APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

5ª edizione

REUMATOLOGIA E MALATTIE NEOPLASTICHE

CURARE ARTRITI E CONNETTIVITI PREVIENE IL RISCHIO ONCOLOGICO?

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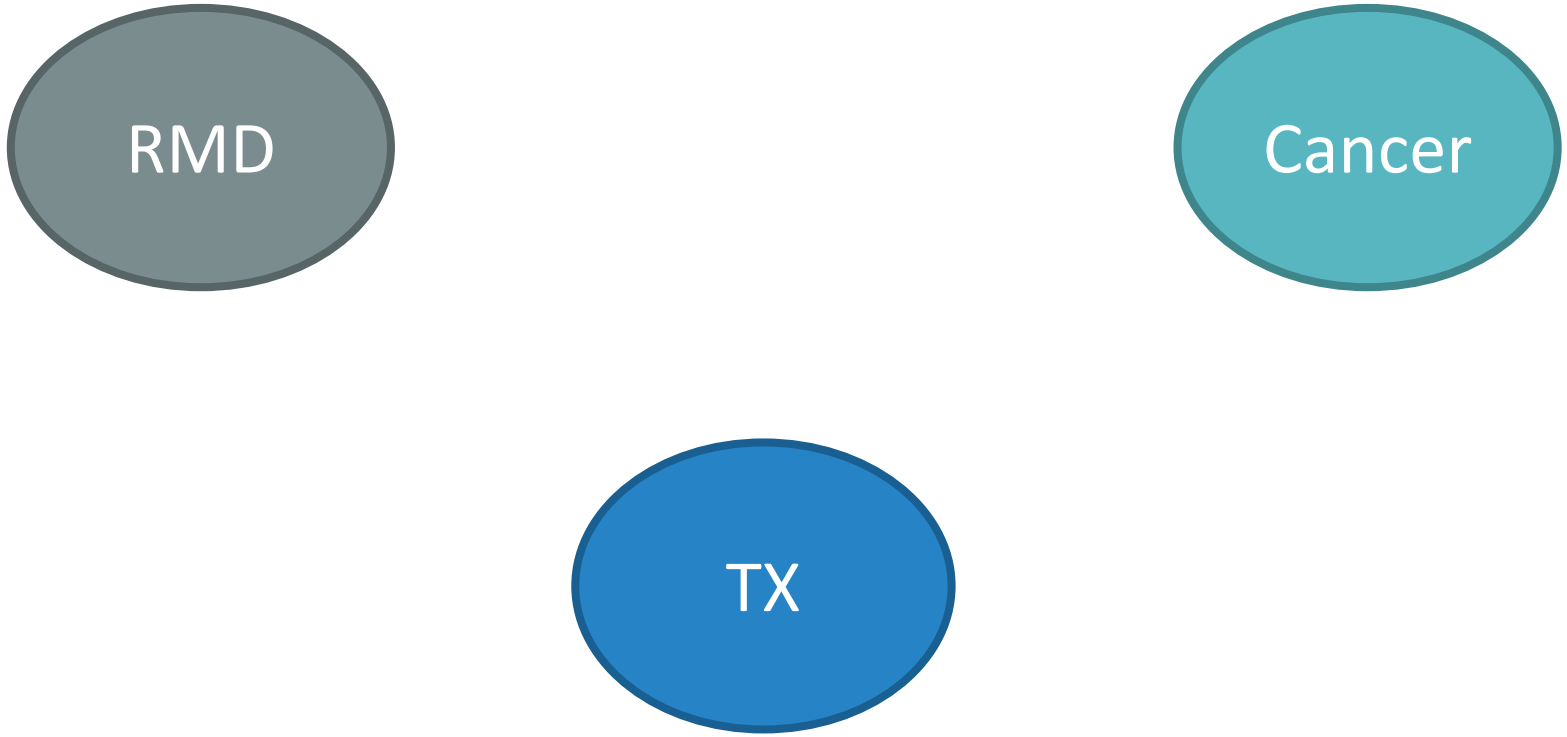
SEZIONE DI REUMATOLOGIA ED EMATOLOGIA - SCUOLA DI SPECIALIZZAZIONE DI REUMATOLOGIA

DIPARTIMENTO DI SCIENZE MEDICHE – DIRETTORE MARCELLO GOVONI

UNIVERSITÀ DEGLI STUDI DI FERRARA

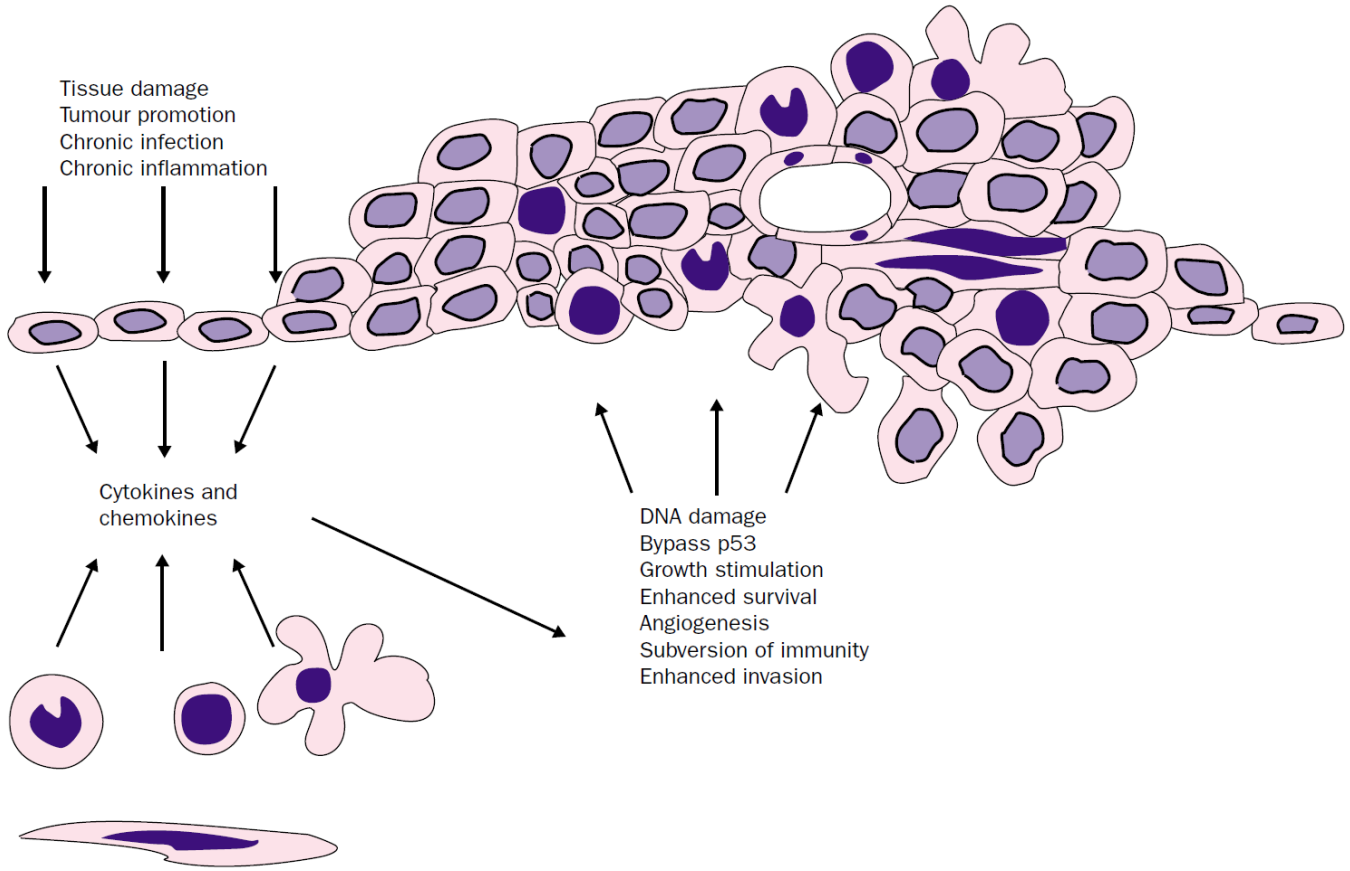
Outline



Causal model

Rationale - Virchow's hypothesis 1863

If genetic damage is the "match that lights the fire" of cancer, some types of inflammation may provide the "fuel that feeds the flames".



Fran Balkwill & Alberto Mantovani, Lancet 2001; 357: 539–45

RMD associated with malignancy

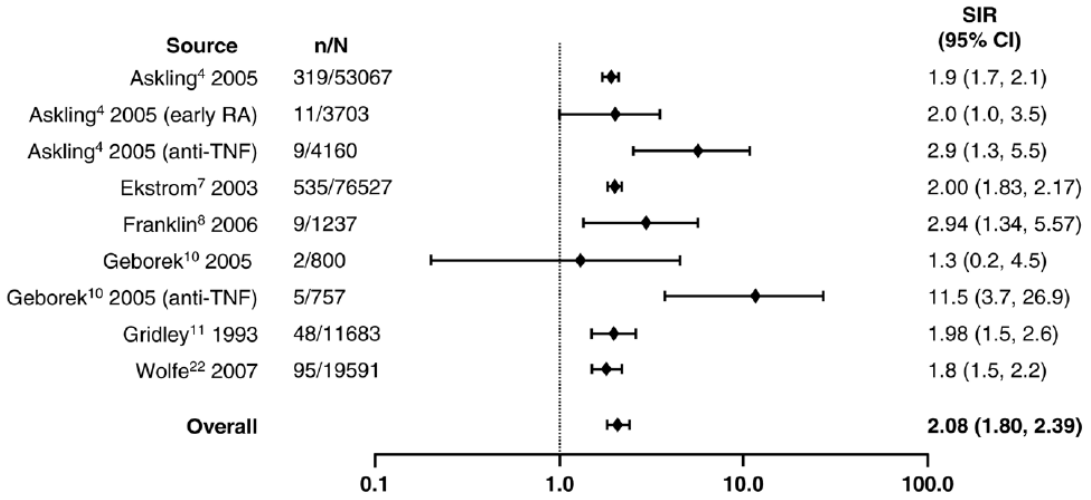
Connective Tissue Disease	Malignancy	Associated Factors	Clinical Alert
Sjögren's syndrome	Lymphoproliferative disorders	Glandular features: lymphadenopathy, parotid or salivary enlargement Extraglandular features: purpura, vasculitis, splenomegaly, lymphopenia, low C4, cryoglobulins	Clues to progression from pseudolymphoma to lymphoma include worsening of clinical features, disappearance of rheumatoid factor, and decline of IgM
Rheumatoid arthritis	Lymphoproliferative disorders	Presence of paraproteinemia, greater disease severity, longer disease duration, immunosuppression, Felty's syndrome	Rapidly progressive; refractory flare in long-standing rheumatoid disease may suggest an underlying malignancy
Systemic lupus erythematosus (SLE)	Lymphoproliferative disorders	—	Non-Hodgkin's lymphoma should be considered in SLE patients who develop adenopathy or masses; lymphoma of the spleen is another cause of splenic enlargement in SLE
Systemic sclerosis (scleroderma)	Alveolar cell carcinoma Nonmelanoma skin cancer Adenocarcinoma of the esophagus	Pulmonary fibrosis, interstitial lung disease Areas of scleroderma and fibrosis in the skin Barrett's metaplasia	Annual chest radiograph after fibrosis is detected Change in skin features or poorly healing lesions should be evaluated If indicated, esophagoscopy and biopsy of distal esophageal constricting lesions
Dermatomyositis	Ovarian, lung, and gastric cancers in Western populations; nasopharyngeal carcinoma in Asian populations	Older age, normal creatinine kinase levels, presence of cutaneous vasculitis; less likely in setting of myositis-specific antibodies	Malignancy evaluation needs to be tailored to individual patient's age, symptoms, and signs

Eric L. Matteson, in Kelley and Firestein's Textbook of Rheumatology, 2-Volume Set, 10th Edition 2017

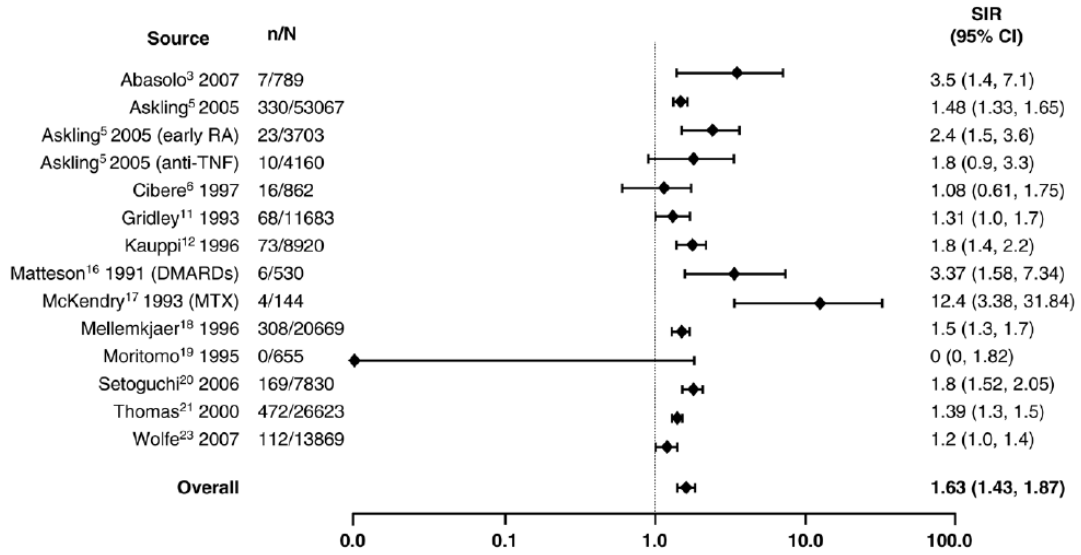
Rheumatoid arthritis and cancer

OVERALL SIR 1.05 (1.01, 1.09)

LYMPHOMA



LUNG CANCER



NH-L 1.95 (1.70, 2.24)

H-L 3.29 (2.56, 4.22)

BREAST 0.77 (0.65, 0.90)

COLORECTAL 0.84 (0.79, 0.90)

Smitten AL, et al. Arthritis Res Ther. 2008;10(2):R45

Rheumatoid arthritis and cancer

OVERALL SIR 1.05 (1.01, 1.09)

LYMPHOMA

LUNG CANCER

RISK FACTORS

Early disease
High disease activity
High cumulative disease activity
Severe disease
Positive Rheumatoid factor
Felty's syndrome
Sjogren's syndrome
Tobacco exposure

NH-L 1.95 (1.70, 2.24)

H-L 3.29 (2.56, 4.22)

BREAST 0.77 (0.65, 0.90)

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Spondyloarthritis and cancer

Author, year	Disease studied	Type of study	No. of AS or PsA patients	No. of lymphoma cases	No. of lymphoma cases with AS	No. of controls	No. of controls with AS	Relative risk or incidence rate (95% CI)[a]
Feltelius et al, 2003	AS	Cohort study	6,621	12	–	–	–	1.3 (0.9–1.9)
Shibata et al, 2004	**AS**	**Cohort study**	**3,262**	**NA**	**–**	**–**	**–**	**2.8 (1.4–5.6)**
Becker et al, 2005	AS	Population-based case–control study	–	710	3	710	1	3.0 (0.1–29)
Askling et al, 2006	AS	Population-based case–control study	–	50,615	23	92,928	41	1.0 (0.6–1.7)
Mellemkjaer et al, 2008	AS	Population-based case–control study	–	25,941	19	58,551	41	1.1 (0.6–1.8)
Anderson et al, 2009	AS	Population-based case–control study	–	33,721	40	122,531	128	1.1 (0.7–1.5)
Rohekar et al, 2008	PsA	Cohort study	665	NA	–	–	–	0.7 (0.3–1.8)
Gross et al, 2011	PsA	Cohort study	2,977	3	–	–	–	0.4 (0.1–1.2)

Psoriatic arthritis and cancer

Toronto cohort 1978-2005
680 Psoriatic arthritis

Malignancy*	SIR (95% CI)†
All cancers	
Both sexes	0.98 (0.77–1.24)
Males	0.81 (0.56–1.15)
Females	1.18 (0.86–1.62)
Hematologic	0.69 (0.26–1.83)
Lung	0.88 (0.46–1.69)
Female breast	1.55 (0.92–2.62)
Prostate	0.65 (0.29–1.44)

*Cancer incidence data were obtained from Cancer Care Ontario and analyzed in 5-year age groups for each calendar year of occurrence from 1978 to 2002. Data on cancer incidence rates for 2003 and 2004 were not available; thus, 2002 data were used.
†95% CI = 95% confidence interval.

Variable	HR (95% CI)
Age at onset of PsA	1.01 (0.99–1.03)
Age at onset of psoriasis	1.00 (0.99–1.02)
ESR, cm/hour	1.13 (1.02–1.25)‡
No. of active joints	1.00 (0.97–1.03)
No. of effused joints	1.04 (1.00–1.09)
No. of clinically deformed joints	0.99 (0.97–1.01)
NSAIDs, past or current use	0.99 (0.48–2.04)
DMARDs, past or current use	1.18 (0.73–1.91)
Immunosuppressive drugs, past or current	1.07 (0.66–1.72)
Methotrexate, past or current use	1.25 (0.77–2.03)
Biologic agents, past or current use	**2.39 (0.58–9.86)**
Intraarticular steroids, past or current use	0.91 (0.56–1.49)

- *95% CI = 95% confidence interval
- †Hazard ratio (HR) reported per 10-cm/hour increase, rather than as 1 mm/hour.
- ‡P = 0.02.

Rohekar S, Arthritis Rheum 2007: 58:82.

Spondyloarthritis and cancer

Toronto cohort 1978-2005
680 Psoriatic arthritis

Malignancy*	SIR (95% CI)†
All cancers	
Both sexes	
Males	
Females	
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RISK FACTORS
None

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•‡P = 0.02.

Rohekar S, Arthritis Rheum 2007: 58:82.

Systemic Lupus Erythematosus and cancer

Author, year	Cancer ascertainment	n	Total cancer SIR (95% CI)	Non-H lymphoma SIR (95% CI)	Other SIR (95% CI)*
Clinical cohort studies					
Pettersson et al, 1992	Tumor registry	205	**2.6 (1.5–4.4)**	**44 (12–111)**	
Sweeney et al, 1995	Self-report	219†	1.4 (0.5–3.0)	10 (0.13–56)	
Abu-Shakra et al, 1996	Chart review	724	1.1 (0.7–1.6)	**5.4 (1.1–16)**	
Ramsey-Goldman et al, 1998	Tumor registry	616	**2.0 (1.4–2.9)**	1.5 (0.02–8.6)	**Lung 3.1 (1.3–7.9)**
Sultan et al, 2000	Chart review	276	1.2 (0.5–2.1)	No cases	
Cibere et al, 2001	Tumor registry	297	**1.6 (1.1–2.3)**	**7.0 (1.9–18)**	**Cervical 8.2 (1.6–23.8)**
Nived et al, 2001	Tumor registry	116	1.5 (0.8–2.6)	**12 (1.3–42)**	
Hospital discharge database studies					
Mellemkjaer et al, 1997	Tumor registry	1,585	**1.3 (1.1–1.6)**	**5.2 (2.2–10)**	**Lung 1.9 (1.1–3.1), Liver 8.0 (2.6–18.6)**
Bjornadal et al, 2002	Tumor registry	5,715	**1.4 (1.3–1.5)**	**2.9 (2.0–4.0)**	**Lung 2.7 (2.1–3.4)**

SLE and cancer

Malignancy	Observed	Expected	SIR	95% CI†
Total cancers	**431**	**373.3**	**1.15**	**1.05–1.27**
Hematologic cancers				
All	**67**	**24.4**	**2.75**	**2.13–3.49**
Non-Hodgkin's lymphoma	**42**			
Hodgkin's lymphoma	5			
Leukemia	7			
Reproductive cancers				
Breast	**73**			
Ovary	9			
Cervix	14			
Vagina	2			
Vulva	2			
Uterus	**6**			
Other cancers				
Lung	**62**			
Hepatobiliary	**10**			
Pancreas	7			
Gastric	9	8.4	1.07	0.49–2.03
Colorectal	40	39.5	1.01	0.72–1.38
Thyroid	9	6.2	1.45	0.66–2.76
Bladder	13	10.5	1.23	0.66–2.11
Prostate	8	11.1	0.72	0.31–1.43
Melanoma	9	9.3	0.97	0.44–1.84

RISK FACTORS

Inflammatory burden
Disease activity
Immunologic defects
overespession of Bcl-2 oncogenes
Viruses (EBV)

Bernatsky S, et al Arthritis Rheum. 2005

Other rheumatic diseases

Poly- dermato-myositis

- The risk of cancer in patients with idiopathic inflammatory myopathies is approximately **five to seven times higher** than in the general population.
- Malignancy is strongly associated with dermatomyositis and, if present, is often detectable at disease outset.
- The most common malignancies in inflammatory myositis are **adenocarcinomas**.
- Suspicion for cancer should be high, especially in patients with **active muscle and skin inflammation but normal creatine kinase levels, age older than 50 years, and periungual erythema**.

Systemic sclerosis

- Risks of **lymphoma, skin cancer, and lung cancer** are **markedly increased** in scleroderma.
- Scleroderma-related risk factors for malignancy include esophageal disease related to **Barrett's esophagus** and lung cancer related to **pulmonary fibrosis**.

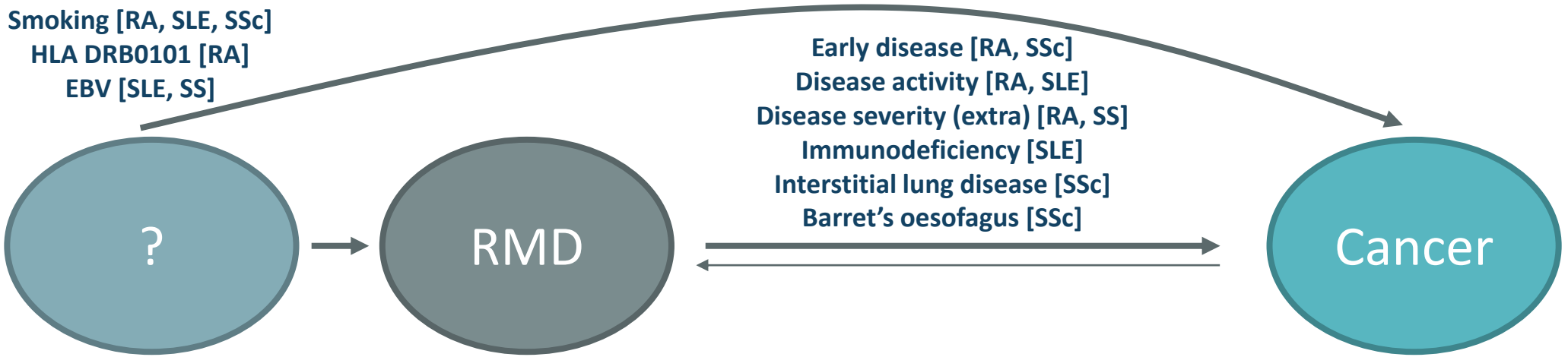
Sjogren's syndrome

- The risk of **lymphoproliferative cancers**, especially various types of lymphoma, is **at least six-fold** increased in patients with primary Sjögren's syndrome.
- Immunologic perturbations, including p53 mutations and B cell activation, as well as **Helicobacter pylori**, are likely predisposing risk factors.

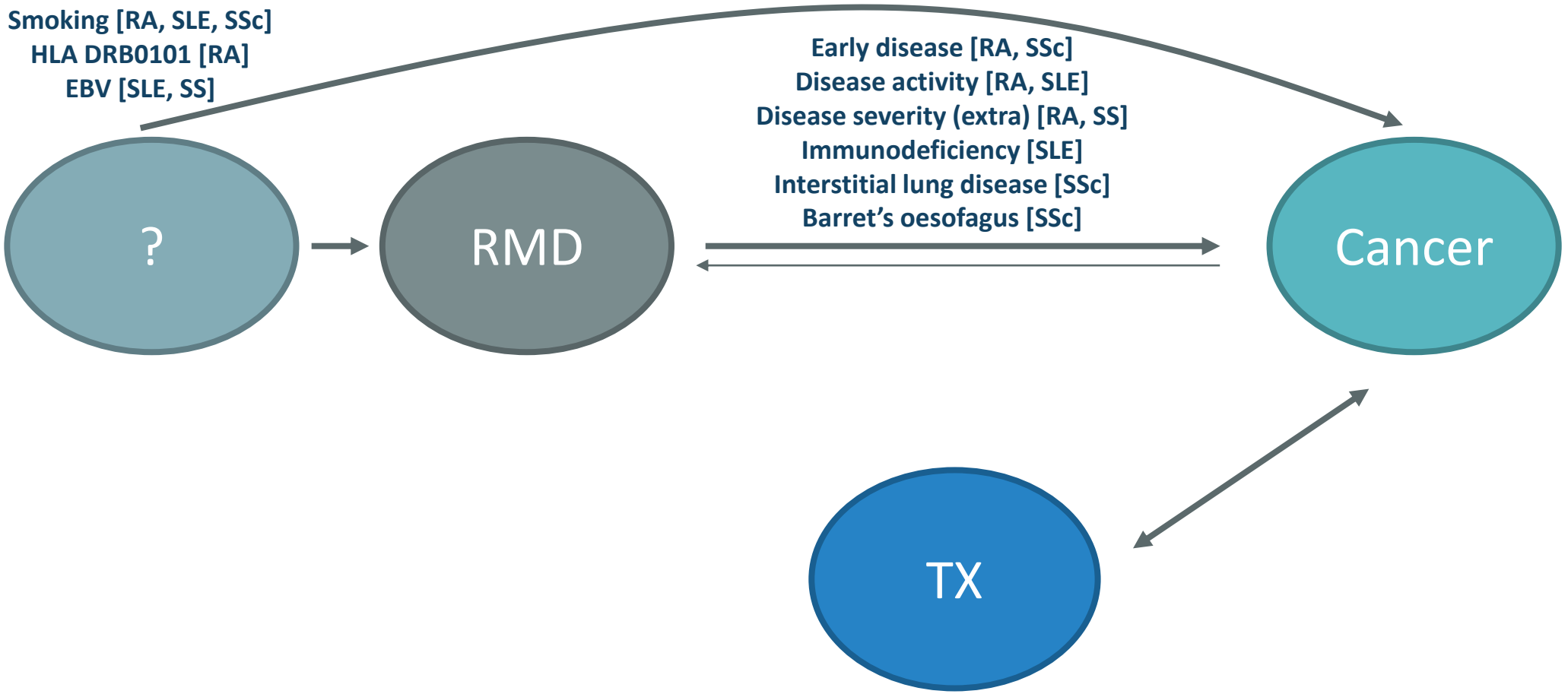
Vasculitis

- It is **unclear** whether the risk of cancer development is increased in vasculitis independent of drug treatment effects.
- HCV+ cryoglobulinemic vasculitis

Causal model

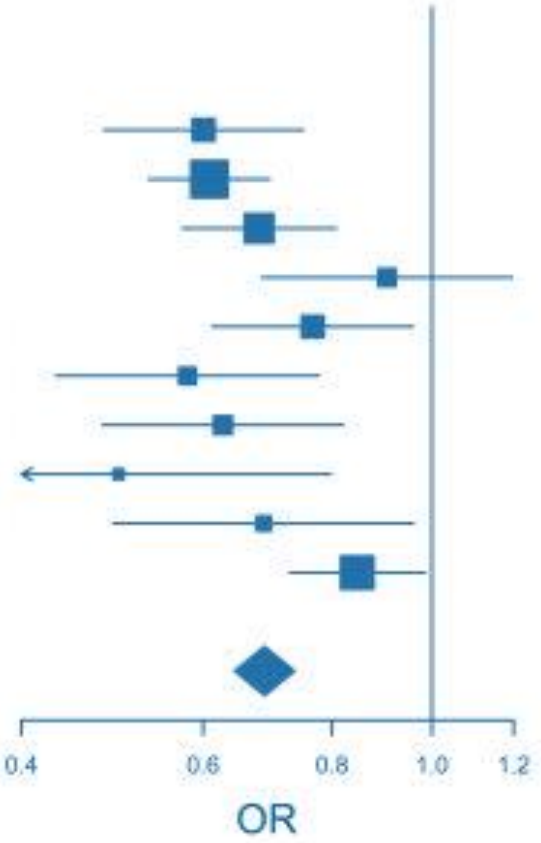


Causal model



NSAIDs and colorectal cancer

Study	Case N (Aspirin and/or NSAIDs, %)	Control N (Aspirin and/or NSAIDs, %)	OR (95% CI)
CCFR	1163 (204, 17.5)	978 (297, 30.4)	0.60 (0.48–0.75)
DACHS	2339 (544, 23.3)	2180 (729, 33.4)	0.61 (0.53–0.70)
DALS	1115 (370, 33.2)	1173 (494, 42.1)	0.68 (0.57–0.81)
HPFS	403 (184, 45.7)	401 (192, 47.9)	0.90 (0.68–1.20)
NHS	553 (172, 31.1)	955 (362, 37.9)	0.77 (0.61–0.96)
OFCCR	553 (101, 18.3)	519 (159, 30.6)	0.58 (0.43–0.78)
PLCO	485 (205, 42.3)	415 (224, 54.0)	0.63 (0.48–0.82)
PMH–CCFR	280 (62, 22.1)	122 (43, 35.2)	0.50 (0.31–0.80)
VITAL	277 (120, 43.3)	279 (147, 52.7)	0.69 (0.49–0.96)
WHI	1466 (493, 33.6)	1531 (574, 37.5)	0.85 (0.73–0.98)
Meta	**8634 (2455, 28.4)**	**8553 (3221, 37.7)**	**0.69 (0.64–0.74)**



Overall p–value=6.20E–28
p for heterogeneity=0.02

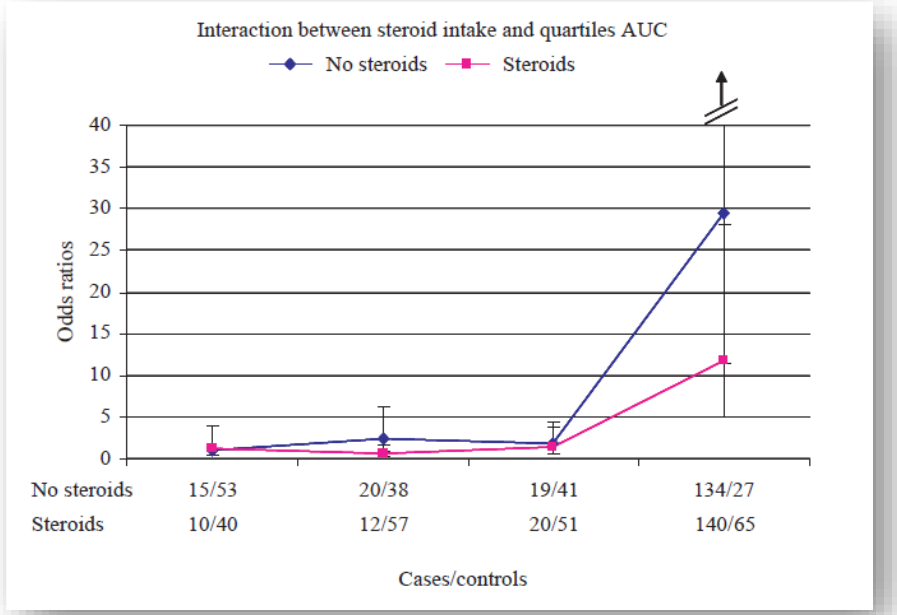
Nan H, eta al. JAMA. 2015 Mar 17;313(11):1133-42.

Glucocorticoids and lymphoma

Characteristics	Cases (n = 378)	Controls (n = 378)
Female/male	208/170	208/170
Age at RA onset, mean (range)	50 (16–83)	53 (18–80)
Age at lymphoma diagnosis, mean (range)	70 (32–91)	
Rheumatoid factor positive*	279/334 (84)	300/360 (83)
Any DMARD†,‡	268 (71)	278 (74)
Cytotoxic drugs†,§	19 (5)	8 (2)
Oral steroid treatment†	183/373 (49)	217 (57)
Intra-articular steroid treatment¶	168 (44)	240 (63)
Oral steroid treatment at lymphoma diagnosis of the case	84 (22)	125 (33)
Confirmed Sjögren's syndrome**	7 (2)	1 (0.3)

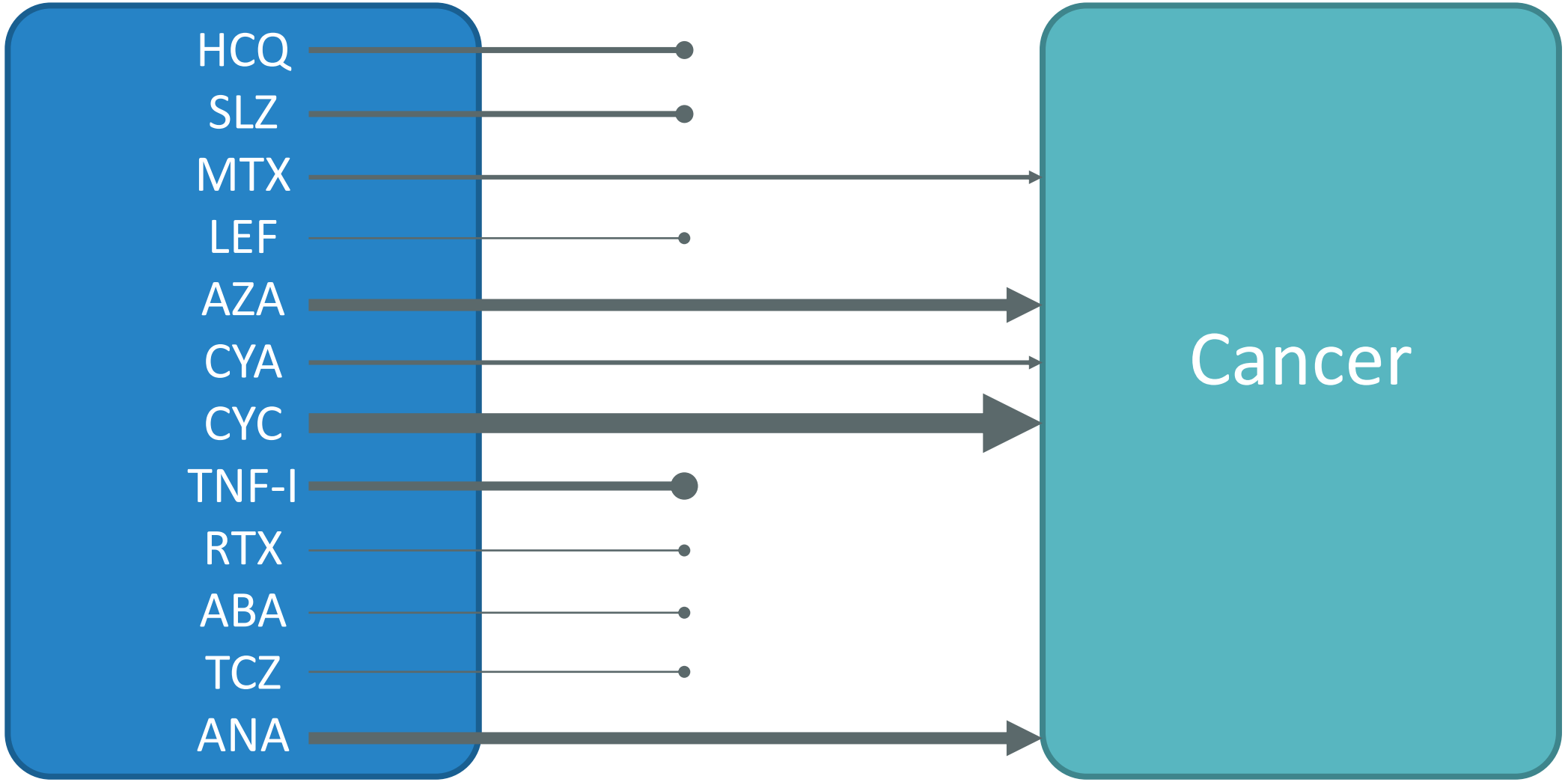
	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Oral steroids/yes†,‡	183	217	0.69 (0.51 to 0.94)	0.58 (0.38 to 0.90)
Duration of treatment with oral steroids				
No steroids	190	161	1.0	1.0
≥4 Weeks–2 years	95	94	0.81 (0.56 to 1.2)	0.87 (0.51 to 1.5)
>2 Years	88	123	0.57 (0.40 to 0.82)	0.43 (0.26 to 0.72)
Initiation of steroids, years after RA onset§				
No steroids	190	161	1.0	1.0
Year 1–5	90	133	0.53 (0.37 to 0.76)	0.58 (0.35 to 0.97)
Year >5	92	84	0.87 (0.60 to 1.3)	0.58 (0.35 to 0.97)
Treatment with intra-articular steroids				
No intra-articular steroids	202	128	1.0	1.0
Intra-articular steroids overall	168	240	0.44 (0.32 to 0.61)	0.35 (0.22 to 0.56)
Intra-articular steroids group A¶	88	222	0.24 (0.16 to 0.36)	0.22 (0.13 to 0.37)
Intra-articular steroids, group B**	80	18	3.1 (1.6 to 5.8)	2.6 (1.1 to 6.2)

*Adjusted for disease-modifying antirheumatic drug treatment and disease activity as area under the curve in quartiles; †information



Hellgren K, et al. Ann Rheum Dis. 2010 Apr;69(4):654-9.

DMARDs and cancer



Methotrexate and cancer

Lymphoproliferative disease

- Several case reports
- No attributable risk
- Dose dependent

Extranodal B cell lymphomas (mostly EBV)

Beneficial impact on mortality

Kameda T, et al. Arthritis Care Res 66:1302, 2014.
Georgescu L, et al Semin Arthritis Rheum 26:794, 1997.

Azathioprine and cancer

Lymphoproliferative disorders

- Overall SIR 8.05
- Lymphoma
  - Dose dependent (>300mg/day)
- Leukemia
  - Not increased in SLE

Matteson EL, J Rheumatol 1991; 18:809.
Silman AJ, et al. Ann Rheum Dis 1988; 47:988.
Nero P, et al. Ann Rheum Dis 2004; 63:325.

Cyclophosphamide and cancer

Rheumatic diseases

- 1.5-4.1 fold increase risk of malignancy

ANCA-associated vasculitis

- Bladder cancer: SIR 4.8
- Leukemia: SIR 5.7
- Lymphoma: SIR 4.2

Vasquez S, et al. J Rheumatol 1992; 19:1625
Radis CD, et al. Arthritis Rheum 1995; 38:1120
Bernatsky S, et al. Arch Intern Med 2008; 168:378

Other immunosuppressants and cancer

Leflunomide

- No signal

Cyclosporin A

- Case reports of EBV-associated lymphomas
- No signal vs other DMARDs

Mycophenolate mofetil

- Case reports lymphoma

Zijlmans JM, et al. N Engl J Med 326:1363, 1992.
Arellano F, et al. Br J Rheumatol 32(Suppl 1):72, 1993.
Dasgupta N, et al. Lupus 14:910, 2005.

Anti-TNF in RA – observational studies

Study, Reference Number	Registry	Intervention	Control nb-DMARDs	Control General Population	Adjusted Hazards Ratio (Intervention vs. Comparator/Control)	Adjusted Hazards Ratio (Intervention vs. General Population)	Risk of Bias
All Types of Cancer							
Askling, 2009[97]	ARTIS	3 TNFi	nb-DMARDs	General population	TNFi vs. pts starting MTX: 1.0 (0.8, 1.2): TNFi vs./ nb-DMARDs combination therapy 1.0 (0.7, 1.4)	1.1 (1.0, 1.3)	Low
Carmona, 2011[98]	BIOBADASER	3 TNFi	nb-DMARDs	General population	0.5 (0.1, 2.5)	0.7 (0.5, 0.9)	Low
Haynes, 2013[99]	Claim database	3 TNFi	nb-DMARDs	N/A	0.8 (0.6, 1.1); ever-analysis 0.9 (0.8, 1.1)	N/A	Moderate
Strangfeld, 2010[100]	RABBIT	3 TNFi + anakinra	nb-DMARDs	General population	TNFi vs. nb-DMARDs 0.7 (0.4, 1.1); ANA vs. nb-DMARDs 1.4 (0.6, 3.5)	0.8 (0.5, 1.0)	Low
Patients with History of Cancer							
Dixon, 2010[110]	BSRBR	3 TNFi	nb-DMARDs	N/A	0.5 (0.1, 2.2); Censoring after firstcancer 0.5 (0.1, 2.2).	N/A	Low
Lymphoma							
Askling, 2009[102]	ARTIS	3 TNFi	nb-DMARDs	General population	1.4 (0.8, 2.1)	2.7 (1.8, 4.1)	Low
Carmona, 2011[98]	BIOBADASER	3 TNFi	nb-DMARDs	General population	N/A	Hodgkin's, 5.3 (0.1, 29.5); non-Hodgkin's, 1.5 (0.31, 4.4)	Low
Haynes, 2013[99]	Claim database	3 TNFi	nb-DMARDs	N/A	0.8 (0.3, 2.1), ever-analysis 1.3 (0.7, 2.2); any lymphoma or leukemia: 0.7 (0.3, 1.5); ever-analysis (1.0 (0.6, 1.6)	N/A	Moderate
Non-Melanoma Skin Cancer							
Amari, 2011[103]	Claim database	3 TNFi	nb-DMARDs	N/A	1.4 (1.2, 1.6); TNFi vs. MTX 1.4 (1.2, 1.7)	N/A	Moderate
Mercer, 2012[104]	BSRBR	3 TNFi	nb-DMARDs	General population	BCC 1.0 (0.5, 1.7), SCC 1.2 (0.4, 3.8); 1st cancer per subject BCC 0.8 (0.5, 1.5)	1.7 (1.4, 2.0)	Low
Haynes, 2013[99]	Claim database	3 TNFi	nb-DMARDs	N/A	0.8 (0.5, 1.4); ever-analysis 1.1 (0.8, 1.5)	N/A	Moderate
Melanoma							
Raaschou, 2013[105]	ARTIS	5 TNFi	nb-DMARDs	N/A	1.5 (1.0, 2.2)	N/A	Low

Eric L. Matteson, in Kelley and Firestein's Textbook of Rheumatology, 2-Volume Set, 10th Edition 2017

Non anti-TNF and tofacitib and cancer

Rituximab

- All malignancy SIR = 1.05 (95% CI, 0.76 to 1.42)

Abatacept

- No signal

Tocilizumab

- No signal

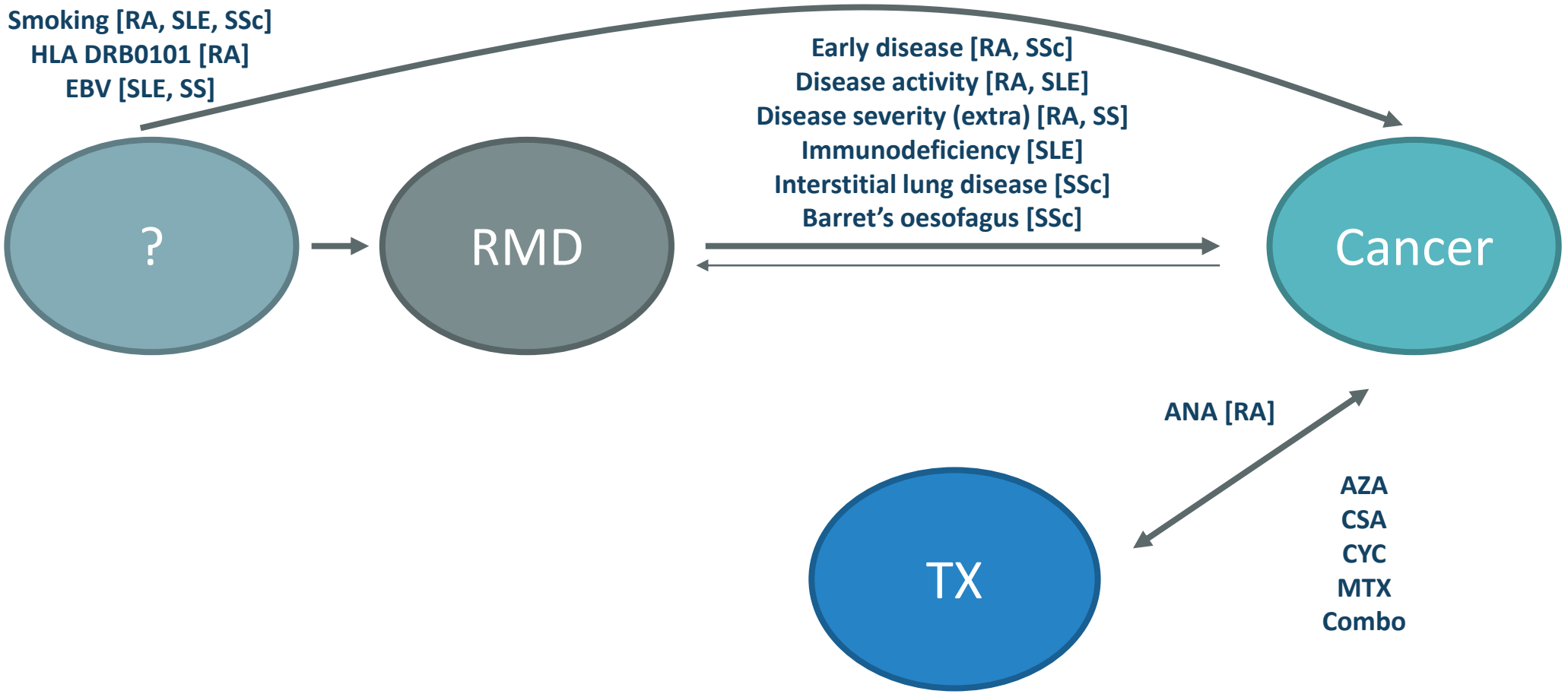
Anakinra

- Lymphoma SIR = 3.71; 95% CI, 0.77 to 11.0)
- A number of solid tumors have also been reported with this agent.

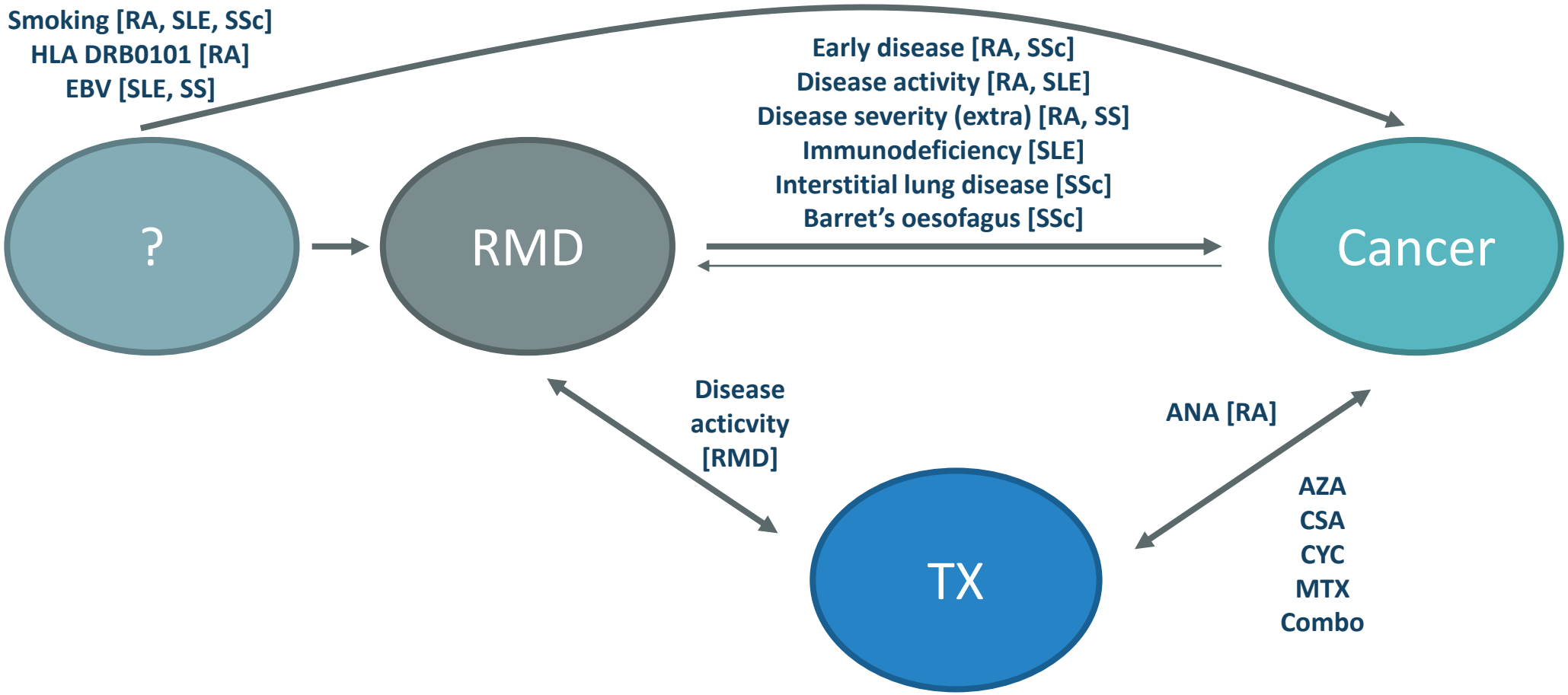
Tofacitinib

- No signal

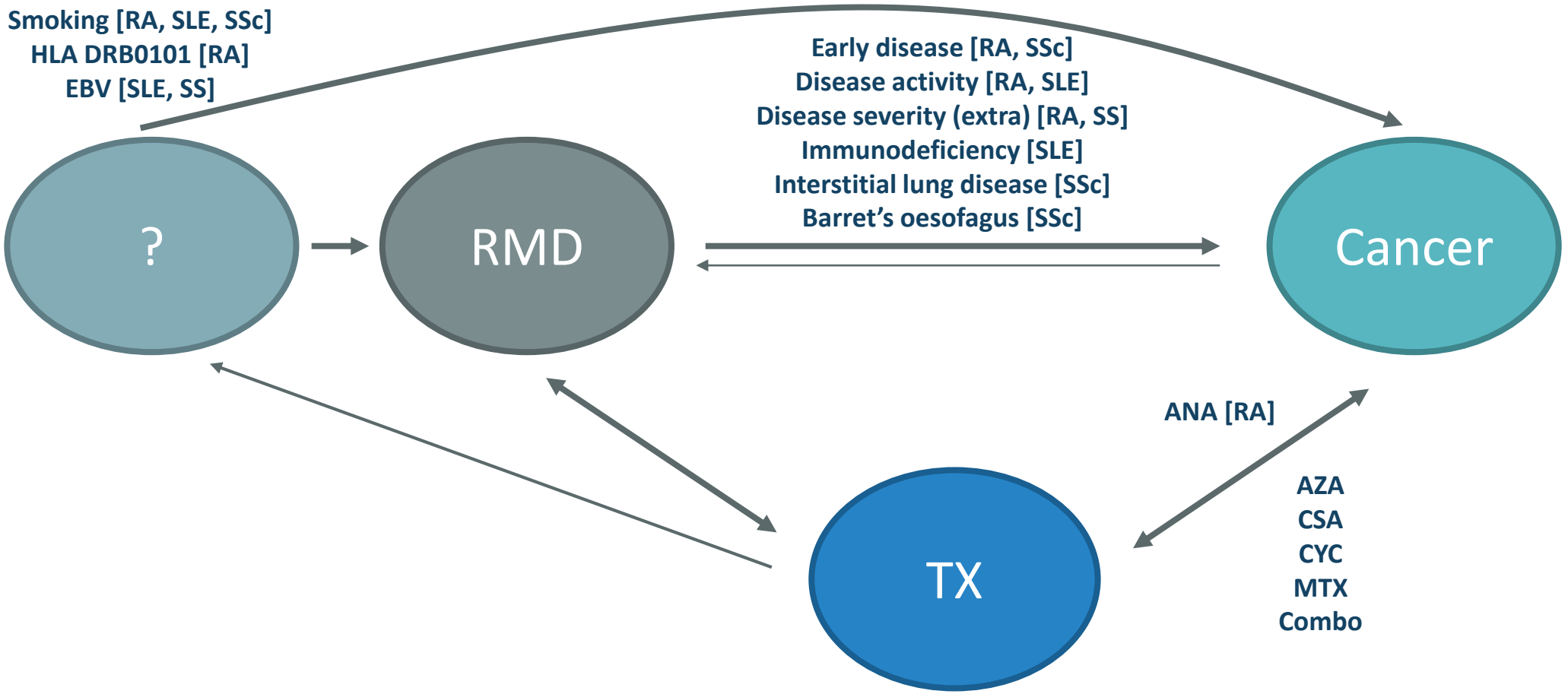
Causal model



Causal model



Causal model



Aromatase inhibitors and RA onset

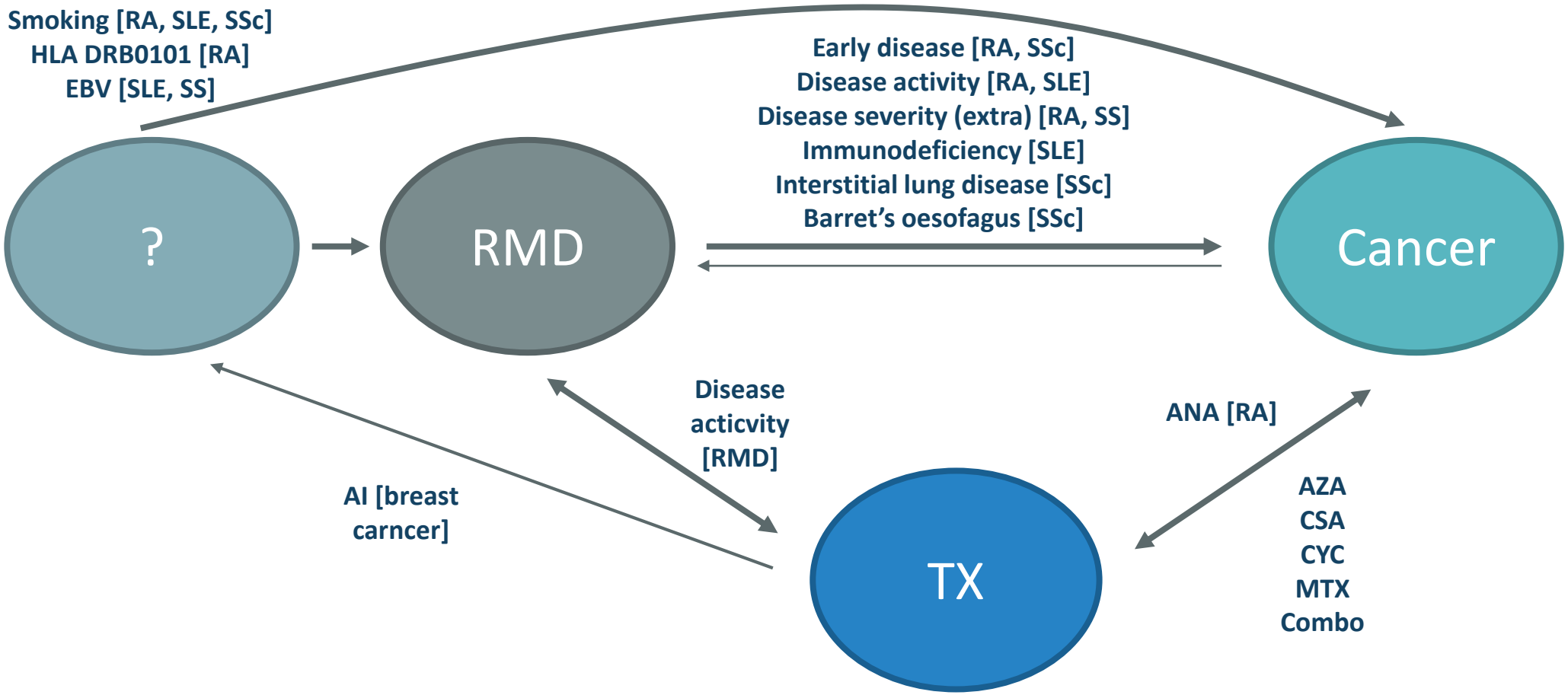
7,533 women with brast cancer starting Tamoxifen or Aromatase inhibitors

	Incident RA	Person-years	Exposure periods	Incident rate *1000/yr (95%CI)	Crude HR	Adjusted HR(95%CI) *	Competitive risk Adjusted HR(95%CI)*§
Tamoxifen	26	8650.2	3,371	3.01 (1.96, 4.40)	reference	reference	reference
Aromatase inhibitors	87	17455.7	6,815	4.98 (3.99, 6.15)	**1.67 (1.08-2.60)**	**1.64 (1.04-2.58)**	**1.62 (1.03-2.56)**
→Anastrozole	50	9457.8	3,170	5.29 (3.92, 6.97)	**1.77 (1.10-2.85)**	**1.73 (1.06-2.81)**	**1.75 (1.07-2.86)**
→Letrozole	30	6626.6	2,785	4.53 (3.05, 6.46)	1.51 (0.89-2.56)	1.49 (0.87-2.56)	1.47 (0.86-2.51)
→Exemestane	7	1371.3	860	5.10 (2.05, 10.5)	1.78 (0.76-4.17)	1.75 (0.74-4.16)	1.47 (0.63-3.43)

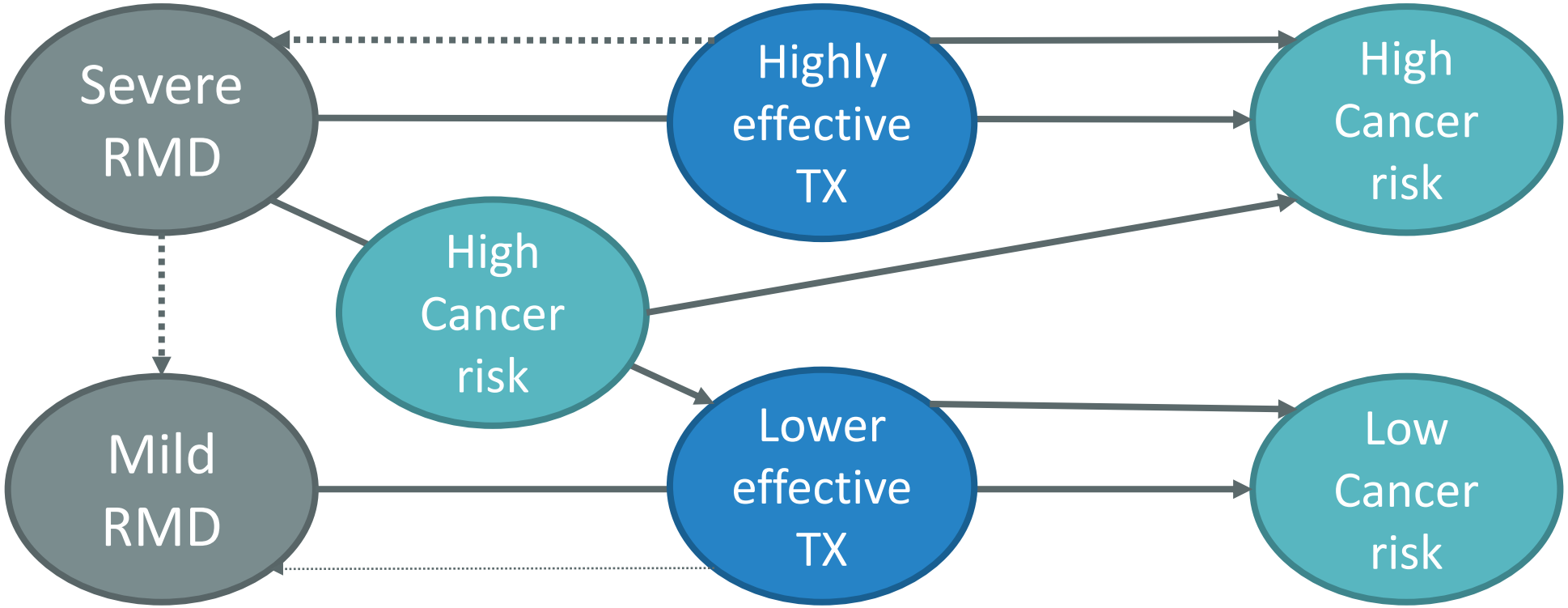
*Adjusted for age at the beginning of the exposure period, level of neoplasia; §Competitive risk survival model

Caprioli M et al. RMD Open 2017 (in press)

Causal model

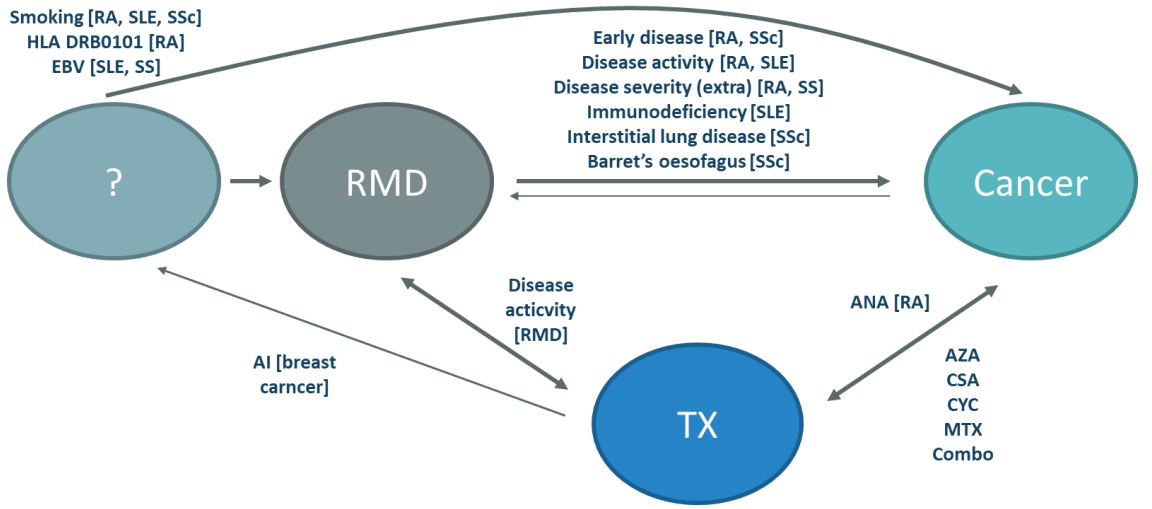


Confounding by indication



Cancer prevention in patients with RMD

- Target the lowest level of clinical disease activity possible using the least intensive treatment regimen
- Routine cancer screening that is appropriate to their age, sex, familial cancer burden, and risk factors such as smoking.
- Surveillance in early phases and based on drug-exposure



Grazie per l'attenzione