Nutraceutica nella prevenzione dei tumori: derivati di origine alimentare come antiinfiammatori

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Rovigo

I° Simposio Nazionale sulla Nutraceutica in Urologia

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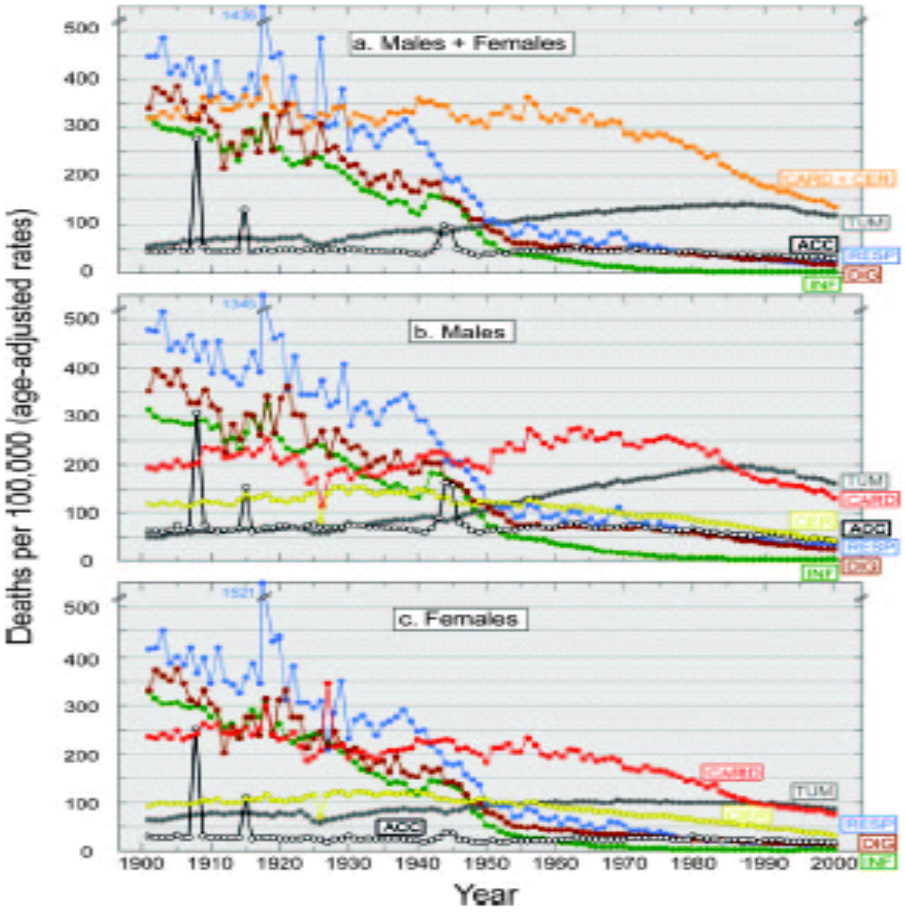
Mortalità dal1901 to 2000: speranza di vita



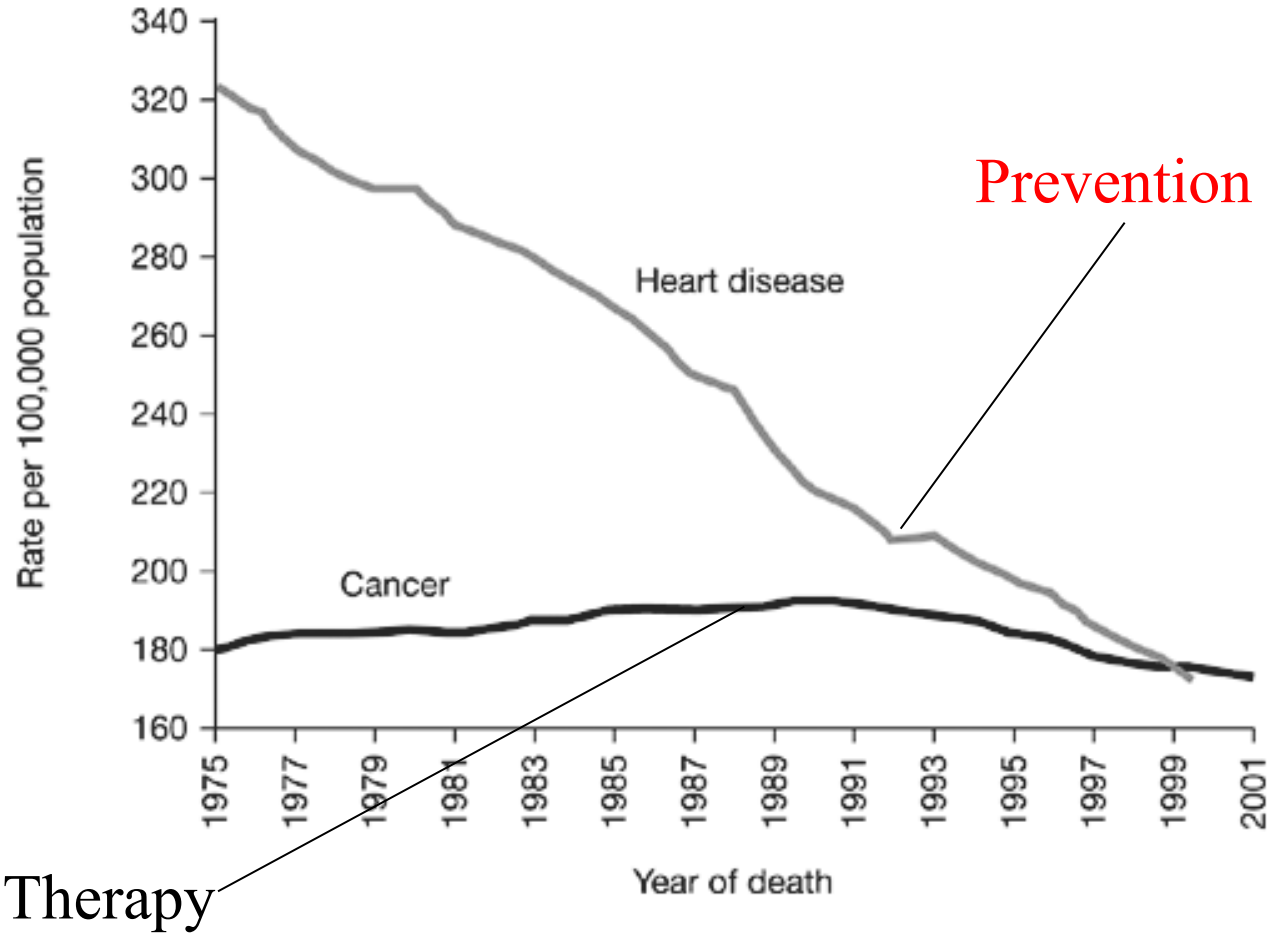
La rivoluzione epidemiologica
Del XIX secolo

Mortality rate from 1901 to 2000 for the principal causes of death:

- **Infectious diseases (INF)**
- **tumors (TUM)**
- **cardiovascular (CARD)**
- **cerebrovascular (CER)**
- **respiratory and flu (RESP)**
- **digestive tract (DIG)**
- **accidents (ACC)**

De Flora S. et al. Faseb J. 2005, Vol 8:892-7

Prevenzione meglio che Terapia



Jemal A *et al*. (2005) Cancer statistics, 2005. *CA Cancer J Clin* **54**: 10–0

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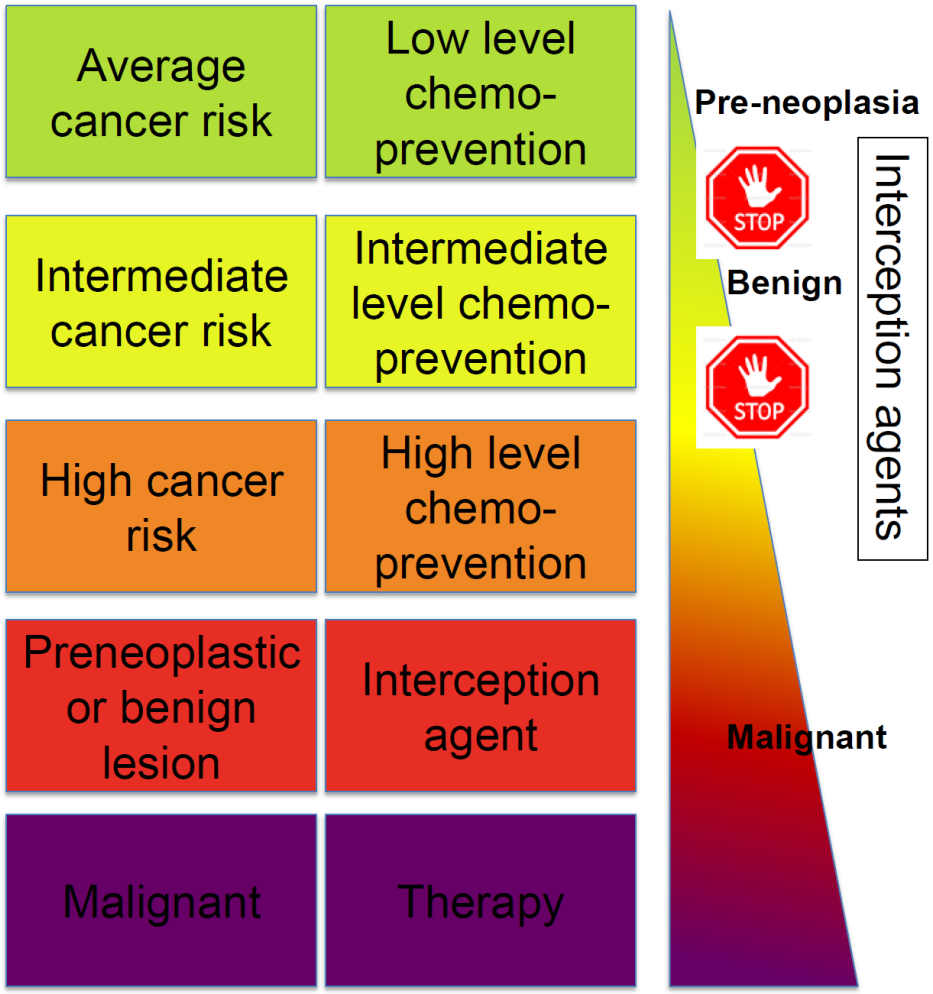
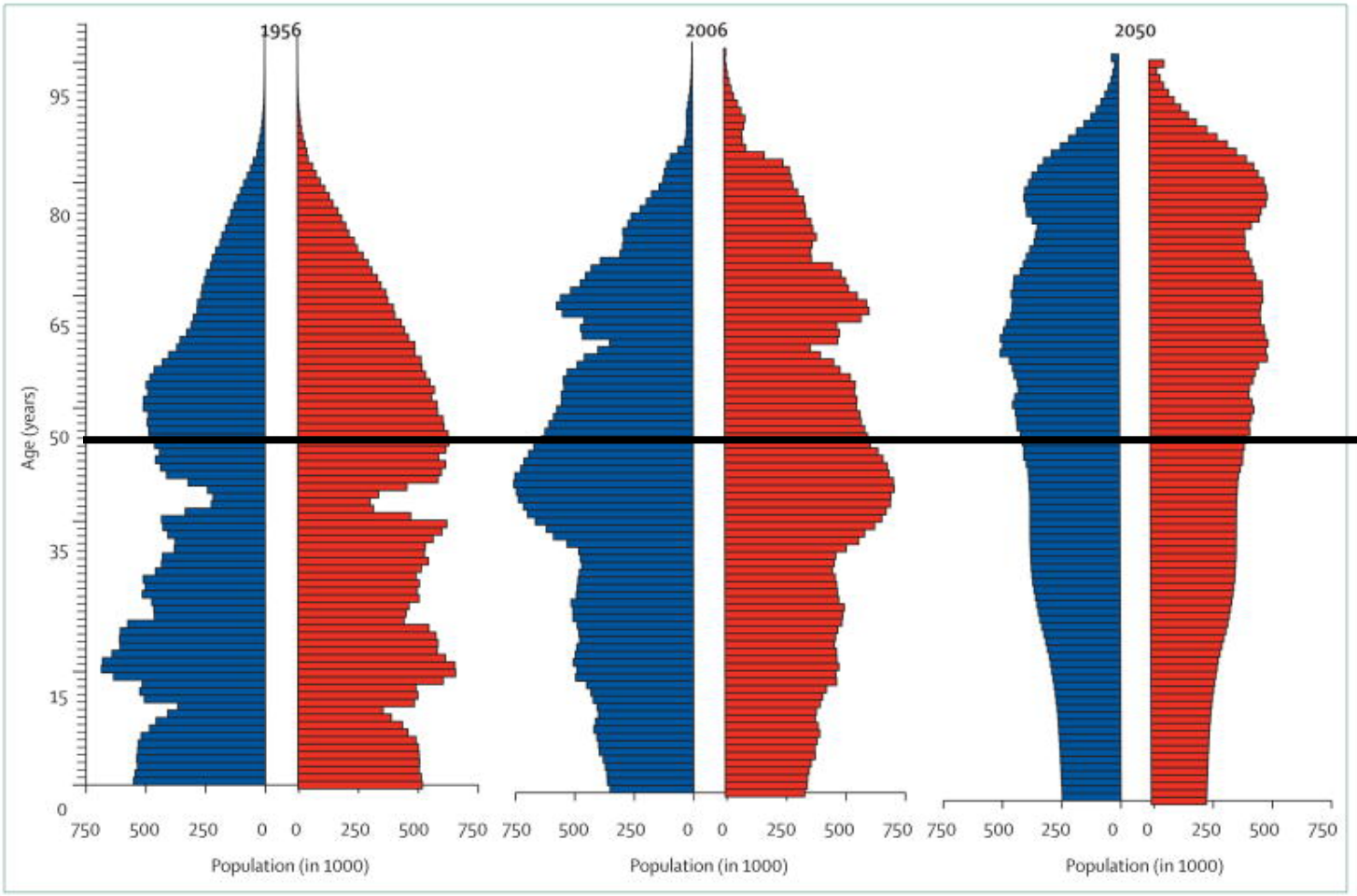


Figure 1: Cancer prevention in the general population at 'lowest' risk of developing cancer must be with low toxicity interventions. As cancer risk level increases, more efficacious drugs with higher side effects are warranted. Interception approaches can be used with pre-neoplastic and even benign lesions.

SPERANZA DI VITA ALLA NASCTA E AUMENTO DELL ETA MEDIA. IN PARTICOLARE LE DONNE VIVONO Più A LUNGO. LONGEVITà DI GENERE



50 anni

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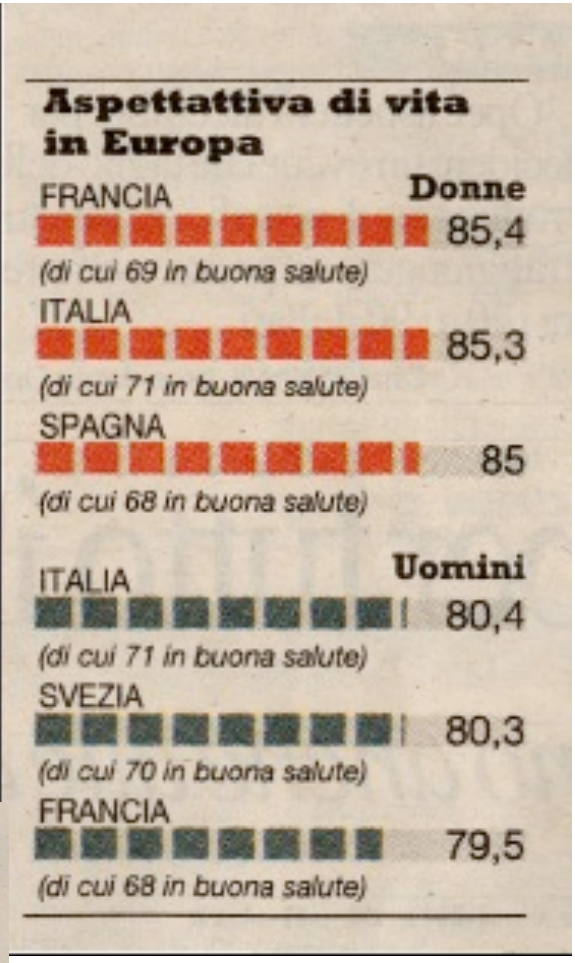
Christensen K, *et al* Lancet. 2009 Oct 3;374(9696):1196-208.

La Repubblica



Gli italiani i più longevi d'Europa

Classifica di Lancet. E gli esperti confermano: "Qui si vive meglio"

(segue dalla prima pagina)

ELENA DUSI

E ANCHE se le donne sono leggermente sopravanzate dalle francesi (85,4 anni contro i nostri 85,3), nel complesso si conferma che il nostro è il paese dove i giorni sono più lunghi.

Lo studio europeo che esce oggi sulla rivista medica *The Lancet* si sofferma sulle ragioni di questo primato. E lo fa in un momento che sembra studiato apposta per farci riflettere. Tra i 25 paesi europei, infatti, si vive più a lungo e si invecchia con meno acciacchi laddove il livello di istruzione è più elevato, il sistema sanitario pubblico è meglio finanziato e le politiche a favore degli anziani sono più supportate da fondi. La correlazione fra ricchezza, educazione e durata della vita è molto stretta, sottolinea la curatrice dello studio, Carol Jagger dell'università inglese di Leicester. E nell'Europa a 25 il nucleo centrale dei quindici offre panorami nettamente migliori rispetto ai dieci paesi arrivati dopo con economie più traballanti.

Livello di istruzione elevato, buon sistema sanitario e aiuti agli anziani

Per Antonio Golini, che insegna Demografia alla Sapienza ed è membro dell'Accademia dei Lincei, il primato italiano ha cause note come dieta, un sistema sanitario che funziona bene nonostante qualche scandalo e una generale condizione di salute che si trasmette per via genetica di padre in figlio. «Siamo abituati ad accentuare i lati negativi della nostra condizione, ma in Italia godiamo di un buon sistema di vita e abbiamo il vantaggio di non avere grandi metropoli. Nelle città medie e piccole che caratterizzano il nostro paesaggio la qualità dell'esistenza è molto migliore».

L'idillio fra The Lancet e l'Italia dura però solo un capitolo. In un paese che invecchia (così come tutto il continente) e ha un pil privo di grinta non esiste altra soluzione — sostengono la Jagger e i suoi ricercatori — che mettere in atto una raccomandazione avanzata dal Consiglio Europeo: portare al 50 per cento il livello di occupazione dei lavoratori con più di 55 anni e far slittare gradualmente l'età pensionabile verso i 70 anni. «È ovvio che la fase di attività di un individuo debba andare di pari passo con l'allungamento della sua vita» dice Golini. Anche perché l'indice della salute — che indica l'età media in cui si presentano i primi acciacchi invalidanti — oltrepassa in Italia l'asticella dei 70 anni.

Con il nostro pil si pone il problema delle pensioni e dovremo lavorare fino a 70 anni

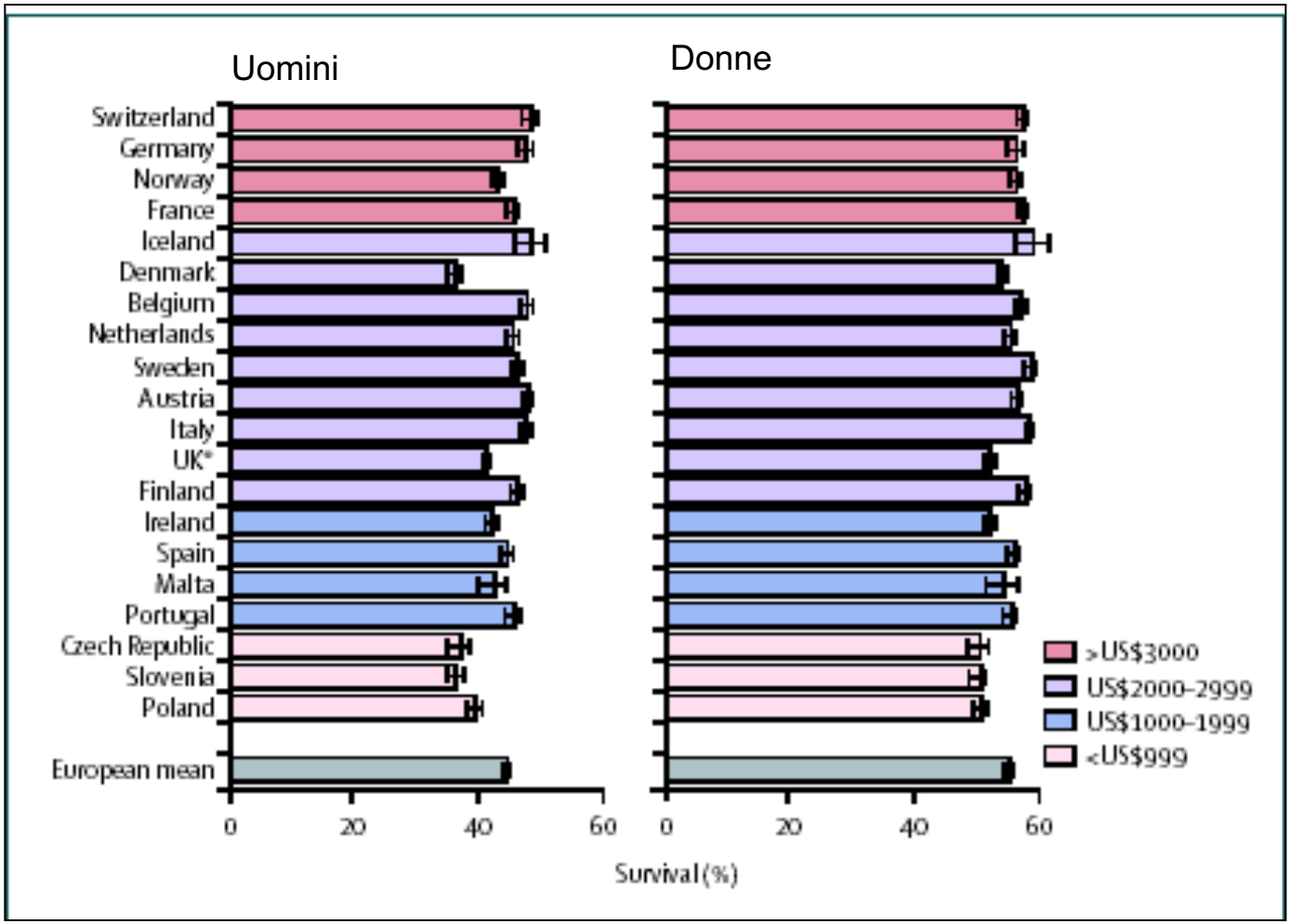
Per ogni anno che passa, al giorno d'oggi, la nostra aspettativa di vita aumenta di almeno tre mesi. «È come se ogni anno durasse per noi quindici mesi» spiega Golini. «Dodici ci sono dati subito, gli altri tre vengono in un certo senso depositati in banca: ne usufruiremo sotto forma di allontanamento della vecchiaia. Ma non è giusto che a pagarne i costi siano solo i giovani e i lavoratori attivi in genere. Anche perché negli ultimi quindici anni l'Europa è cresciuta a un ritmo mediamente doppio rispetto all'Italia, mentre India e Cina ci hanno sopravanzato di circa dieci volte. La strada persa si recupera soltanto lavorando di più, non solo nel corso della settimana ma anche in quello della vita». Sembra sia il modo migliore per arrivare a cent'anni.

Mortalità per Tumore: Uomini e Donne a confronto

Tabella: Tassi di Mortalità per anno per Tumore – riferiti a 10.000 persone in tutta Italia

FASCE ETA'	UOMINI	DONNE
Fino 30 anni	0.58	0.48
30-40 anni	1.68	1.98
40-50 anni	6.85	6.99
50-60 anni	27.31	17.92
60-70 anni	75.38	36.74
70-80 anni	167.35	74.66
80 e oltre	282.19	142.19
Tasso std	28.18	19.58

5-year relative survival (RS) by country for all cancers combined, with area-weight mean European survival (EUROCARE 4 study)



Source: The Lancet Oncology 2007, 23 Aug Berrino Franco et al.
"Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study"

Epidemiological evidence for cancer prevention

MORTALITY (over 100.000 people) FOR CANCER IN SEVERAL COUNTRIES (ACS)

	Italia	Germania	DK	UK	USA	Giapp.	Cina	Uganda
Totale								
Uomini	170,9	161.8	179.2	162.3	152.6	154.3	159.8	123.6
Donne	95,2	110.4	104.1	122.7	119.9	82.2	86.7	118.5
Polmone e bronchi								
Uomini	50,1	42.4	45.2	42.9	48.7	32.4	36.7	3.3
Donne	8.5	10.8	27.8	21.1	26.8	9.6	16.3	2.1
Colon e retto								
Uomini	16.5	19.5	23.3	17.5	15.2	17.3	7.9	7.0
Donne	10,9	15.7	19.2	12.4	11.6	11.1	5.3	6.2
Mammella	18,9	21.6	27.8	24.3	19.0	8.3	5.5	13.4
Prostata	12,2	15.8	22.6	17.9	15.8	5.7	1.0	32.5
Stomaco								
Uomini	12,6	10.3	5.4	8.7	4.8	28.7	32.7	6.6
Donne	6,5	6.4	3.3	4.0	2.2	12.7	15.1	5.2
Esofago								
Uomini	3.4	5.0	7.0	9.0	5.1	7.5	21.6	12.5
Donne	0.7	1.0	1.9	4.1	1.2	1.1	9.6	11.3
Cervice Uter.	2.2	3.8	5.0	3.1	2.3	2.8	3.8	29.2
Fegato								
Uomini	12,6	4.9	3.4	2.8	4.4	21.0	35.3	6.1
Donne	4,8	2.1	2.3	1.5	2.0	6.7	13.1	5.0

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Angiopreventive compounds

a

soy beans and genistein

b

red clover and daidzein

c

Sylibum m. and silybinin

d

appies and quercetin

e

red grapes and wine, and resveratrol

f

Camelia s. and EGCG

g

Curcuma l. and curcumin

h

Hypericum p. and hyperforin

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Araldi EM *et al*. Curr Cancer Drug Targets. 2008, 8(2):146-55

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Angiopreventive compounds

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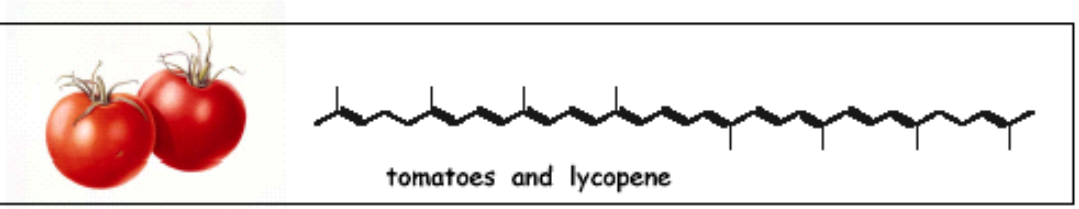

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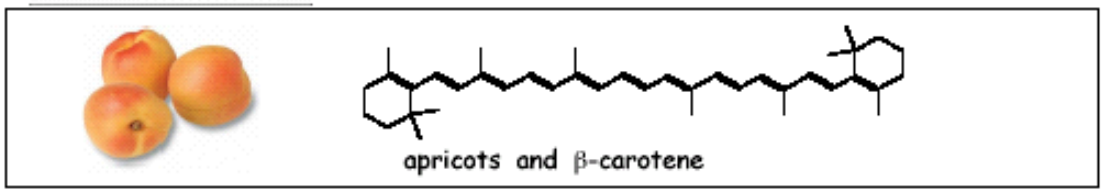

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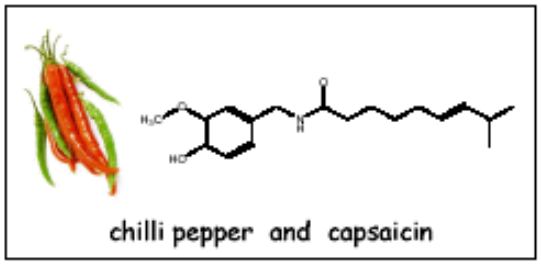

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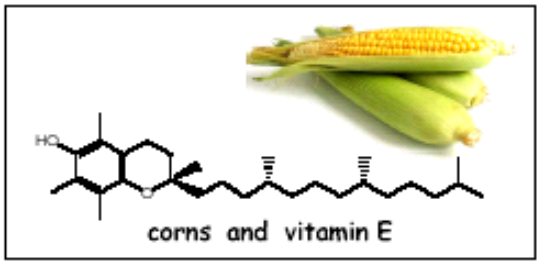

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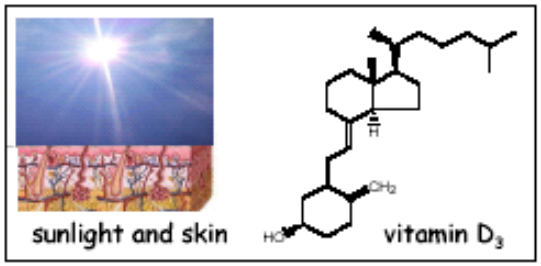

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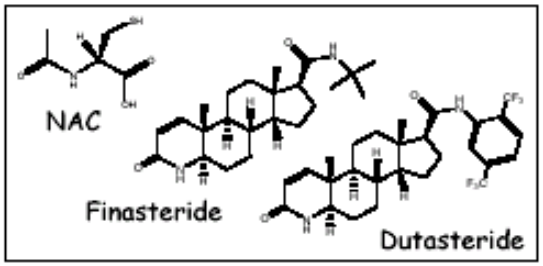

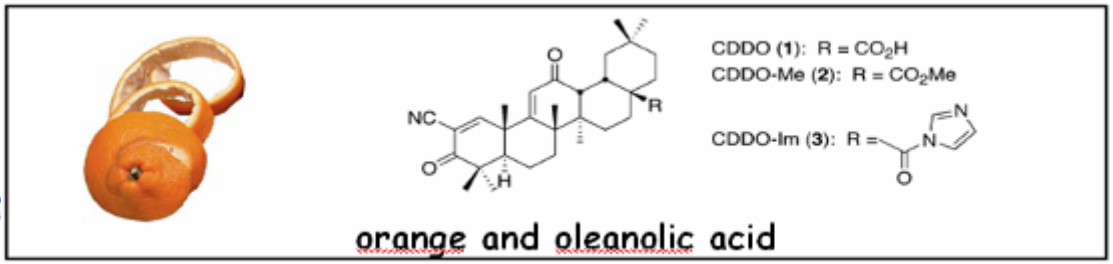

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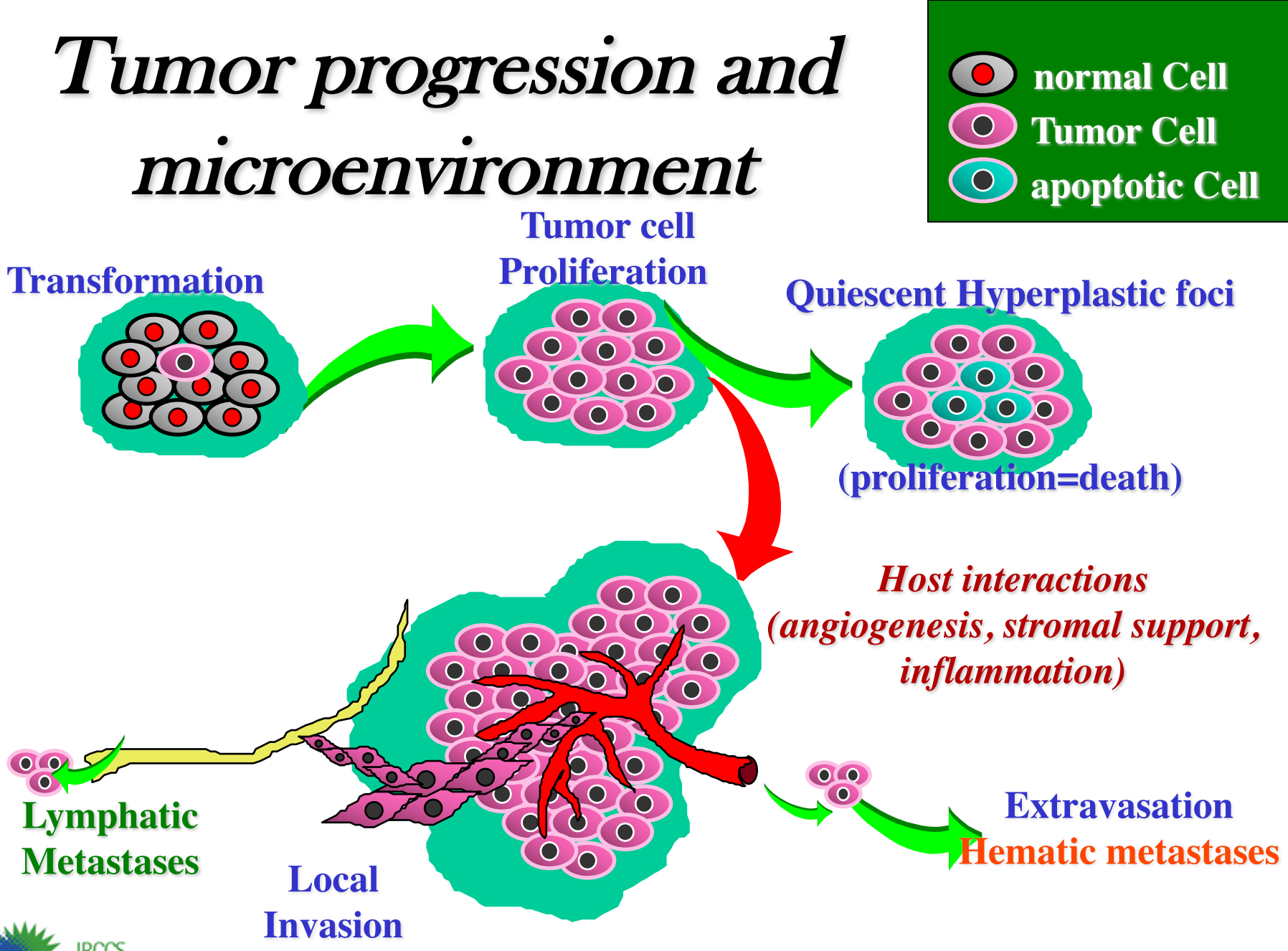
PHYTOCHEMICALS	FOOD	MAIN CHEMOPREVENTIVE ACTIVITIES
Ellagic acid	strawberries, grape, blueberries,	Antioxidant
Phenolic acids	coffee and red grapes	Antioxidant
Omega-3 fatty acids	fish oil (mackerel, salmon, trout)	may decrease risk of heart disease, anti-inflammatory
Allylic sulfide (allicin)	garlic	intercepts and detoxifies
Anthocyanins	blackberries, cherries, raspberries, red grapes and strawberrie	Antioxidant
Capsaicin	red peppers	antiinflammatory
Catechins	green tea and black tea, hop, dark chocolate	antiangiogenic, antibacteric, antiinflammatory, inhibits the activation of carcinogens
Curcumin	turmaric, curry, mustard	antiangiogenic, antiinflammatory, antioxidant
Epicatechine	tea, dark chocolate , peach and plums	antiangiogenic, antibacteric, antiinflammatory, inhibits the activation of carcinogens
Hesperidin	oranges, lemons, citrus fruits	Aids a healthy heart
Fibre	cereal bran	prevents intestinal neoplasia
Genistein	tofu, soy milk, soy beans	Phyto-estrogen, anti-angiogenic
Gingerol	ginger	Antioxidant
Isothiocyanates, Indoles	broccoli, cauliflower, cabbage, kale	blocks carcinogens from damaging a cell; interferes with the action of a precancerous form of estrogen
Limonene and Terpenes	orange and lemon peel	inhibits malignant cell growth
Lignans	flax seed	interferes with estrogen action and may reduce breast, colon and ovarian cancer
Lycopene	tomatoes and kiwi	prevent prostate cancer risk, antiangiogenic
Polyphenols	apples, broccoli, cereal bran, green tea, spinach	Antioxydant, antiangiogenic
Procyanadin	red and blue fruits and vegetables	prevents infections
Quercetin	cherry tomatoes, red onions, apples	Antioxydant, inhibits the proliferation of several tumor cells
Teaflavine	black tea	antiangiogenic, antibacteric, antiinflammatory, inhibits the activation of carcinogens
B- C Vitamins	citrus fruits	reinforce immune system

Tumor progression and microenvironment



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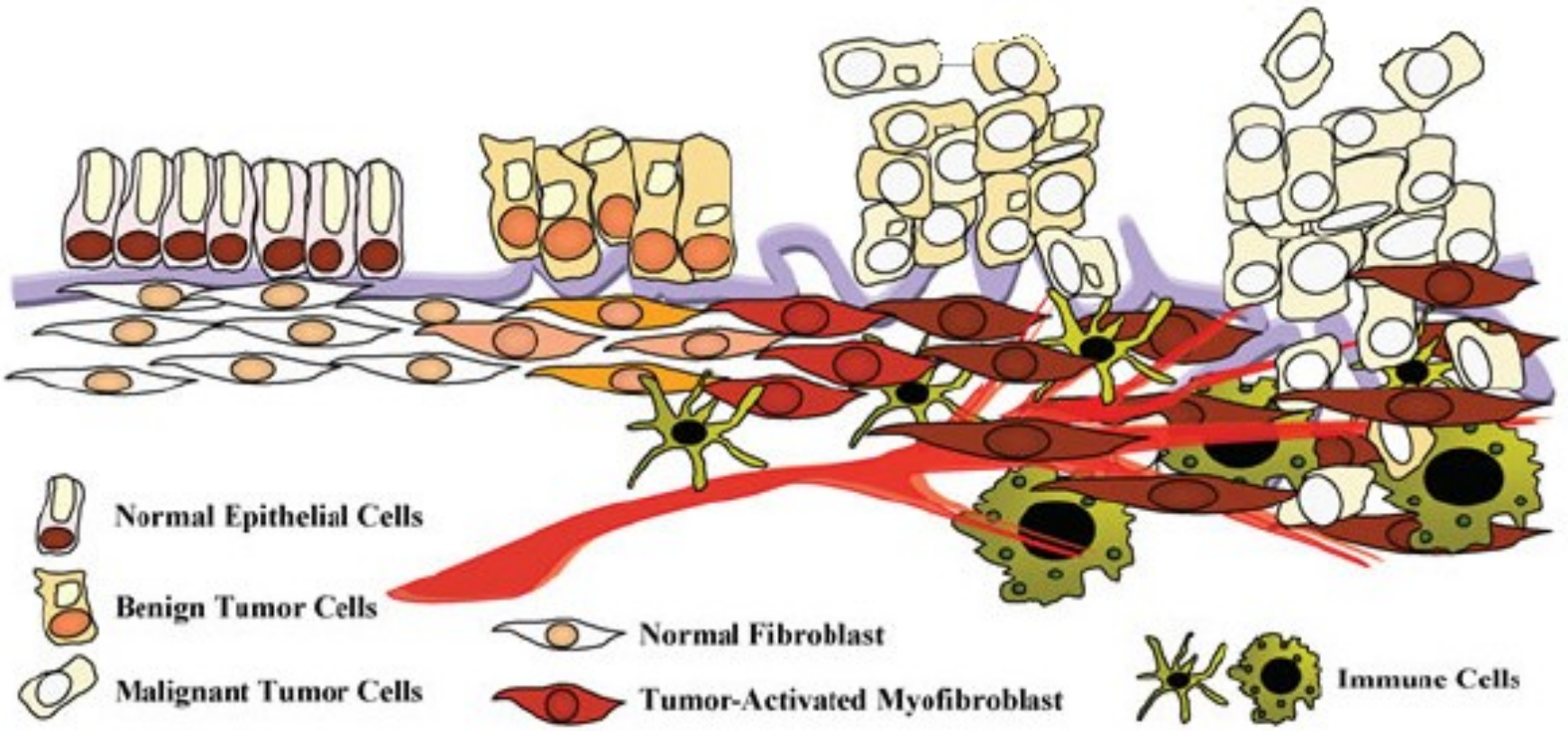
Tumors are tissues



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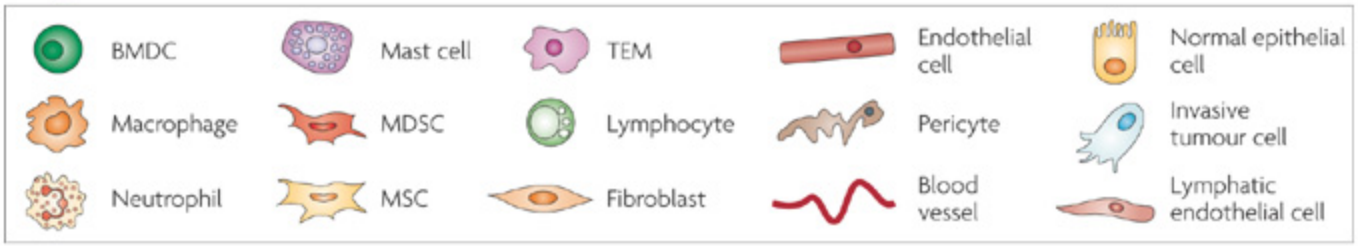
Suh et al. Clin Cancer Res 13: 121–31, 2007

The tumor microenvironment



Nature Reviews | Cancer

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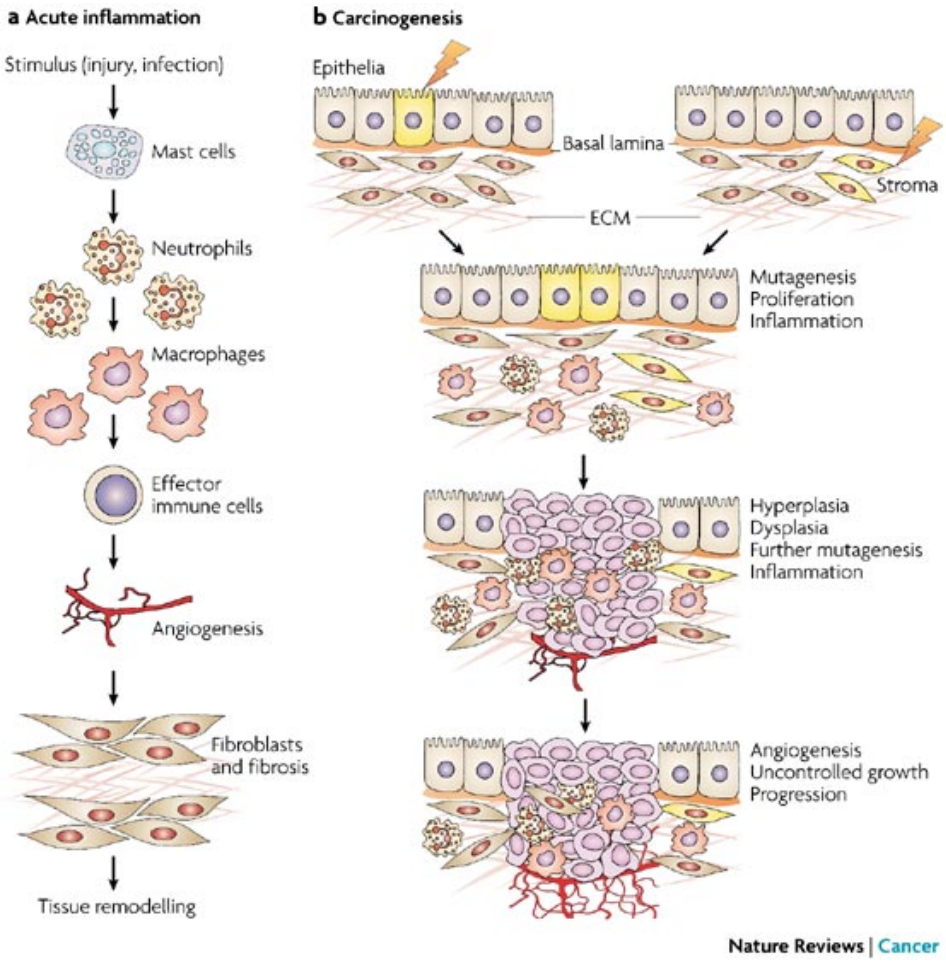
Johanna A. Joyce & Jeffrey W. Pollard
Nature Reviews Cancer **9, 239-252 (April 2009)**
doi:10.1038/nrc2618

In inflammation and in tumor progression similar cellular activations occur in the microenvironment



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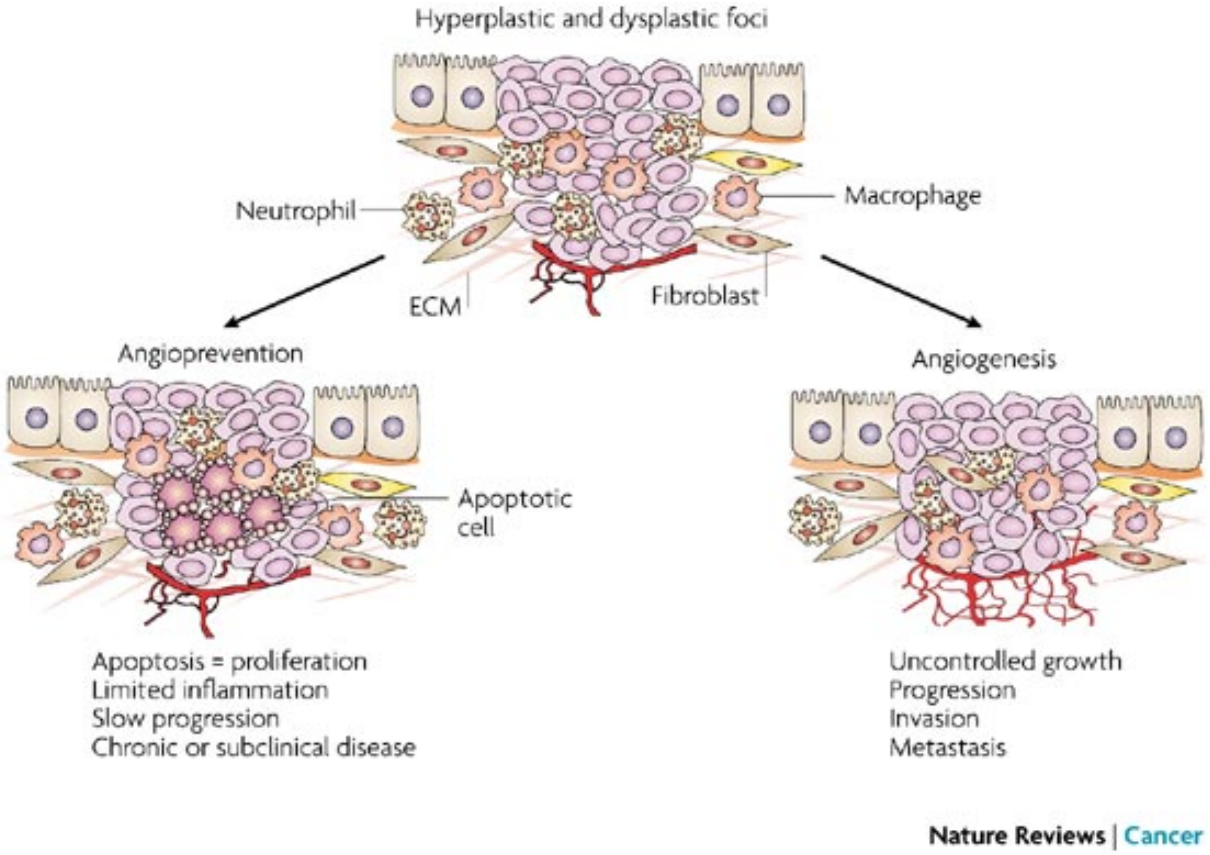
Albini A, Sporn MB. The tumour microenvironment as a target for chemoprevention. Nat Rev Cancer. 7:139-47; 2007

INFLAMMATORY ANGIOGENESIS IS A TARGET OF CHEMOPREVENTION



Albini A, Sporn MB. The tumour microenvironment as a target for chemoprevention. Nat Rev Cancer. 7:139-47; 2007

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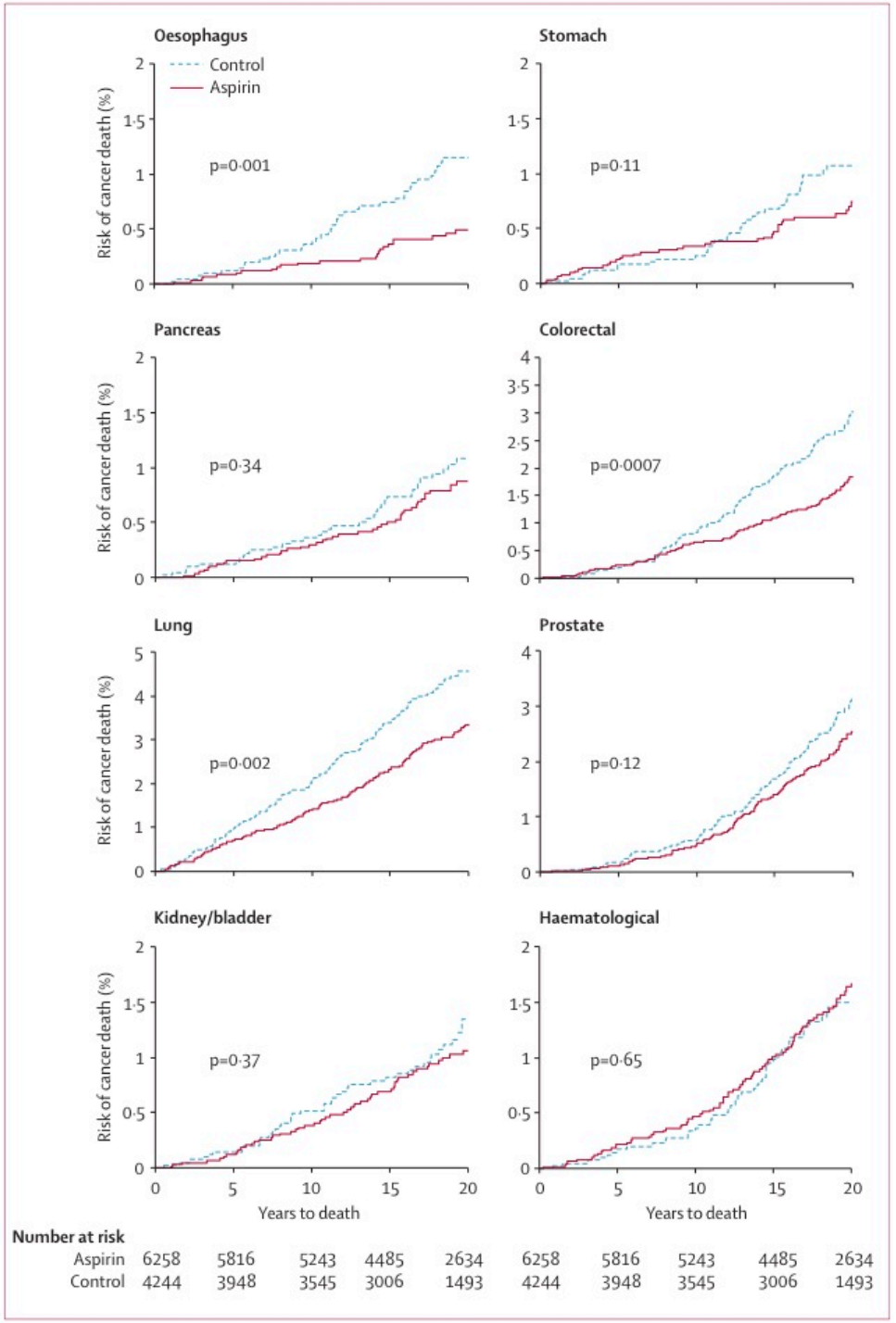
nature REVIEWS CANCER

Aspirin in Chemoprevention

Targeting inflammation: Several types of cancers are prevented

Warfarin had no effect over the same time period



Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials **Rothwell PM et al** **Lancet. 2011;377(9759):31-41**

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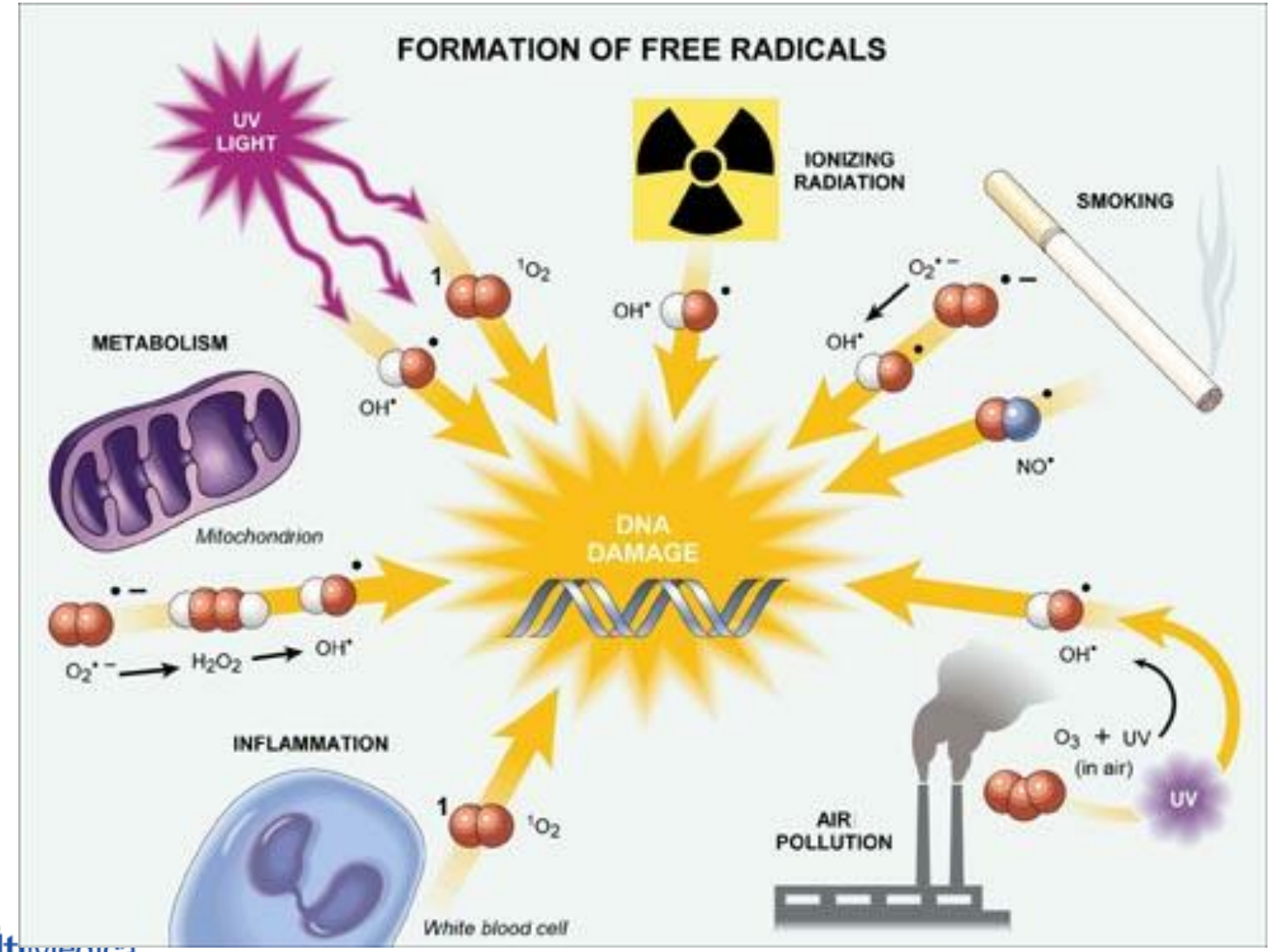
Effetti antiossidanti-anti radicali liberi



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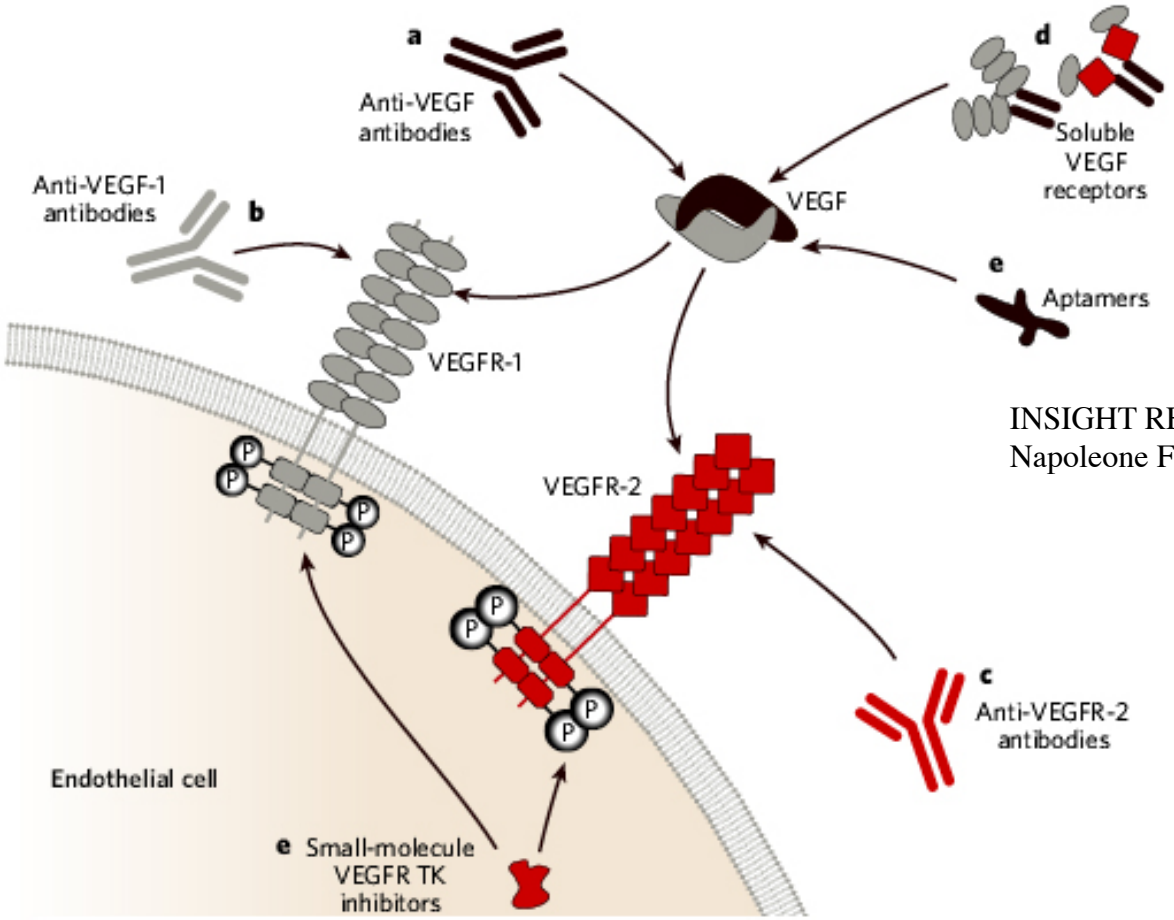
VEGF-VEGF receptor inhibition for antiangiogenesis



INSIGHT REVIEW NATURE 438: 967
Napoleone Ferrara & Robert S. Kerbel

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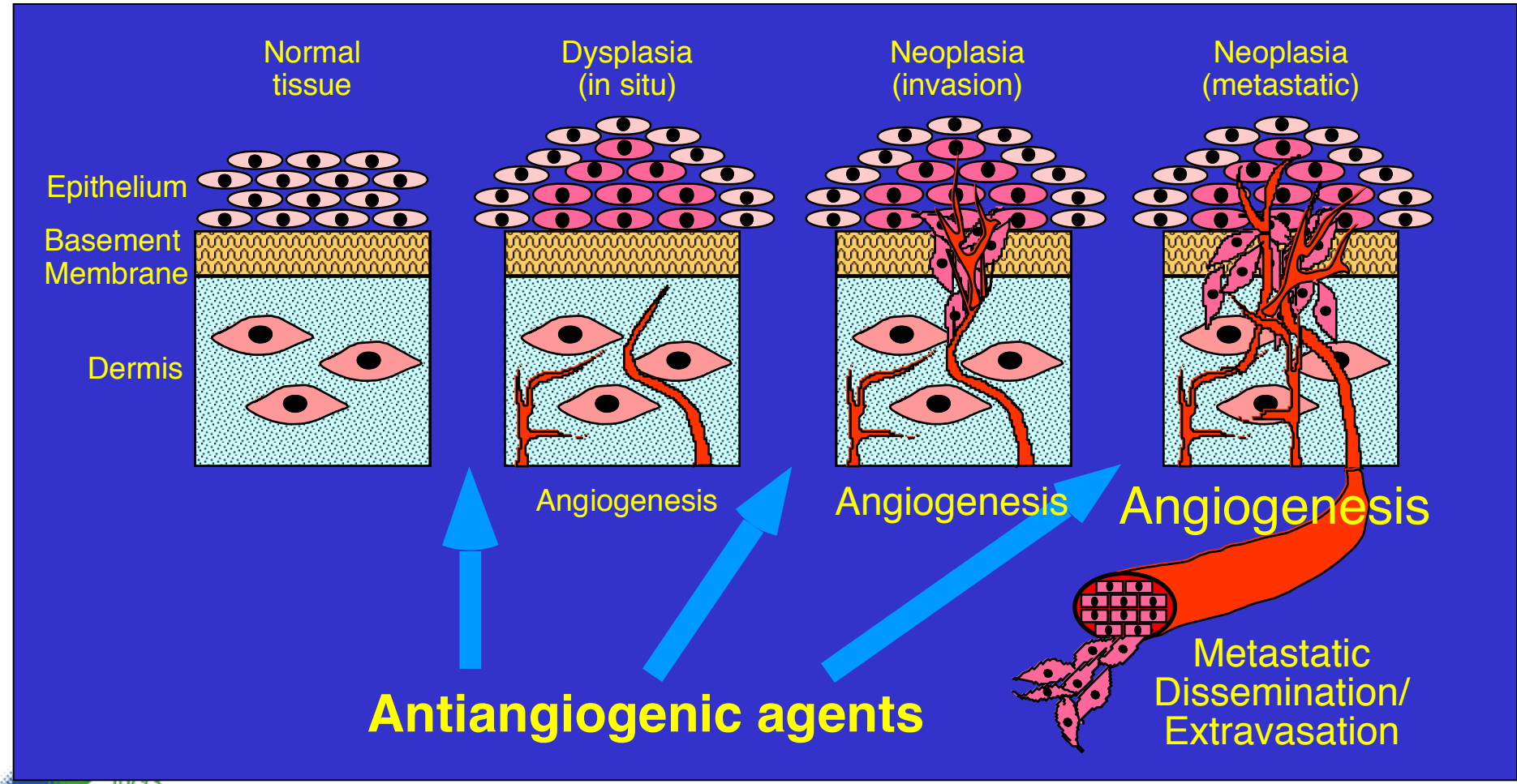
Anti- angiogenesis in multistage tumorigenesis: Angiogenic switch is an EARLY event



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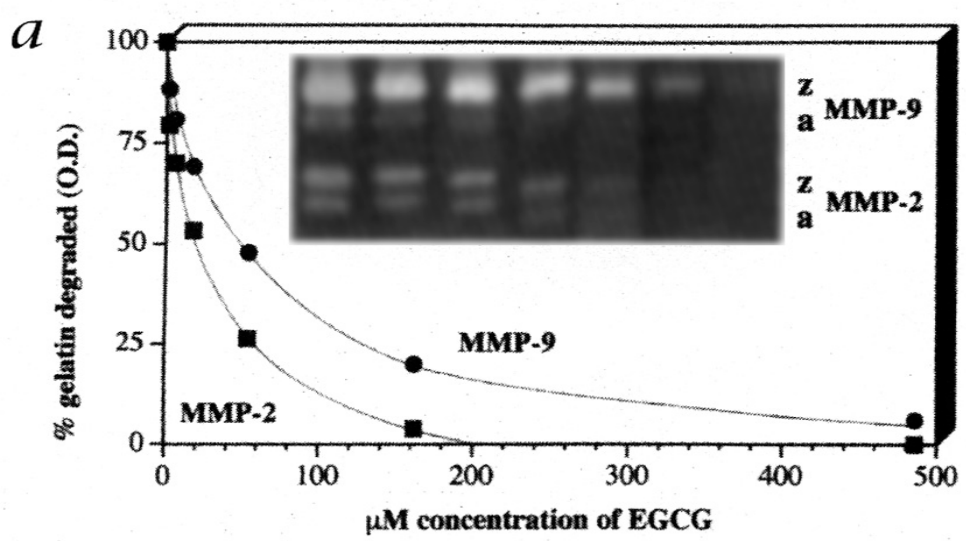
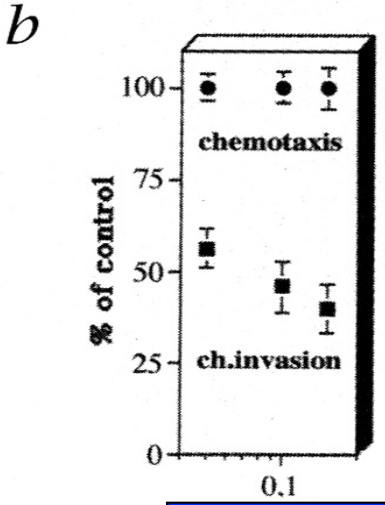
Effect of Celecoxib on Cardiovascular Events in two trials for the prevention of colorectal adenomas

	APC, n (%)			PreSAP, n (%)	
	Placebo (n=679)	200 mg BID (n=685)	400 mg BID (n=671)	Placebo (n=628)	400 mg QD (n=933)
Total cardiovascular deaths	1 (0.1)	5 (0.7)	6 (0.9)	4 (0.6)	4 (0.4)
Total noncardiovascular deaths	5 (0.7)	3 (0.4)	3 (0.4)	3 (0.5)	6 (0.6)
Total deaths	6 (0.9)	8 (1.2)	9 (1.3)	7 (1.1)	10 (1.1)
Fatal and nonfatal myocardial infarction	3 (0.4)	12 (1.8)	10 (1.5)	4 (0.6)	9 (1.0)
Fatal and nonfatal stroke	3 (0.4)	3 (0.4)	6 (0.9)	7 (1.1)	9 (1.0)
Nonfatal events					
Myocardial infarction	3 (0.4)	9 (1.3)	9 (1.3)	4 (0.6)	9 (1.0)
Stroke	3 (0.4)	3 (0.4)	5 (0.7)	5 (0.8)	9 (1.0)
Heart failure	2 (0.3)	1 (0.1)	4 (0.6)	0	3 (0.3)
Resuscitated sudden death	0	0	1 (0.1)	0	0
Thromboembolic event	1 (0.1)	3 (0.4)	4 (0.6)	1 (0.2)	0
Hospitalization for unstable angina	5 (0.7)	6 (0.9)	2 (0.3)	5 (0.8)	8 (0.9)
Arrhythmia	9 (1.3)	4 (0.6)	7 (1.0)	2 (0.3)	5 (0.5)
Cardiovascular procedure	7 (1.0)	10 (1.5)	7 (1.0)	2 (0.3)	9 (1.0)
Other cardiovascular	9 (1.3)	11 (1.6)	14 (2.1)	5 (0.8)	11 (1.2)

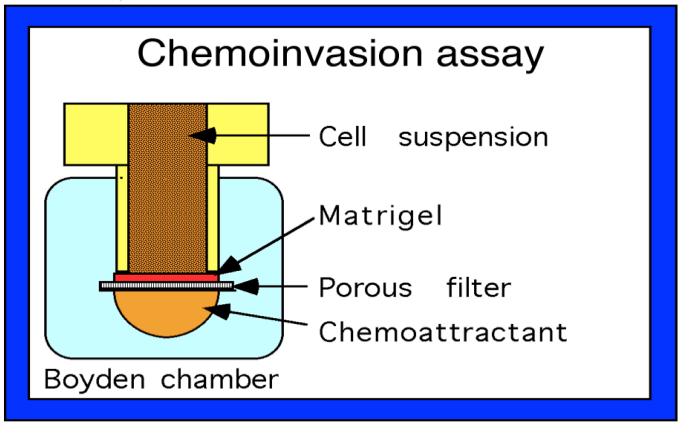
Solomon et al, "Journal of the American Heart Association, 2006

Green Tea?
Yes please!





The green tea flavonoid EGCG inhibits MMP activity
Garbisa… *Albini.*, Nature Medicine, 5:1216, 1999.



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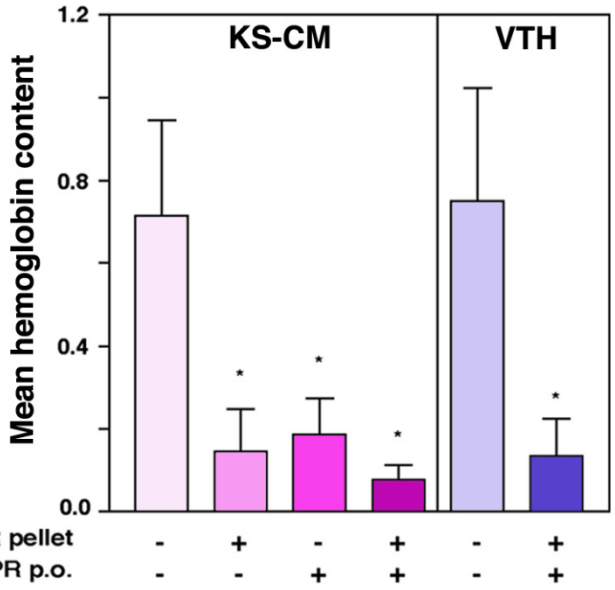
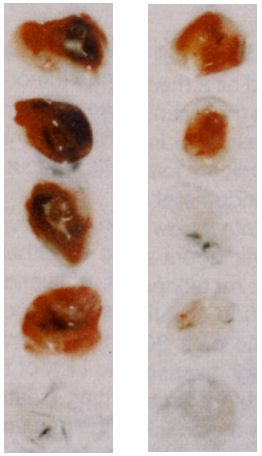
Albini et al Cancer Res 1987-Nature protocols 2007

Angiogenesis *in vivo*

A

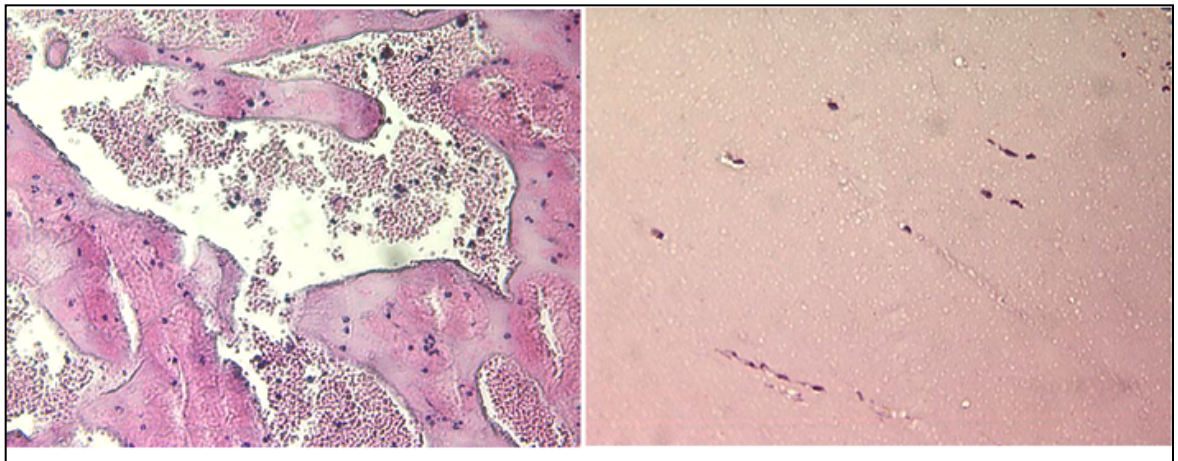




VTH +NAC

B

Angiogenic stimulus **Stimulus + angioprevention**



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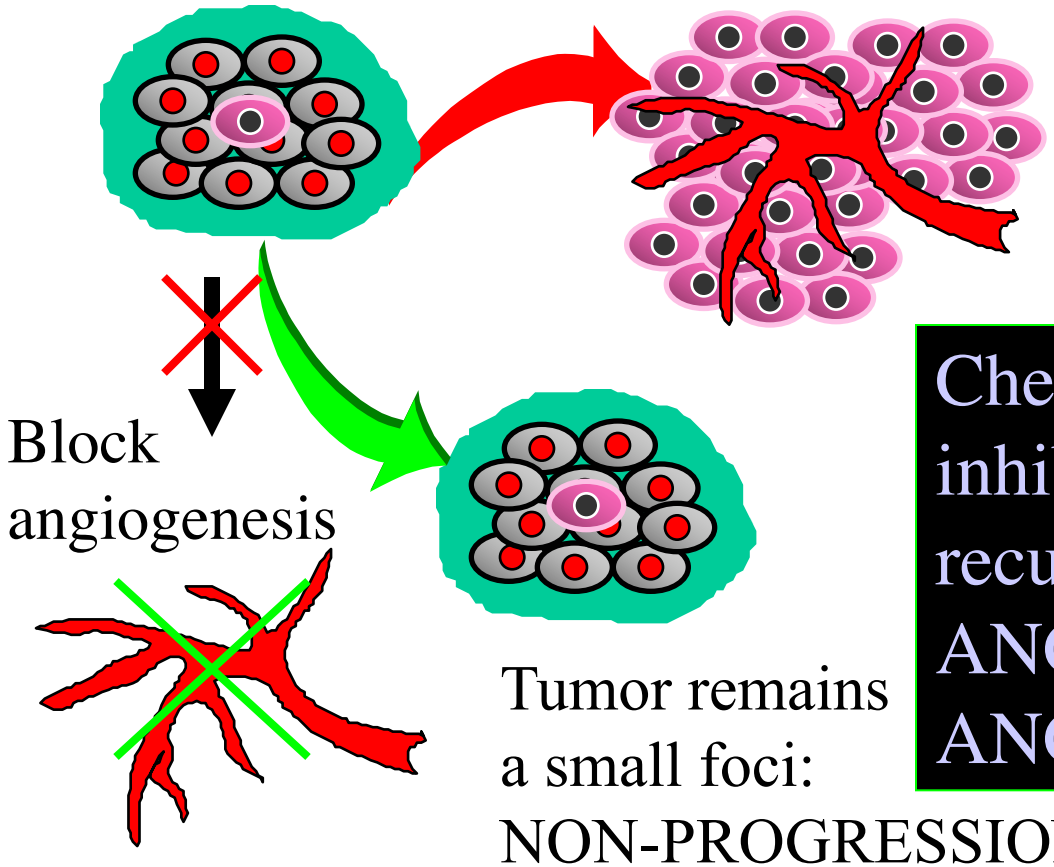
Chemoprevention and anti-Angiogenesis



Chemopreventive drugs inhibit small tumor growth or recurrency: could acting on ANGIOGENESIS: ANGIOPREVENTION

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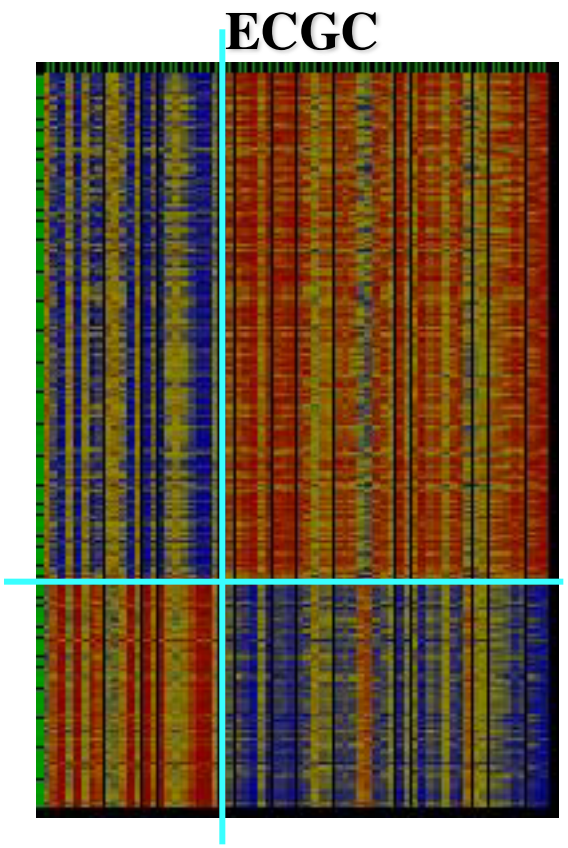
Tosetti and Albini, FASEB J 2002

Benelli and Albini FASEB J 2002

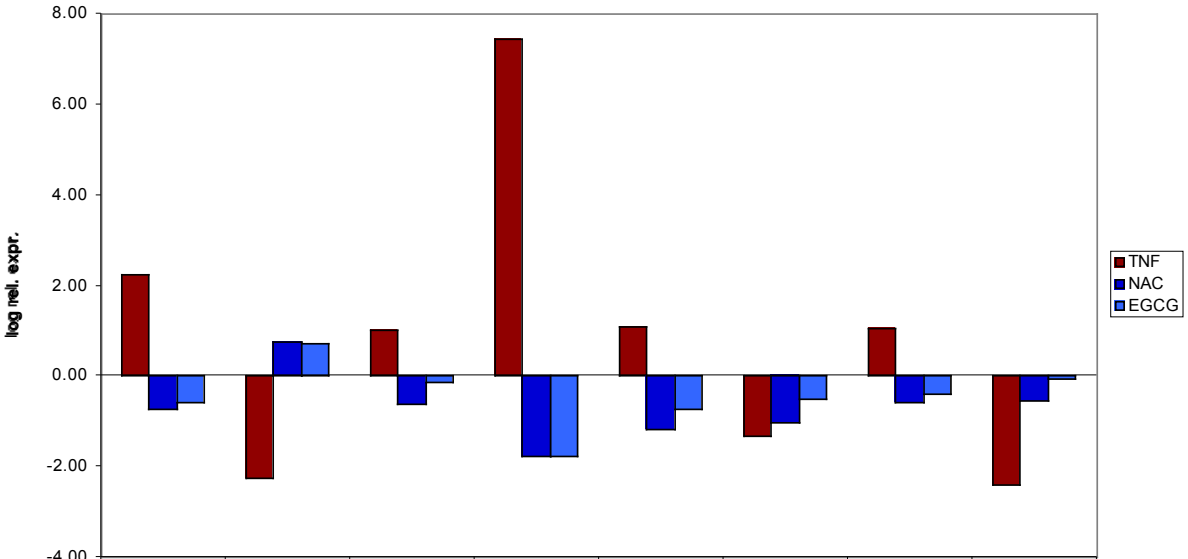
Genes regulated by NAC and EGCG

Correlations



NF-κB

TNF alpha responsive genes



	GBP1	MKP2	uPA	ESEL	ART4	HOXA4	jagged	WSX1
TNF	2.23	-2.26	1.01	7.46	1.09	-1.32	1.07	-2.40
NAC	-0.74	0.77	-0.62	-1.79	-1.18	-1.03	-0.58	-0.54
EGCG	-0.60	0.73	-0.14	-1.79	-0.74	-0.49	-0.40	-0.06

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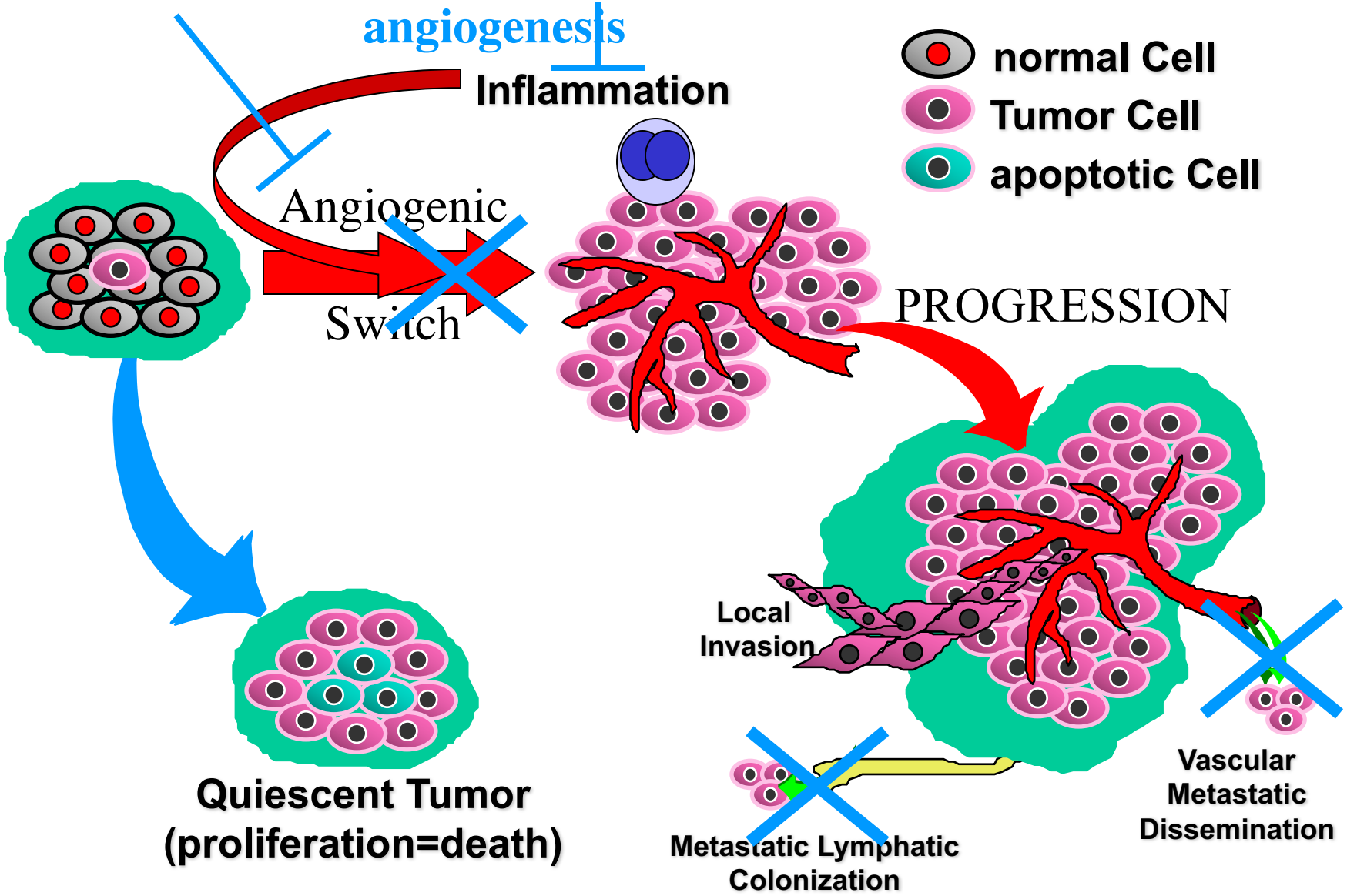
EGCG and NAC Responsive Angiogenesis Related Genes

Probe set	fold expression		Gene ID	description	Acc. #
	EGCG	NAC			
35799_at	1,86	4,94	HSP40 hmlg.	chaperone	AL080081
39790_at	1,52	1,84	SERCA2	ATPase	M23115
1788_s_at	1,66	1,7	MKP2	MAP kinasse phosphatase	U48807
38824_at	0,83	0,71	TIP30	HIV-1 Tat interactive protein 2	AF039103
37294_at	0,8	0,71	BTG1	B-cell translocation gene 1	X61123
32214_at	0,81	0,71	TXL	thioredoxin-like	AF003938
1211_s_at	0,86	0,69	CRADD	death receptor adaptor protein	U84388
37844_at	0,96	0,69	WSX1	class I cytokine receptor	AI263885
39734_at	0,98	0,68	EMAP2	endothelial monocyte-activating	U10117
35414_s_	0,76	0,67	jagged1	ligand for the Notch receptor	U77914
35317_at	0,9	0,67	MEA5	hyaluronoglucosaminidase	AB014579
39071_at	0,82	0,66	VNRA	integrin, alpha V	M14648
39333_at	0,77	0,66	COL4A1	collagen, type IV, alpha 1	M26576
37310_at	0,91	0,65	uPA	plasminogen activator, urokinase	X02419
36606_at	0,74	0,65	CPE	carboxypeptidase E	X51405
39361_f_	0,9	0,65	TSPAN-6	transmembrane 4 superfamily member 6	AF043906
1593_at	0,85	0,63	FGFB	basic fibroblast growth factor	J04513
39742_at	0,79	0,59	I-TRAF	TRAF interacting factor	U59863
483_g_at	0,8	0,58	CDHH	cadherin 13	U59289
33227_at	0,96	0,58	IL10RB	interleukin 10 receptor, beta	AI984234
34767_at	0,78	0,57	MAP-1	modulator of apoptosis 1	AI670788
1069_at	0,69	0,56	hCox-2	cyclo-oxygenase 2	U04636
37574_at	0,71	0,54	CAS-L	cas-like docking	L43821
41419_at	0,64	0,53	CED-6	CED-6 protein	AL080142
40687_at	0,41	0,53	CX37	gap junction protein, alpha 4	M96789
41362_at	0,76	0,52	ABCG1	ATP-binding cassette, sub-family G	X91249
1715_at	0,57	0,31	TRAIL	tumor necrosis factor (ligand) superfamily, member 10	U37518
265_s_at	0,29	0,29	ESEL	selectin E (endothelial adhesion molecule 1)	M24736

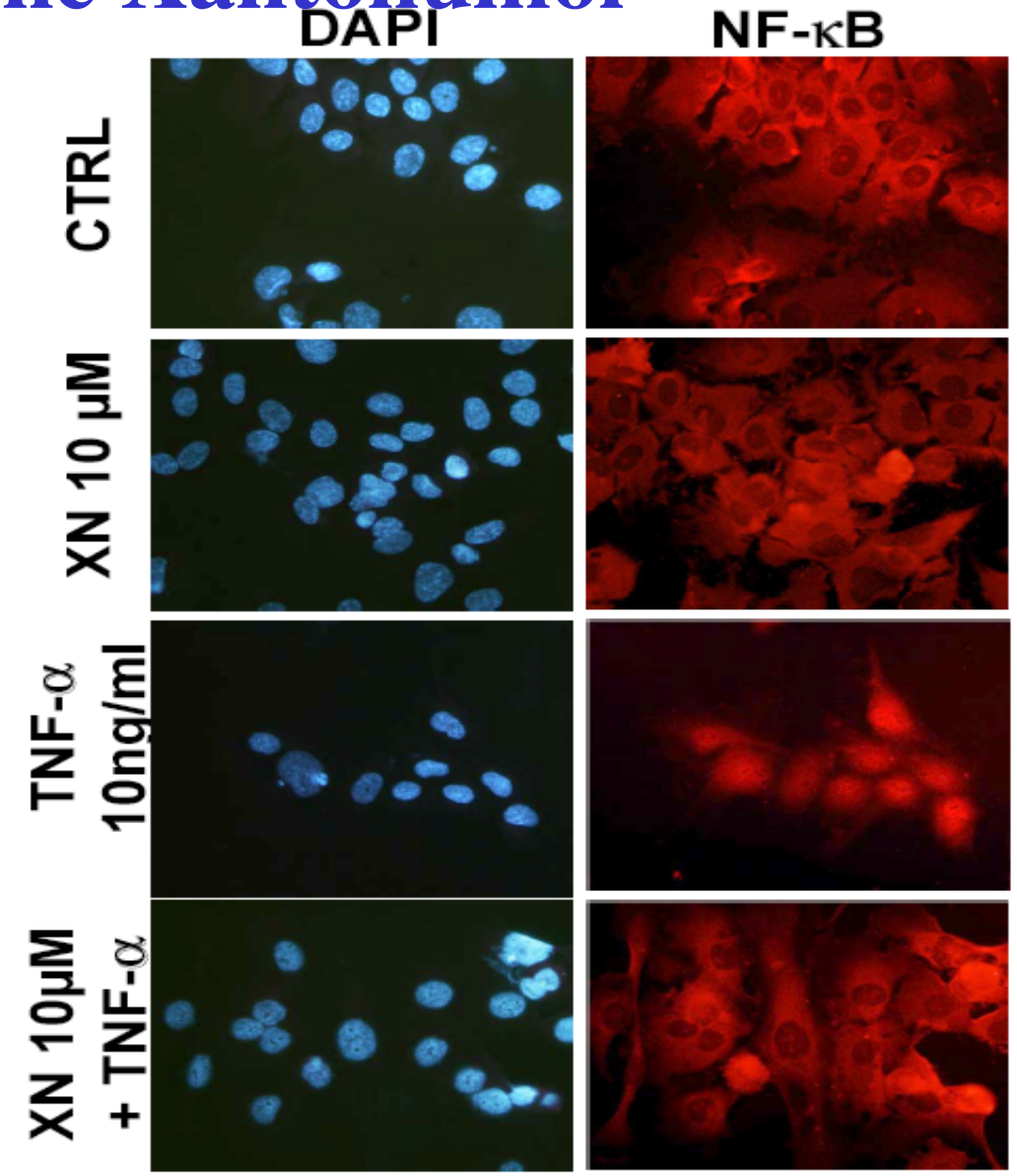
ANGIOPREVENTION: Chemoprevention of angiogenesis



Tosetti F, Ferrari N, De Flora S, Albini A. Angioprevention': angiogenesis is a common and key target for cancer chemopreventive agents. Faseb J. 16:2-14.; 2002

Inhibition of NF-kB Translocation by Bier hop isoflavone Xantohumol

Xantohumol from bier hop:
A new "angiopreventive" agent



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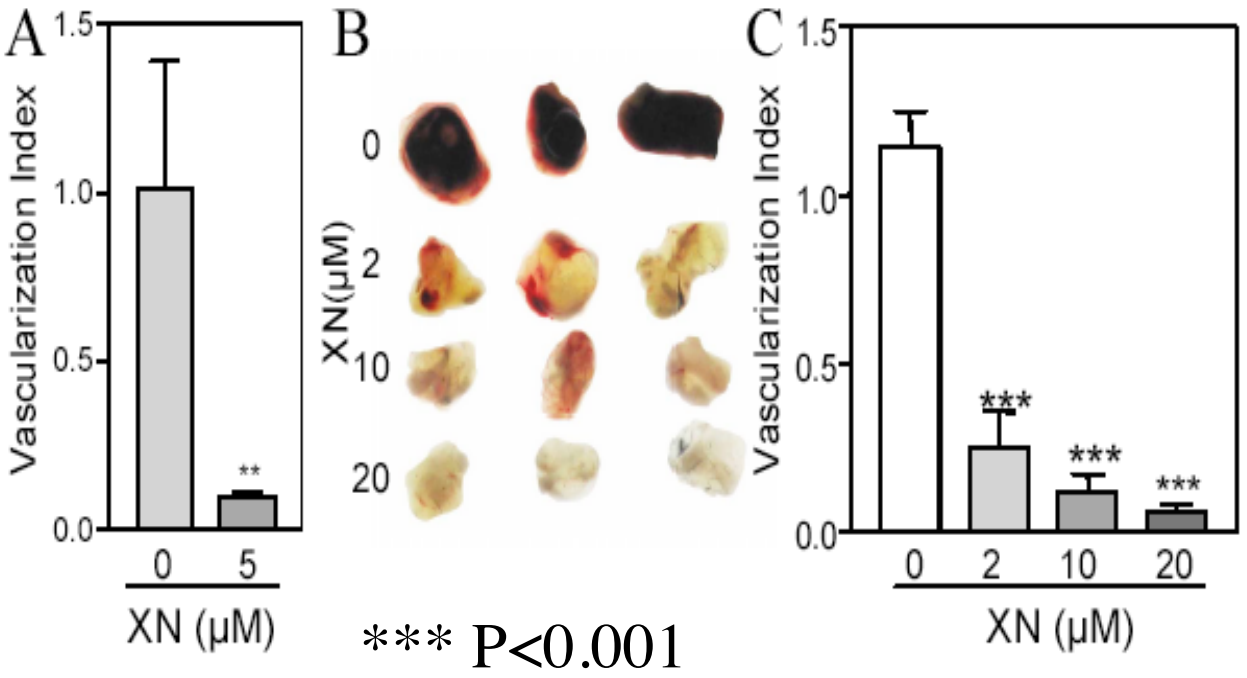
Xanthohumol inhibits angiogenesis in matrigel pellets in vivo



*** P<0.001

Xanthohumol is a chalcone found in beer hops; it has been shown to be a candidate chemopreventive agent and to have anti-angiogenic properties

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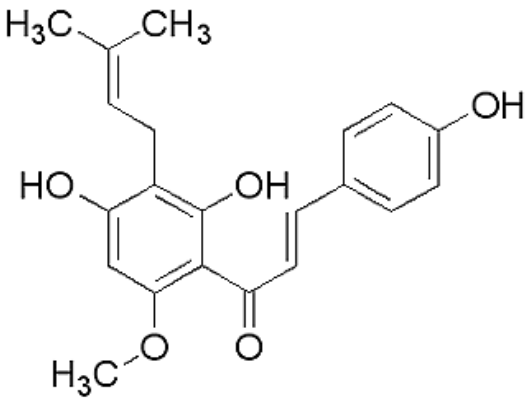
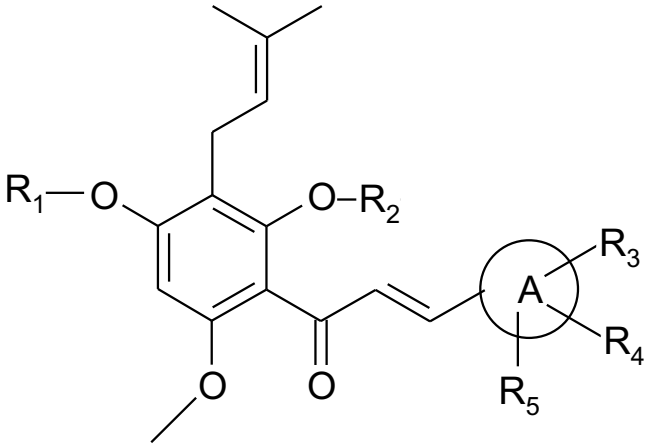
xanthoumol



Anti-angiogenic activity of xanthoumol-derived compounds: patent pending

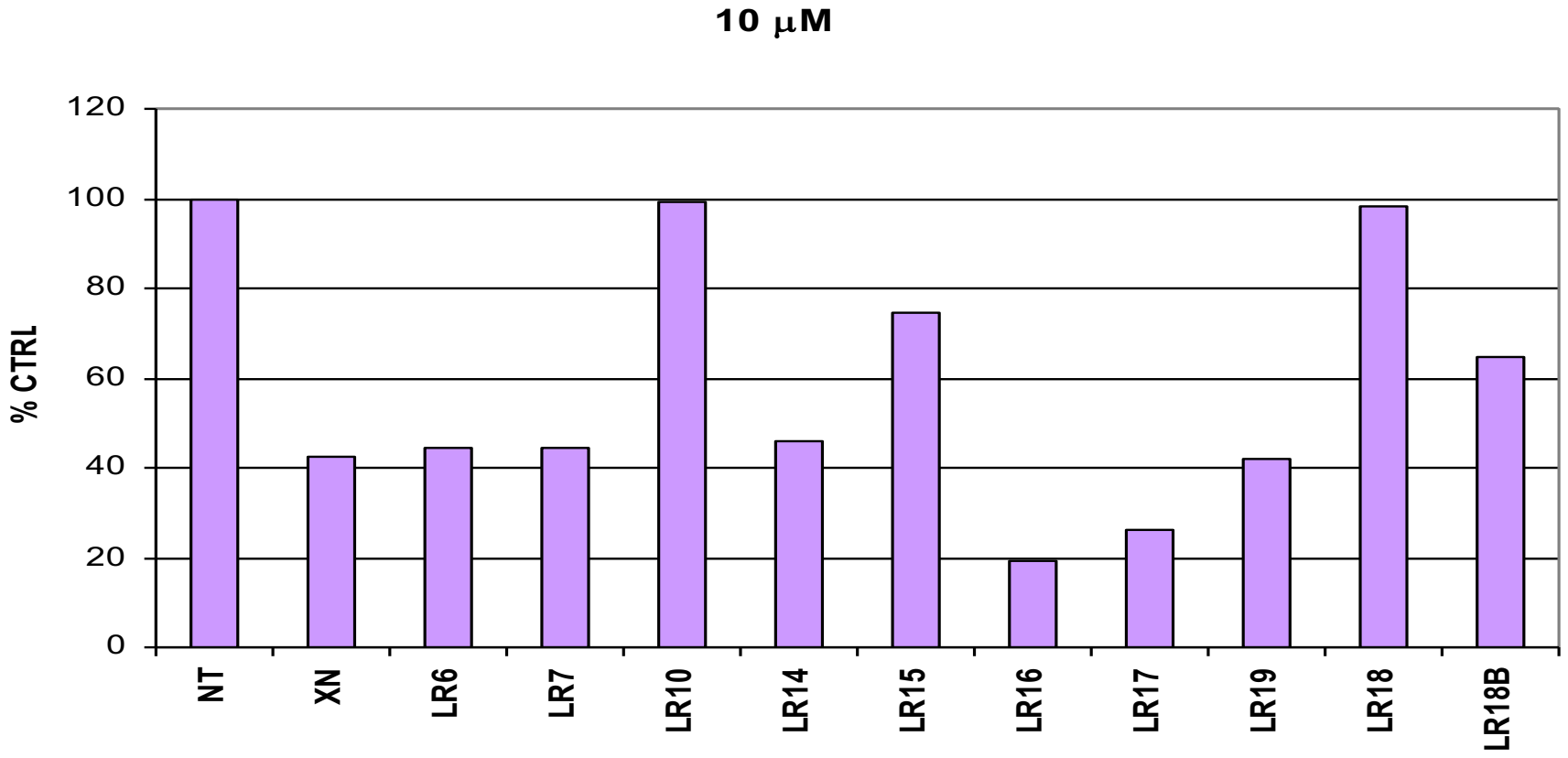
(I) New synthetic xanthoumols



R1= H, CH3OCH2–, …
R2= H, CH3OCH2–, …
A= fenile o un anello aromatico
R3= Cl, F, NO2, CH3CONH-, …
R4= H, Cl, F, …
R5= H, F, …

Anti-angiogenic activity of xanthoumol-derived compounds

Invasion assay
HUVEC pretreated 24h



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European Journal of Medicinal Chemistry 138 (2017) 890–899

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Research paper

Synthesis and antiangiogenic activity study of new hop chalcone Xanthohumol analogues

Elisa Nuti [a, g, 1], Barbara Bassani [b, 1], Caterina Camodeca [a], Lea Rosalia [a], AnnaRita Cantelmo [c], Cristina Gallo [d], Denisa Baci [b], Antonino Bruno [b], Elisabetta Orlandini [a, e, g], Susanna Nencetti [a, g], Douglas M. Noonan [b, f], Adriana Albini [b, *, 2], Armando Rossello [a, g, **, 2]

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[d] Laboratory of Translational Research, Arcispedale S. Maria Nuova-IRCCS, Viale Risorgimento 80, 42121 Reggio Emilia, Italy
[e] Dipartimento di Scienze Della Terra, Università di Pisa, Via Santa Maria 53, 56126 Pisa, Italy
[f] Department of Biotechnologies and Life Sciencies, University of Insubria, Viale O. Rossi 9, 21100 Varese, Italy
[g] Centro Interdipartimentale di Ricerca "Nutraceutica e Alimentazione per la Salute", Università di Pisa, Via Del Borghetto 80, 56124 Pisa, Italy

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Chemopreventive agents

ABSTRACT

Angiogenesis induction is a hallmark of cancer. Antiangiogenic properties of Xanthohumol (XN), a naturally occurring prenylated chalcone from hops, have been widely reported. Here we describe the synthesis and study the antiangiogenic activity *in vitro* of a series of XN derivatives, where different substituents on the B-ring of the chalcone scaffold were inserted. The new XN derivatives inhibited human umbilical-vein endothelial cell (HUVEC) proliferation, adhesion, migration, invasion and their ability to form capillary-like structures *in vitro* at 10 μM concentration. The preliminary results indicate that the phenolic OH group in R, present in natural XN, is not necessary for having antiangiogenic activity. In fact, the most effective compound from this series, **13**, was characterized by a para-methoxy group in R and a fluorine atom in R_2 on B-ring. This study paves the way for future development of synthetic analogues of XN to be used as cancer angiopreventive and chemopreventive agents.

mentelocalemilano
...cosa fare nel tuo tempo libero

Bevete la birra, previene il cancro. Una nuova scoperta

Da uno studio, tutto italiano, è risultato che nuovi derivati di sintesi dello Xantumolo, molecola contenuta nel luppolo della birra, sono in grado di **contrastare l'angiogenesi**, meccanismo alla base della **proliferazione dei tumori.** Pubblicato dalla rivista scientifica *European Journal of Medicinal Chemistry*, lo studio, tutto italiano, è stato condotto dall'**IRCCS MultiMedica di Milano**, dall'**Università di Pisa** e dall'**Università dell'Insubria di Varese**.


Adriana Albini e la sua équipe

***Affamare* le cellule tumorali contrastando l'angiogenesi**. Sono queste le capacità *anticancro* individuate, da uno studio made in Italy, per un gruppo di nuove molecole derivate da un fitocomposto contenuto nel luppolo della birra. La ricerca è frutto di una collaborazione tra istituti di ricerca italiani: il laboratorio di Biologia Vascolare e Angiogenesi di MultiMedica, diretto dalla dottoressa **Adriana Albini**, il professor **Armando Rossello**, del Dipartimento di Farmacia dell'Università di Pisa e il professor **Douglas Noonan** dell'Università dell'Insubria di Varese. Più nel dettaglio, lo studio, durato quattro anni, ha evidenziato una **capacità di riduzione dell'angiogenesi**, da parte dei nuovi Xantumoli, dell'80% in test sperimentali.

Lo **Xantumolo** possiede anche un'azione antiossidante, anti radicali liberi, ed è in grado di combattere le cellule che presentano un alterato equilibrio ossidoriduttivo, come quelle tumorali. Di qui l'importanza di svilupparne una serie di varianti sintetiche con proprietà farmacologiche più spiccate. Albini, direttrice del laboratorio di Biologia Vascolare e Angiogenesi di MultiMedica e direttore scientifico della Fondazione MultiMedica Onlus illustra le fasi del progetto di ricerca che ha portato alla scoperta delle proprietà di queste nuove molecole: «abbiamo intrapreso una collaborazione con un team di chimici farmaceutici del Dipartimento di Farmacia dell'Università di Pisa, coordinati da Armando Rossello, che hanno progettato e sviluppato modificazioni strutturali della **molecola base contenuta nel luppolo**, per renderla più efficace e utilizzabile a concentrazioni più basse. Si tenga presente che il luppolo è utilizzato nella preparazione della birra sin dal VII secolo, non solo per le sue qualità rinfrescanti e aromatiche, ma anche per la sua capacità di garantire una più lunga conservazione, caratteristica legata alle sue proprietà antibiotiche».

Per scoprire se la sostanza possa essere utilizzata per la terapia e la prevenzione di tumori, sia solidi che ematologici, dopo un'analisi dell'attività biologica dei singoli, i gruppi di ricerca sono riusciti a identificare due tra i 13 nuovi derivati dello Xantumolo da loro brevettati, che sono in grado di esercitare un'attività anti-angiogenica ancora maggiore rispetto al principio naturale base dello XN.

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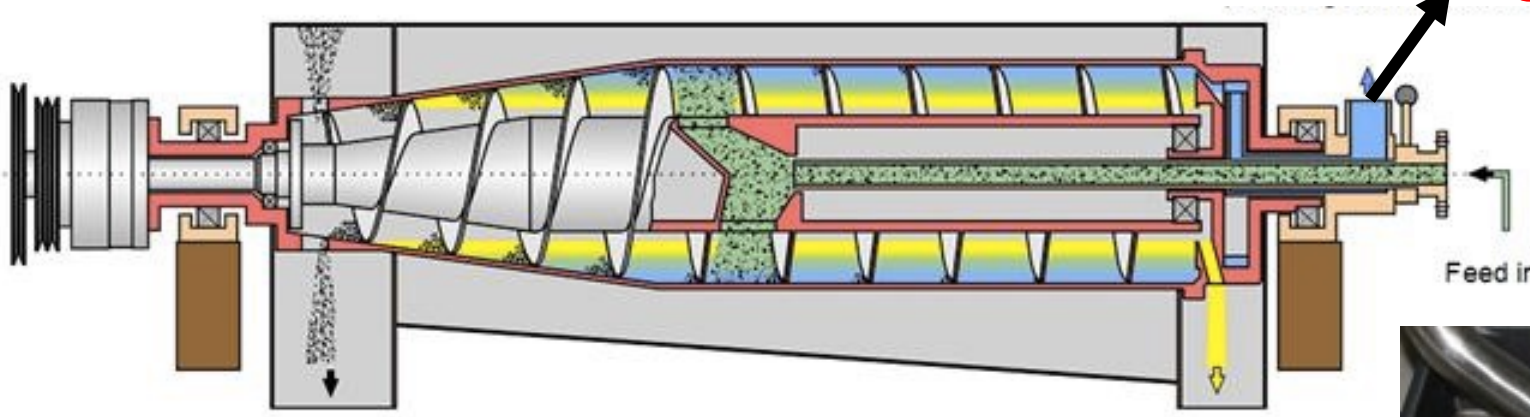
«Abbiamo testato i derivati neo-sintetizzati che sono risultati particolarmente efficaci nell'interferire con funzioni chiave della cellula endoteliale, il mattone fondamentale che costituisce i vasi sanguigni tumorali, quali la proliferazione, l'adesione, la migrazione, l'invasione e la formazione di strutture simil-capillari. Lo studio - conclude Albini -apre la strada per lo **sviluppo futuro su più ampia scala di analoghi sintetici dello Xantumolo da sperimentare come possibili agenti chemiopreventivi**. Il passo successivo sarà quello di testare i più attivi derivati brevettati del luppolo in modelli cellulari complessi e individuare i principali interruttori molecolari coinvolti nel loro effetto anti-angiogenico e anti-tumorale come possibili bersagli da colpire, sia in approcci terapeutici sia di prevenzione».

La ricerca è stata condotta da giovani ricercatori dei laboratori partecipanti (Antonino Bruno, Barbara Bassani e Denisa Baci per l'IRCCS MultiMedica, Elisa Nuti, Caterina Camodeca, Lea Rosalia, Elisabetta Orlandini e Susanna Nencetti, per l'Università di Pisa, Cristina Gallo per l'IRCCS Arcispedale Santa Maria Nuova Reggio Emilia) ed è stata realizzata grazie al supporto di un finanziamento da parte dell'Associazione Italiana per la Ricerca sul Cancro (AIRC), di una Borsa dellaFondazione Umberto Veronesi (FUV) e di fondi di ricerca dell'Università di Pisa (Fondi di Ateneo 2009-2010 e PRA-Progetti di Ricerca di Ateneo 2016/27).

Antioxidants from Olive Mill Waste Waters



Olive oil waste water

The Olive oil process

Solid waste

The centrifuge separates the oil from the water

Olive oil

BEVERAGES FROM OMWW

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Polyphenols in OMWW

A009 PHENOLIC COMPOSITION

Phenolic compound (g/L)	A009 batch 1	A009 batch 2
Hydroxytyrosol glucoside	ND	1,69
Hydroxytyrosol	2.7	5.72
Tyrosol	0.2	ND
Chlorogenic acid	0.12	0.1
B-hydroxyverbascoside isomer 1	0.35	0.14
B-hydroxyverbascoside isomer 2	0.32	0.17
Verbascoside	0.84	1.32
caffeyol ester of secologanoside	ND	0,2
Decarboxymethyloleuropeinaglycon	1.99	0.28
Oleouropein aglycon	ND	0.22
6'-p-coumaroyl secologanoside	ND	0.4
Rutin	0.11	ND
luteolin-7-o-glucoside	0.22	ND

Table S1: Phenolic quantification in OMWW extract. Quantification of the phenolic presence in A009 was performed using an highperformance liquid chromatography (HPLC) analysis. Results are expressed as g/L. N.D. Not detected.

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Vol. 26, No. 5
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Antimicrobial Properties of Oleuropein and Products of Its Hydrolysis from Green Olives[1]

H. P. FLEMING, W. M. WALTER, JR., AND J. L. ETCHELLS

U.S. Food Fermentation Laboratory, Agricultural Research Service, United States Department of Agriculture, and Department of Food Science, North Carolina State University, Raleigh, North Carolina 27607

Combinatory effects

Single compund effects

7636 *J. Agric. Food Chem.* **2003,** *51,* 7636–7641

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Antioxidizing Potency of Phenol Compounds in Olive Oil Mill Wastewater

ALFONSO RANALLI,* LUCIA LUCERA, AND STEFANIA CONTENTO

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Food and Chemical Toxicology

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

ELSEVIER

Anti-apoptotic activity of hydroxytyrosol and hydroxytyrosyl laurate

Sabrina Burattini[a,*], Sara Salucci[a], Valentina Baldassarri[a], Augusto Accorsi[b], Elena Piatti[b], Andres Madrona[c], Josè L. Espartero[c], Manila Candiracci[b,c], Giovanni Zappia[b], Elisabetta Falcieri[a,d]

Tested on U937, C2C12

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European Journal of Pharmaceutical Sciences

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

Tested on leukemia cells

Enhanced chemopreventive activity of hydroxytyrosol on HL60 and HL60R cells by chemical conversion into thio derivatives

Maria Vittoria Sepporta [a,1], M. Ángeles López-García [b,1], Roberto Fabiani [a,*], Inés Maya [b], José G. Fernández-Bolaños [b,*]

Tested on PC12 cells

Contents lists available at ScienceDirect

Pharmacological Research

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

Cytoprotective effects of olive mill wastewater extract and its main constituent hydroxytyrosol in PC12 cells

Sebastian Schaffer [1], Walter E. Müller, Gunter P. Eckert *

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Journal of Functional Foods 27 (2016) 236–248

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

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

Potential chemopreventive activities of a polyphenol rich purified extract from olive mill wastewater on colon cancer cells

Barbara Bassani [a,1], *Teresa Rossi* [b,1], *Daniela De Stefano* [a], *Daniele Pizzichini* [c], *Paola Corradino* [a], *Nicoletta Macrì* [a], *Douglas M. Noonan* [a,d], *Adriana Albini* [a,*,1], *Antonino Bruno* [a,1]

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[b] *Laboratory of Translational Research, IRCCS Arcispedale Santa Maria Nuova, Viale Risorgimento, 80, Reggio Emilia 42123, Italy*

[c] *ENEA, Casaccia Research Center, Via Anguillarese, 301, Rome 00123, Italy*

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OMWW-Purified Extract A009 as a Potential Chemopreventive Agent on Prostate Cancer Cells

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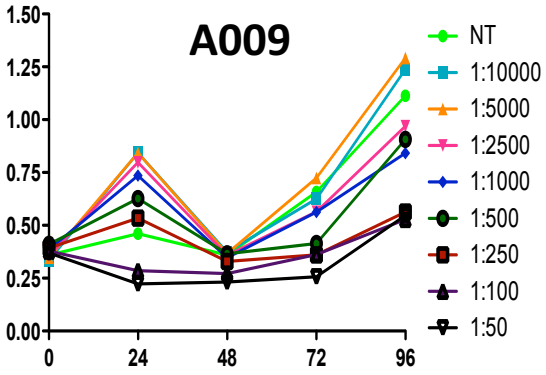
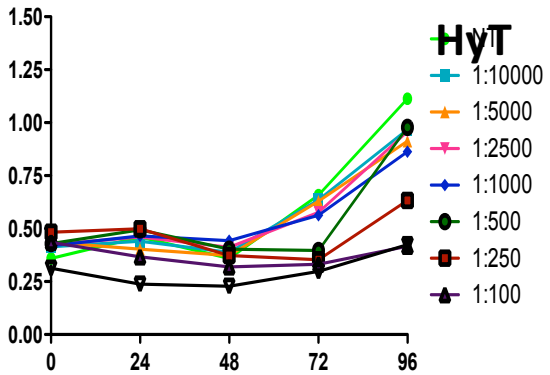
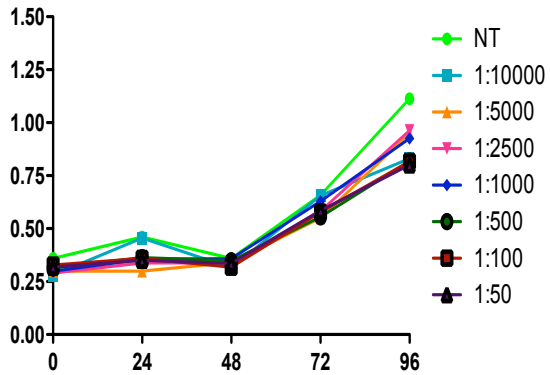
A009 REDUCES PROSTATE CANCER (PCa) CELL PROLIFERATIC

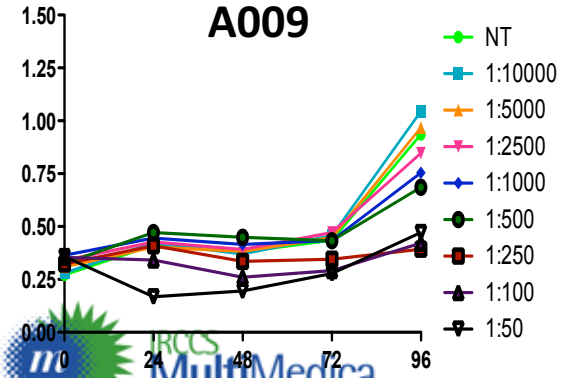
PC-3

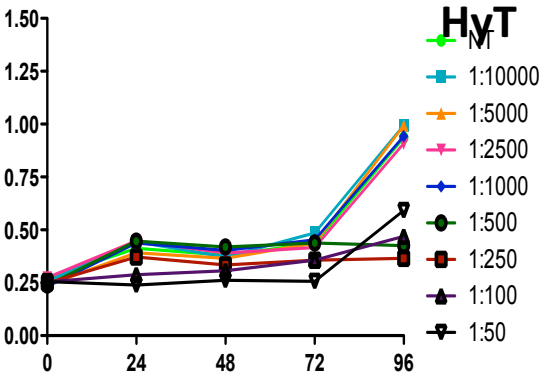


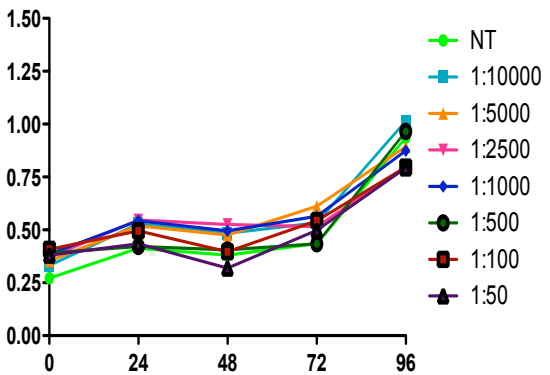




DU-145







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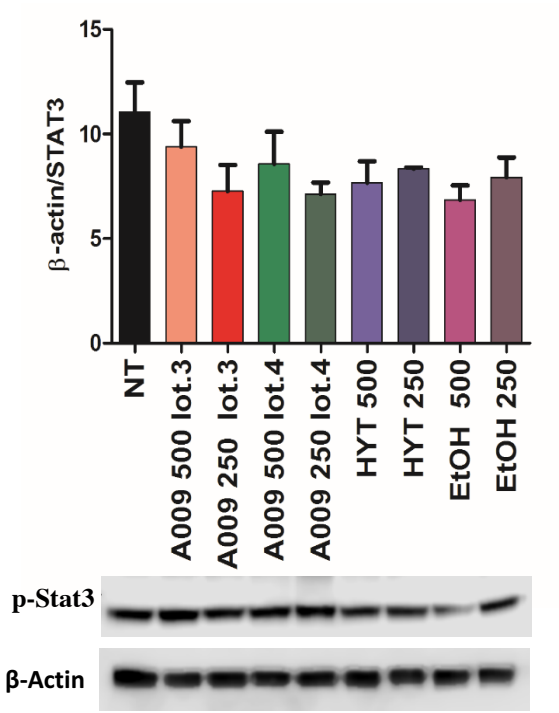
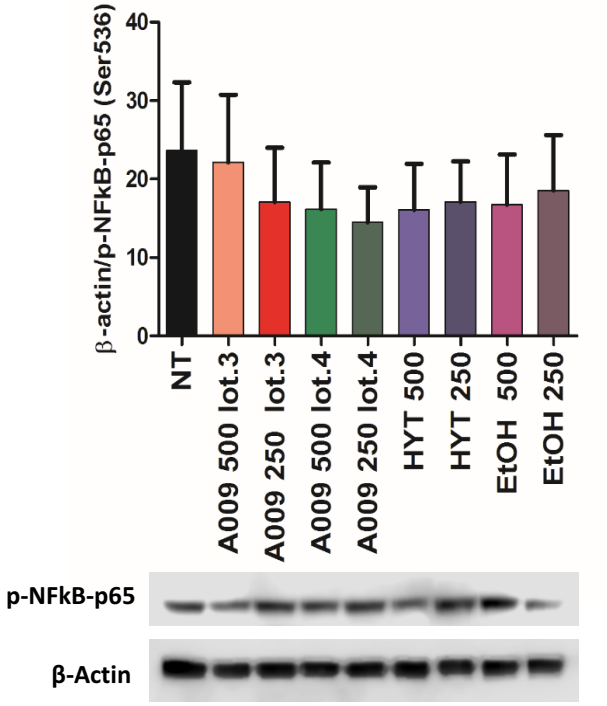
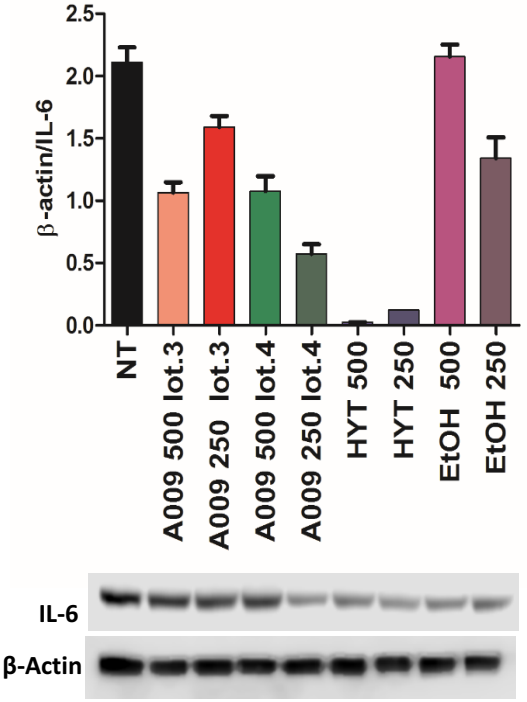
PC3 IL-6/STAT3/NF-κB axis







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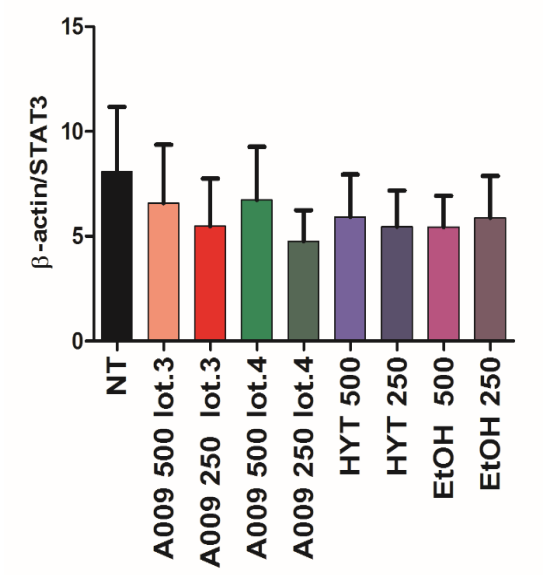
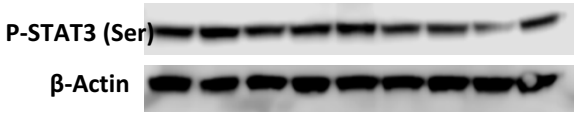
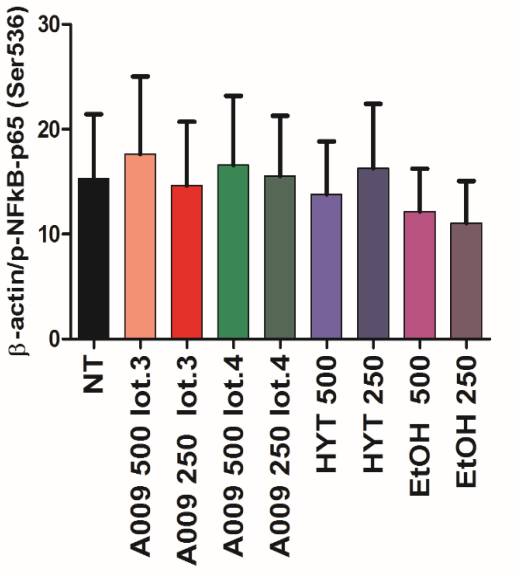
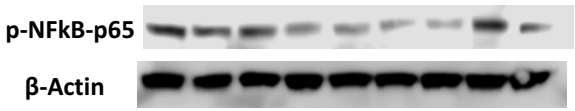
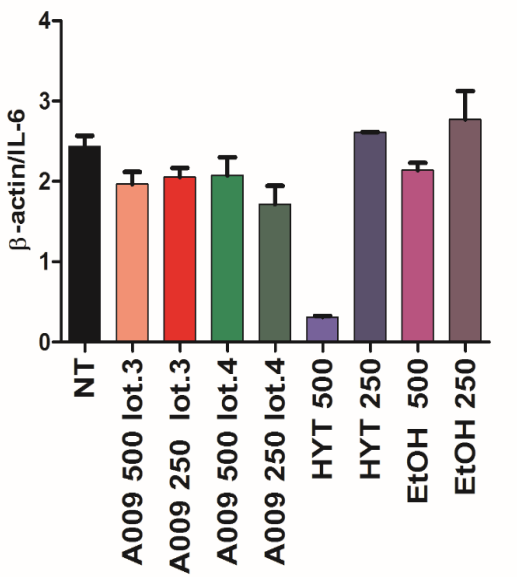
DU IL-6/STAT3/NF-κB axis

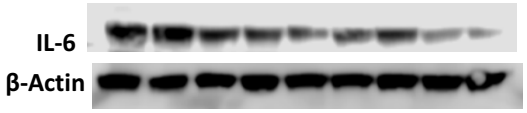












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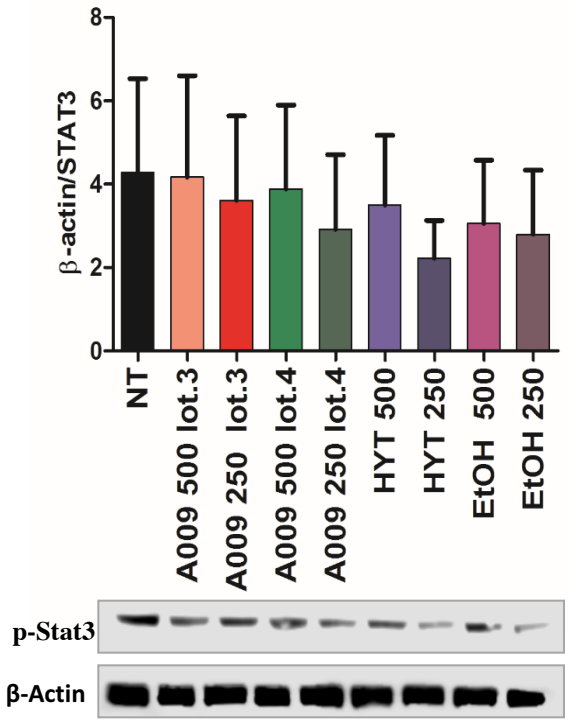
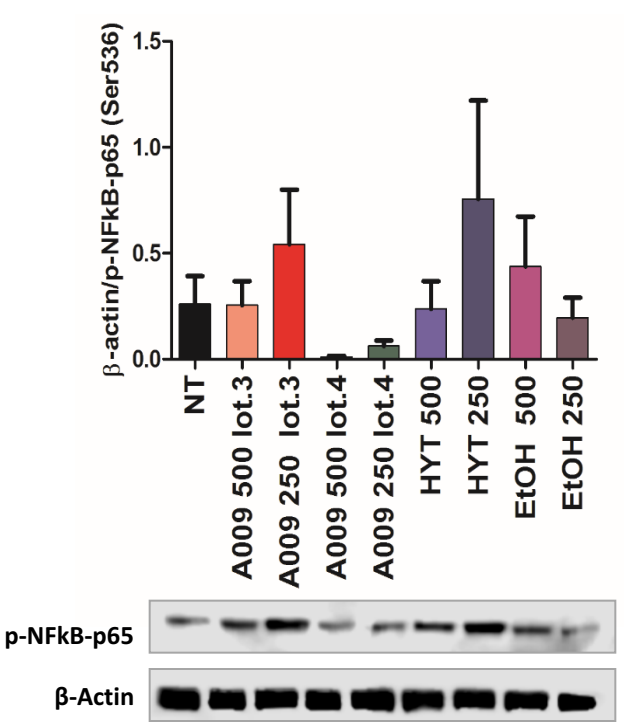
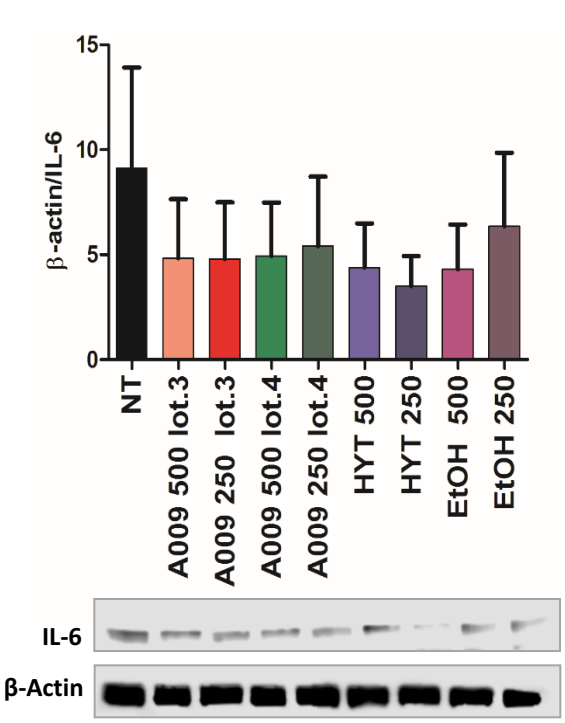
LnCAP IL-6/STAT3/NF-κB axis







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Curcumin

Phytoestrogens are plant derived substances that have estrogenic activity. They bind to the estrogen receptor with an affinity 1000-10000 fold lower than that of the endogenous hormone and initiate estrogendependent transcription. According to their chemical structures phytoestrogens are classified into six main groups: flavones, flavonones, isoflavones, coumestans, lignans, and stilbenes.

Several secondary metabolites from herbal nutrient products act as weak estrogens (phytoestrogens), competing with endogenous estrogen for binding to the estrogen receptors and inhibiting steroid converting enzymes.

Phytoestrogens have been proposed for chemoprevention and as a substitute of hormone replacement therapy], because it can be assumed that they compete with the endogenous hormone for binding to the estrogen receptor, thereby reducing the proliferative effects of endogenous estrogens.

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Effects of 100nM Curcumin on gene expression in MCF7 cells (after 72 hours of treatment with 100nM of curcumin was analyzed by microarray hybridization.)

Effects of 100nM Curcumin on Gene Expression in MCF7 Cells

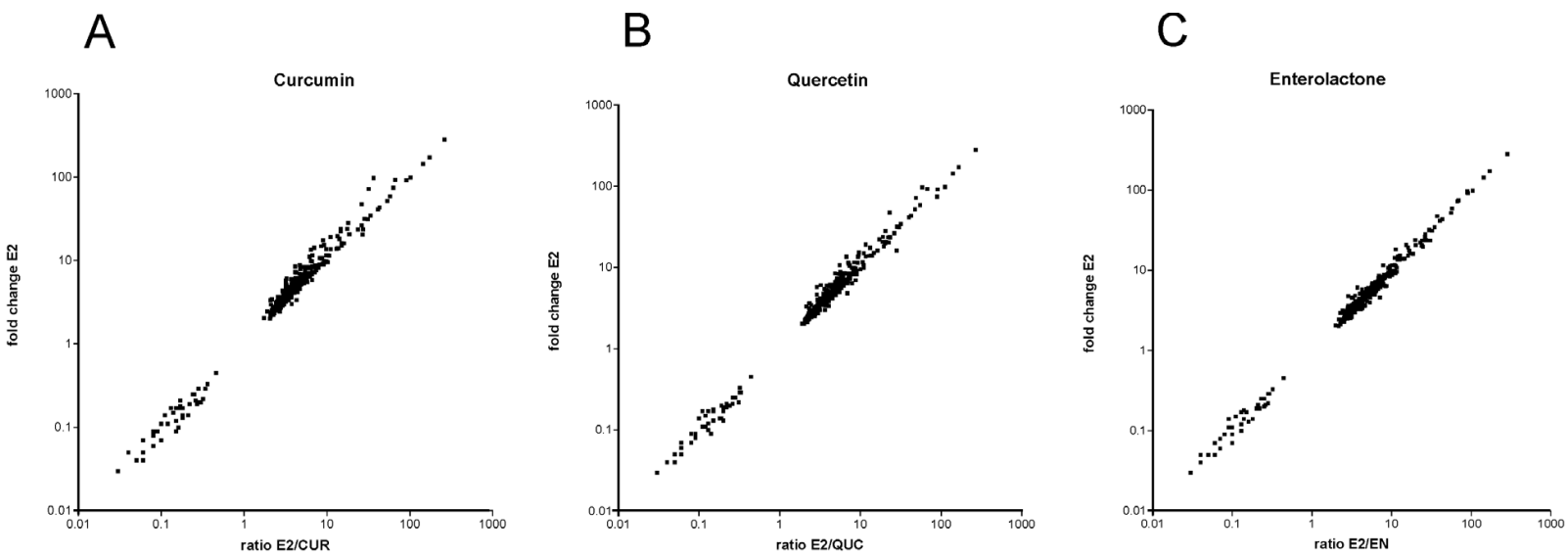
Affy ID	*Gene symbol*	*Description*	*p-value*	*FC_CUR*	*FC_E2*
213906_at	MYBL1	v-myb myeloblastosis viral oncogene homolog (avian)-like 1	0.0192	2.71	100.64
224428_s_at	CDCA7	cell division cycle associated 7	0.0147	2.05	13.05
1559966_a_at	NA	NA	0.0120	2.01	1.54
214519_s_at	RLN2	relaxin 2	0.0481	1.92	6.32
202094_at	BIRC5	baculoviral IAP repeat-containing 5 (survivin)	0.0035	1.87	16.47
207828_s_at	CENPF	centromere protein F, 350/400ka (mitosin)	0.0205	1.84	6.02
218585_s_at	DTL	denticleless homolog (Drosophila)	0.0136	1.79	10.80
234987_at	SAMHD1	SAM domain and HD domain 1	0.0343	1.78	2.73
205046_at	CENPE	centromere protein E, 312kDa	0.0447	1.76	21.09
226712_at	SSR1	signal sequence receptor	0.0332	1.76	1.50
219000_s_at	DCC1	NA	0.0205	1.74	11.67
203438_at	STC2	stanniocalcin 2	0.0311	1.69	2.53
202134_s_at	WWTR1	WW domain containing transcription regulator 1	0.0123	1.69	1.72
228711_at	ZNF37A	zinc finger protein 37a (KOX 21)	0.0340	1.68	1.59
225655_at	UHRF1	ubiquitin-like, containing PHD and RING finger domains, 1	0.0022	1.65	7.06
220651_s_at	MCM10	MCM10 minichromosome maintenance deficient 10	0.0230	1.64	23.92
234863_x_at	FBXO5	F-box protein 5	0.0072	1.64	9.15
218859_s_at	C20orf6	chromosome 20 open reading frame 6	0.0469	1.63	1.78
223413_s_at	LYAR	NA	0.0445	1.62	5.92
205440_s_at	NPY1R	neuropeptide Y receptor Y1	0.0320	1.62	5.80
1554696_s_at	TYMS	thymidylate synthetase	0.0082	1.61	7.65
1553269_at	ZNF718	zinc finger protein 718	0.0467	1.58	2.14
205283_at	FCMD	Fukuyama type congenital muscular dystrophy (fukutin)	0.0428	1.58	1.58
204983_s_at	GPC4	glypican 4	0.0119	1.58	0.81
208859_s_at	ATRX	alpha thalassemia/mental retardation syndrome X-linked	0.0466	1.56	0.96
229304_s_at	MLF1IP	MLF1 interacting protein	0.0161	1.55	4.79
225664_at	COL12A1	collagen, type XII, alpha 1	0.0312	1.54	3.24
219654_at	PTPLA	protein tyrosine phosphatase-like, member A	0.0024	1.54	1.35
209409_at	GRB10	growth factor receptor-bound protein 10	0.0276	1.52	1.04
219959_at	MOCOS	molybdenum cofactor sulfurase	0.0221	1.51	4.71
219544_at	FLJ22624	NA	0.0277	1.50	5.67
1555495_a_at	SDCCAG10	serologically defined colon cancer antigen 10	0.0365	1.50	1.64

IRCCS MultiMed

Bachmeier BE *et al*, Cell Physiol Biochem. 2010;26(3):471-82.

There is an almost perfect linear correlation for Curcumin, Quercetin and Enterolact

The ratios between the fold changes (17-β-estradiol versus control divided by phytoestrogen versus control) are plotted over the 17-β-estradiol fold change values.



All three compounds tested at the physiological concentration of 100 nM regulate many E2 genes in the same direction like 17- β -estradiol yet the extent of regulation is very limited. The comparison between untreated controls and phytoestrogen treated cells does not yield statistically significant gene regulation events. However, the gene expression profile elicited by the phytoestrogens shows a significant correlation with the profile in response to 17- β -estradiol. Interestingly, Curcumin showed the strongest effects and the most significant correlation.

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Bachmeier BE *et al*, Cell Physiol Biochem. 2010;26(3):471-82.

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Rapid Communications in Mass Spectrometry

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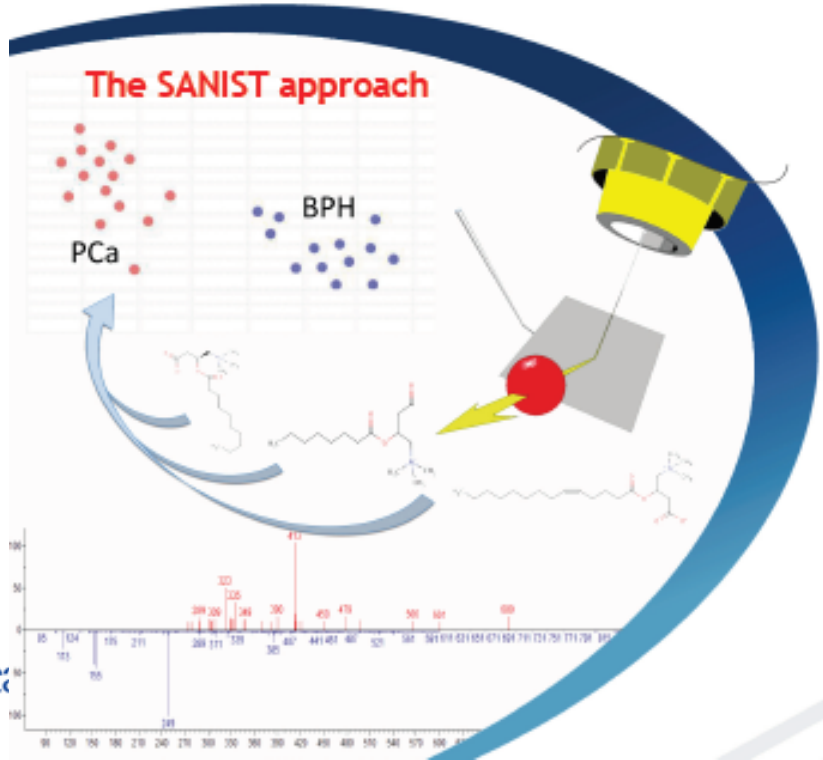
SANIST: a rapid mass spectrometric SACI/ESI data acquisition and elaboration platform for verifying potential candidate markers

by Adriana Albini, Daniela Briga, Matteo Conti, Antonino Bruno, Daniela Farioli, Sara Cavali, Ilaria Sogno, Gioacchino D'Ambrosio, Paolo Consonni and Douglas M. Noonan



Research Article

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Rapid Commun. Mass Spectrom. **2015**, *29*, 1703–1710
(wileyonlinelibrary.com) DOI: 10.1002/rcm.7270

SANIST: a rapid mass spectrometric SACI/ESI data acquisition and elaboration platform for verifying potential candidate biomarkers

Adriana Albini[1*†], Daniela Briga[2†], Matteo Conti[3], Antonino Bruno[2], Daniela Farioli[1], Sara Canali[2], Ilaria Sogno[2], Gioacchino D'Ambrosio[2], Paolo Consonni[2†] and Douglas M. Noonan[2,4†]

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RATIONALE: Surface-Activated Chemical Ionization/Electrospray Ionization mass spectrometry (SACI/ESI-MS) is a technique with high sensitivity and low noise that allows accurate biomarker discovery studies. We developed a dedicated SACI/ESI software, named SANIST, for both biomarker fingerprint data acquisition and as a diagnostic tool, using prostate cancer (PCa) as the disease of interest.
METHODS: Liquid chromatography (LC)/SACI/ESI-MS technology was employed to detect a potential biomarker panel for PCa disease prediction. Serum from patients with histologically confirmed or negative prostate biopsies for PCa was employed. The biomarker data (*m/z* or Thompson value, retention time and extraction mass chromatogram peak area) were stored in an ascii database. SANIST software allowed identification of potential biomarkers. A Bayesian scoring algorithm developed in house allowed sample separation based on comparison with samples in the database.
RESULTS: Biomarker candidates from the carnitine family were detected at significantly lower levels in patients showing histologically confirmed PCa. Using these biomarkers, the SANIST scoring algorithm allowed separation of patients with PCa from biopsy negative subjects with high accuracy and sensitivity.
CONCLUSIONS: SANIST was able to rapidly identify and perform a preliminary evaluation of the potential diagnostic efficiency of potential biomarkers for PCa.

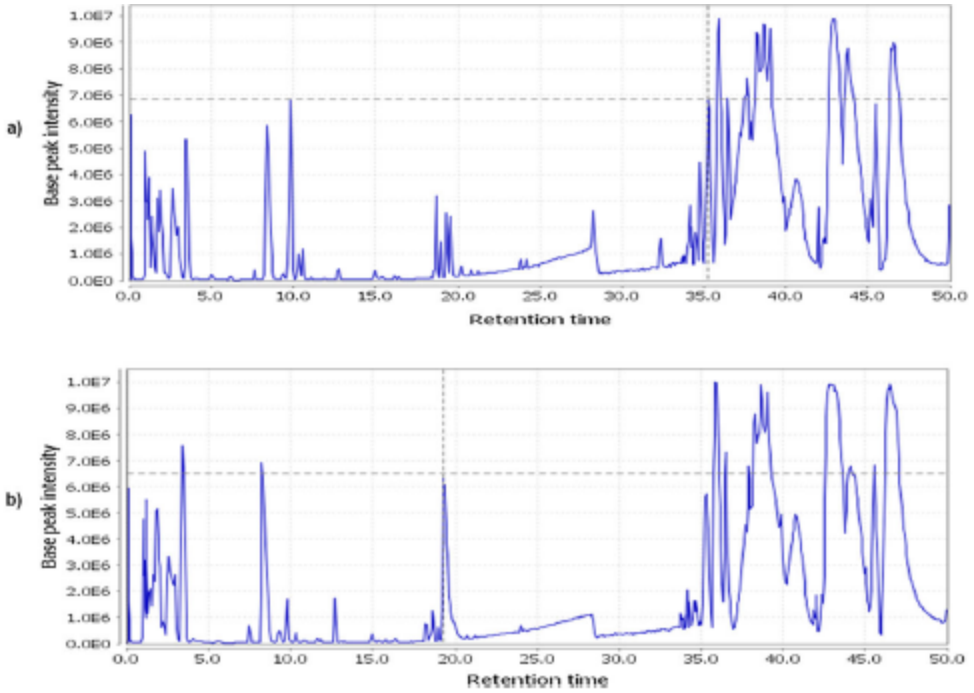


Figure 1. Representative full scan (base peak) extracted ion 'SANIST' mass chromatograms of (a) biopsy negative (BPH) and (b) biopsy positive (PCa) subjects.

Table 1. Ions that were differentially expressed between serum samples from BPH and positive prostate cancer (PCa positive) subjects in the discovery study and their corresponding metabolites

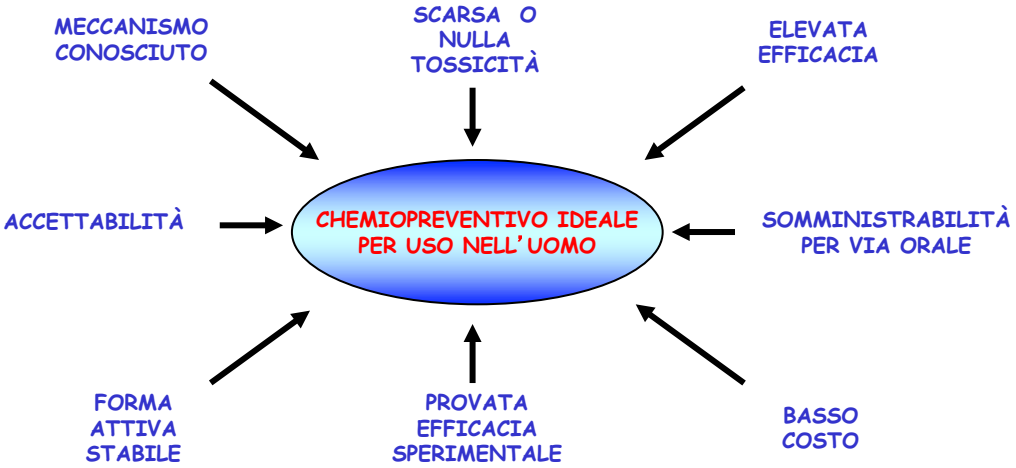
m/z value	Ion species	Metabolite name	Fold (Patient area/ Control area)	*p* value
316.256	$[M+H]^+$	Decanoyl-L-carnitine	0.76	0.0001
288.217	$[M+H]^+$	Octanoyl-L-carnitine	0.85	0.0003
370.295	$[M+H]^+$	5-*cis*-Tetradecenoyl carnitine	0.72	0.0004

Table 2. Classification percent identity score and absolute identity score obtained on the basis of the SANIST platform and the three identified carnitine biomerkers. All prostate cancer patient (PCa positive) profiles are similar to another prostate cancer, while benign prostate hyperplasia (BPH) are closest to other BPH subjects

Sample	SANIST sample classification	Absolute identity (‰)	Percent identity score (%)
P1	PCa Positive	904	91
P2	PCa Positive	911	92
P3	PCa Positive	903	90
P4	PCa Positive	905	94
P5	PCa Positive	912	92
P7	PCa Positive	920	91
P8	PCa Positive	903	91
P9	PCa Positive	907	92
P10	PCa Positive	904	93
P14	PCa Positive	903	92
P16	PCa Positive	906	92
P17	PCa Positive	905	93
P18	PCa Positive	901	94
P19	PCa Positive	902	93
P29	PCa Positive	913	91
C21	BPH	923	90
C23	BPH	908	91
C24	BPH	909	91
C29	BPH	905	93
C31	BPH	904	94
C32	BPH	914	93
C33	BPH	905	90
C34	BPH	914	91
C35	BPH	903	91
C36	BPH	906	90
C38	BPH	907	92
C39	BPH	903	92
C40	BPH	903	93

Chemioprevenzione farmacolgica e alimentare

- La chemioprevenzione prevede la somministrazione cronica di specifiche molecole per prevenire l'insorgenza di forme tumorali o impedirne la recidivanza
- Le caratteristiche del chemiopreventivo ideale sono:elevata tollerabilità, assenza di effetti collaterali o da accumulo, facilità di somministrazione, basso costo.
- Molti componenti della dieta, del cibo, hanno proprietà chemiopreventive



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OSSIAZIONE E INFIAMMAZIONE NELL INVECCHIAMENTO

Redox Biology 11 (2017) 482–501

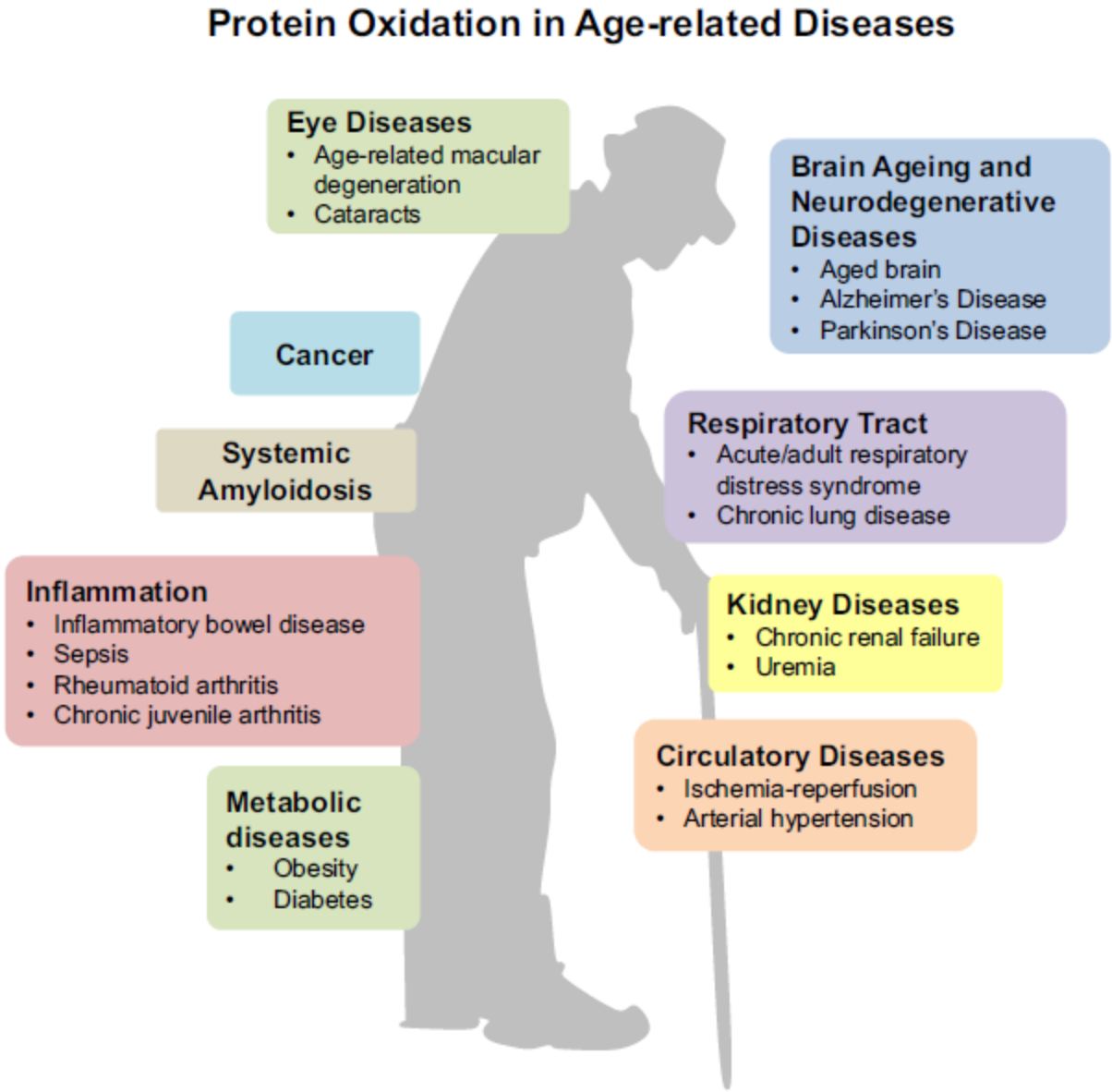

Fig. 9. Protein oxidation in age-related diseases. This figure shows the numerous diseases in which protein oxidation has been demonstrated so far. Protein oxidation may be the cause or consequence of these diseases which affect nearly all organ systems.

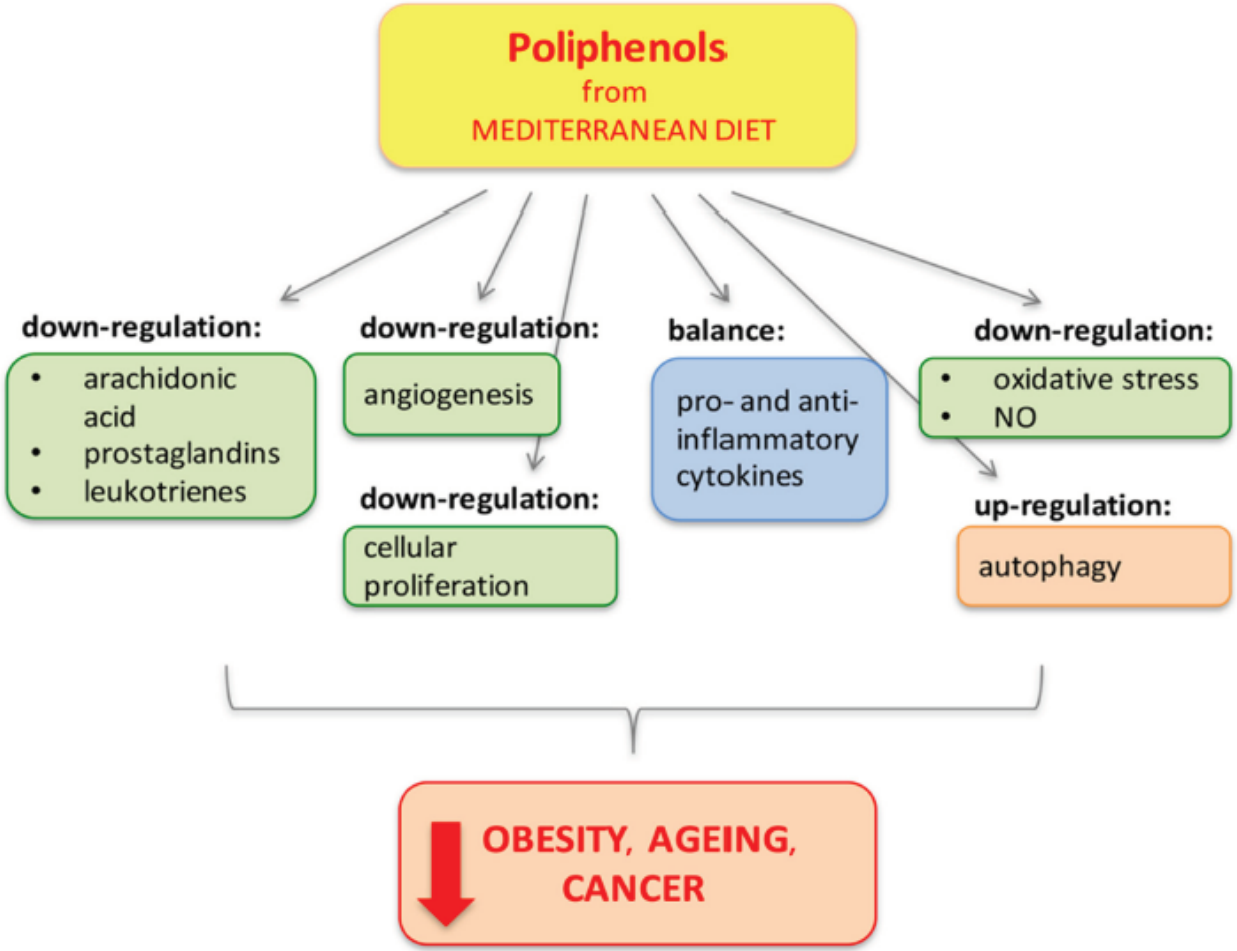

Figure 2: Polyphenols from Mediterranean Diet. Polyphenols protect and reduce inflammation by different pathways (through mechanisms of down-regulation, balance and up-regulation) preventing obesity, cancer and age-related diseases, in which inflammation has an important pathological role [240].

Clinical Trials Of Chemoprevention With AntiAngiogenic Molecules

Table 1 | Clinical trials of chemoprevention with antiangiogenic principles*

Compound	Molecular target or mechanism	Condition (ClinicalTrials.gov identifier)	Phase	Study type or design
Metabolic regulators				
Metformin	VEGF, mTOR, AMPK, MMP-2, MMP-9[78–80,87,90,117]	Barretts's metaplasia (NCT01447927) Colorectal adenoma or high BMI (NCT01312467) Prostate cancer (NCT01433913)	II II II	I, R, DB I, NR, OL I, R, DB
Pioglitazone	PPARγ agonist, bFGF, VEGF, IL-8, CXCL5, CXCL1[71]	Lung cancer (NCT00780234)	II	I, R, DB
Anti-inflammatory agents				
Aspirin and tea polyphenols	COX inhibitor, VEGF, COX-independent MOA[120–124]	Oesophageal squamous cell carcinoma (NCT01496521)	III	I, R, DB
Aspirin and esomeprazole	COX inhibitor, VEGF, COX-independent MOA[120–124]	Barretts's metaplasia (NCT00357682)	III	I, R, OL
Aspirin and eflornithine	COX inhibitor, VEGF, COX-independent MOA[120–124]	Familial adenomatous polyposis (NCT00983580)	II	I, R, DB
Sulindac‡	COX-2 inhibitor[54,56,60]	Oral premalignant lesions (NCT00299195)	P	I, R, DB
Sulindac and eflornithine	COX-2 inhibitor[54,56,60]	Colorectal premalignant or nonmalignant lesions (NCT00118365)	III	I, R, DB
Celecoxib‡	COX-2 inhibitor[54,56,126,127,129]	Cervical intraepithelial neoplasia (NCT00081263)	II	I, R, DB
Phytochemicals and derivatives				
Curcumin	NF-κB, VEGF, mTOR, miR-21[3,53,86,110,138,139]	Familial adenomatous polyposis (NCT00927485) Colorectal cancer (NCT01333917)	– I	I, R, DB I, OL, SG, Ph
Polyphenon E	MMPs, STAT3, VEGF[3,34,35,41,130,131]	Prostatic intraepithelial neoplasia (NCT00596011) Ductal carcinoma *in situ* (NCT01060345) Bronchial dysplasia (NCT00611650) Cervical intraepithelial neoplasia (NCT00303823)	II P II II	I, R, DB I, NR, SG, OL I, R, DB I, R, DB
Resveratrol	NF-κB, IGF axis, EGF, VEGF[54,61,140–142]	Healthy adult smokers (NCT01492114) Impaired glucose tolerance (NCT01375959)	III P	I, R, DB, CS I, R, DB, CS
Genistein	NF-κB, AP-1, uPA, FAK, VEGF, HIF-1α, PTEN[42,52,84]	Type II diabetes mellitus (NCT00951912) High risk for breast cancer (NCT00290758)	– IIb	I, R, DB I, R, DB
Genistein and vitamin D	NF-κB, AP-1, uPA, FAK, VEGF, HIF-1α, PTEN[42,52,84]	Early stage prostate cancer (NCT01325311)	II	I, R, DB
Black raspberry	COX-2, iNOS[92]	Head and neck cancer (NCT01469429)	I–II	I, R, OL
Sulforaphane	HDAC, Nrf2, VEGF, HIF-1α, MMPs[3,66,95]	Prostate cancer (NCT01265953) Prostate cancer (NCT00946309)	– I–II	I, R, DB I, R, DB
Other compounds				
Propranolol	VEGF, MMP-2, MMP-9, NF-κB[64]	Infantile haemangioma (NCT01074437)	II	I, R, DB
Imiquimod	MMP-9, interferons[46,47]	Lentigo maligna (NCT01088737)	II–III	I, NR, SG, OL
Everolimus	mTOR[75]	Skin cancer (NCT00799188)	III	I, R, OL
Fenretinide	IGF-1/IGFBPs[113,114]	High risk for breast cancer (NCT01479192)	III	I, R, DB
Tamoxifen	Oestrogen receptor, angiogenin, VEGF, endostatin[49–52]	Breast cancer (NCT01357772)	III	I, R, DB

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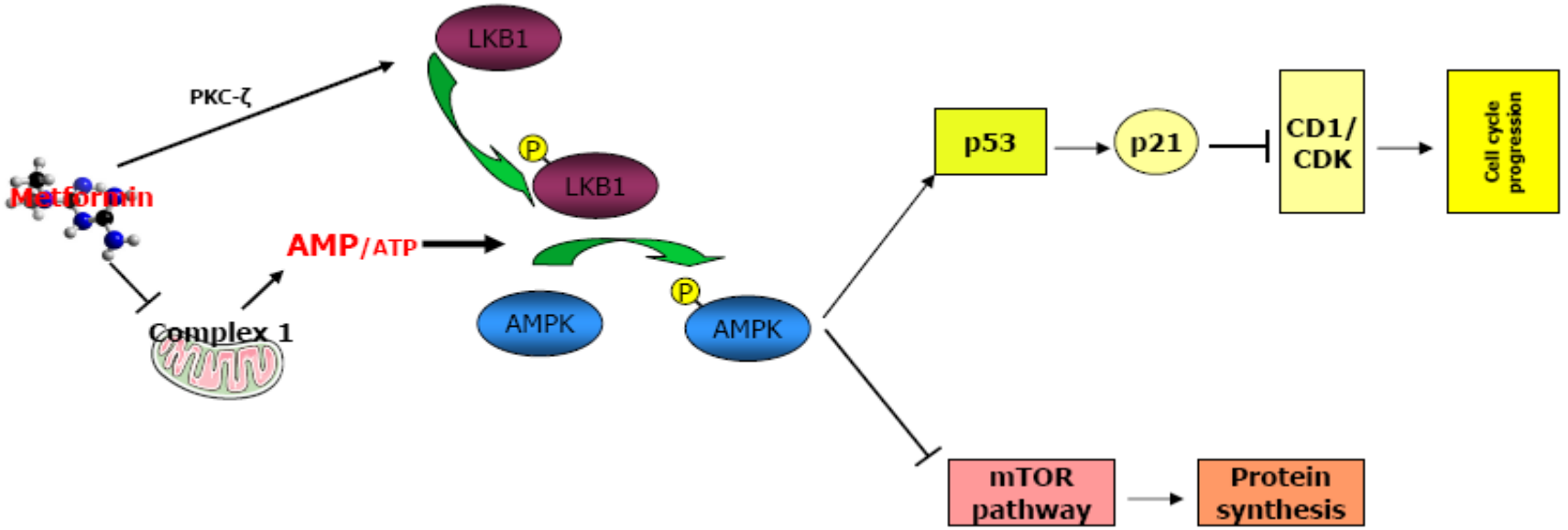
Albini et al, Nat Rev Clin Oncol. 2012 Aug 14;9(9):498-509

From diabetes cure to cancer prevention … via angioprevention?

METFORMIN



A decreased risk of breast cancer was observed in female patients with type 2 diabetes using metformin on a long-term basis.

Bodmer M et al, Diabetes Care 2010

Epidemiological studies have confirmed that metformin, but not other anti-diabetic drugs, significantly reduces cancer incidence and improves cancer patients' survival in tipe 2 diabetics.

Evans JM et al. BMJ 2005
Landman GW et al. Diabetes Care 2010

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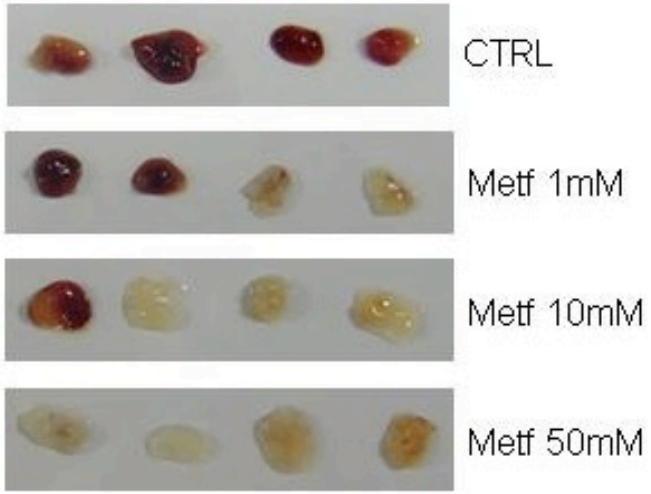
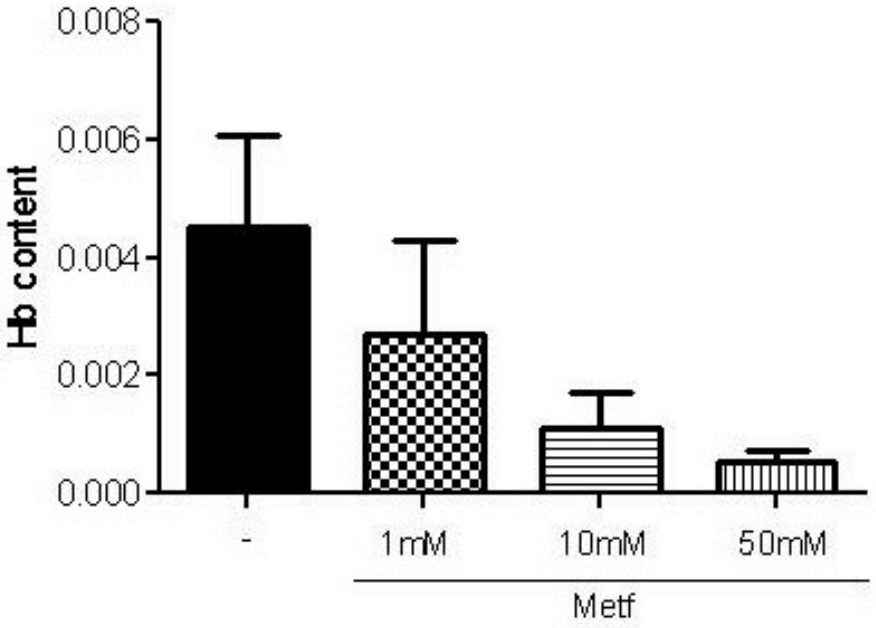
Metformin inhibits angiogenesis in vivo





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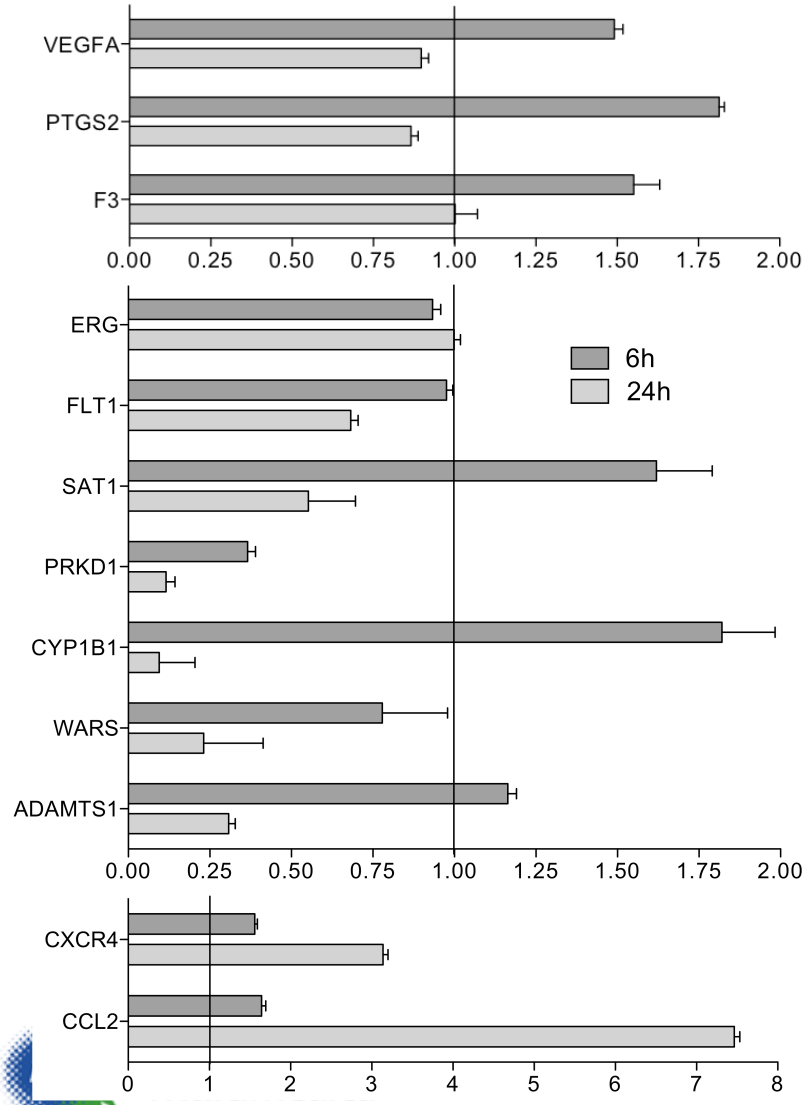
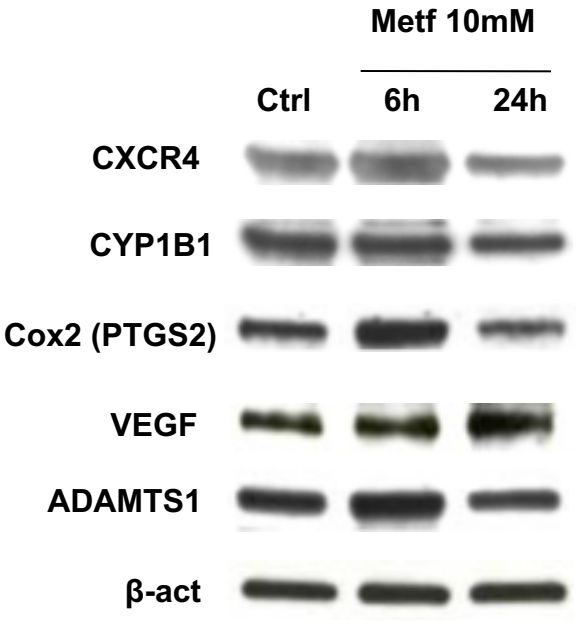
Metformin modulates several angiogenesis associated genes

qRT-PCR



Protein (WB)



Protein	CTR	6h	24h
CXCR4	-	Up	Down
CYP1B1	-	-	Down
Cox2 (PTGS2)	-	Up	Down
VEGF	-	-	Up
ADAMTS1	-	Up	Down

Combination Chemoprevention (to the micreonvironment): Metformin + Aspirin?

www.nature.com/scientificreports

OPEN

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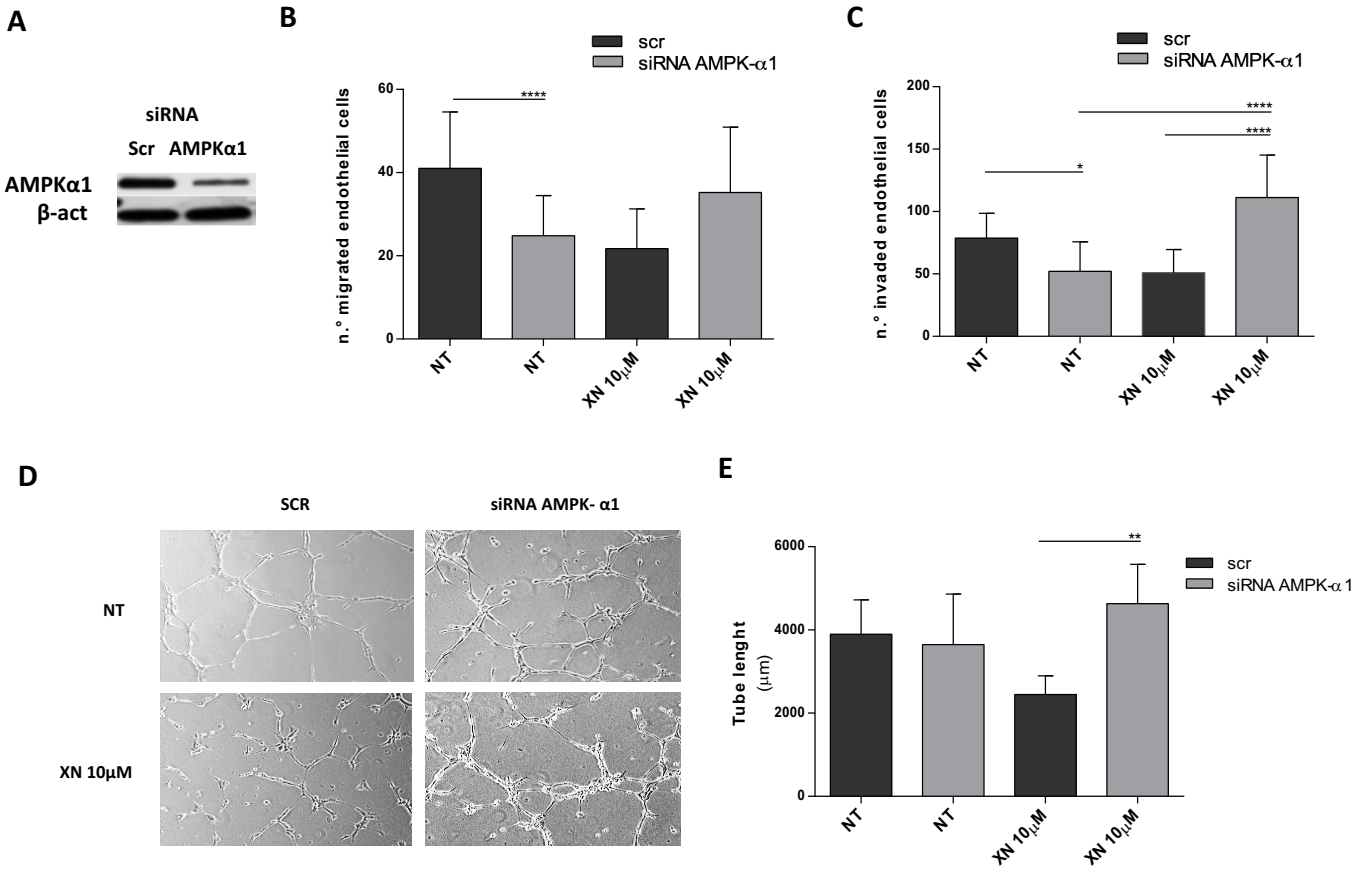
Aspirin and atenolol enhance metformin activity against breast cancer by targeting both neoplastic and microenvironment cells

Giovanna Talarico[1,*], Stefania Orecchioni[1,*], Katiuscia Dallaglio[2], Francesca Reggiani[1], Patrizia Mancuso[1], Angelica Calleri[1], Giuliana Gregato[1], Valentina Labanca[1], Teresa Rossi[2], Douglas M. Noonan[3,4], Adriana Albini[3,*] & Francesco Bertolini[1,*]

Metformin can induce breast cancer (BC) cell apoptosis and reduce BC local and metastatic growth in preclinical models. Since Metformin is frequently used along with Aspirin or beta-blockers, we investigated the effect of Metformin, Aspirin and the beta-blocker Atenolol in several BC models. *In vitro*, Aspirin synergized with Metformin in inducing apoptosis of triple negative and endocrine-sensitive BC cells, and in activating AMPK in BC and in white adipose tissue (WAT) progenitors known to cooperate to BC progression. Both Aspirin and Atenolol added to the inhibitory effect of Metformin against complex I of the respiratory chain. In both immune-deficient and immune-competent preclinical models, Atenolol increased Metformin activity against angiogenesis, local and metastatic growth of HER2+ and triple negative BC. Aspirin increased the activity of Metformin only in immune-competent HER2+ BC models. Both Aspirin and Atenolol, when added to Metformin, significantly reduced the endothelial cell component of tumor vessels, whereas pericytes were reduced by the addition of Atenolol but not by the addition of Aspirin. Our data indicate that the addition of Aspirin or of Atenolol to Metformin might be beneficial for BC control, and that this activity is likely due to effects on both BC and microenvironment cells.

AMPK requirement for XN-induced anti-angiogenic effects



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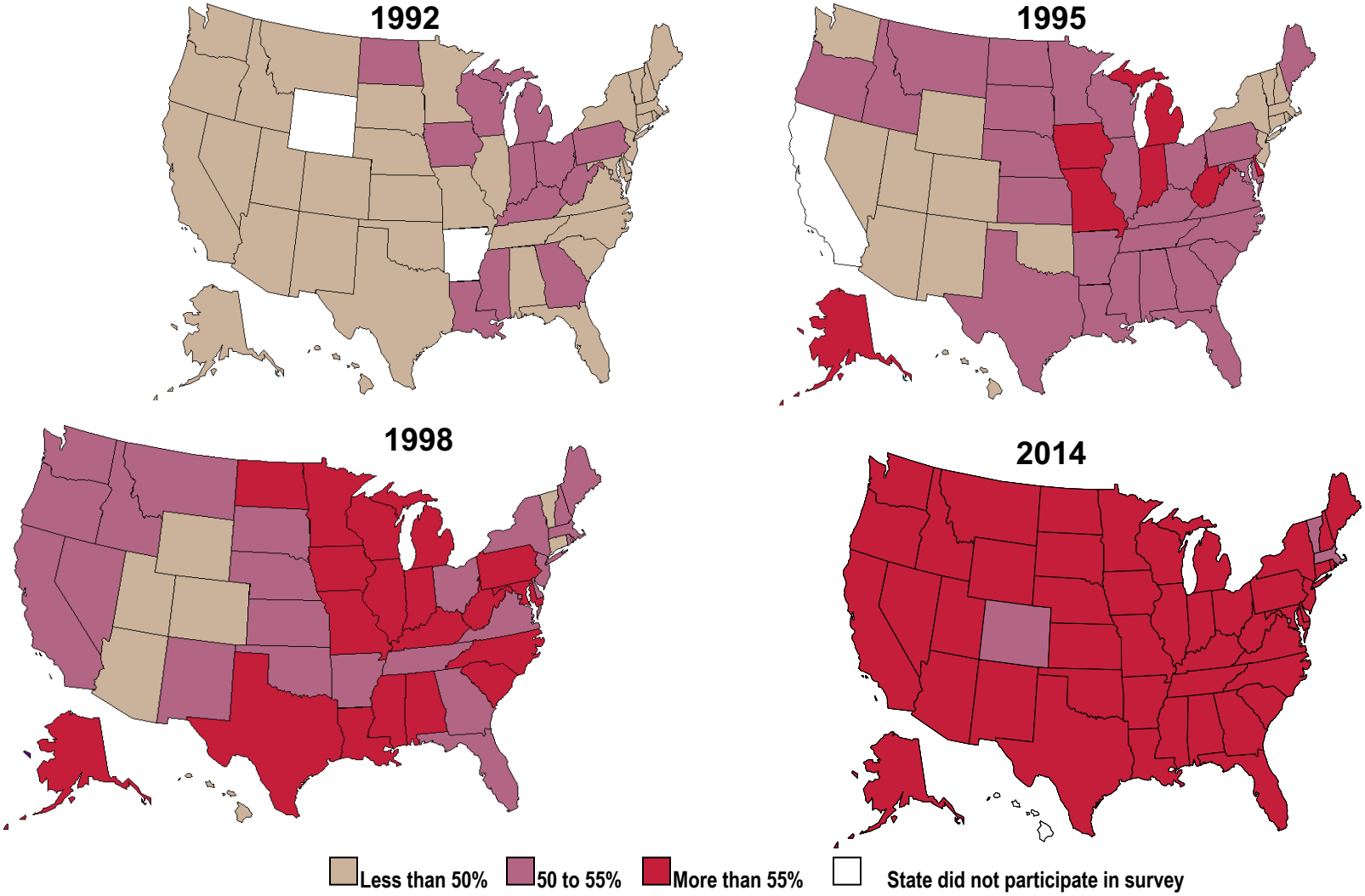
Hop derived flavonoid xanthohumol inhibits endothelial cell functions *via* AMPK activation

Cristina Gallo[1], Katiuscia Dallaglio[1], Barbara Bassani[2], Teresa Rossi[1], Armando Rossello[3], Douglas M. Noonan[4], Gabriele D'Uva[2], Antonino Bruno[2], Adriana Albini[2]

Aumento della Percentuale di persone in sovappeso USA negli ultimi venti anni



*Body mass index of 25.0 kg/m^{2}or greater. Source: Behavioral Risk Factor Surveillance System, CD-ROM (1984-1995, 1998) and Public Use Data Tape (2004), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 1997, 2000, 2005.

DIETA MEDITERRANEA

- **Povera in carni e ricca di vegetali;**
- **comprende alimenti e condimenti i cui effetti benefici sulla salute sono ampiamente riconosciuti;**
- **Nelle aree italiane dove più si conserva la tradizione alimentare mediterranea, l'incidenza di alcuni tumori è significativamente inferiore**

MEDITERRANEAN DIET IN ITALY IN THE FIFTIES

"… a hearty dish of beans and short lengths of macaroni (pasta e fagioli);
… lots of bread (never served with any kind of spread);
… great quantities of fresh vegetables;
… a modest portion of meat or fish (perhaps twice a week);
… wine;
… always fresh fruits for dessert.

"…. for the possible prevention of CHD, it would be hard to do better than imitate the diet of the common folk of Naples in the early 1950s"

Ancel and Margaret Keys. HOW TO EAT WELL AND STAY WELL: THE MEDITERRANEAN WAY 1975

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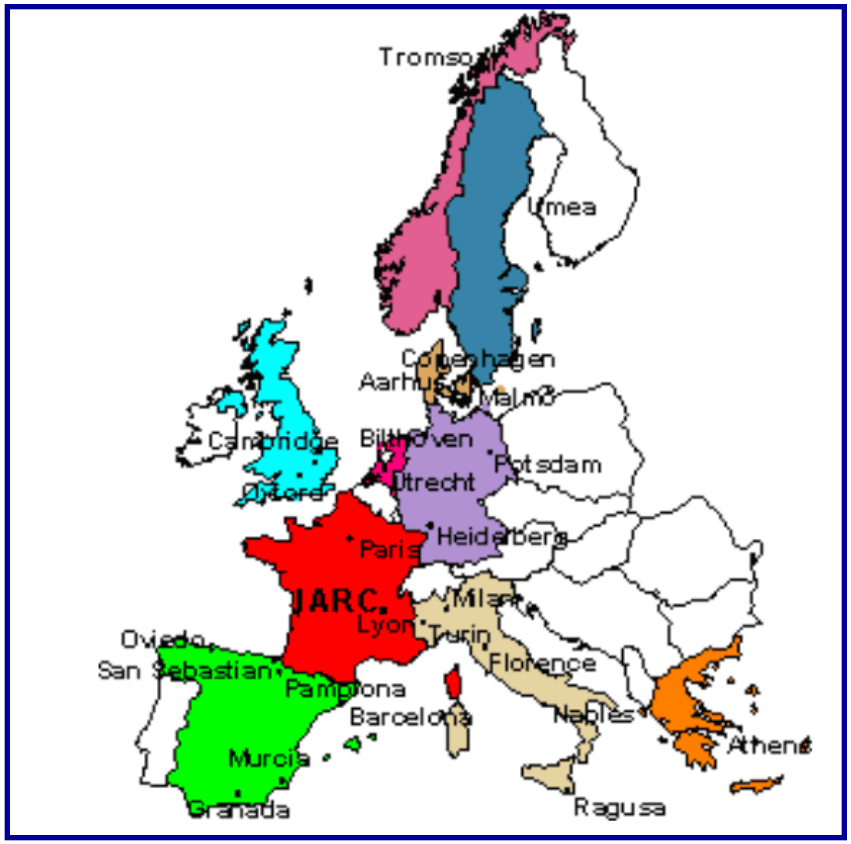
Lo studio EPIC

European Prospective Investigation into Cancer and nutrition



OBIETTIVO: studiare il ruolo dei fattori alimentari e legati allo stile di vita nell'eziologia dei tumori e di altre malattie cronico-degenerative.

Raccolta dei dati

- Questionario anamnestico → stile di vita
- FFQ → dieta
- Misure antropometriche
- Prelievo

EPIC Italia: ~ 47,000 volontari in 5 centri

~ 520,000 volontari reclutati in 10 Paesi Europei

Mediterranean dietary pattern and cancer risk in the EPIC cohort

E Couto[1,2], P Boffetta[*,1,3,4], P Lagiou[5], P Ferrari[6], G Buckland[7], K Overvad[8], CC Dahm[9], A Tjønneland[10], A Olsen[10], F Clavel-Chapelon[11,12], M-C Boutron-Ruault[11,12], V Cottet[11,12], D Trichopoulos[4,13,14], A Naska[5], V Benetou[5], R Kaaks[15], S Rohrmann[15], H Boeing[16], A von Ruesten[16], S Panico[17], V Pala[18], P Vineis[19,20], D Palli[21], R Tumino[22], A May[23], PH Peeters[23], HB Bueno-de-Mesquita[24,25], FL Büchner[24,26], E Lund[27], G Skeie[27], D Engeset[27], CA Gonzalez[7], C Navarro[28,29], L Rodríguez[30], M-J Sánchez[28,31], P Amiano[28,32], A Barricarte[28,33], G Hallmans[34], I Johansson[35], J Manjer[36], E Wirfärt[37], NE Allen[38], F Crowe[38], K-T Khaw[39], N Wareham[39], A Moskal[1], N Slimani[1], M Jenab[1], D Romaguera[19], T Mouw[19], T Norat[19], E Riboli[19] and A Trichopoulou[4,5]

Br J Cancer (2011) 104, 1493 – 1499

Table 3 Hazard ratios for all cancers associated with categories of the Mediterranean diet score

Score	Cohort members	Cases	HR[a] (95% CI)
Both sexes			
0–3	154 052	10 349	1.00
4	105 936	6849	0.96 (0.93–0.99)
			0.92 (0.89–0.95)
			0.93 (0.90–0.96)
			...end = 0.0001
			1.00
4	30 770	2121	0.99 (0.93–1.04)
5	29 766	2049	0.97 (0.92–1.03)
6–9	38 908	2455	0.93 (0.88–0.99)
			P for trend = 0.02
Women			
0–3	110 891	7305	1.00
4	75 166	4728	0.95 (0.91–0.98)
5	69 906	4176	0.90 (0.87–0.94)
6–9	79 910	4853	0.93 (0.89–0.96)
			P for trend = 0.0001

8% di tumori in meno per punteggi medio alti

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Italian Mediterranean Index and risk of colorectal cancer in the Italian section of the EPIC cohort

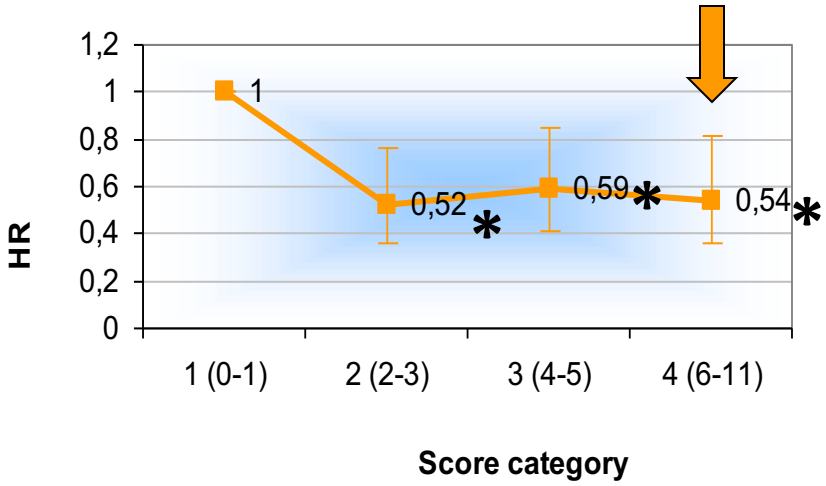
Claudia Agnoli[1], Sara Grioni[1], Sabina Sieri[1], Domenico Palli[2], Giovanna Masala[2], Carlotta Sacerdote[3,4], Paolo Vineis[4,5], Rosario Tumino[6], Maria Concetta Giurdanella[6], Valeria Pala[1], Franco Berrino[7], Amalia Mattiello[8], Salvatore Panico[8] and Vittorio Krogh[1]

Int. J. Cancer: **132**, 1404–1411 (2013) © 2012 UICC

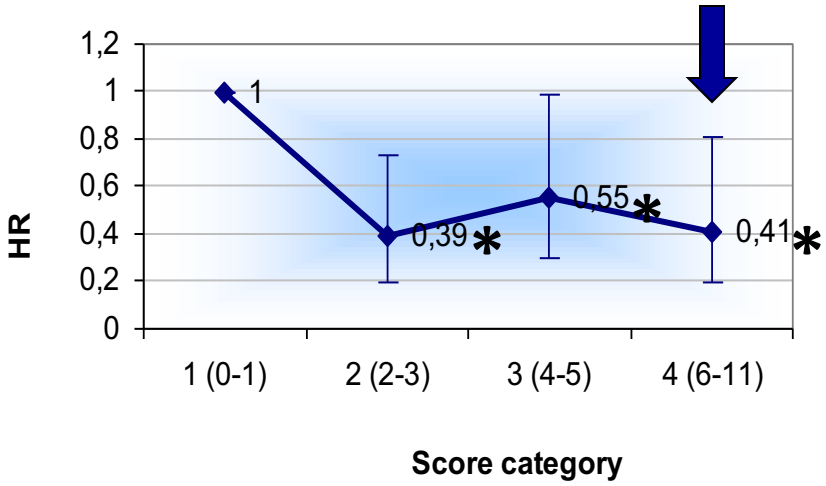
Risultati

Tumori del colon e del retto

Tumore del Colon



Tumore del Retto



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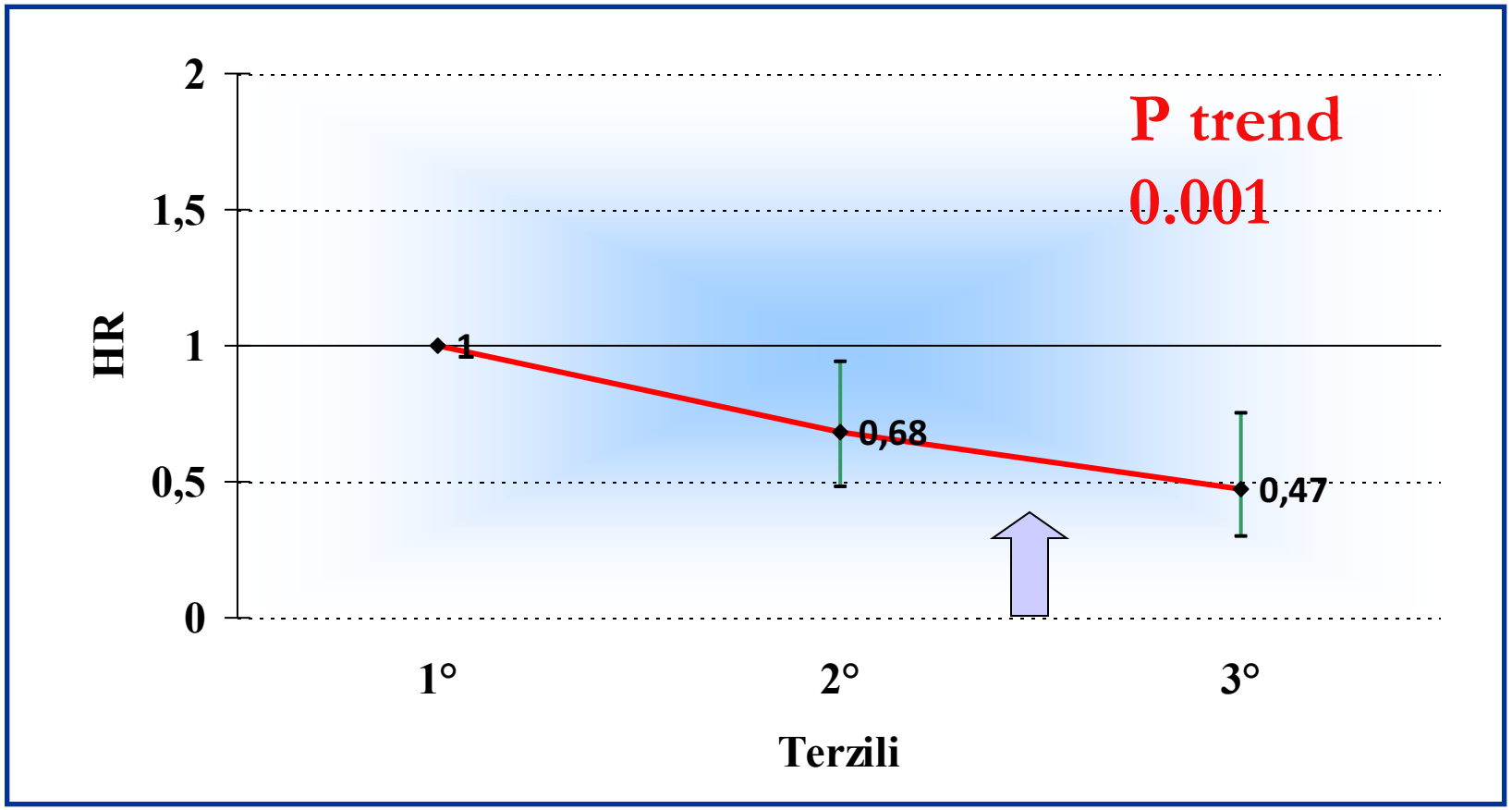
A Priori–Defined Dietary Patterns Are Associated with Reduced Risk of Stroke in a Large Italian Cohort[1–3]

Claudia Agnoli,[4] Vittorio Krogh,[4]* Sara Grioni,[4] Sabina Sieri,[4] Domenico Palli,[6] Giovanna Masala,[6] Carlotta Sacerdote,[7,8] Paolo Vineis,[9,10] Rosario Tumino,[11,12] Graziella Frasca,[11] Valeria Pala,[4] Franco Berrino,[5] Paolo Chiodini[13] Amalia Mattiello,[14] and Salvatore Panico[14]

J. Nutr. 141: 1552–1558, 2011

Indice Mediterraneo Italiano e Ictus



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Agnoli et al. *J.Nutr.* 2011; 141:1552-1558.

La "personalità" della Dieta Mediterranea è caratterizzata da:

- Consumi sostenuti di vegetali, legumi, frutta fresca e secca, cereali integrali
- Predominanza di consumo di olio di oliva a fronte di un basso consumo di grassi animali
- Consumo abituale di pesce
- Consumo moderato di prodotti caseari
- Consumo moderato di carni
- Consumo regolare ma piuttosto moderato di alcol, essenzialmente come vino e durante i pasti

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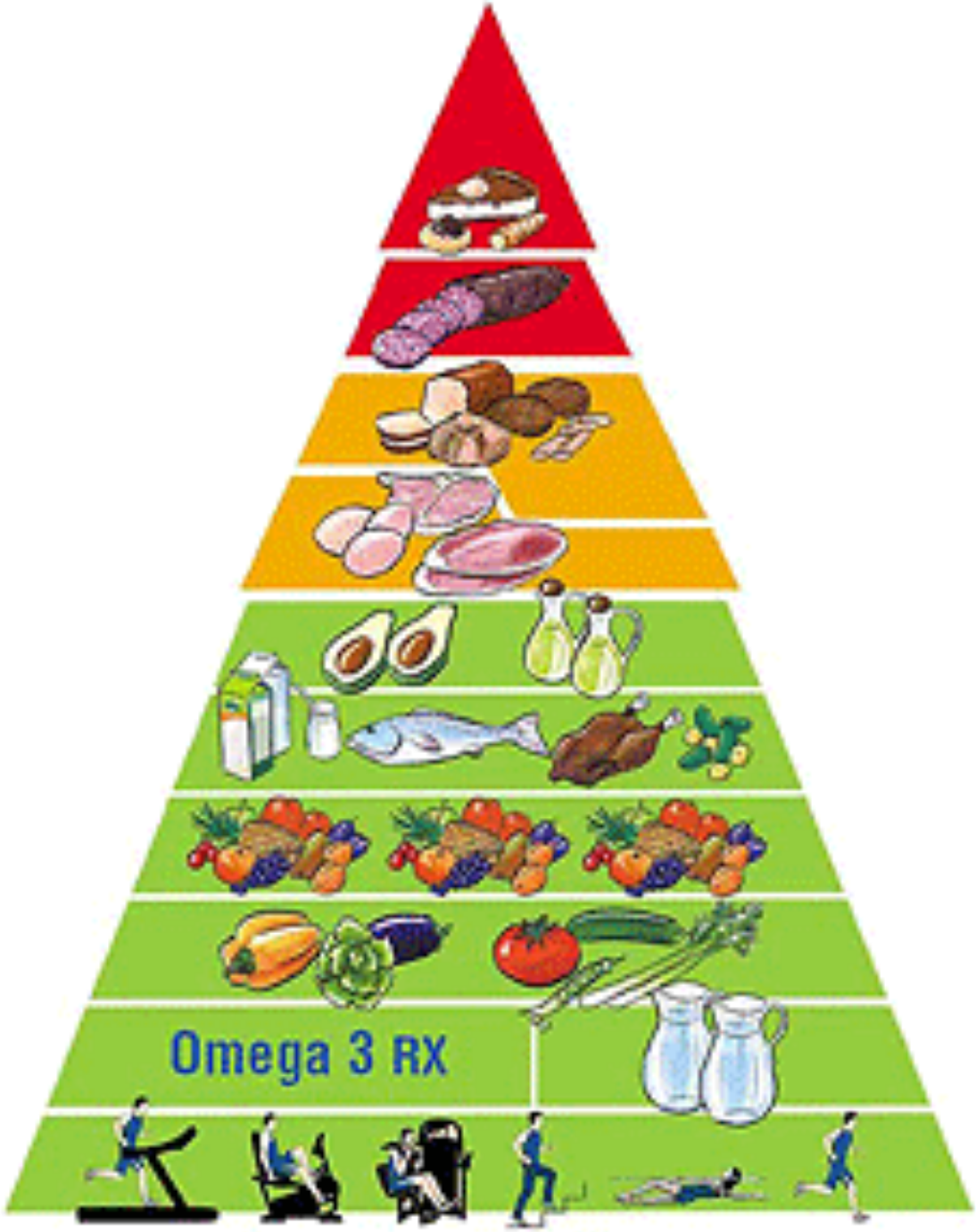
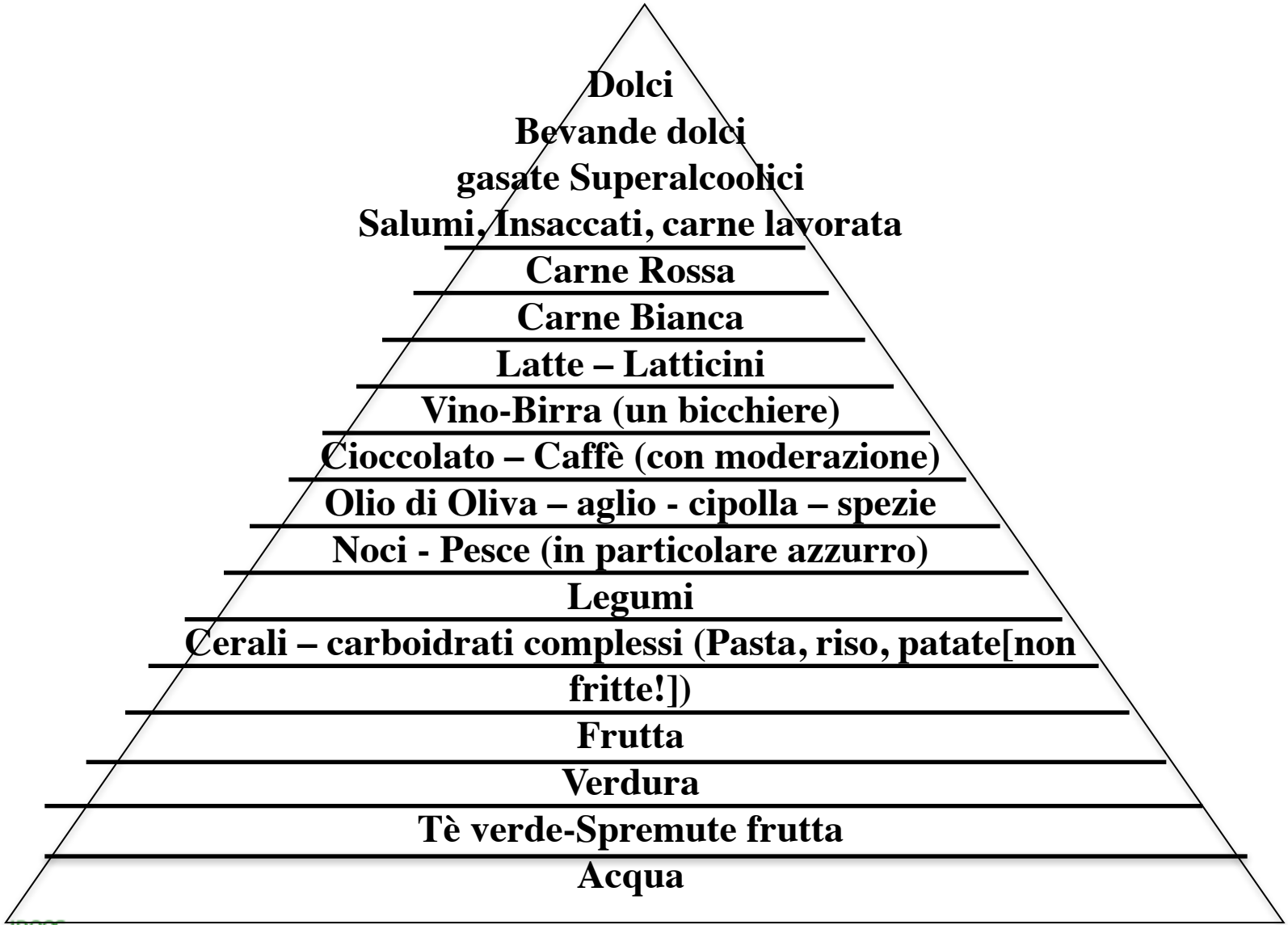
Piramide Alimentare

Gruppo 1: carboidrati a lento assorbimento(pane, pasta, polenta, riso, legumi, cereali in genere, ecc.).
Gruppo 2 e 3: verdura e frutta rappresentano le fonti principali di vitamine e minerali.
Gruppo 4: costituito dal latte e i suoi derivati, sono la fonte principale di calcio e altri minerali escluso il ferro, i formaggi invece forniscono anche un buon apporto proteico.
Gruppo 5: carni, pesci e uova rappresentano la fonte proteica più elevata e di maggiore valore qualitativo.
Gruppo 6: tutti i tipi di olio, burro, margarina e simili, rappresentano la fonte principali di grassi.
Gruppo 7: da evitare: bibite carbonate, lardo e strutto, superalcolici


Omega 3 RX



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Unhealthy life style …can be prevented…

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Perspective

Clinical Cancer Research

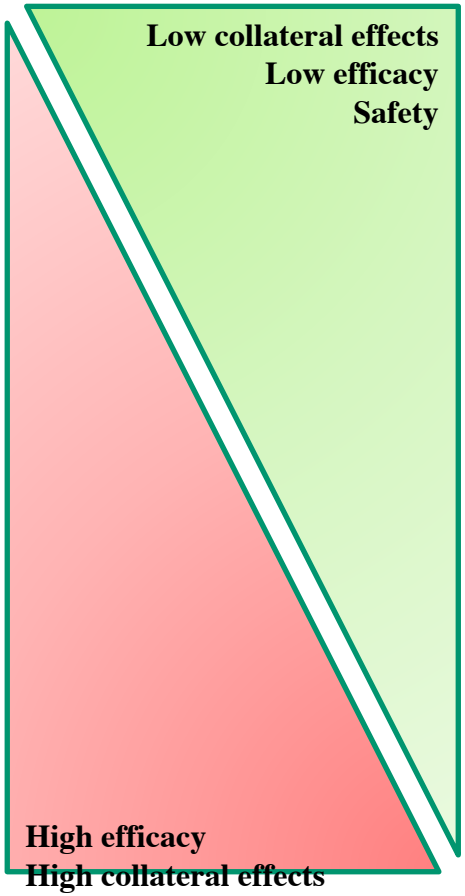
Cancer Prevention and Interception: A New Era for Chemopreventive Approaches

Adriana Albini[1], Andrea DeCensi[2], Franco Cavalli[3], and Alberto Costa[4]

Table 1. A potential "to do" list in cancer prevention and preventive interception

	Prevention	Interception
1	Do not smoke.	-Quit smoking (often requires a multitask, structured intervention). Take low-dose aspirin or other chemoprevention measures.
2	Avoid chemical carcinogens in the environment and at work place. Make your environment smoke free.	-Fight for your rights: receive attention if you have been exposed to asbestos, PAH, and other carcinogens in the work place or environment.
3	Avoid physical carcinogens, example: overexposure to sunlight and other sources of UV.	-Do periodic screening for premalignant skin lesions.
4	Avoid biologic carcinogens. Vaccines for virally induced cancer (example: HPV).	-Antibiotics for bacterial-associated cancer (example: *Helicobacter pylori*). Do periodic screening for premalignant lesions in the uterine cervix
5	Avoid overweight and obesity, eat properly	-Lose weight, change dietary habits
6	Avoid foods that might be potentially carcinogenic	-Limit salt, red and processed meat; avoid soft drinks
7	Limit alcohol. Do not overcome 1 glass per day in women and 2 glasses in men	-Cut back or quit drinking
8	Keep your gut flora and your microbiota "healthy"	-Restore your intestinal flora with a healthy life style and diet. Near future: dietary supplements containing "healthy" microbiome components
9	Avoid a sedentary lifestyle, be physically active	-Get on an exercise program
10	Control risk factors: inflammation, metabolic syndrome	-With low level risk conditions, take some chemopreventive strategies with few side effects: aspirin, metformin, flavonoids, curcumin
11	Prefer breast feeding your children rather than using formula	-Monitor changes in your body (e.g., breast lumps).
12	If there are familial cases of cancer, get genetic counseling and do relevant chemoprevention for the cancers at risk.	-Do periodic screening for premalignant lesions for breast, colon and prostate. With high risk consider a chemoprevention trial. Near future: precision prevention.

Abbreviations: PAH, polycyclic aromatic hydrocarbons; UV, ultraviolet light.



Primary Prevention

- **In healthy individuals**
  - **Reduce DNA damage**
    - **Anti-oxidant**
    - **Anti-inflammation**
  - **Live with hyperplastic foci**
    - **Anti-angiogenesis**
    - **Anti-inflammation**

Secondary Prevention

- **In patients with benign disease**
  - **early detection and intervention**
    - **reverse, halt or retard the condition**

Tertiary Prevention

- **In patients with malignant disease after treatment**
  - **Anti-metastatic procedures**

Quaternary Prevention

- **In patients with malignant disease during treatment**
  - **Enhancement of efficacy (ie sensitizing CSCs)**
  - **Protection of normal cells from the damage of chemotherapy**

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Conclusions

- Chemopreventive drugs target angiogenesis, endothelial and inflammatory cells.
- Endothelial cell cultures show alterations in gene expression when treated with chemopreventive drugs
- Numerous angiogenesis-and inflammation associated genes were among those most regulated upon treatment.
- A group of genes regulated by ECGC and NAC that show an overlap in regulation
- The chemoprevention drugs tested have anti-inflammatory angiogenesis properties and act on the microenvironment
- The NfκB pathway is affected leading to reduced expression of several genes that are related to inflammation and/or angiogenesis, i.e. selectin-E and urokinase plasminogen activator.

Reduction of inflammation, ROS and EC activation can explain the preventive effects observed.

Diet derived molecules are potential chemopreventive angiopreventive agents

The microenvironment can provide markers for progression

The microenvironment can be involved in cancer drugs vascular and cardiac toxicity

ANGIOGENESIS AND THE MICROENVIRONMENT CAN BE TARGETED NOT ONLY IN THERAPY BUT IN PREVENTION

Industry and Diet Derivatives Chemoprevention and Angioprevention

Prevention Clinical trials are hampered by:

- Need for large patient groups
  - Identification of risk groups
  - Risk-risk vs risk-benefit
- Need for long follow-up
- Comparisons with off patent drugs
- Identification of drug complications with long term use

High Cost

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Future directions for prevention

- Development of a true nutriceutical industry
- Modification of "natural" compounds or targeted compounds to improve:
  - Stability
  - Activity
  - Efficacy
- Identification of risk factors and monitoring capacity
- **The nutriceutical Industry needs to develop a monitoring system for efficacy**

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