Τελευταία δεδομένα σχέσης βιολογικών παραγόντων και καρκίνου

Εαρινές Ημέρες Ρευματολογίας 2018

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Σύγκρουση συμφερόντων

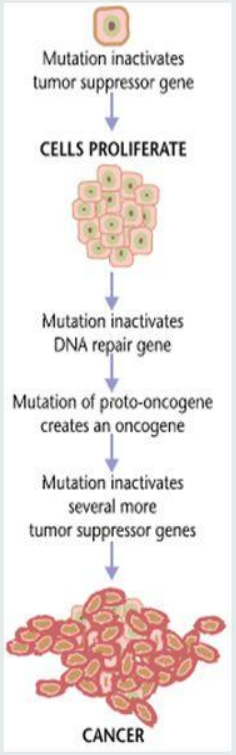
- Τιμητική αμοιβή για ομιλίες και συμμετοχή σε advisory boards από τις εταιρείες UCB, Pfizer, Novartis, BMS, MSD, Janssen, Abbvie

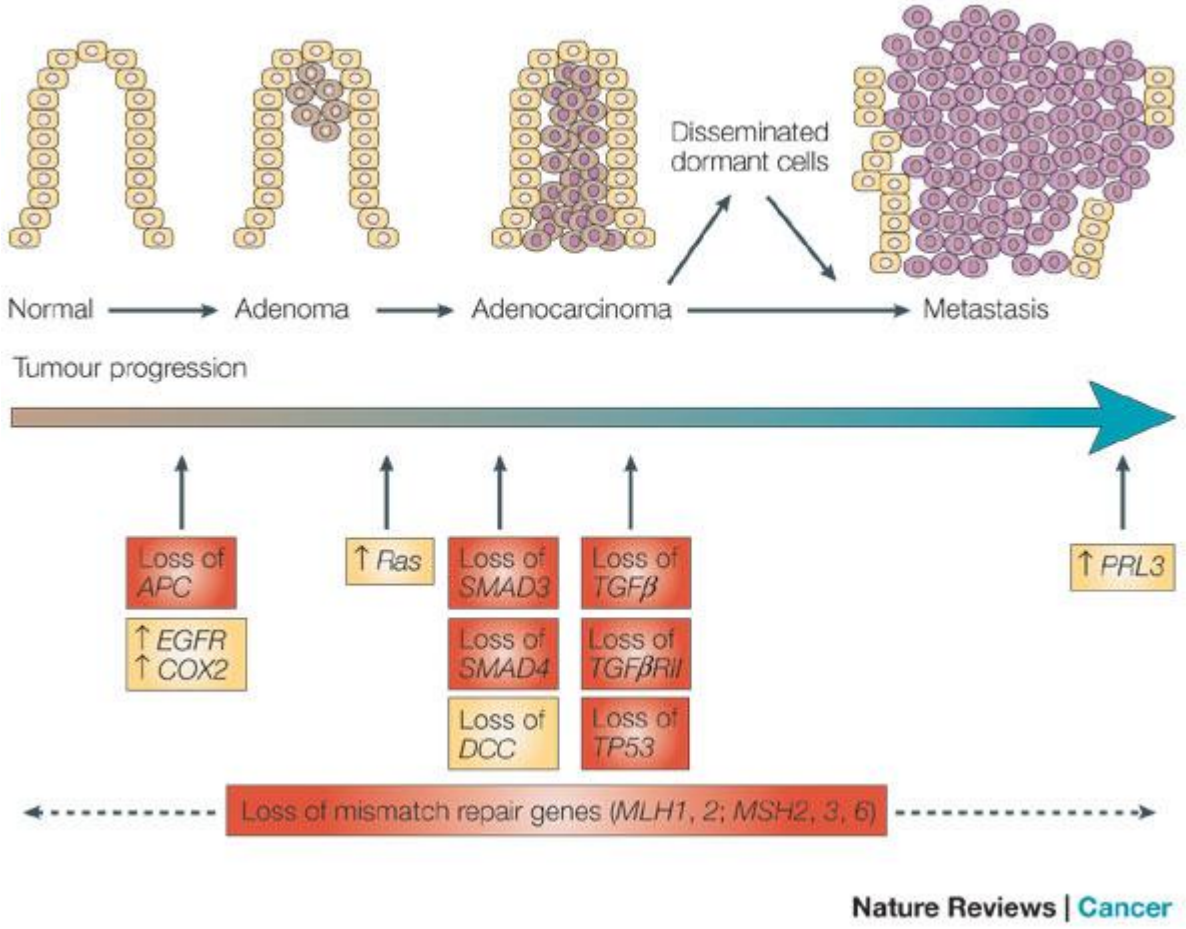
- Σχέση ανοσολογικού συστήματος-καρκίνου
- Σχέση χρόνιας φλεγμονής-καρκίνου

Η ογκογένεση είναι μια αργή διαδικασία…

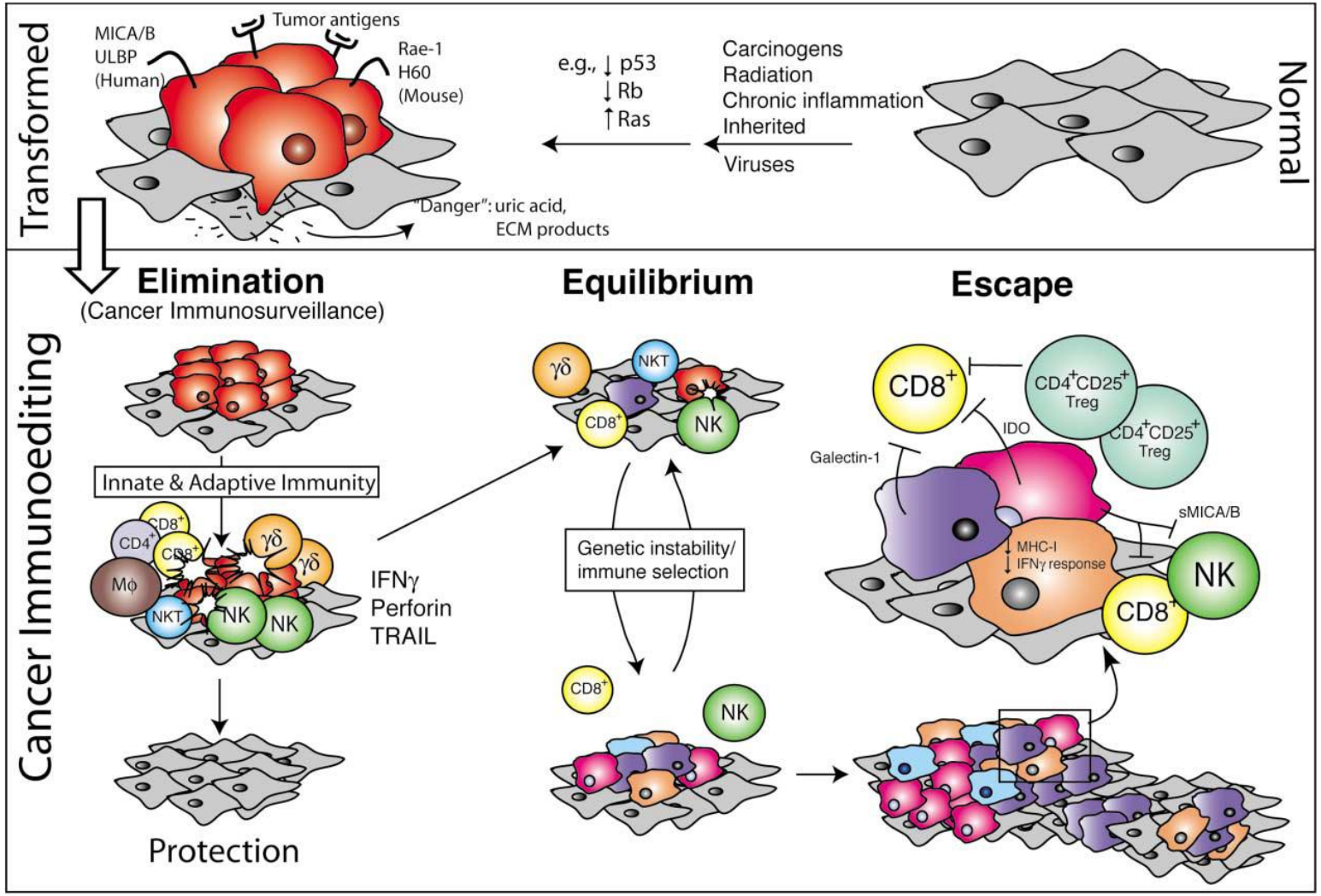
Tumorigenesis is a multi-step process

- Tumorigenesis is a multi-step process by which normal cells are transformed into cancer cells by acquiring genetic changes.
- It is characterized by a progression of changes on cellular and genetic level that ultimately reprogram a cell to undergo uncontrolled cell division and a malignant mass (neoplasm) is formed.
- Three to six genetic changes are usually required for a normal cell to transform into a cancer cell.

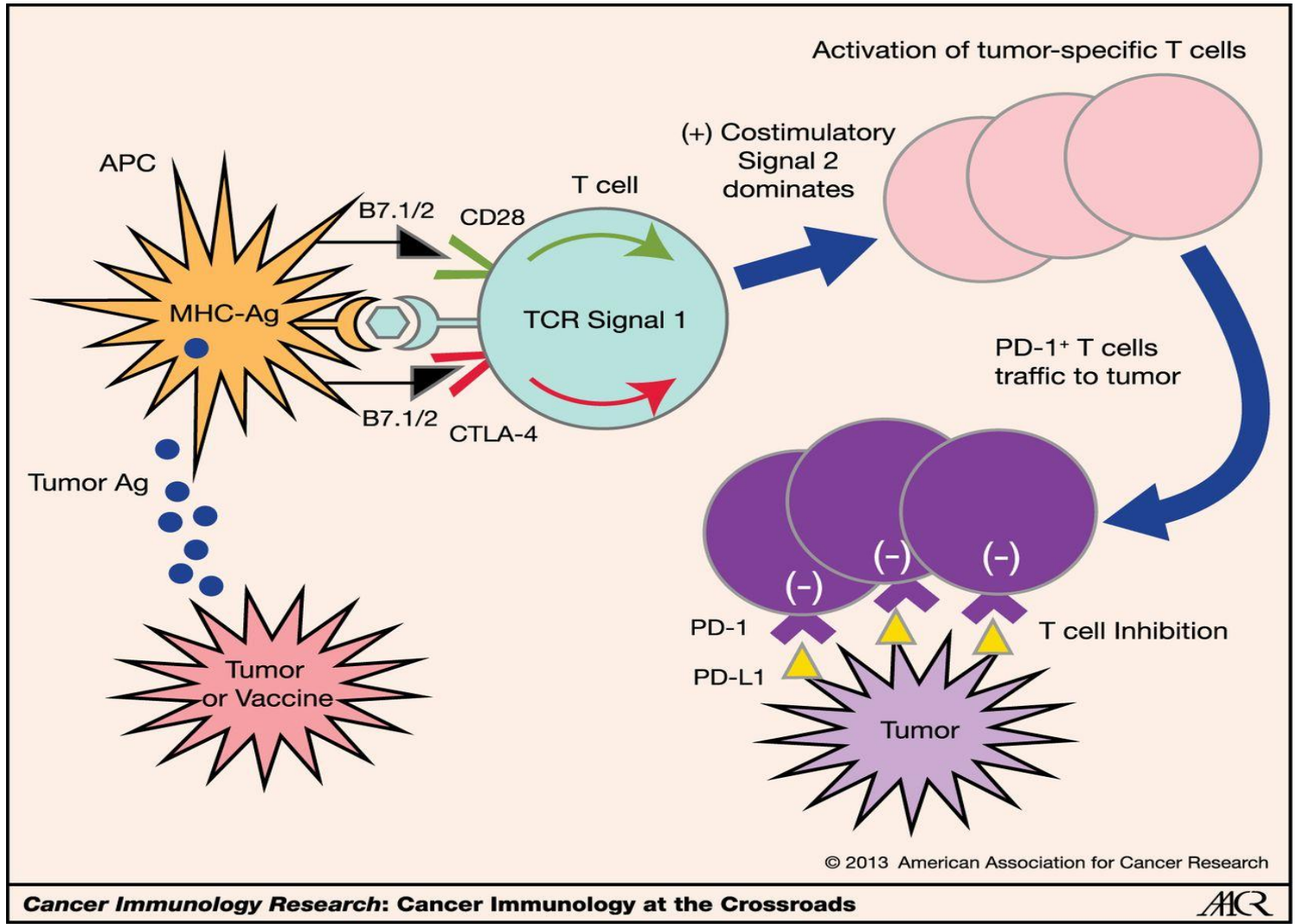


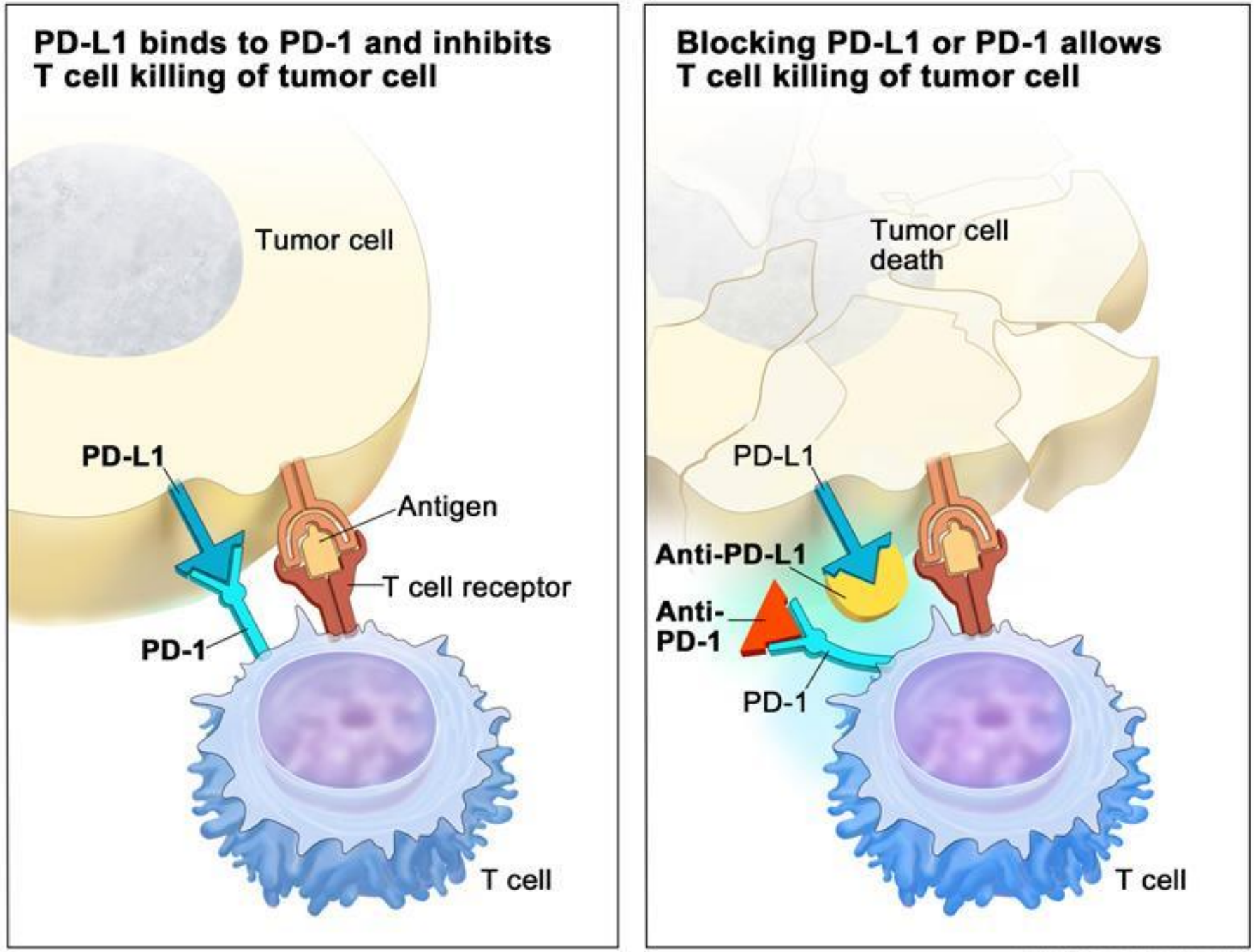


Ανοσολογικό σύστημα και καρκίνος
Μια περίπλοκη, στενή σχέση

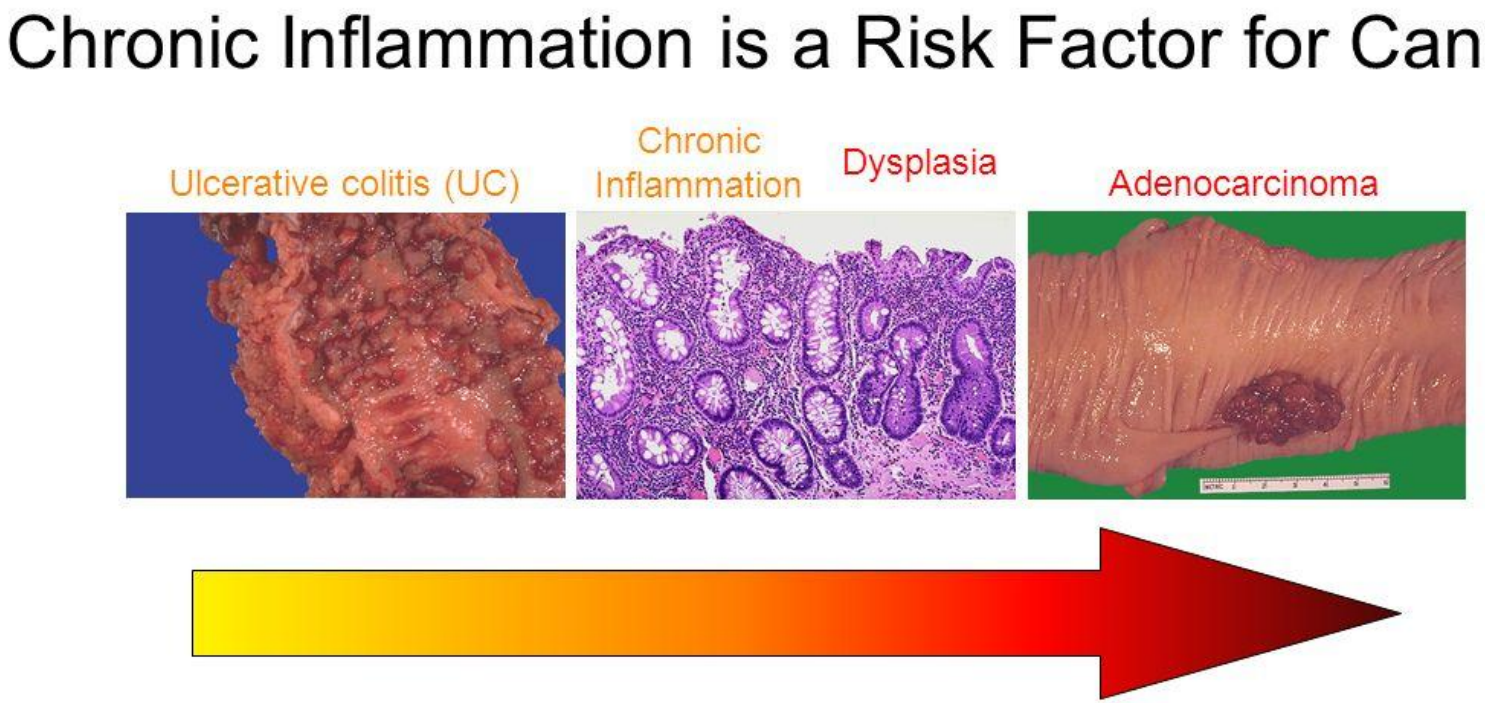


Θα μπορούσαμε να ενισχύσουμε την ανοσολογική απάντηση έναντι του όγκου?
Η εποχή της αντικαρκινικής ανοσοθεραπείας έχει ξεκινήσει





Χρόνια φλεγμονή και καρκίνος…



- Χρόνια φλεγμονή ωε προδιαθεσικός παράγοντας καρκίνου
  - Hepatitis B/C
  - Helicobacter pylori
  - IBD

Η ΡΑ είναι τυπική χρόνια φλεγμονώδης νόσος. Αυξάνεται η πιθανότητα κακοήθειας?

- Κατά βάση όχι
- Σχετικός κίνδυνος 1.1-1.15
- Η μικρή αυτή αύξηση αφορά αιματολογικές κακοήθειες

ARTHRITIS & RHEUMATISM
Vol. 63, No. 2, February 2011, pp 352–358
DOI 10.1002/art.30134

The Risk of Cancer in Patients With Rheumatoid Arthritis

A Nationwide Cohort Study in Taiwan

Yi-Ju Chen,[1] Yun-Ting Chang,[2] Chang-Bi Wang,[3] and Chun-Ying Wu[4]

- Η PA ως νόσος σχετίζεται με αυξημένη πιθανότητα εμφάνισης λεμφώματος

Table 2. SIRs and 95% CIs for cancers, according to age, sex, and duration of followup in Taiwanese patients with rheumatoid arthritis*

Characteristic	All cancers†				Hematologic cancers			
	No. observed	No. expected	SIR	95% CI	No. observed	No. expected	SIR	95% CI
All patients	935	762.19	1.23	1.22–1.23	75	27.35	2.74	2.68–2.81
Women	634	535.40	1.18	1.17–1.19	39	18.90	2.06	2.00–2.13
Men	301	228.13	1.32	1.30–1.33	36	8.23	4.38	4.23–4.52
Age, years								
15–39	43	18.33	2.35	2.28–2.42	2	1.30	1.54	1.33–1.77
40–69	698	442.85	1.58	1.56–1.59	52	14.90	3.49	3.40–3.59
≥70	194	188.66	1.03	1.01–1.04	21	7.22	2.91	2.79–3.04
Followup, years								
<1	160	2.71	58.96	58.13–59.96	14	0.10	139.08	132.76–147.53
1–2	150	8.25	18.19	17.89–18.48	13	0.30	42.67	41.01–45.75
2–4	246	102.85	2.39	2.36–2.42	17	3.71	4.59	4.37–4.81
4–6	165	156.57	1.05	1.04–1.07	18	5.62	3.21	3.06–3.35
6–8	128	165.15	0.78	0.76–0.79	7	5.88	1.19	1.10–1.28
≥8	86	273.97	0.31	0.31–0.32	6	9.72	0.62	0.57–0.67

* SIRs = standardized incidence ratios; 95% CI = 95% confidence interval.
† Includes hematologic cancers.

Table 4. SIRs for hematopoietic malignancies in Taiwanese patients with rheumatoid arthritis*

Cancer type	No. observed	No. expected	SIR	95% CI
All	75	27.35	2.74	2.68–2.81
Leukemia	15	10.12	1.48	1.41–1.56
Hodgkin's lymphoma	1	0.56	1.76	1.45–2.17
Non-Hodgkin's lymphoma and others†	59	16.66	3.54	3.45–3.63

* SIRs = standardized incidence ratios; 95% CI = 95% confidence interval.

Simon et al. Arthritis Research & Therapy (2015) 17:212
DOI 10.1186/s13075-015-0728-9

arthritis research&therapy

RESEARCH ARTICLE Open Access

Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis

Teresa A. Simon[1*], Adam Thompson[1], Kunal K. Gandhi[1], Marc C. Hochberg[2] and Samy Suissa[3]

Overall malignancy

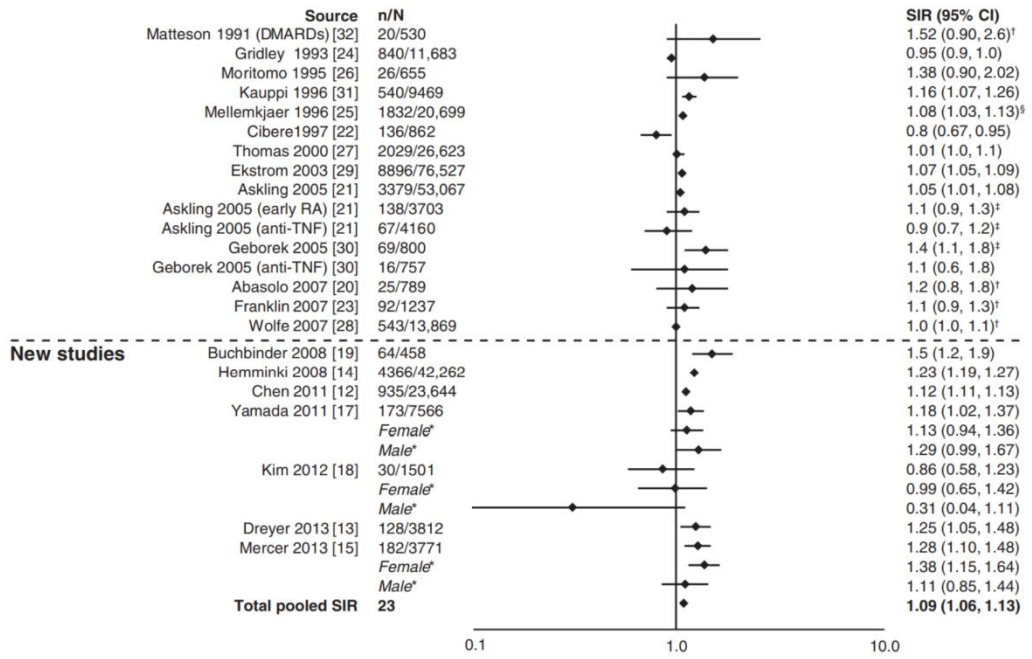


Fig. 2 Relative risk of overall malignancy in patients with rheumatoid arthritis (RA) compared with the general population. CI, confidence interval; DMARD, disease-modifying antirheumatic drug; n, number of malignancies; N, population size; RR, relative risk; SIR, standardized incidence ratio; TNF, tumor necrosis factor. *SIRs by sex are not included in the total pooled SIR. †Excluding non-melanoma skin cancer. ‡All solid tumors. §Excluding lymphatic and hematopoietic

lymphoma

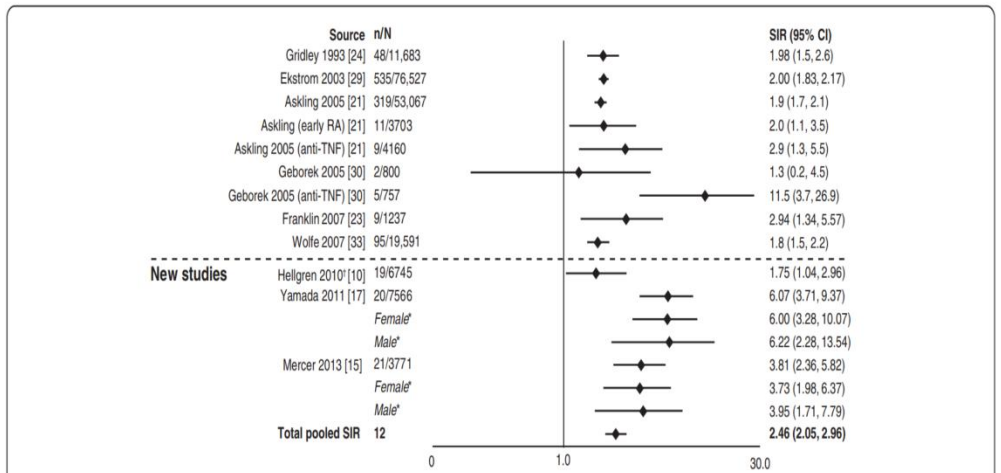


Fig. 3 Relative risk of malignant lymphoma in patients with rheumatoid arthritis (RA) compared with the general population. CI, confidence interval; n, number of malignancies; N, population size; OR, odds ratio; SIR, standardized incidence ratio; TNF, tumor necrosis factor. *SIRs by sex are not included in the total pooled SIR. †Reported as odds ratio

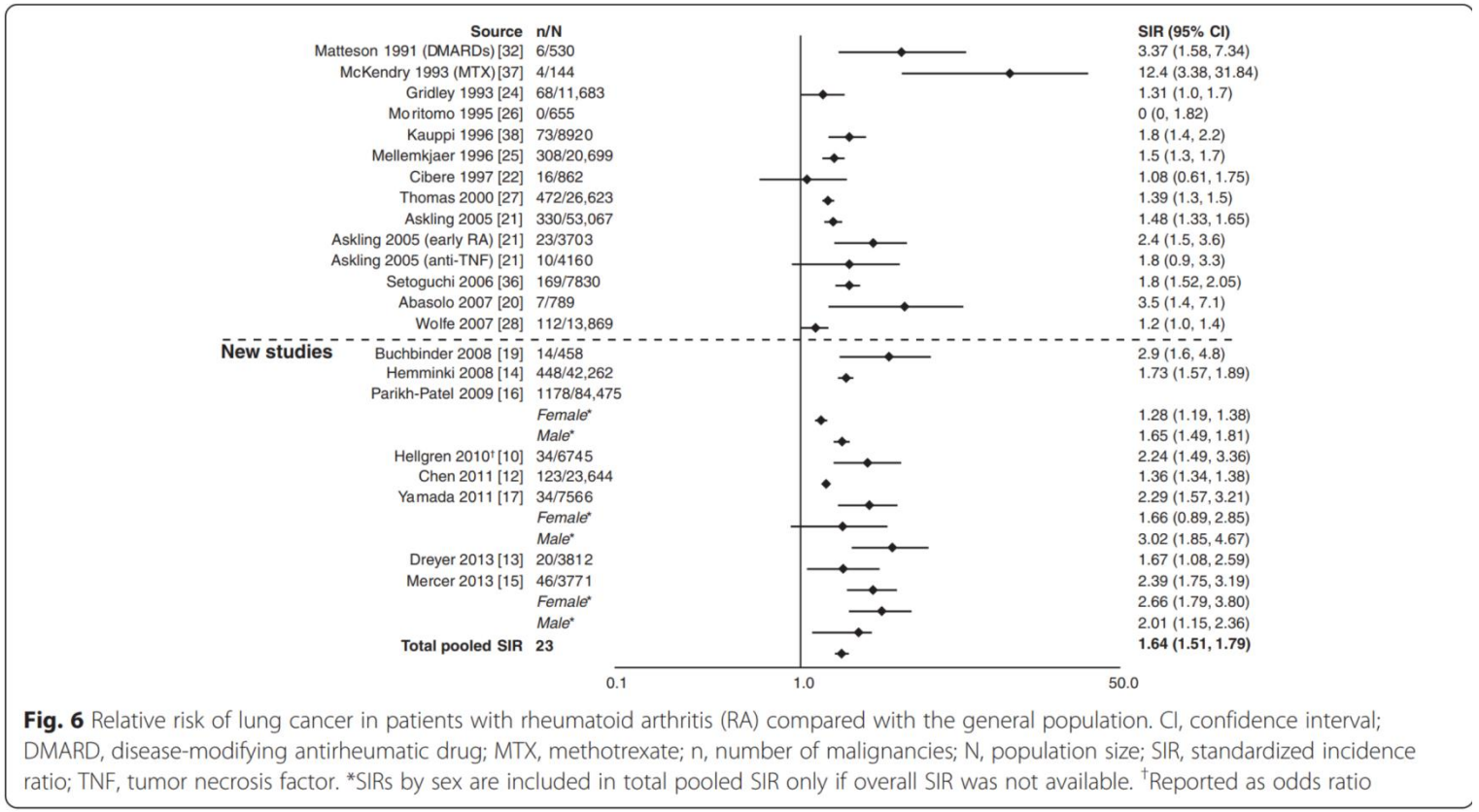


Fig. 6 Relative risk of lung cancer in patients with rheumatoid arthritis (RA) compared with the general population. CI, confidence interval; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; n, number of malignancies; N, population size; SIR, standardized incidence ratio; TNF, tumor necrosis factor. *SIRs by sex are included in total pooled SIR only if overall SIR was not available. †Reported as odds ratio

- Αυξημένη πιθανότητα για καρκίνο πνεύμονα?
- Κοινός προδιαθεσικός παράγοντας το κάπνισμα

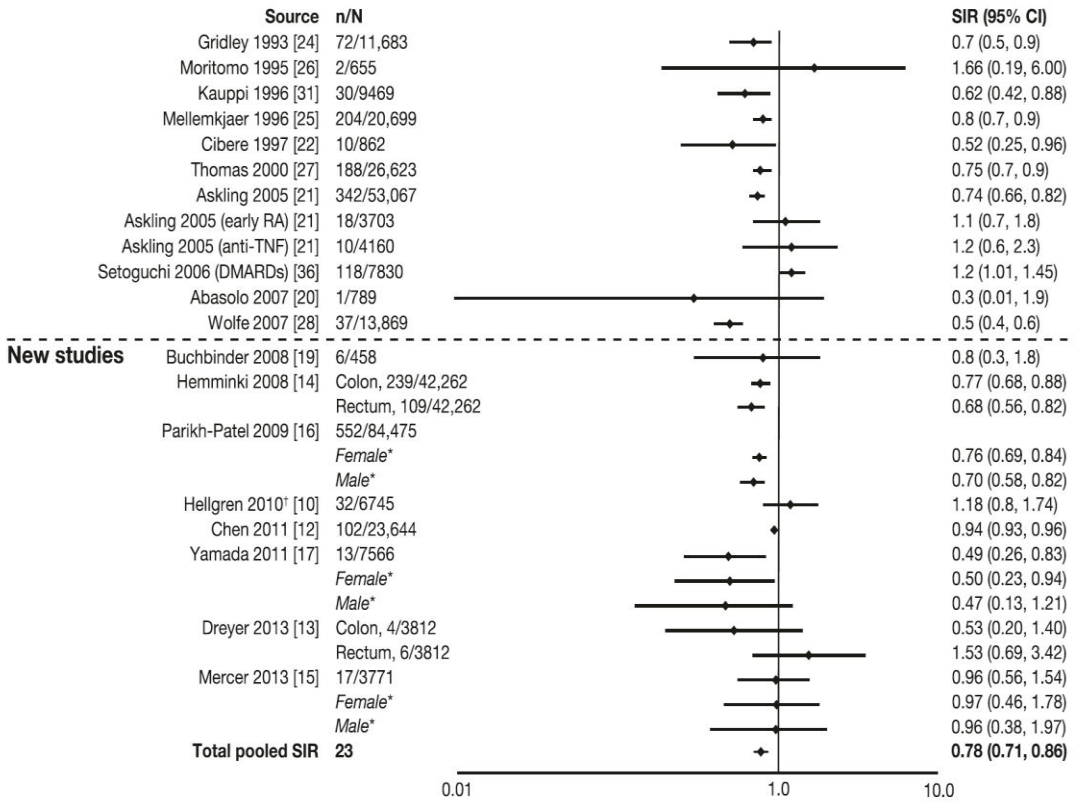


Fig. 7 Relative risk of colorectal cancer in patients with rheumatoid arthritis (RA) compared with the general population. CI, confidence interval; DMARD, disease-modifying antirheumatic drug; n, number of malignancies; N, population size; SIR, standardized incidence ratio; TNF, tumor necrosis factor. *SIRs by sex are included in total pooled SIR only if overall SIR was not available. †Reported as odds ratio

- Μειωμένη πιθανότητα για καρκίνο εντέρου?
- Λόγω ΜΣΑΦ?

Βιολογικοί παράγοντες και καρκίνος…

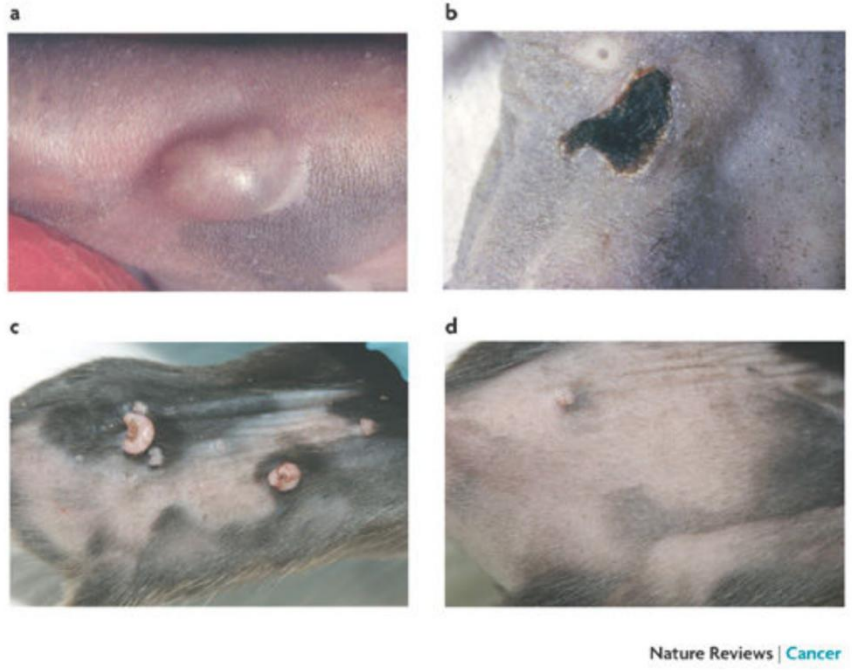
- Περισσότερα δεδομένα για τους TNF αναστολείς
- In vitro ο TNF καταστρέφει καρκινικά κύτταρα
- In vivo όμως τα πράγματα είναι πιο περίπλοκα….

Timeline

Tumour necrosis factor and cancer

Frances Balkwill

Figure 2: The pro- and anti-tumour actions of tumour necrosis factor (TNF) in mouse models of cancer.



Direct TNF administration to tumor

TNF-/- mice resistant to tumor development

Είναι πολύ δύσκολο να ξεκαθαρισθεί εαν υπάρχει σχέση μεταξύ αντι-TNF και καρκίνου

- Η ίδια η νόσος (PA) αυξάνει λίγο την πιθανότητα για καποιους τύπους καρκίνου
- Συγχορηγούμενα φάρμακα μπορεί να επηρεάζουν
- Ασθενείς υψηλού κινδύνου για κακοήθεια αποκλείσθηκαν απο τις μελέτες
- Δεν είναι τόσο συχνός ο καρκίνος ειδικά μέσα στον στενό χρονικό ορίζοντα των μελετών

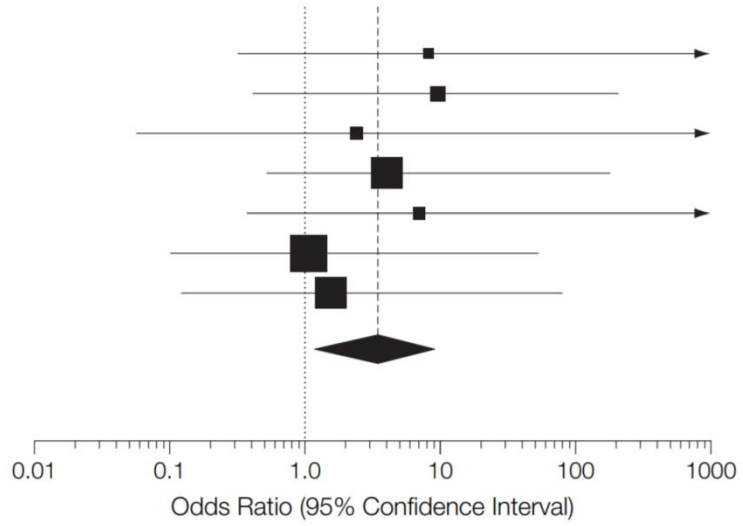
Η βασική μελέτη που «ενοχοποίησε» τα αντι-TNF….

Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies
Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials

Figure 2. Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Malignancies in Patients With Rheumatoid Arthritis

Source	Malignancies, No./Total: Anti-TNF	Malignancies, No./Total: Placebo	Odds Ratio (95% Confidence Interval)
Lipsky et al,[9] 2000	5/342	0/86	7.57 (0.30-Infinity)
Furst et al,[8] 2003	4/318	0/318	9.11 (0.40-199.49)
Weinblatt et al,[11] 2003	1/209	0/62	2.29 (0.06-Infinity)
Keystone et al,[6] 2004	8/419	1/200	3.87 (0.51-172.73)
St Clair et al,[7] 2004	4/749	0/291	6.58 (0.36-Infinity)
Van de Putte et al,[33] 2004	4/434	1/110	1.01 (0.10-50.39)
Westhovens et al,[34] 2004	3/721	1/361	1.50 (0.12-79.18)
Total	**29/3192**	**3/1428**	**3.29 (1.19-9.08)**

Test for overall effect:
Mantel-Haenszel $\chi^2 = 5.2$; $P = .02$



TNF indicates tumor necrosis factor. Size of the data markers is proportional to the statistical weight of the trial.

The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events

J P Leombruno,[1] T R Einarson,[1] E C Keystone[2]

Table 7 Rates of adverse events in placebo and recommended dose anti-TNF groups of randomised controlled trials in RA

Outcome	Unadjusted event rate per 1000 subjects (controlled portions of trials only)		Meta-analysis OR (95% CI)	Exposure-adjusted event rate per 1000 subject/years (controlled portions of trials only)		Meta-analysis RR (95% CI)	Exposure-adjusted event rate per 1000 subject/years (controlled and uncontrolled portions of trial)		Simple pooled RR (95% CI)
	Placebo	Biological		Placebo	Biological		Placebo	Biological	
Death	4.1	5.6	1.39 (0.74 to 2.62)	5.2	6.0	1.23 (0.66 to 2.29)	5.2	5.9	1.13 (0.57 to 2.27)
Serious adverse event	118.0	139.3	1.11 (0.94 to 1.32)	177.0	164.6	0.94 (0.77 to 1.15)H	177.0	177.4	1.00 (0.87 to 1.16)
Serious infection	27.5	32.5	1.21 (0.89 to 1.63)	34.0	35.7	1.07 (0.81 to 1.43)	34.0	36.7	1.08 (0.81 to 1.43)
Lymphoma	0.4	1.0	1.26 (0.52 to 3.06)	0.5	1.2	1.26 (0.53 to 3.01)	0.5	1.2	2.41 (0.37 to 15.59)
Non-cutaneous cancers and melanoma	3.7	5.4	1.31 (0.69 to 2.48)	5.1	6.4	1.21 (0.63 to 2.32)	5.1	7.1	1.40 (0.69 to 2.83)
Non-melanoma cutaneous cancer	1.4	2.1	1.27 (0.67 to 2.42)	1.8	1.9	1.01 (0.43 to 2.38)	1.7	2.4	1.41 (0.41 to 4.91)

H, Evidence of heterogeneity with fixed effects method, random effects analysis shown. OR, odds ratio; RA, rheumatoid arthritis; RR, risk ratio; TNF, tumour necrosis factor.

ARTHRITIS & RHEUMATISM
Vol. 63, No. 6, June 2011, pp 1479–1485
DOI 10.1002/art.30310

Tumor Necrosis Factor Therapy and the Risk of Serious Infection and Malignancy in Patients With Early Rheumatoid Arthritis

A Meta-Analysis of Randomized Controlled Trials

Andrew E. Thompson,[1] Scott W. Rieder,[2] and Janet E. Pope[1]

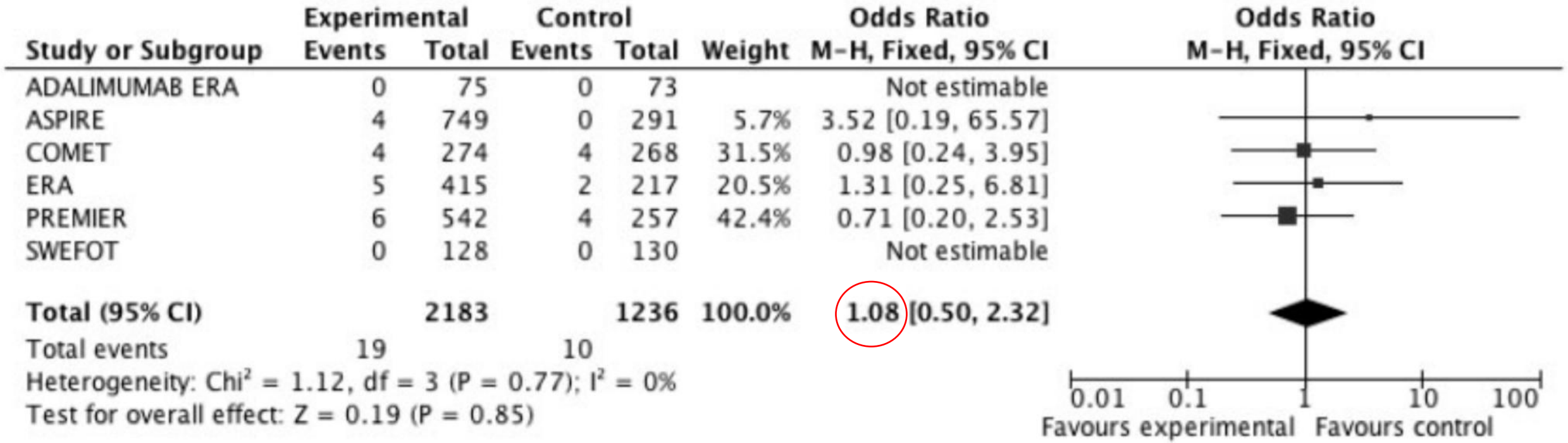
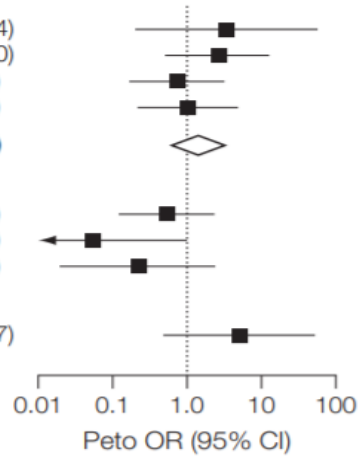


Figure 2. Effect of anti–tumor necrosis factor antibody therapy (experimental group), compared with control therapy, on the occurrence of malignancy in patients with rheumatoid arthritis. Results are shown as forest plots, with values expressed as the pooled odds ratio with 95% confidence interval, determined using the Mantel-Haenszel test. See Figure 1 for definitions.

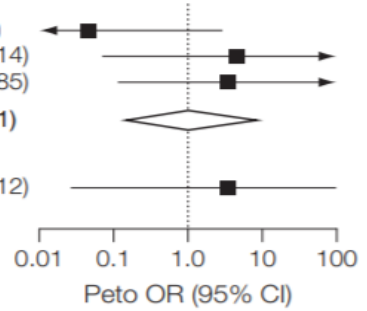
Skin cancer, nonmelanoma[a]

BRMs	No. of Studies	Peto OR (95% CI)	*P* Value
TNF inhibitors			
Certolizumab[53]	1	3.52 (0.21-58.74)	.38
Etanercept[56-61]	3	2.68 (0.55-13.00)	.22
Golimumab[62-66]	5	0.76 (0.18-3.22)	.70
Infliximab[25, 37, 38, 70-72]	3	1.07 (0.22-5.11)	.93
Overall	**12**	**1.37 (0.59-3.19)**	**.46**
Non-TNF inhibitors			
Abatacept[20, 25, 75]	3	0.54 (0.13-2.31)	.41
Anakinra[80]	1	0.06 (0.00-0.94)	.05
Tocilizumab[87, 88]	2	0.22 (0.02-2.44)	.22
Combination			
Abatacept + etanercept/BRM[20]	1	5.16 (0.50-53.67)	.17



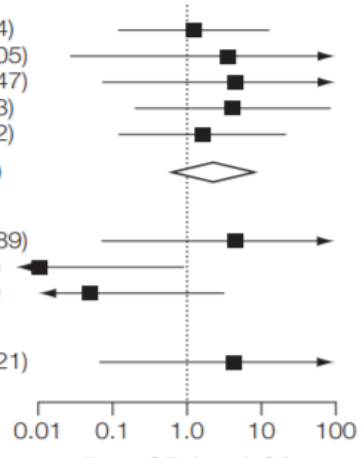
Skin cancer, melanoma[a]

BRMs	No. of Studies	Peto OR (95% CI)	*P* Value
TNF inhibitors			
Adalimumab[44]	1	0.04 (0.00-2.97)	.15
Etanercept[58, 60, 61]	1	4.50 (0.07-286.14)	.48
Infliximab[70-72]	1	3.51 (0.11-111.85)	.48
Overall	**3**	**1.08 (0.11-10.21)**	**.95**
Non-TNF inhibitors			
Anakinra[80]	1	3.50 (0.03-464.12)	.62



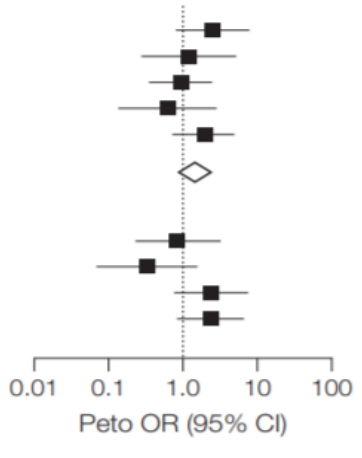
Lymphoma

BRMs	No. of Studies	Peto OR (95% CI)	*P* Value
TNF inhibitors			
Adalimumab[44, 45, 49]	3	1.23 (0.12-13.14)	.86
Certolizumab[53]	1	3.51 (0.03-458.05)	.61
Etanercept[55]	1	4.59 (0.07-284.47)	.47
Golimumab[62, 65]	2	4.18 (0.20-88.53)	.36
Infliximab[37, 38, 68, 70-72]	3	1.64 (0.12-21.92)	.71
Overall	**10**	**2.14 (0.55-8.38)**	**.28**
Non-TNF inhibitors			
Abatacept[76]	1	4.51 (0.07-285.89)	.48
Anakinra[80]	1	0.01 (0.00-0.94)	.05
Tocilizumab[88]	1	0.05 (0.00-3.19)	.16
Combination			
Anakinra + etanercept[21]	1	4.45 (0.07-287.21)	.48



Solid tumors[b]

BRMs	No. of Studies	Peto OR (95% CI)	*P* Value
TNF inhibitors			
Adalimumab[36, 43, 44, 47, 49]	5	2.35 (0.75-7.36)	.14
Certolizumab[51, 53]	2	1.14 (0.26-4.98)	.86
Etanercept[55, 58-61]	3	0.89 (0.33-2.39)	.81
Golimumab[62-66]	5	0.59 (0.13-2.76)	.50
Infliximab[25, 37, 38, 68-72]	5	1.82 (0.69-4.78)	.23
Overall	**20**	**1.31 (0.78-2.20)**	**.31**
Non-TNF inhibitors			
Abatacept[20, 25, 76, 77]	4	0.82 (0.22-3.01)	.76
Anakinra[78-81]	4	0.31 (0.07-1.49)	.14
Rituximab[26, 32, 82, 83]	4	2.28 (0.72-7.25)	.16
Tocilizumab[41, 86, 88, 89]	4	2.22 (0.79-6.20)	.13

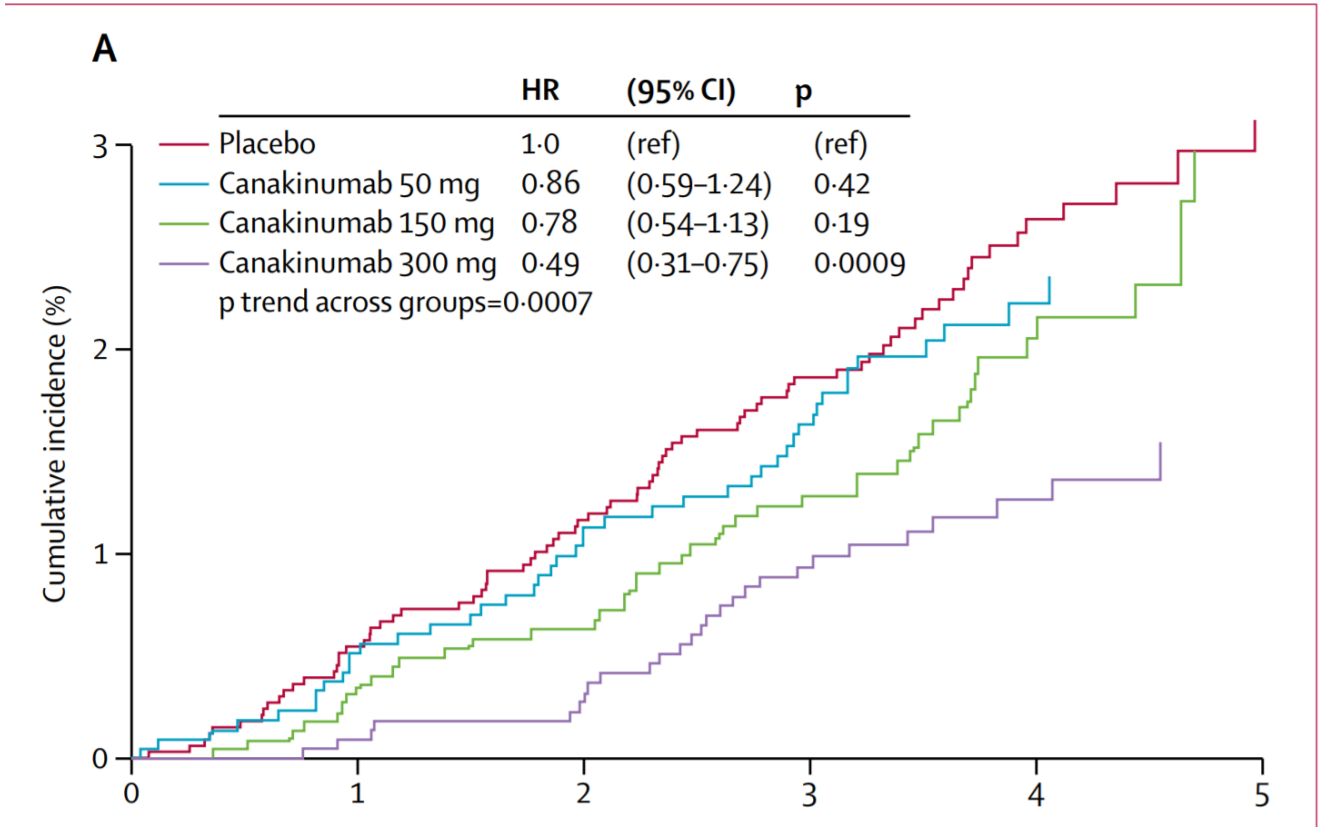


- JAMA 2012

Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

Paul M Ridker, Jean G MacFadyen, Tom Thuren, Brendan M Everett, Peter Libby, Robert J Glynn*, on behalf of the CANTOS Trial Group†*

- Η αναστολή της IL-1 μειώνει την πιθανότητα καρκίνου πνεύμονα!



Cho et al. Arthritis Research & Therapy (2017) 19:277
DOI 10.1186/s13075-017-1482-y

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

The risk of malignancy and its incidence in early rheumatoid arthritis patients treated with biologic DMARDs

Soo-Kyung Cho[1,2], Jiyoung Lee[2], Minkyung Han[2], Sang-Cheol Bae[1,2] and Yoon-Kyoung Sung[1,2*]

Η πιο πρόσφατη μετα-ανάλυση

Table 4 Risk factors for the development of malignancy in early RA patients[a]

Variable	Malignancies		Hematologic malignancies	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Age	1.04 (1.03–1.05)	1.04 (1.03–1.04)	1.02 (0.99–1.06)	1.02 (0.98–1.05)
Male sex	1.90 (1.59–2.27)	1.88 (1.57–2.25)	1.55 (0.59–4.07)	1.41 (0.53–3.74)
Comorbidities	1.66 (1.39–1.99)	1.34 (1.11–1.61)	2.42 (0.87–6.73)	2.29 (0.80–6.52)
Medications				
bDMARD ever use	0.41 (0.24–0.70)	0.42 (0.25–0.73)	1.91 (0.44–8.27)	1.69 (0.38–7.59)
Methotrexate use	0.90 (0.76–1.07)	0.93 (0.78–1.12)	1.21 (0.49–2.97)	1.06 (0.41–2.74)
Corticosteroid use	1.03 (0.86–1.25)	1.05 (0.86–1.28)	1.12 (0.40–3.11)	1.02 (0.35–2.95)
NSAID use	1.22 (0.88–1.71)	1.16 (0.83–1.63)	1.61 (0.22–12.09)	2.00 (0.26–15.48)

RA rheumatoid arthritis, *OR* odds ratio, *CI* confidence interval, *bDMARD* biologic disease-modifying anti-rheumatic drug, *NSAID* nonsteroidal anti-inflammatory drugs
[a]Adjusted by type of healthcare utilization including insurance, type of institution, type of department

CONCISE REPORT

Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides – a follow-up study from the DANBIO Registry

Lene Dreyer,[1] Lene Mellemkjær,[2] Anne Rødgaard Andersen,[3] Philip Bennett,[4] Uta Engling Poulsen,[5] Torkell Juulsgaard Ellingsen,[6] Torben Høiland Hansen,[7] Dorte Vendelbo Jensen,[8] Louise Linde,[3] Hanne Merete Lindegaard,[9] Anne Gitte Rasmussen Loft,[10] Henrik Nordin,[11] Emina Omerovic,[12] Claus Rasmussen,[13] Annette Schlemmer,[14] Ulrik Tarp,[15] Merete Lund Hetland[3 16]

- Τα registries πιθανά δίνουν καλύτερες πληροφορίες
  - Περισσότεροι ασθενείς
  - Μακροχρόνια παρακολούθηση

Δεδομένα από αρχεία...

Variable	No of cancers among treated†	TNF-I treated versus non-treated HR‡ (95% CI)	p Value*
Ever TNF-I treatment			
Overall effect	152	1.02 (0.80 to 1.30)	
Plus adjustment for HAQ§		0.95 (0.74 to 1.22)	
Plus adjustment for CRP§		0.99 (0.77 to 1.26)	
Plus adjustment for DAS28§		0.96 (0.74 to 1.24)	
Men	48	0.83 (0.55 to 1.26)	p=0.24
Women	104	1.13 (0.83 to 1.53)	
Time since treatment initiation, years			
<1	41	1.04 (0.72 to 1.50)	
1–4	97	1.03 (0.79 to 1.35)	p=0.86
5+	14	0.88 (0.51 to 1.54)	
1+	111	1.01 (0.78 to 1.30)	
Cumulative duration of treatment, years			
<1	43	1.04 (0.73 to 1.48)	
1–2	39	1.19 (0.83 to 1.71)	p=0.69
2–3	29	1.09 (0.72 to 1.63)	
4+	41	0.86 (0.60 to 1.22)	
Age at treatment start, years			
<50	12	0.83 (0.38 to 1.82)	
50–64	69	0.97 (0.68 to 1.37)	p=0.76
≥65	71	1.10 (0.80 to 1.50)	

OPEN ACCESS

EXTENDED REPORT

Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

Louise K Mercer, Mark Lunt, Audrey L S Low, William G Dixon, Kath D Watson, Deborah P M Symmons, Kimme L Hyrich, BSRBR Control Centre Consortium

Table 4 Incidence and risk of individual solid cancer subtypes

	sDMARD N=3249	TNFi N=11 767	ETA N=4073	INF N=3457	ADA N=4327
Lung cancer					
Number	40	103	49	25	29
Incidence rate per 10 000 patient-years (95% CI)	34 (24 to 47)	20 (16 to 24)	22 (16 to 29)	20 (13 to 30)	16 (11 to 23)
Unadjusted HR (95% CI)	Referent	0.57 (0.40 to 0.82)	0.64 (0.42 to 0.98)	0.59 (0.36 to 0.97)	0.49 (0.29 to 0.76)
Age and sex adjusted HR (95% CI)	Referent	0.81 (0.56 to 1.17)	0.95 (0.62 to 1.46)	0.81 (0.49 to 1.35)	0.64 (0.40 to 1.04)
PD-adjusted HR (95% CI)	Referent	0.85 (0.52 to 1.39)	1.02 (0.58 to 1.76)	0.92 (0.50 to 1.71)	0.69 (0.39 to 1.23)
Female breast cancer					
Number	22	73	30	18	25
Incidence rate per 10 000 patient-years (95% CI)	34 (20 to 48)	18 (14 to 22)	17 (11 to 23)	19 (10 to 28)	17 (10 to 23)
Unadjusted HR (95% CI)	Referent	0.72 (0.45 to 1.17)	0.70 (0.40 to 1.22)	0.76 (0.41 to 1.42)	0.74 (0.42 to 1.31)
Age adjusted HR (95% CI)	Referent	0.83 (0.51 to 1.35)	0.83 (0.47 to 1.45)	0.86 (0.46 to 1.61)	0.83 (0.47 to 1.48)
PD-adjusted HR (95% CI)	Referent	0.58 (0.32 to 1.06)	0.56 (0.28 to 1.10)	0.59 (0.28 to 1.24)	0.59 (0.31 to 1.15)
Colorectal cancer					
Number	19	43	16	10	17
Incidence rate per 10 000 patient-years (95% CI)	16 (9 to 25)	8 (6 to 11)	7 (4 to 12)	8 (4 to 15)	9 (5 to 15)
Unadjusted HR (95% CI)	Referent	0.52 (0.30 to 0.89)	0.46 (0.24 to 0.90)	0.50 (0.23 to 1.07)	0.59 (0.31 to 1.14)
Age and sex adjusted HR (95% CI)	Referent	0.71 (0.41 to 1.23)	0.66 (0.33 to 1.29)	0.67 (0.31 to 1.44)	0.79 (0.41 to 1.52)
PD-adjusted HR (95% CI)	Referent	0.51 (0.24 to 1.06)	0.45 (0.19 to 1.05)	0.47 (0.19 to 1.20)	0.57 (0.26 to 1.27)
Gastro-oesophageal cancer					
Number	12	20	8	5	7
Incidence rate per 10 000 patient-years (95% CI)	10 (5 to 18)	4 (2 to 6)	4 (2 to 7)	4 (1 to 9)	4 (2 to 8)
Unadjusted HR (95% CI)	Referent	0.35 (0.17 to 0.73)	NR	NR	NR
Age and sex adjusted HR (95% CI)	Referent	0.51 (0.24 to 1.05)	NR	NR	NR
PD-adjusted HR (95% CI)	Referent	0.59 (0.23 to 1.52)	NR	NR	NR

NR, not reported (indicates fewer than 10 events in each cohort so comparative analyses were not performed).
ADA, adalimumab; ETA, etanercept; INF, infliximab; PD, propensity score stratified into deciles; sDMARD, synthetic disease modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitors.

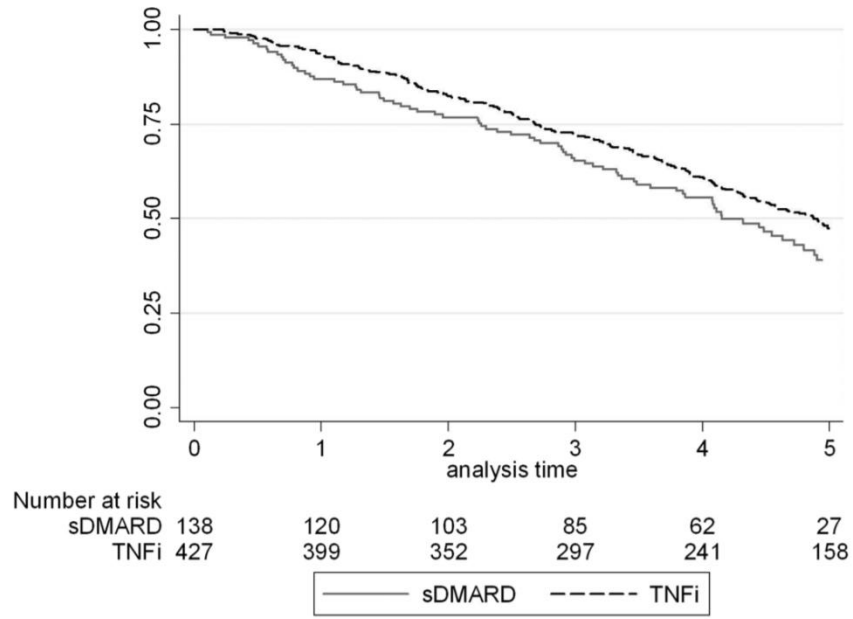


Figure 2 Kaplan-Meier survival curves for death following diagnosis with solid cancer in the BSRBR-RA. sDMARD, synthetic disease modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor.

Που καταλήγουμε όσον αφορά την σχέση TNF αναστολέων και καρκίνου?

- Ο συνολικός κίνδυνος είναι πολύ χαμηλός
- Φαίνεται ίσως κάποια αύξηση στον κίνδυνο λεμφώματος. Όμως...
  - Η ίδια η νόσος αυξάνει τον κίνδυνο
  - Channeling bias? Οι ασθενείς εκείνοι που έχουν την υψηλότερη πιθανότητα εμφάνισης νόσου (υψηλή ενεργότητα...) είναι και αυτοί που επιλέγονται για βιολογική θεραπεία

Καρκίνος δέρματος-Μελάνωμα

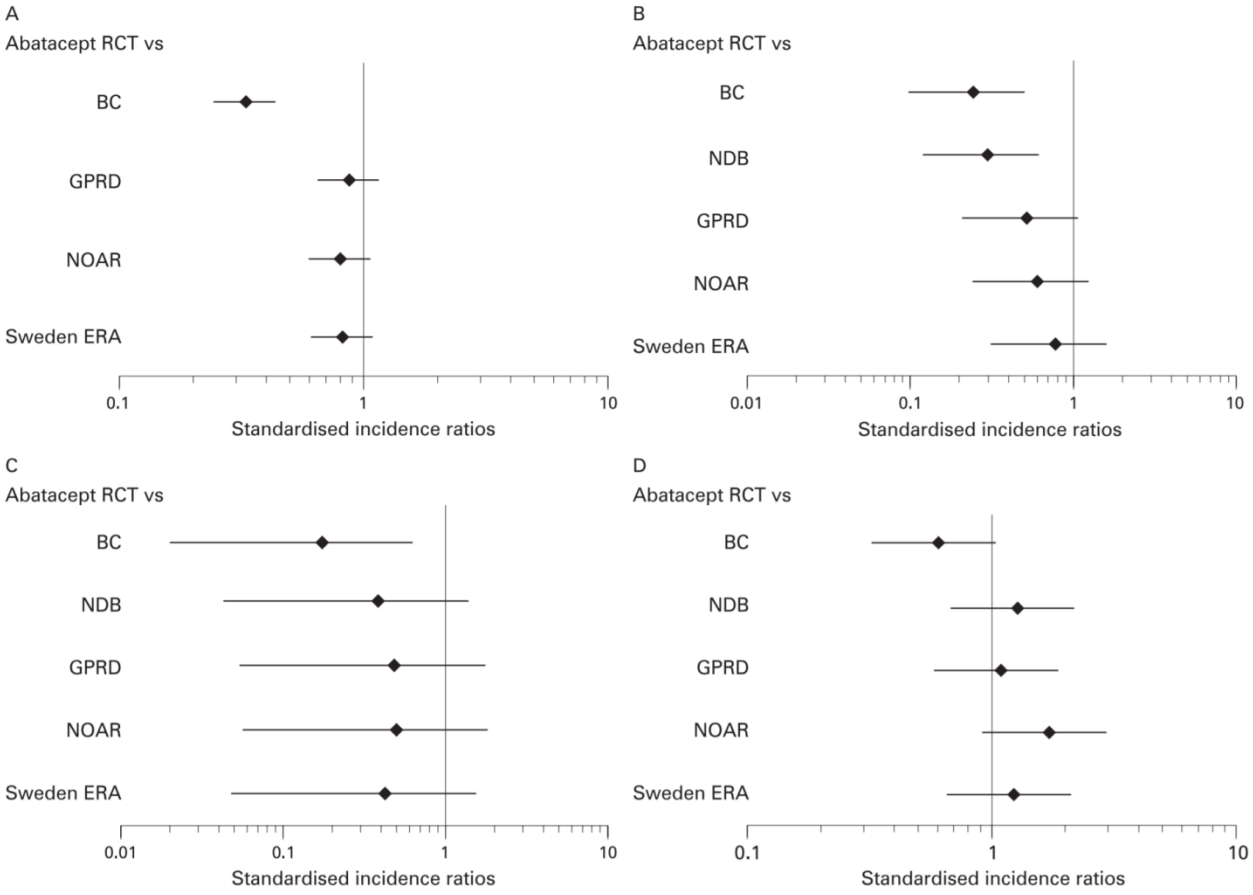
- Οι κλινικές μελέτες έδειξαν αύξηση στον μη μελανωματικό καρκίνο δέρματος (HR 2)
- Αυτό πάντως δεν επιβεβαιώθηκε από τα αρχεία βιολογικών θεραπειών (DANBIO, BSRBR-RA). Εκεί βρέθηκε αυξημένος κίνδυνος για όλους τους ασθενείς με PA ανεξάρτητα θεραπείας (ανάγκη για screening?).
- Οριακή η συσχέτιση για μελάνωμα. Ο συνολικός κίνδυνος εξαιρετικά χαμηλός

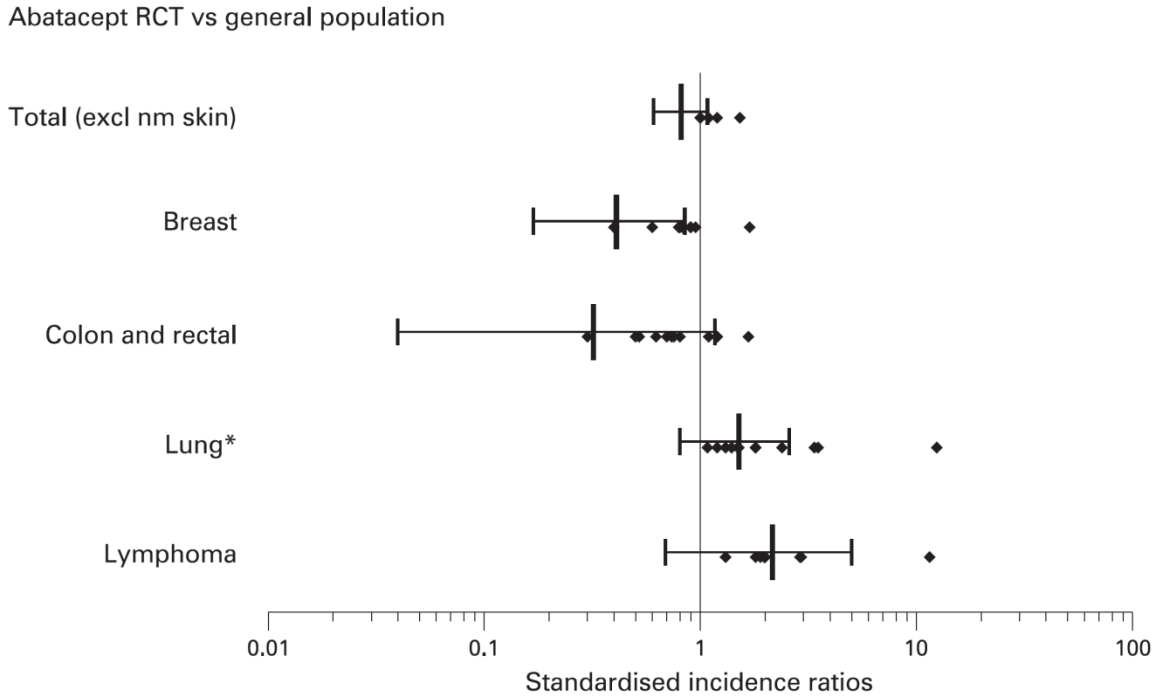
Παιδιά και έφηβοι ίσως αποτελούν εξαίρεση

- 48 περιστατικά κακοήθειας σε 10 χρόνια (JIA και IBD). Τα περισσότερα λεμφώματα. Μερικά περιστατικά ηπατοσπληνικού Τ λεμφώματος. Πολλοί ασθενεις έπαιρναν ταυτόχρονα και AZA..
- Box Warning...

Malignancies in the rheumatoid arthritis abatacept clinical development programme: an epidemiological assessment

T A Simon,[1] A L Smitten,[1] J Franklin,[2] J Askling,[3] D Lacaille,[4] F Wolfe,[5] M C Hochberg,[6] K Qi,[7] S Suissa[8]





- A Total
- B Breast
- C Colorectal
- D Lung

Schiff et al. Arthritis Research & Therapy 2011, 13:R141
http://arthritis-research.com/content/13/5/R141

arthritis research&therapy

RESEARCH ARTICLE Open Access

Integrated safety in tocilizumab clinical trials

Michael H Schiff[1*], Joel M Kremer[2], Angelika Jahreis[3], Emma Vernon[4], John D Isaacs[5] and Ronald F van Vollenhoven[6]

Table 1 Serious adverse events reported at a rate of ≥ 0.3 per 100 patient-years in any group (all-control population)

		All-control population *n* = 4,199	
	Control *n* = 1,555	**Tocilizumab 4 mg/kg + DMARDs *n* = 774**	**Tocilizumab 8 mg/kg + DMARDs *n* = 1,870**
Rate per 100 PY (number of events)			
Pneumonia	0.6 (5)	0.7 (4)	0.9 (11)
Cellulitis	0.2 (2)	–	0.9 (11)
Gastroenteritis	0.2 (2)	0.5 (3)	0.1 (1)
Urinary tract infection	0.5 (4)	0.2 (1)	0.1 (1)
Sepsis	0.1 (1)	0.4 (2)	0.2 (2)
Herpes zoster	0.1 (1)	–	0.3 (4)
Fall	0.1 (1)	–	0.3 (4)
Pulmonary embolism	0.2 (2)	–	0.3 (3)
Basal cell carcinoma	0.1 (1)	0.4 (2)	0.1 (1)
Spinal compression fracture	0.1 (1)	–	0.3 (3)
Coronary artery disease	–	0.2 (1)	0.3 (3)
Back pain	0.1 (1)	–	0.3 (3)
Rheumatoid arthritis	0.4 (3)	–	–
Gastroenteritis viral	0.1 (1)	0.4 (2)	–
Prostate cancer	0.1 (1)	0.4 (2)	–
Neutropenia	–	0.4 (2)	0.1 (1)
Syncope	–	0.4 (2)	–
Tendon rupture	–	0.4 (2)	–
Interstitial lung disease	–	0.4 (2)	–
Anaphylactic reaction	–	0.4 (2)	–

DMARD, disease-modifying antirheumatic drug; PY, patient-years.

Το rituximab?

- Πρόκειται ουσιαστικά για αντικαρκινικό φάρμακο

Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years

Ronald F. van Vollenhoven, Roy M. Fleischmann, Daniel E. Furst, Stuart Lacey, and Patricia B. Lehane

Seminars in Arthritis and Rheumatism 43 (2014) 489–497

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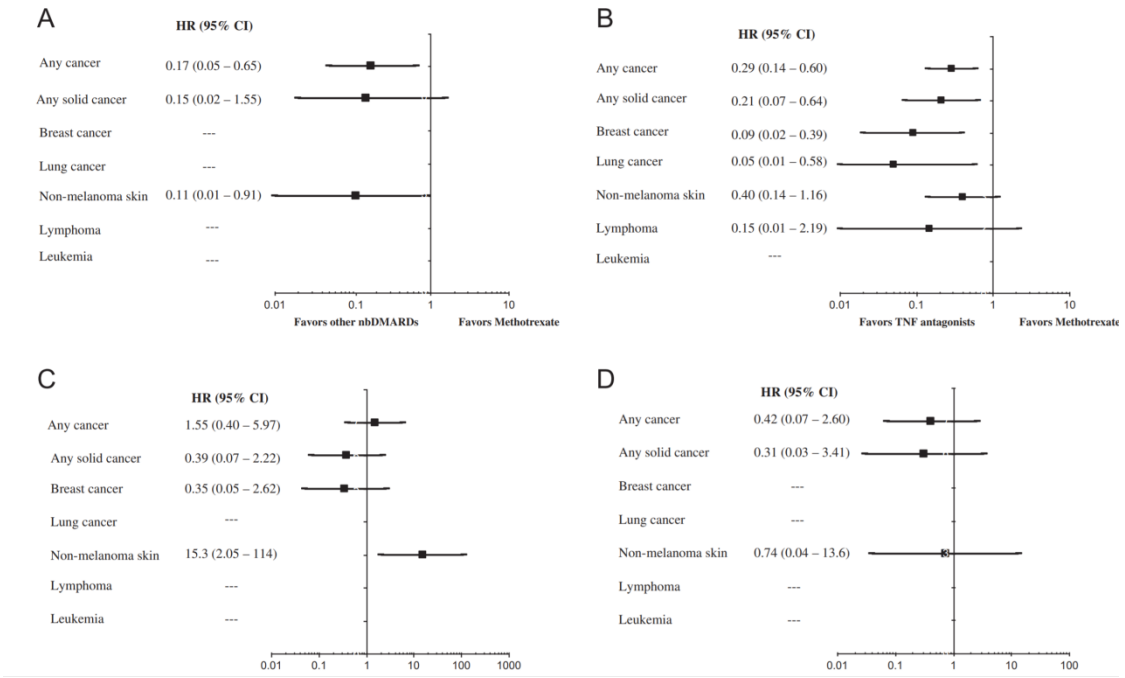
journal homepage: www.elsevier.com/locate/semarthrit

Comparative cancer risk associated with methotrexate, other non-biologic and biologic disease-modifying anti-rheumatic drugs

Daniel H. Solomon, MD, MPH[a,b,*], Joel M. Kremer, MD[c], Mark Fisher, MD[d], Jeffrey R. Curtis, MD, MPH[e], Victoria Furer, MD, MPH[i], Leslie R. Harrold, MD, MPH[f], Marc C. Hochberg, MD, MPH[g], George Reed, PhD[h], Peter Tsao, MSc[a], Jeffrey D. Greenberg, MD, MPH[i]



Ο ρόλος της MTX

- A Other DMARD
- B anti-TNF
- C ABA
- D RTX

Μπορούμε να δώσουμε βιολογικό σε ασθενείς με ιστορικό κακοήθειας?

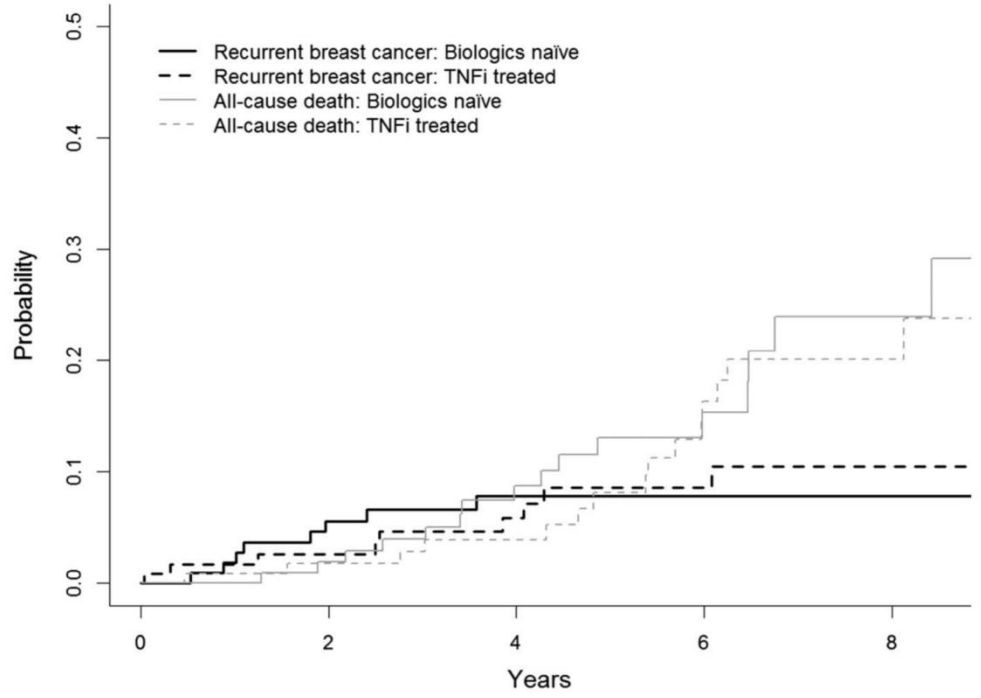
Clinical and epidemiological research

EXTENDED REPORT

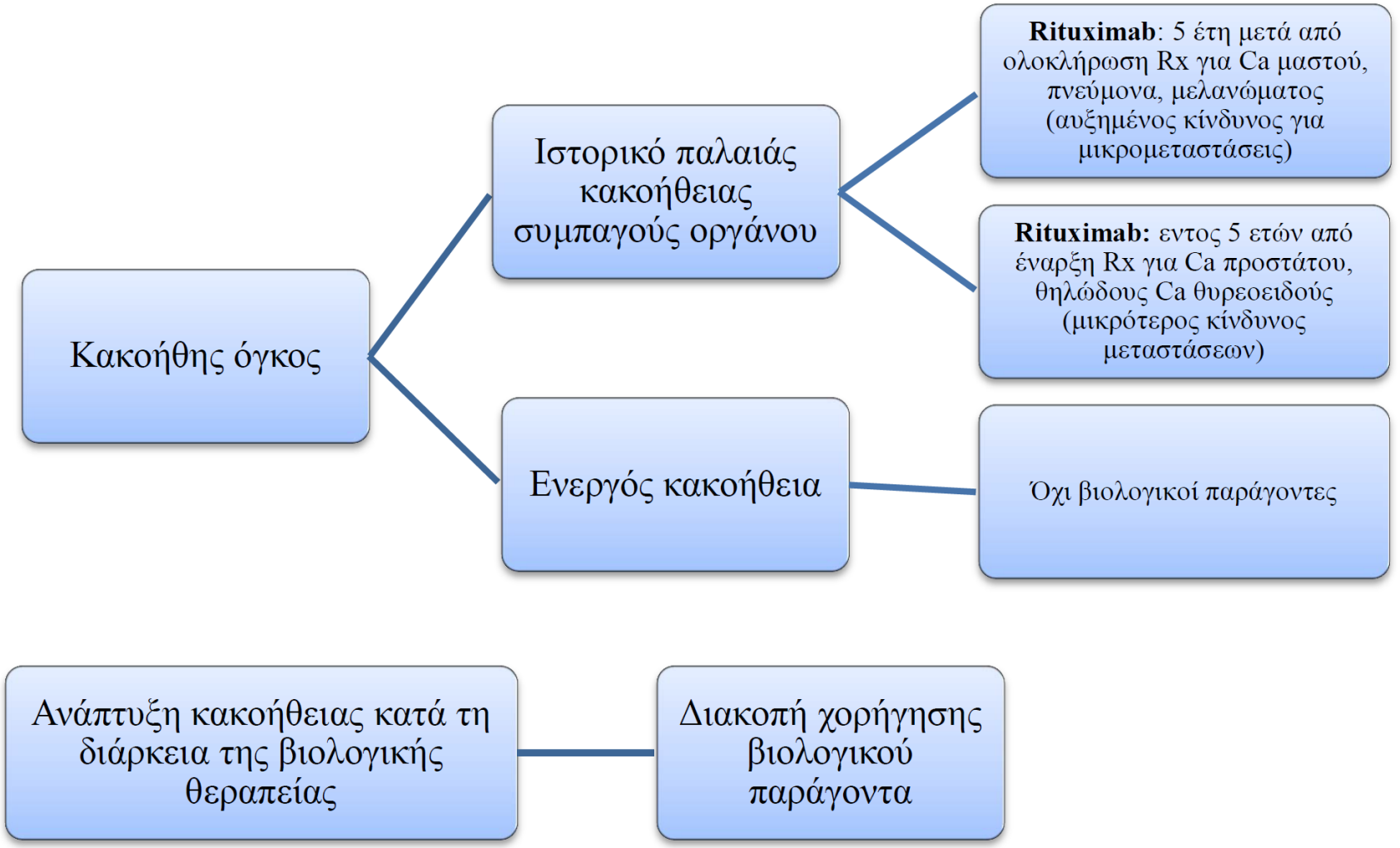
TNF inhibitor therapy and risk of breast cancer recurrence in patients with rheumatoid arthritis: a nationwide cohort study

Pauline Raaschou,[1,2] Thomas Frisell,[1] Johan Askling,[1,3] for the ARTIS Study Group

- Η χρήση TNF αναστολέων σε ασθενείς με ιστορικό καρκίνου μαστού δεν φαίνεται να αύξησε τον κίνδυνο υποτροπής (χορήγησε μετά από 9.4 έτη από την διαγνωση)



Ας είμαστε επιφυλακτικοί….



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