results have not been replicated and studies were limited by non-representative populations, lack of temporality in regard to symptom onset and lack of adjustment for potential confounding variables (such as duration of breast implants).

Study (Year) Location, study period	Biomarker	Rheumatic disease, symptom or severity	No. with biomarker / No. with outcome	Measure of effect	Time from implant to testing	Notes	NOS	\$
<b>Jensen et al. (2003)</b> Denmark, 1997-1999	Anti-silicate antibody	Soft tissue rheumatism (n=27)	Median level: 4 Range: 1-167	$r_s = -0.09$ , $p=0.06$	>16 years (median)	- Women in national hospital registry with soft tissue rheumatism after SBI surgery - Comparator matched on age and date of BI surgery	7	NR
		No soft tissue rheumatism (n=23)	Median level: 7 Range: 1-21	$r_s = 0.11$ , $p=0.14$				
<b>Zandman-Goddard et al. (1999)</b>	Collagen I/II/IV	Asymptomatic (n=86)	7% / 9% / 3%	–	8.2 years (mean)	Cf. Above	5	No
		Symptomatic (n=116)	12% / 10% / 13%	–	15.0 years (mean)			
<b>De Jong et al. (2004)</b>	Anti-polymer antibodies	Limited symptoms	7/65 (11%)	–	17-20 years (mean)	Cf. Above	4	NR
		Mild symptoms	1/8 (13%)	–				
		Moderate symptoms	0/4 (0%)	–				
		Advanced symptoms	0/7 (0%)	–				
<b>Tenenbaum et al. (1997)</b>	Anti-polymer antibodies	Limited symptoms	1/34 (3%)	Comparator	NR	Cf. Above	3	No
		Mild symptoms	2/26 (8%)	NS				
		Moderate symptoms	7/16 (44%)	$P < 0.01$				
		Advanced symptoms	13/19 (68%)	OR 71.5 (7.7- 665)				
		SLE, systemic sclerosis or Sjögren's	3/15 (20%)	NS				
<b>Kossovsky et al. (1995)</b> United States, NR	Anti-SSAA(x)	Arthritis	70%/34 SSAA+; 54%/199 SSAA-	NS	10-12 years (mean)	- Self-referred symptomatic SBI	3	Yes
		Myalgia	70%/10 SSAA-fbgn+; 41%/199 SSAA-	NS				
<b>Kossovsky et al. (1996)</b> United States, NR	Anti-SSAA(fn) / Anti-SSAA(col1) / Anti-SSAA(col3) / Anti-SSAA(fbgn)	Symptomatic (n=310)	17.4% / 12.9% / 7.4% / 7.1%	$P < 0.005$ / NS / $P < 0.005$ / $P < 0.005$	11 years (mean)	- Serum samples submitted by collaborating physicians - Symptoms not defined	2	Yes
		Asymptomatic (n=11)	0% / 9% / 0% / 0%					
<b>Smalley et al. (1995)</b> United States, NR	Silicone lymphocyte stimulation index (# x control mean)	Symptomatic	171/942 (18%) (2.5- 5x) 316/942 (34%) (5-10x) 373/942 (40%) (>10x)	–	NR	- Symptoms include fatigue, flu- like symptoms, arthralgia, myalgia, sicca, Raynaud and others	2	NR
		Asymptomatic	19/34 (56%) (2.5-10x) 3/34 (9%) (>10x)	–				
<b>Shen et al. (1996)</b> United States, NR	Anti-silicate antibodies	Symptomatic	12/40 (30%)	–	NR	- Symptoms include fatigue, fibromyalgia, insomnia, skin disorders, joint pains, muscle cramps, arthritis, allergies, arrhythmia - Remnant samples from previous studies	2	NR
		Asymptomatic	8/91 (9%)	–				

### C) IMMUNOPATHOLOGICAL STUDIES

One study reported no association between breast and capsular tissue silicone levels and presence of CTD signs or symptoms.

Study (Year) Location, study period	Biomarker	Rheumatic disease, symptom or severity	No. with biomarker / No. with outcome	Measure of effect	Time from implant to testing	Notes	NOS	\$
<b>Weinzweig et al. (1998)</b> United States, 1990-1995	Breast tissue silicon	No symptoms or signs of CTD	Median level: 33 Range: 5-144	P = 0.489	9.8-13.9 years (mean)	- SBI removal due to media-related fear, rupture, contracture or asymmetry - Signs of CTD: diagnosis or physical exam findings of SLE, vasculitis, scleroderma or rheumatoid arthritis; or positive ANA or rheumatoid factor. - 10 patients with signs of CTD included: 3 SLE, 2 rheumatoid arthritis, 1 scleroderma, 1 Raynaud's	3	NR
		Symptoms, no signs of CTD	Median level: 26 Range: 11-216					
		Symptoms and signs of CTD	Median level: 53 Range: 14-297					
	Capsular tissue silicon	No symptoms or signs of CTD (n=13)	Median level: 5344 Range: 410-45,532	P = 0.532				
		Symptoms, no signs of CTD (n=6)	Median level: 13,062 Range: 749-41,844					
		Symptoms and signs of CTD (n=10)	Median level: 5410 Range: 146-28,474					

### D) GENETIC STUDIES

In a case-control study, O'Hanlon et al. identified an immunogenetic profile for myositis developing after silicone breast implantation, distinct from the profile in autoimmune myositis and that in breast implant users without myositis. This suggests that some susceptibility genes may contribute to the development of myositis among breast implant users. In a cross-sectional study, Young et al. identified an immunogenetic profile common to fibromyalgia patients with and without breast implants, suggesting that susceptibility genes may contribute to the development of fibromyalgia; however, this study does not demonstrate a contributory role of breast implants in disease development.

Study (Year) Location, study period	Biomarker	Rheumatic disease, symptom or severity	No. with biomarker / No. with outcome	Measure of effect	Time from implant to testing	Notes	NOS	\$
<b>O'Hanlon et al. (2004)</b> United States, NR	HLA-DQA1*0102	MASI (n=37)	54.1%	MASI vs. SIC: OR 2.4 (95% CI 1.18-5.11); MASI vs. IIM: OR 2.6 (95% CI 1.25-5.46)	MASI: 15.1 years (mean); SIC: 18.0 years (mean)	- Case-control study - From collaborating sites or advertisements - MASI: myositis after silicone implants - SIC: silicone implant controls, matched on age, ethnicity, BI duration - IIM: idiopathic inflammatory myopathies (no BI), matched on age, ethnicity	7	No
		SIC (n=555)	32.4%					
		IIM (n=453)	31.1%					
	HLA-DRB1*0301	MASI	18.9%	MASI vs. SIC: OR 0.9 (0.34- 2.24); MASI vs. IIM: OR 0.2 (95% CI 0.08-0.49)				
		SIC	20.0%					
		IIM	53.1%					
	HLA-DQA1*0501	MASI	29.7%	MASI vs. SIC: OR 0.6 (0.26- 1.27); MASI vs. IIM: OR 0.2 (95% CI 0.11-0.54)				
		SIC	41.6%					
		IIM	62.9%					
	HLA-DRB1*EYSTS	MASI	51.4%	MASI vs. SIC: OR 0.8 (0.40- 1.71); MASI vs. IIM: OR 0.3 (95% CI 0.16-0.69)				
		SIC	56.1%					
		IIM	76.3%					
<b>Young et al. (1995)</b> United States, 1992-1994	HLA-DR53 (HLA-DRB4 gene)	Symptomatic (BI)	52/77 (68%)	P = 0.007	Symptom: 1 2.1 years (mean) Asymptomatic: 10.3 years (mean)	- Cross-sectional study - Self-referred to plastic surgery post-mediatisation - Symptomatic: at least 1 of: breast pain, chronic fatigue, upper torso pain, myalgias, arthralgias for >4 months - Asymptomatic: matched on age and BI duration - Fibromyalgia: no BI, matched on age and race, from rheumatology practices - DR53 in strong linkage disequilibrium with DR4/DR7	6	No
		Asymptomatic (BI)	13/37 (35%)					
		Fibromyalgia (no BI)	20/31 (65%)					
		Asymptomatic (no BI)	28/54 (52%)					
	HLA-DR7 (HLA-DRB1 gene)	Symptomatic (BI)	26/77 (34%)	P = 0.046				
		Asymptomatic (BI)	4/37 (11%)					
		Fibromyalgia (no BI)	9/31 (29%)					
		Asymptomatic (no BI)	11/54 (20%)					
	HLA-DR4 (HLA-DRB1 gene)	Symptomatic (BI)	34/77 (44%)	P = 0.188				
		Asymptomatic (BI)	10/37 (27%)					
		Fibromyalgia (no BI)	14/31 (45%)					
		Asymptomatic (no BI)	17/54 (31%)					
HLA-DR1	Symptomatic (BI)	14/77 (18%)	P = 0.048					
	Asymptomatic (BI)	14/37 (38%)						
	Fibromyalgia (no BI)	8/31 (26%)						
	Asymptomatic (no BI)	8/54 (15%)						

ANA: anti-nuclear antibody; Anti-SSAA: antibodies to silicone-associated surface antigens; BI: breast implant; CTD: connective tissue disease; ENA: autoantibodies to extractable nuclear antigens; GBM: glomerular basement membrane; MCTD: mixed connective tissue disease; NOS: Newcastle-Ottawa scale (range 0 to 9); NR or -: not reported; NS: not statistically significant; OR: odds ratio; PM: polymyositis; RA: rheumatoid arthritis; RF: rheumatoid factor; RNP: ribonucleoprotein; rs: correlation with symptom severity; SBI: silicone breast implants; SLE: systemic lupus erythematosus; ssDNA: single-stranded DNA; \$: potential financial or other conflict of interest.