Vitamina C
e neoplasie

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The beginning….

Proc. Natl. Acad. Sci. USA
Vol. 73, No. 10, pp. 3685–3689, October 1976
Medical Sciences

Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer*

(vitamin C)

EWAN CAMERON† AND LINUS PAULING‡

Table 2. Ratios of average survival times for ascorbate patients and matched controls, with statistical significance

A	B (Days)	C (Days)	D	E (Days)	F (%)	G (%)	H	I
Bronchus (15)	136	38.5	3.53	47	47	8.7	24.5	<<0.0001
Colon (13)	282	37.0	7.61	59	54	20	7.63	<0.003
Stomach (13)	98.9	37.9	2.61	43	46	17	6.41	<0.006
Breast (11)	367	64.0	5.75	91	55	22	5.74	<0.026
Kidney (9)	333	64.0	5.21	88	67	22	8.35	<0.002
Bladder (7)	196	43.6	4.49	57	57	20	4.90	<0.028
Rectum (7)	226	55.5	4.10	71	86	33	7.57	<0.003
Ovary (6)	148	71.0	2.08	78	83	30	6.83	<0.005
Others (19)	172	56.8	3.03	67	53	27	5.28	<0.027
All (100)	209.6	50.4	4.16	65	60	25.7	55.02	<<0.0001

A, Type of cancer and, in parentheses, number of ascorbate patients. There are 10 matched controls for each ascorbic acid patient. B, Average days of survival for ascorbate patients. C, Average days of survival for controls. D, The ratio B/C. E, Average days of survival for all subjects in group. F, Percentage of ascorbate patients surviving longer than E. G, Percentage of controls surviving longer than E. H, Value of


…and the end.

Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial.

Studio controllato in doppio cieco su 150 pz con neoplasia avanzata randomizzati ad elevate dosi di vitamina C (10 g/die) vs placebo.
Nessuna differenza in PS, appetito, peso, e sintomi.
La sopravvivenza mediana in entrambi i gruppi è stata di 7 settimane, le curve di sopravvivenza nei 2 gruppi erano essenzialmente sovrapponibili.

Creagan E.T. et al. N. Engl J Med 1979

High-Dose Vitamin C versus Placebo in the Treatment of Patients with Advanced Cancer Who Have Had No Prior Chemotherapy — A Randomized Double-Blind Comparison

Studio in doppio cieco su 100 pazienti con neoplasia avanzata del colon non precedentemente trattati con CHT, randomizzat a vit C (10g/die) vs placebo.

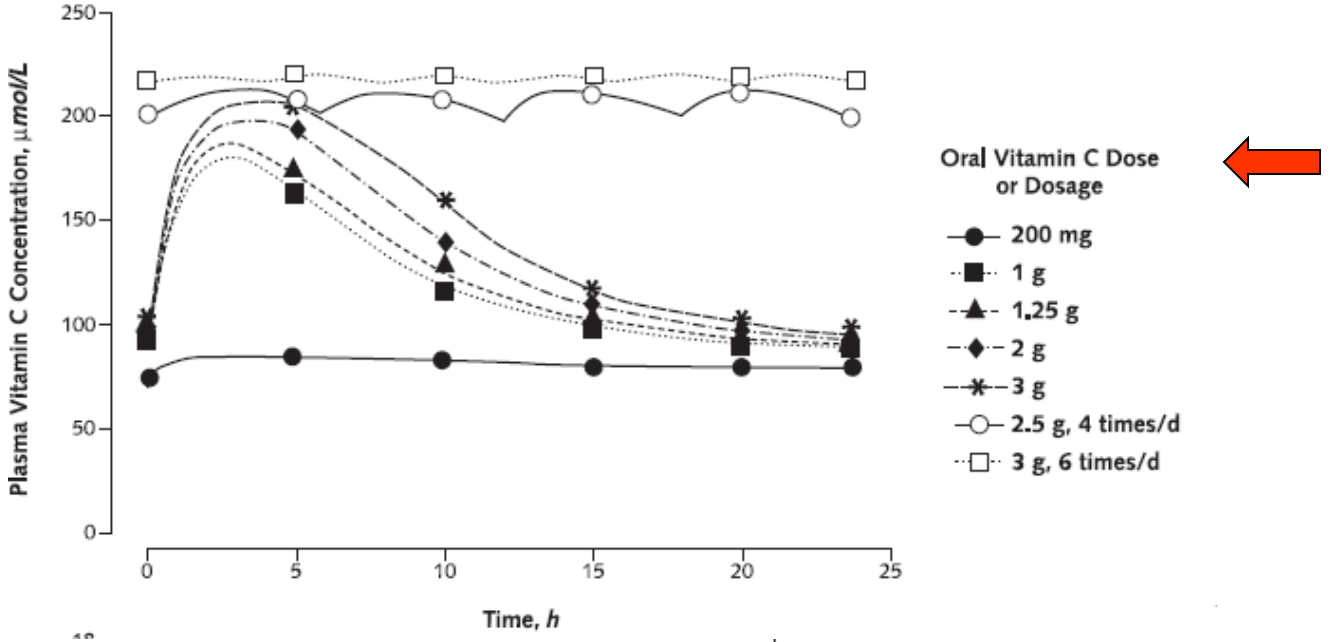
Nessun vantaggio rispetto al placebo nella progressione di malattia e nella sopravvivenza.

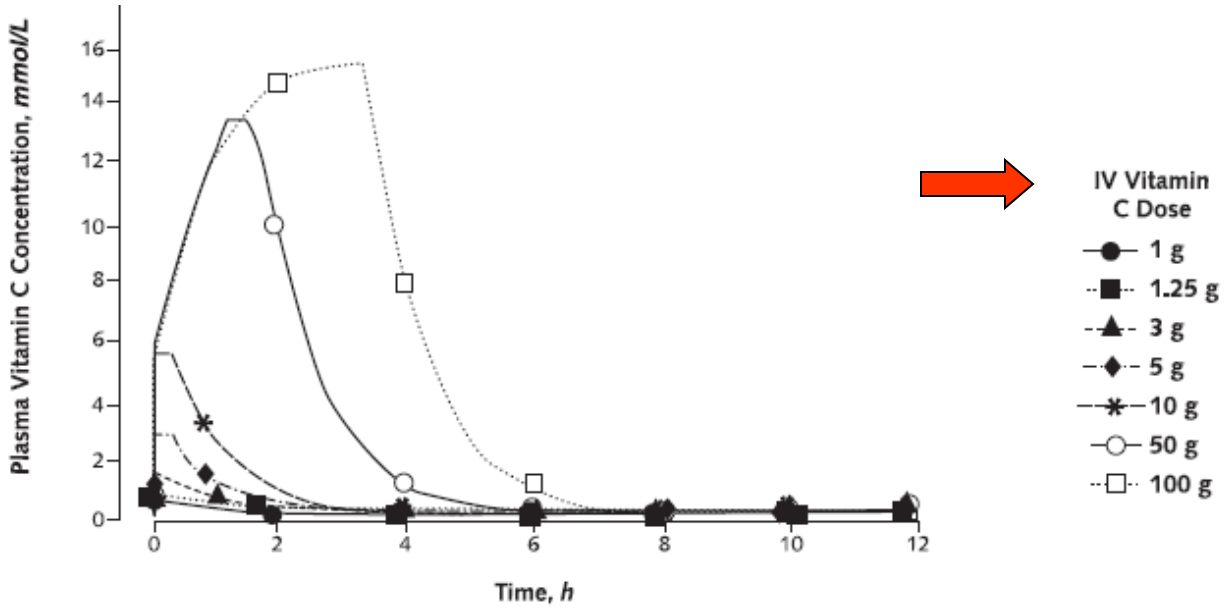
Nessuna risposta in pazienti con malattia misurabile.

Moertel, C.G et al. N Engl J Med 1985

Whas it really the end?

Pharmacokinetics matters!





Padayatty S. J.
Annals Intern Med 2004

Ascorbic Acid and Cancer: A Review

Ewan Cameron, Linus Pauling and Brian Leibovitz

Cancer Res 1979;39:663-681.

Ascorbic acid in the blood of cancer patients

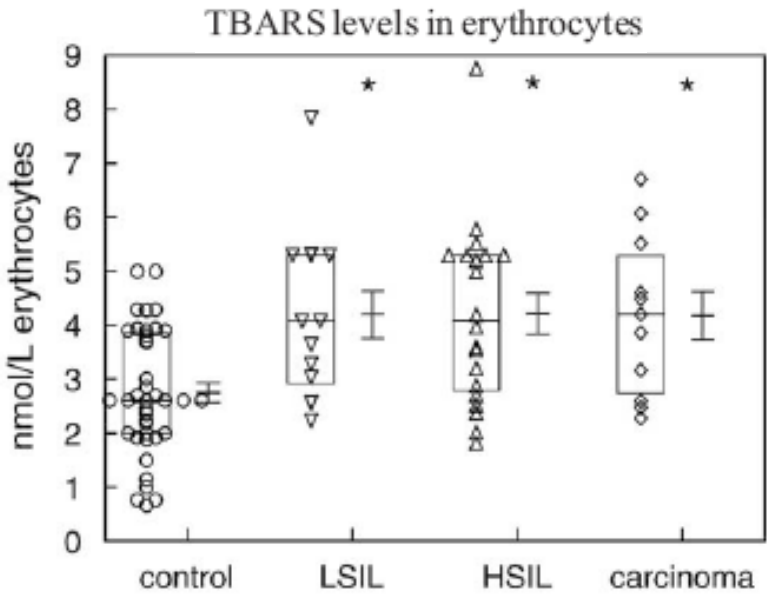
Investigator	Type of cancer studied	No. of cancer patients	Plasma levels (mg/dl)		Leukocyte levels (μg/10^8 cells)	
			Cancer	Controls	Cancer	Controls
Bodansky *et al*. (38)	Miscellaneous cancers	69	0.48	0.79	27.0[a]	36.1[a]
Waldo and Zipf (333)	Miscellaneous cancers	30	0.10	0.80		35.0
Freeman and Hafkesbring (124)	Miscellaneous cancers	5	0.62[b]	0.88[b]		
Krasner and Dymock (183)	Miscellaneous cancers	50			11.5	29.5
Kakar and Wilson (165)	Advanced breast cancer	1	0.13	0.47	12.5	26.0
Basu *et al*. (18)	Advanced breast cancer	22			12.0	33.0
Cameron (49)	Miscellaneous cancers	24	0.26	0.96	11.2	24.3
Waldo and Zipf (333)	Leukemia	42	0.18	0.80	8.2	35.0
Barkhan and Howard (14)	Leukemia	5	0.21	0.69		
Lloyd *et al*. (198)	Acute leukemia	8	0.3	0.79	12.0[c]	35.0[c]
Lloyd *et al*. (198)	Chronic leukemia	8	0.7	0.79	31.0[c]	35.0[c]
Kakar *et al*. (166)	Acute lymphatic leukemia	10	0.40	0.95	35.9	56.4
Basu *et al*. (18)	Miscellaneous cancers	22			17.0	33.0

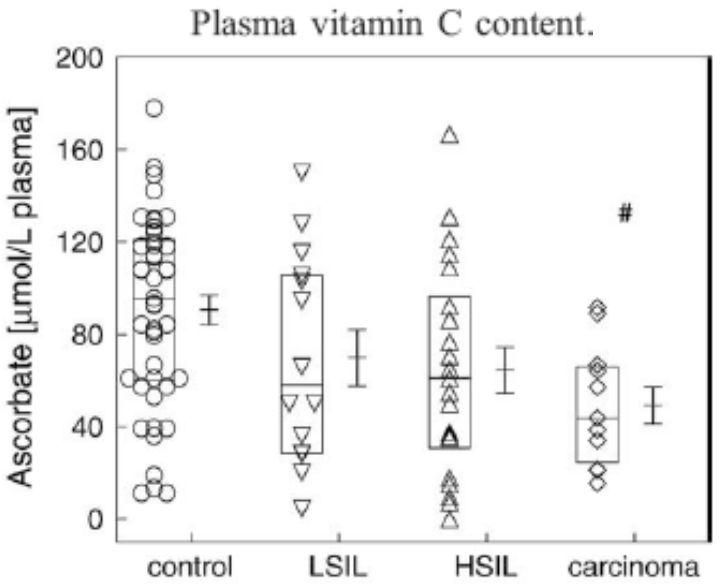
Involvement of oxidative stress in the pre-malignant and malignant states of cervical cancer in women

Clinical Biochemistry 38 (2005)

Thissiane L. Gonçalves [a,b], Fernando Erthal [a], Cristiane L.D. Corte [a], Liz G. Müller [a], Clarice M. Piovezan [c], Cristina W. Nogueira [a], João B.T. Rocha [a,*]

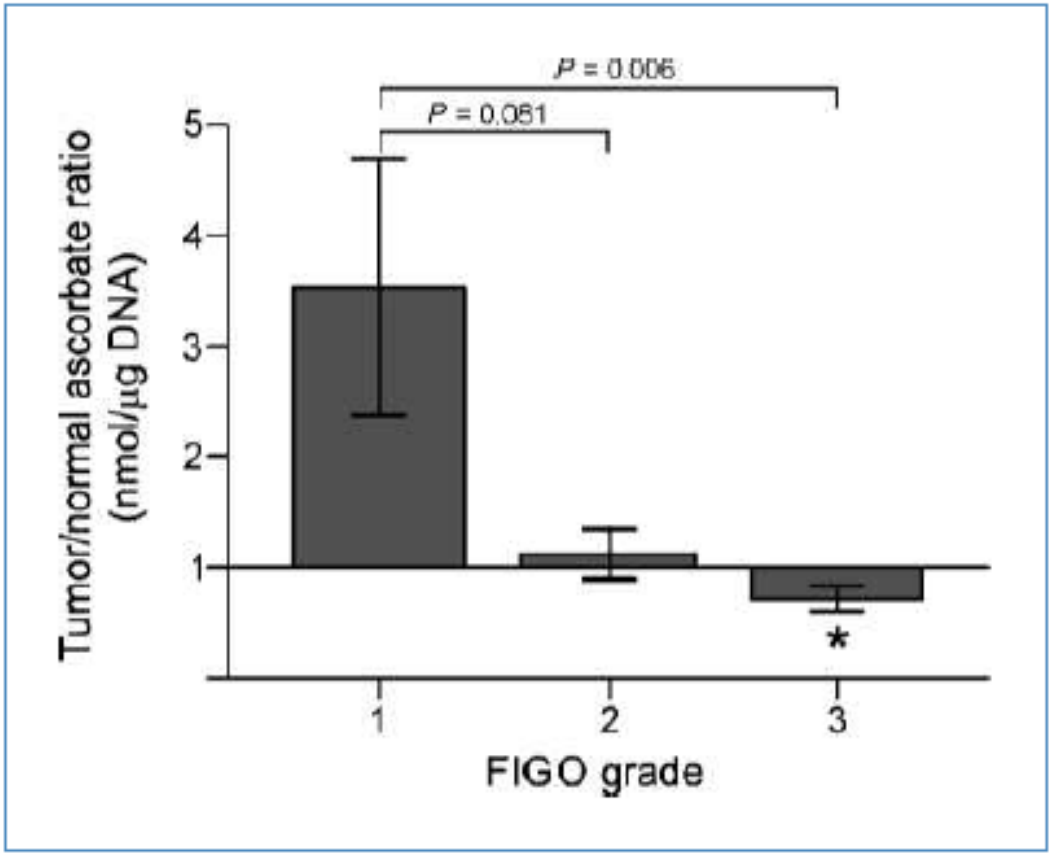
	Control	LSIL	HSIL	Carcinoma
TBARS	2.74 (2.37–3.11) $n = 40$	4.20 (3.24–5.15) $n = 13$	4.21 (3.42–5.00) $n = 20$	4.18 (3.18–5.18) $n = 11$
Vitamin C	90.5 (78.1–102.8) $n = 45$	69.9 (43.6–96.2) $n = 14$	64.2 (43.5–84.9) $n = 20$	49.3 (31.5–67.1) $n = 11$

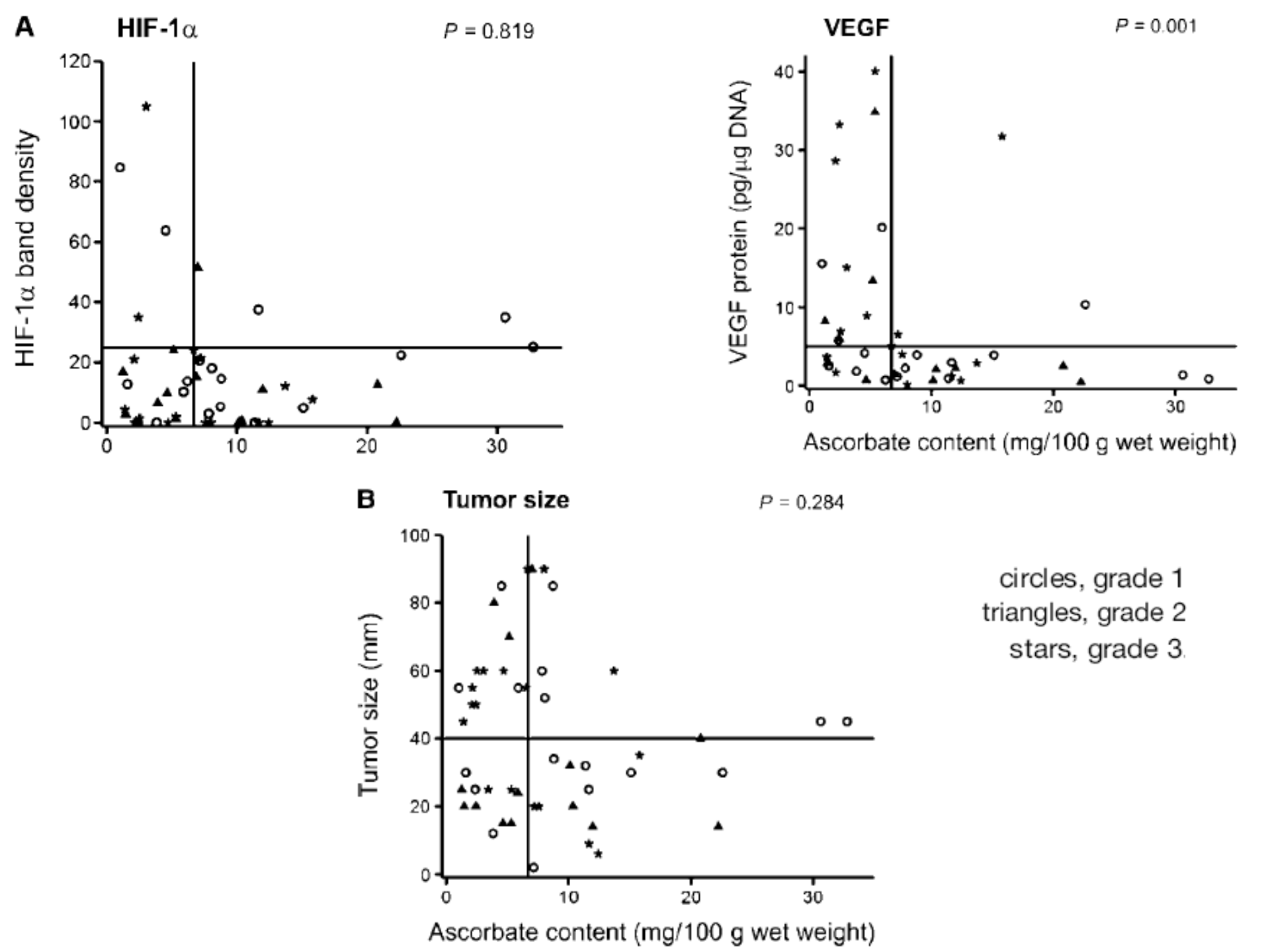


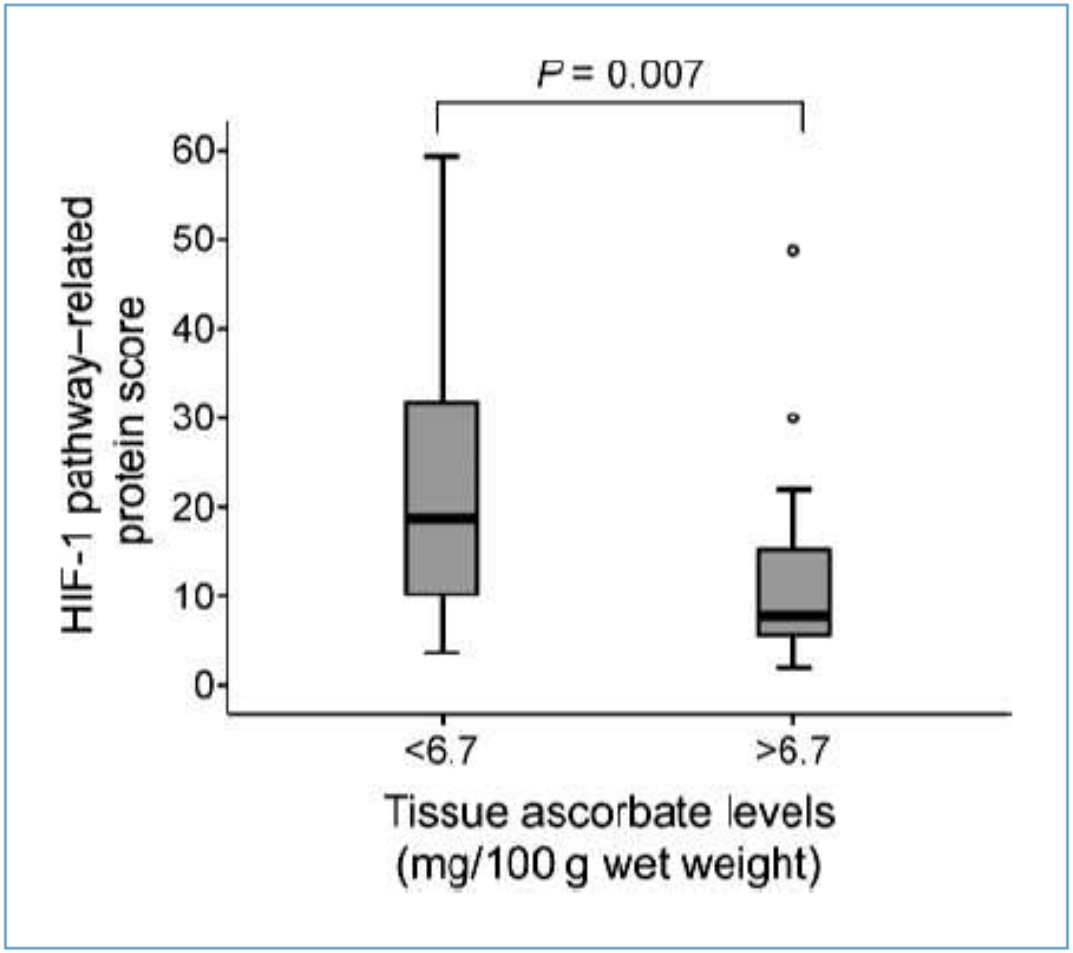


Low Ascorbate Levels Are Associated with Increased Hypoxia-Inducible Factor-1 Activity and an Aggressive Tumor Phenotype in Endometrial Cancer

Caroline Kuiper, Ilona G.M. Molenaar, Gabi U. Dachs, et al. *Cancer Res* 2010;70:5749-5758.

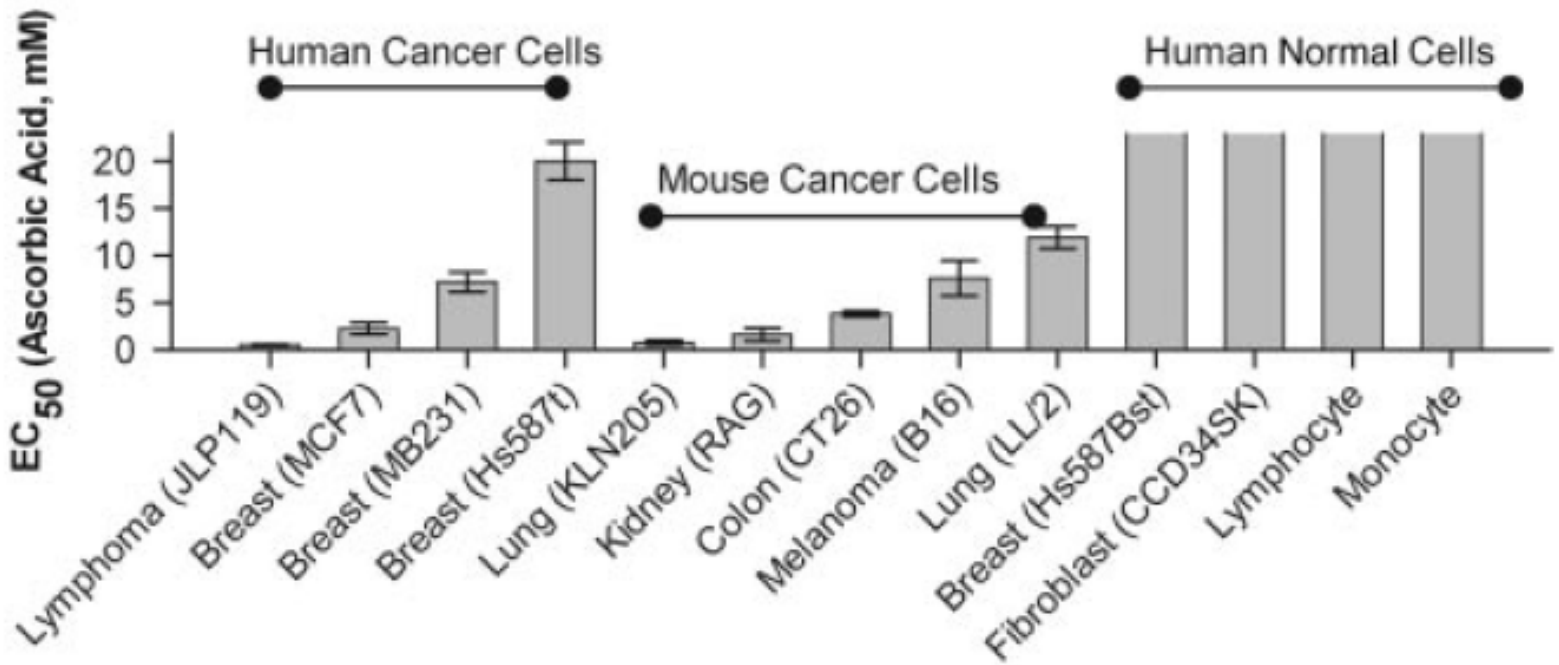


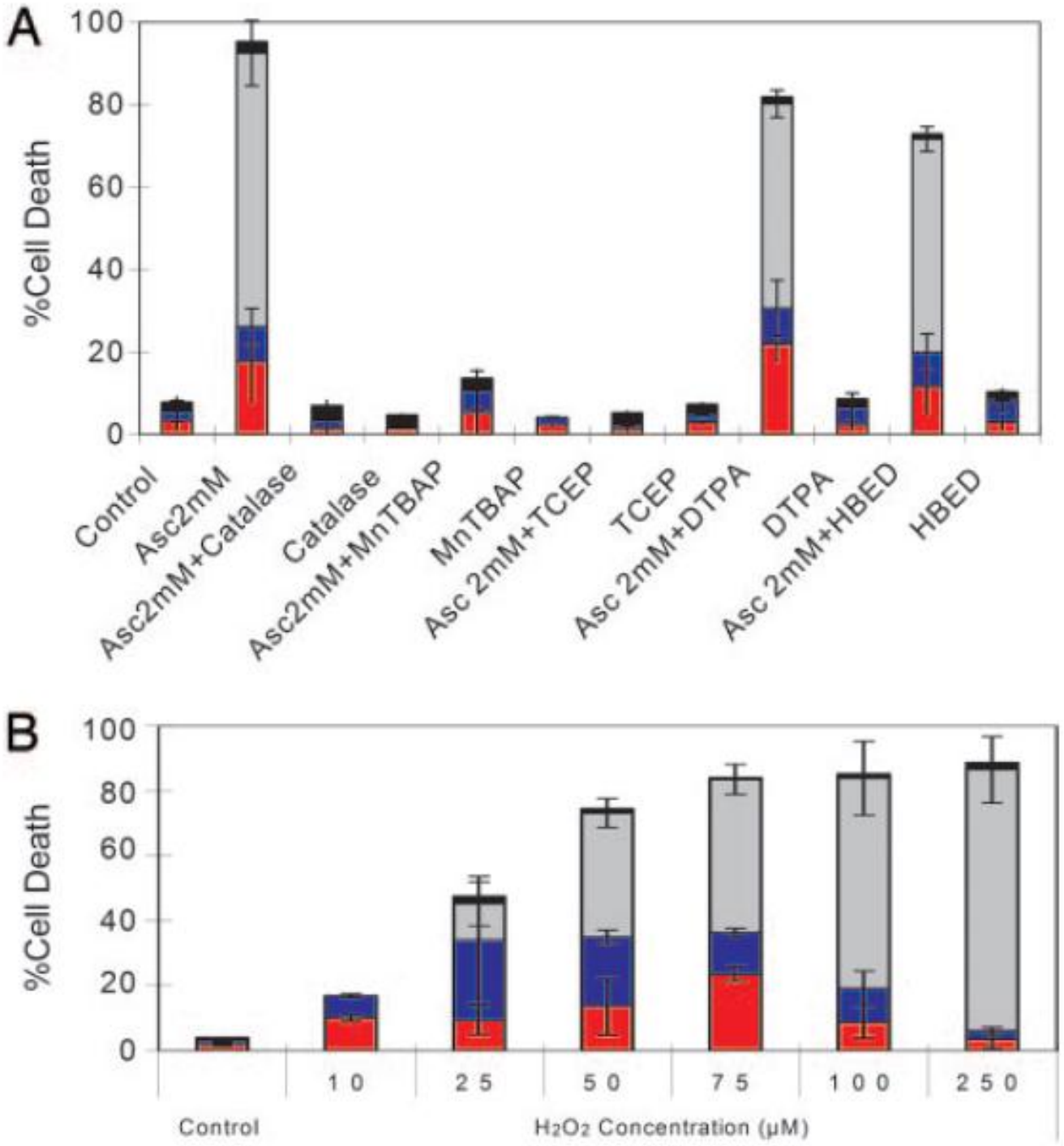

A
HIF-1α
P = 0.819
HIF-1α band density
VEGF
P = 0.001
VEGF protein (pg/μg DNA)
Ascorbate content (mg/100 g wet weight)
B
Tumor size
P = 0.284
Tumor size (mm)
Ascorbate content (mg/100 g wet weight)
circles, grade 1
triangles, grade 2
stars, grade 3

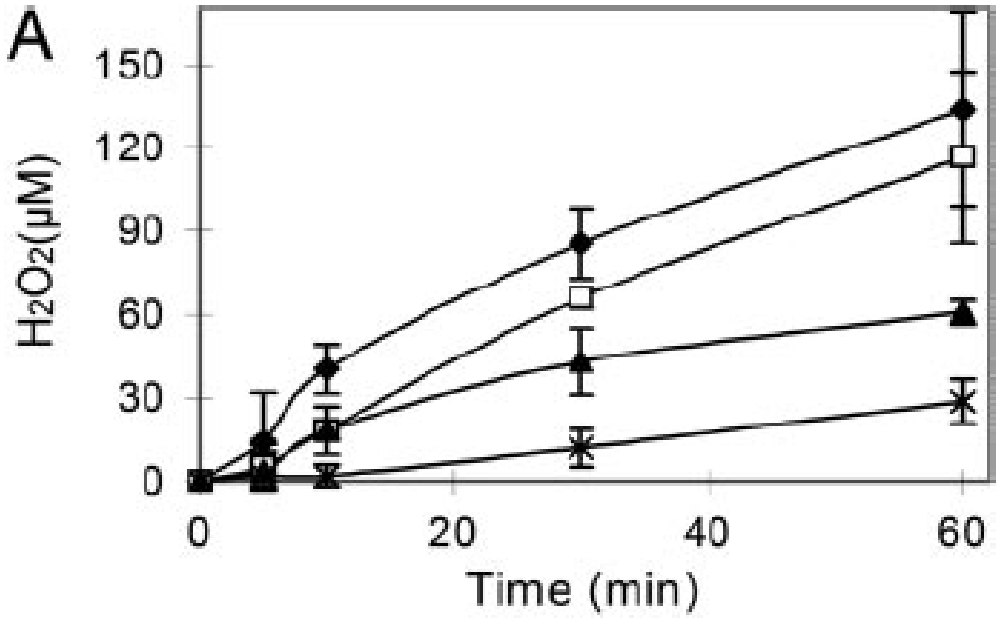

P = 0.007
HIF-1 pathway–related protein score
60
50
40
30
20
10
0
<6.7
>6.7
Tissue ascorbate levels
(mg/100 g wet weight)

Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues

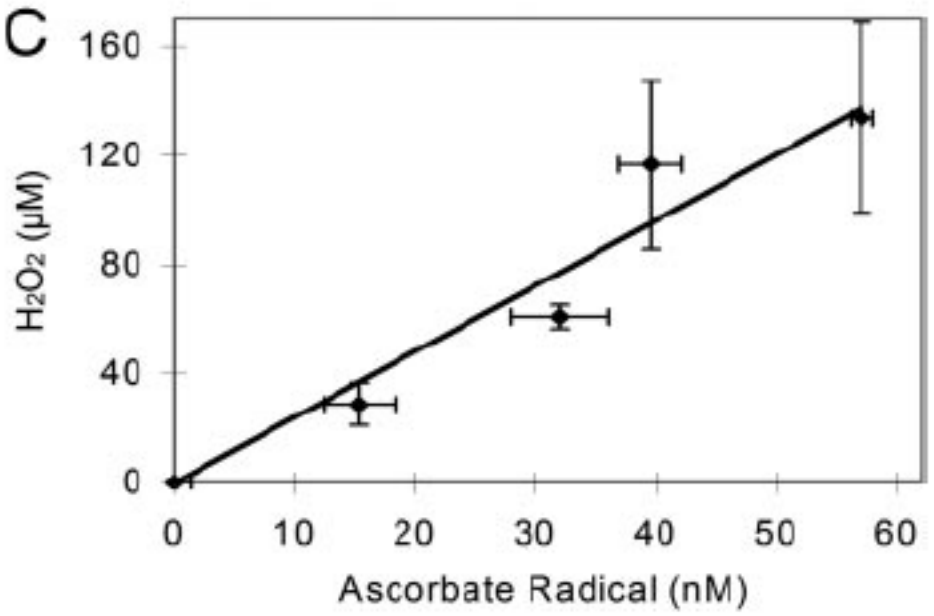
Qi Chen*†, Michael Graham Espey‡, Murali C. Krishna‡, James B. Mitchell‡, Christopher P. Corpe*, Garry R. Buettner§, Emily Shacter†, and Mark Levine*¶




A
%Cell Death
100
80
60
40
20
0
Control
Asc2mM
Asc2mM+Catalase
Catalase
Asc2mM+MnTBAP
MnTBAP
Asc 2mM+TCEP
TCEP
Asc 2mM+DTPA
DTPA
Asc 2mM+HBED
HBED
B
%Cell Death
100
80
60
40
20
0
Control
10
25
50
75
100
250
H2O2 Concentration (μM)



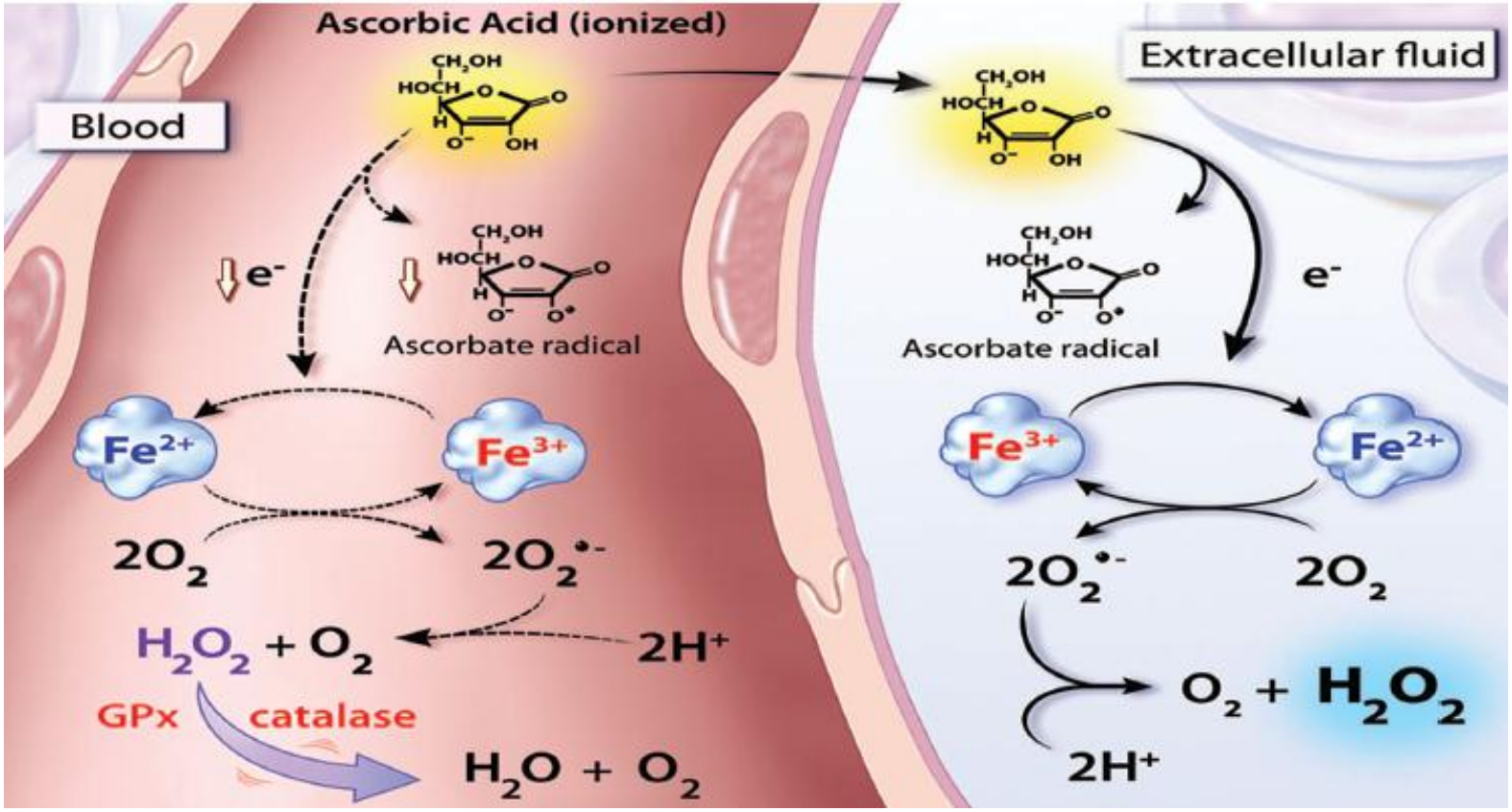
Formazione di H2O2 in funzione del tempo e della conc di ascorbato: 0.2 mM (x), 0.5 mM (▲), 1.0 mM (□), 2.0 mM (◆)



Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid *in vivo*

Qi Chen*, Michael Graham Espey†, Andrew Y. Sun*, Je-Hyuk Lee*, Murali C. Krishna†, Emily Shacter‡, Peter L. Choyke§, Chaya Pooput¶, Kenneth L. Kirk¶, Garry R. Buettner‖, and Mark Levine*,**

PNAS | May 22, 2007

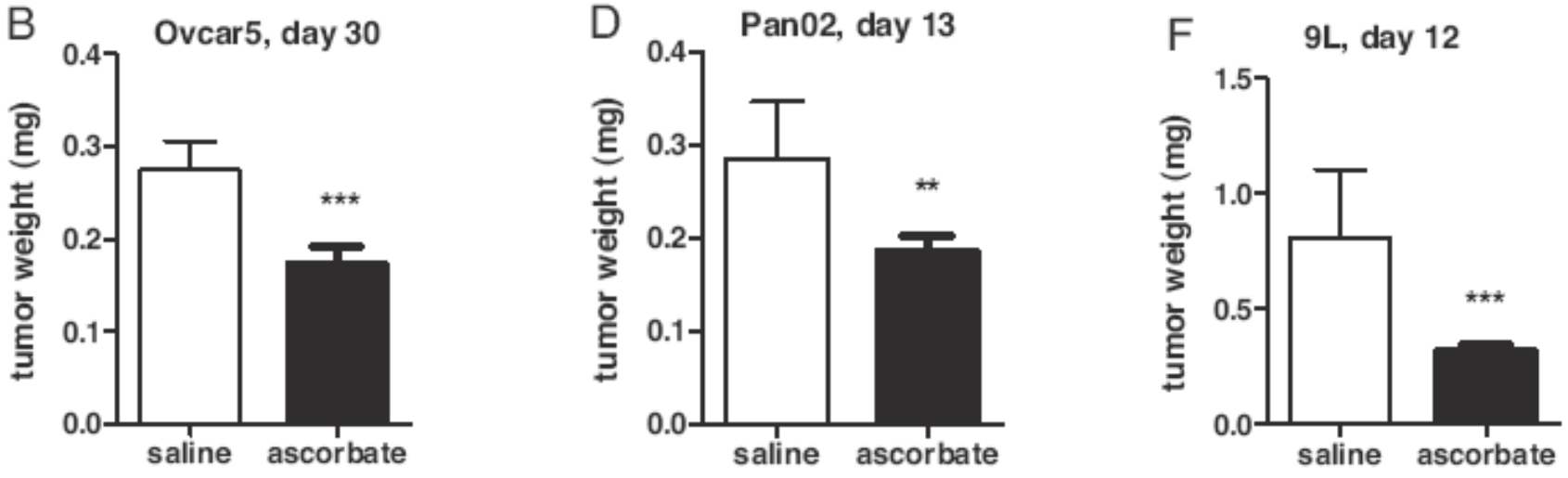


Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice

Qi Chen*†, Michael Graham Espey*†‡, Andrew Y. Sun*, Chaya Pooput§, Kenneth L. Kirk§, Murali C. Krishna¶, Deena Beneda Khoshǁ, Jeanne Driskoǁ, and Mark Levine*‡

PNAS | August 12, 2008

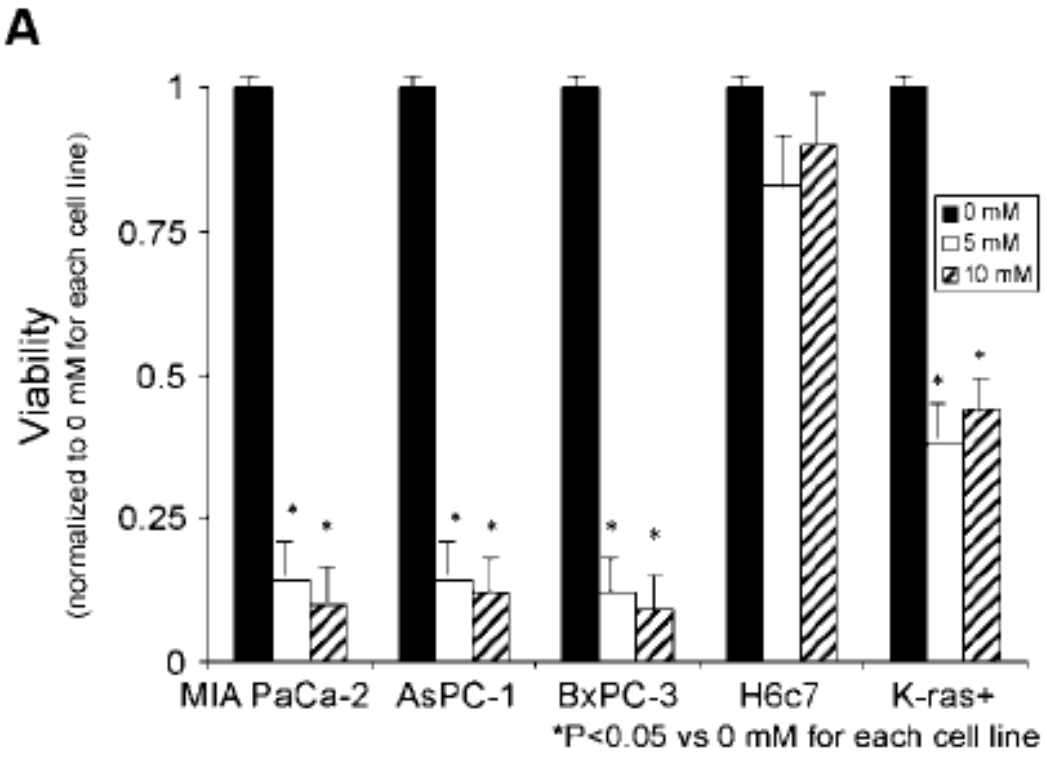
Dosi farmacologiche giornaliere di ascorbato inibiscono significativamente la crescita di neoplasie ovariche, pancreatiche e glioblastomi in topi atimici

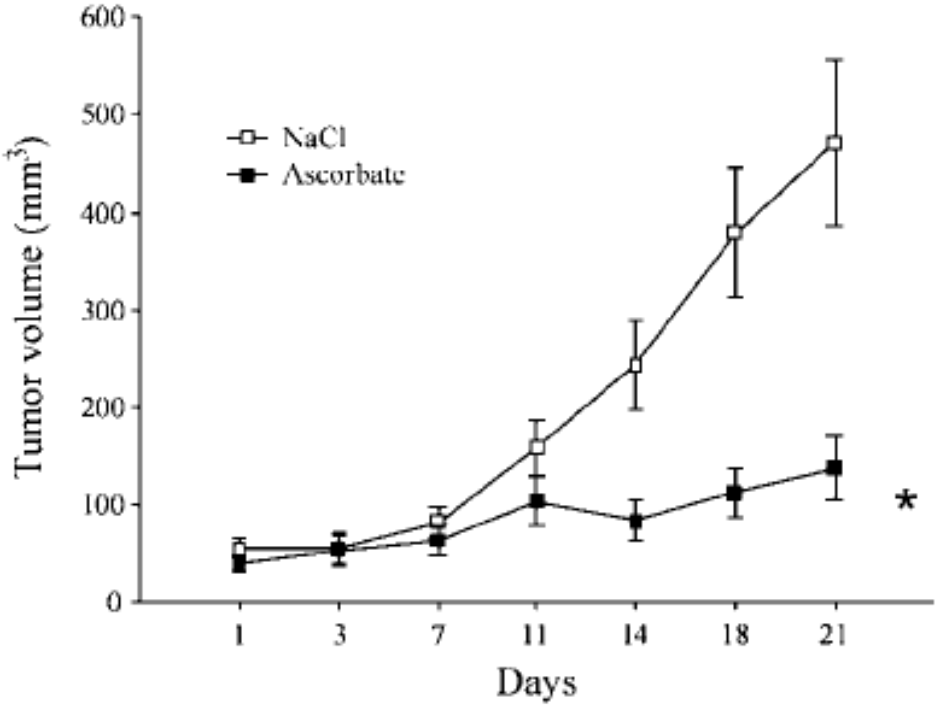


Clinical Cancer Research

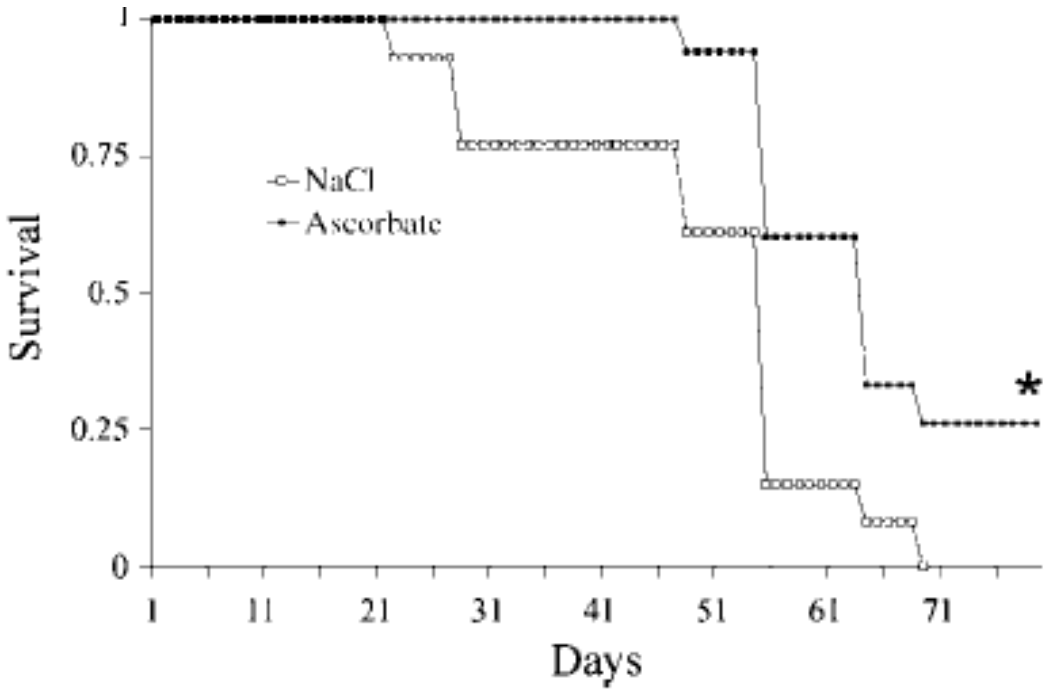
Mechanisms of Ascorbate-Induced Cytotoxicity in Pancreatic Cancer

Juan Du[2], Sean M. Martin[3], Mark Levine[6], Brett A. Wagner[2], Garry R. Buettner[2,4], Sih-han Wang[3], Agshin F. Taghiyev[3], Changbin Du[2], Charles M. Knudson[3], and Joseph J. Cullen[1,2,4,5]



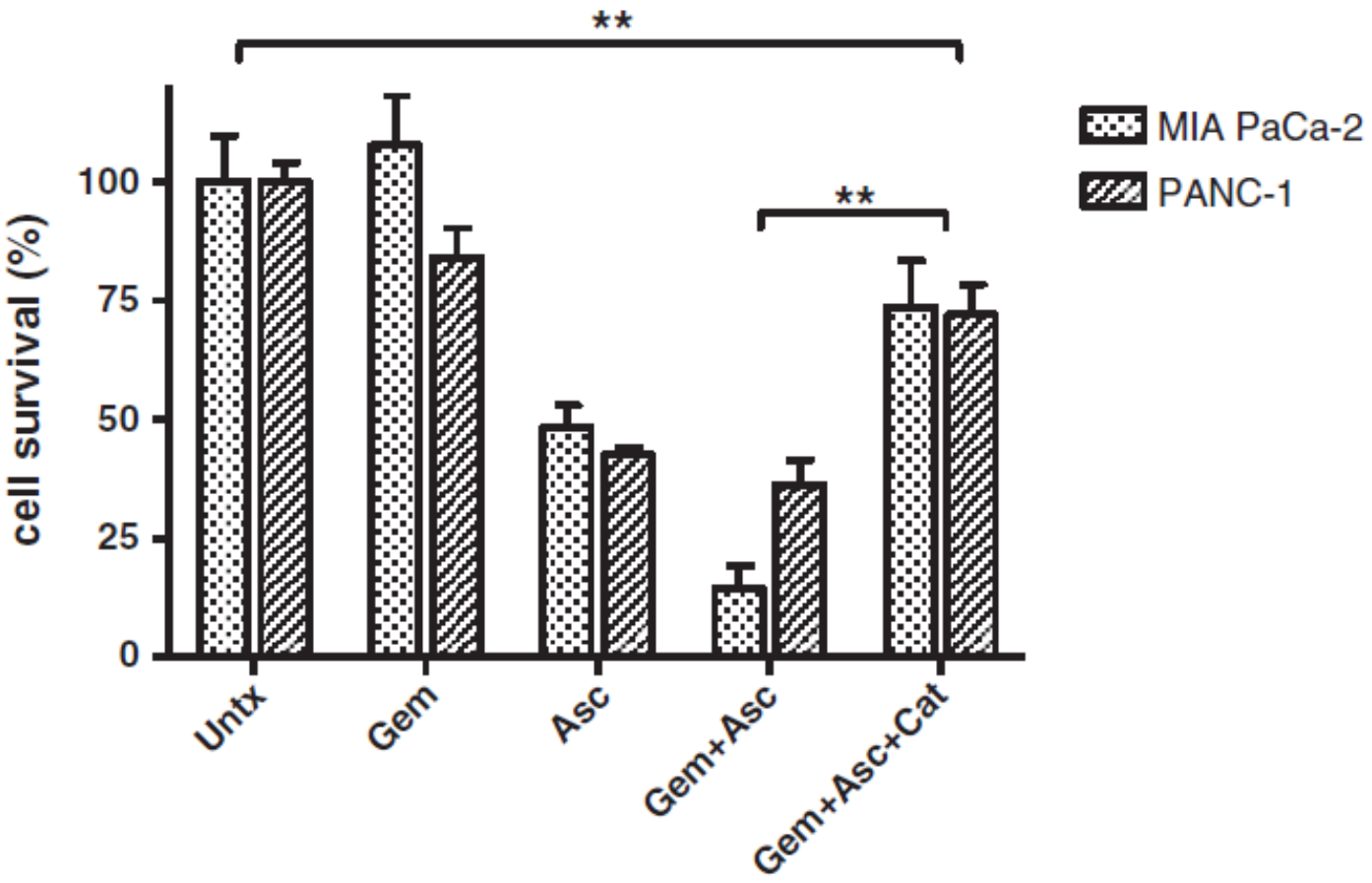

600
500
400
300
200
100
0
Tumor volume (mm3)
NaCl
Ascorbate
*
1
3
7
11
14
18
21
Days

(*, $P < 0.001$)


1
0.75
0.5
0.25
0
Survival
NaCl
Ascorbate
*
1
11
21
31
41
51
61
71
Days

Pharmacologic ascorbate synergizes with gemcitabine in preclinical models of pancreatic cancer

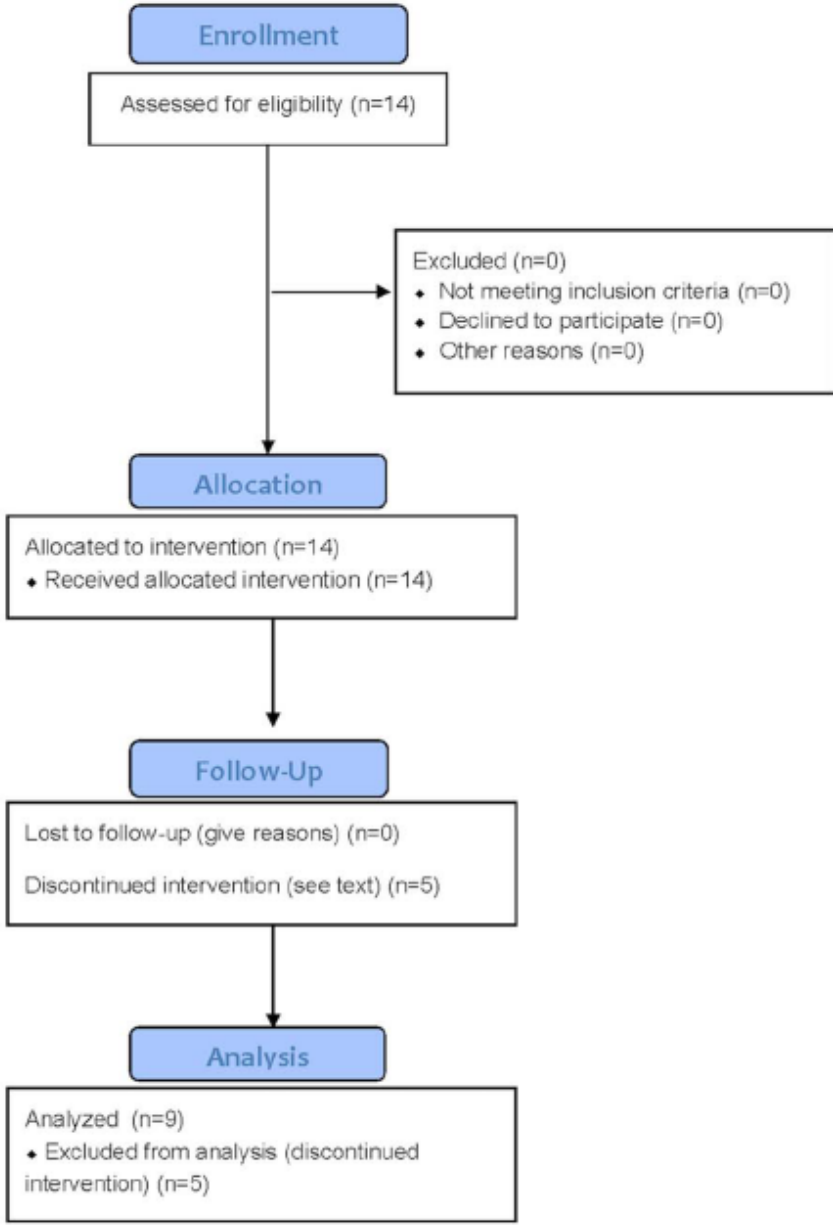
Michael Graham Espey [a], Ping Chen [b,c], Brian Chalmers [b], Jeanne Drisko [b], Andrew Y. Sun [a], Mark Levine [a], Qi Chen [b,*]



Free Radical Biology & Medicine 50 (2011) 1610–1619

Phase I Evaluation of Intravenous Ascorbic Acid in Combination with Gemcitabine and Erlotinib in Patients with Metastatic Pancreatic Cancer

Daniel A. Monti[1], Edith Mitchell[2], Anthony J. Bazzan[1], Susan Littman[2], George Zabrecky[1] Yeo[3], Madhaven V. Pillai[2], Andrew B. Newberg[1], Sandeep Deshmukh[4], Mark Levine[5]*



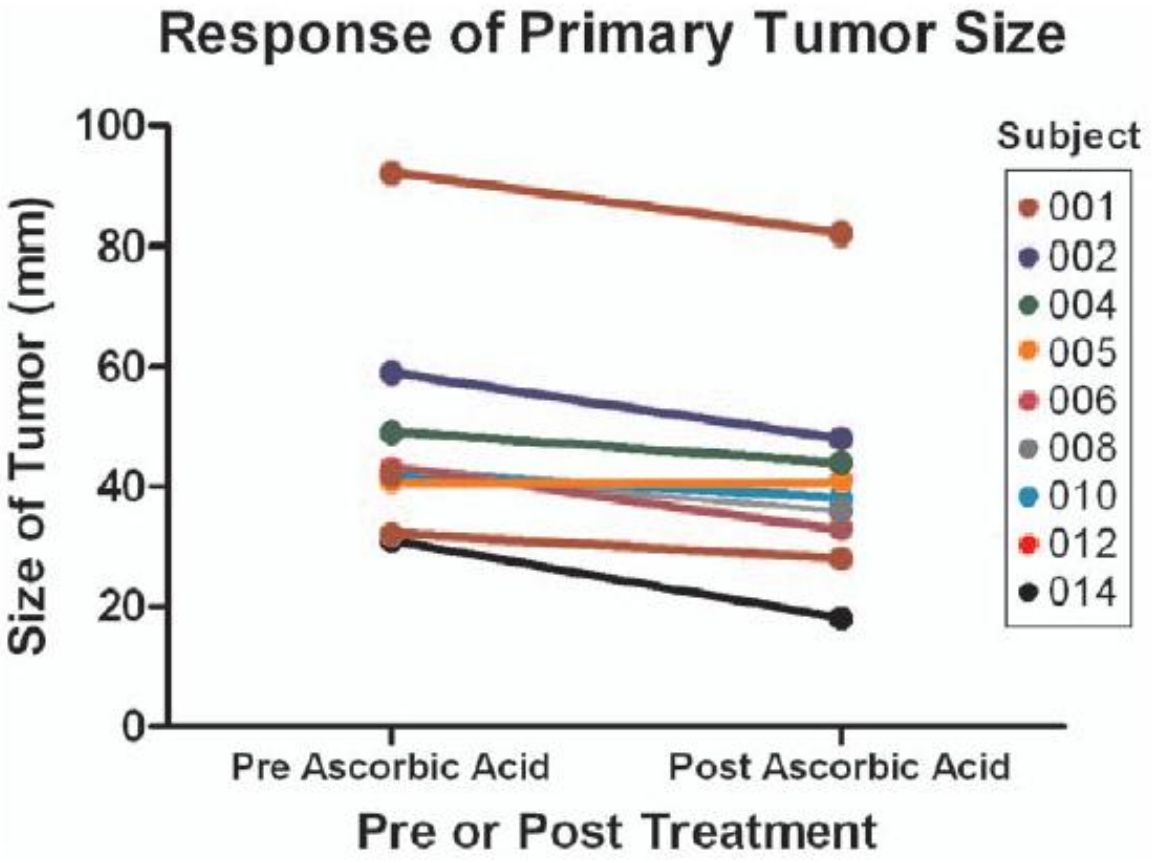
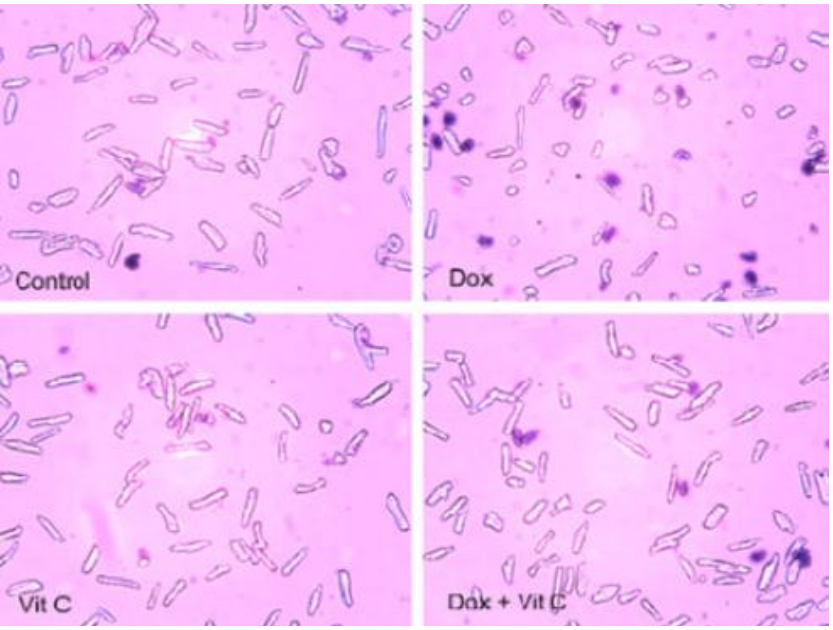


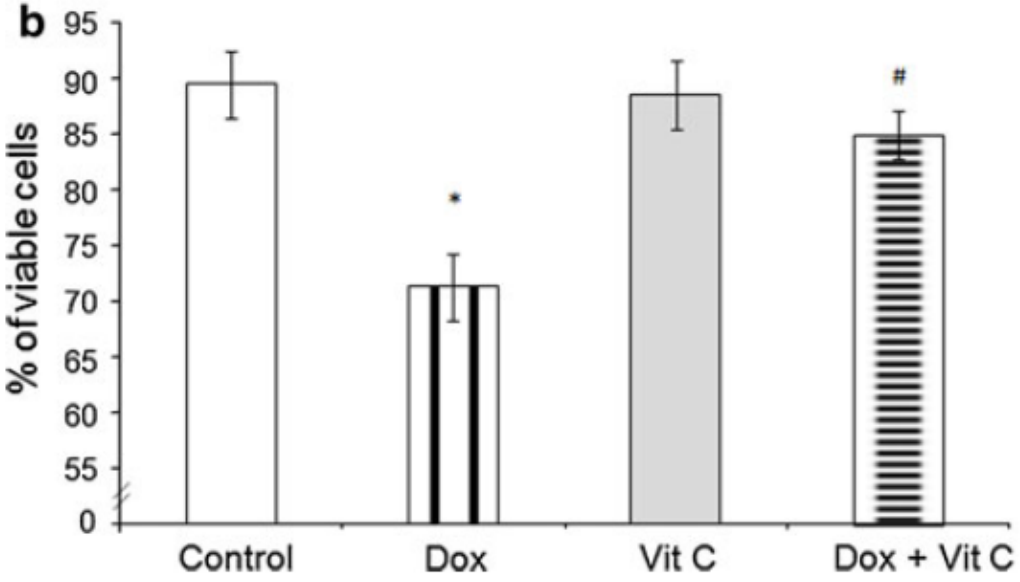
Figure 3. Tumor size initially and after 8 weeks of treatment with ascorbic acid, gemcitabine, and erlotinib for each of the patients who completed the study.

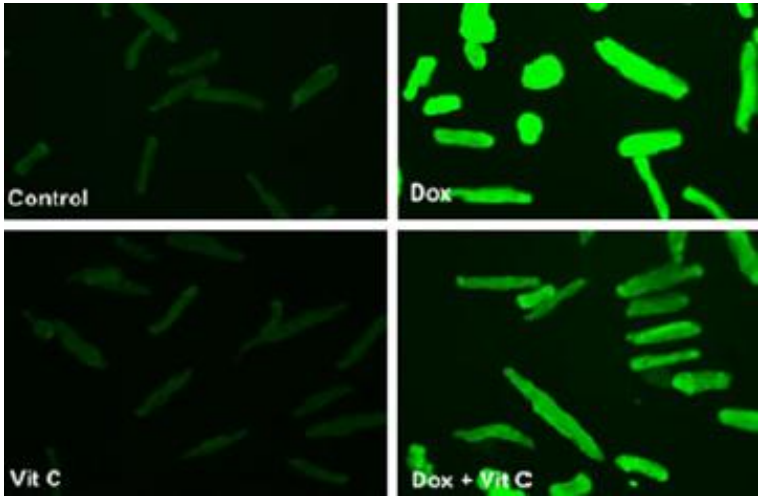
Subcellular basis of vitamin C protection against doxorubicin-induced changes in rat cardiomyocytes

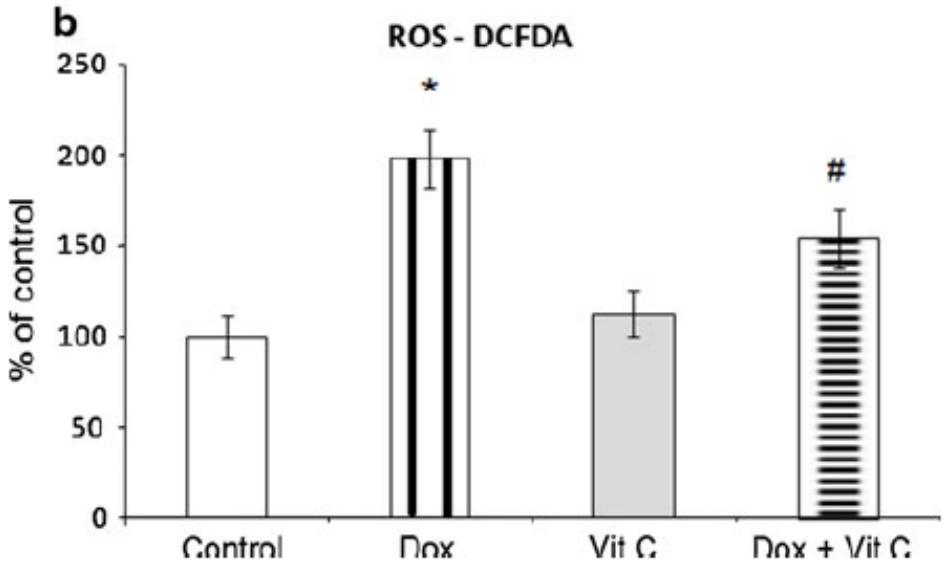
Ana Ludke · Anita K. Sharma · Ashim K. Bagchi · Pawan K. Singal

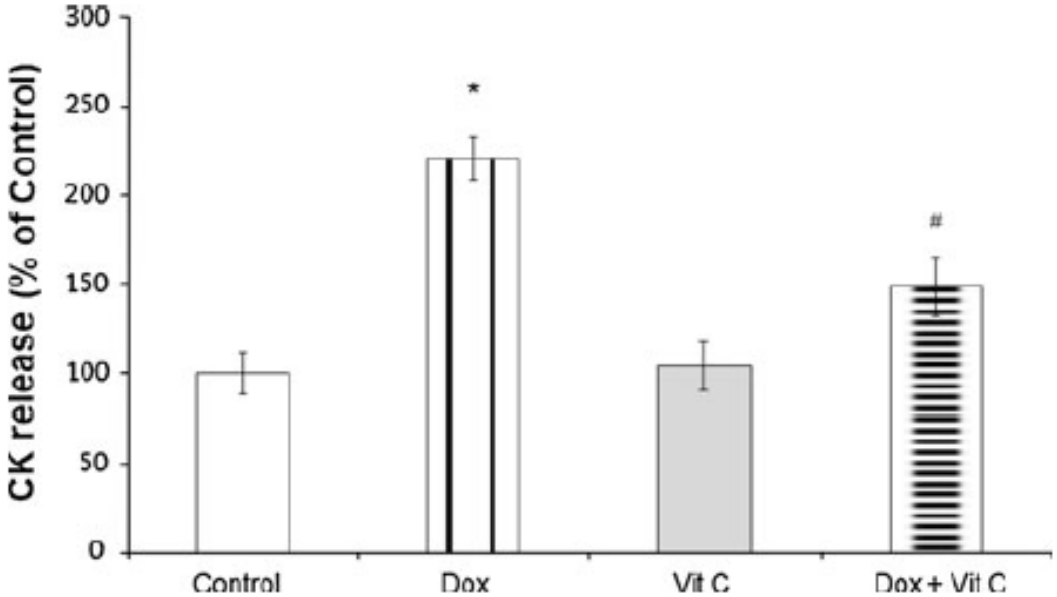
Mol Cell Biochem (2012) 360:215–224





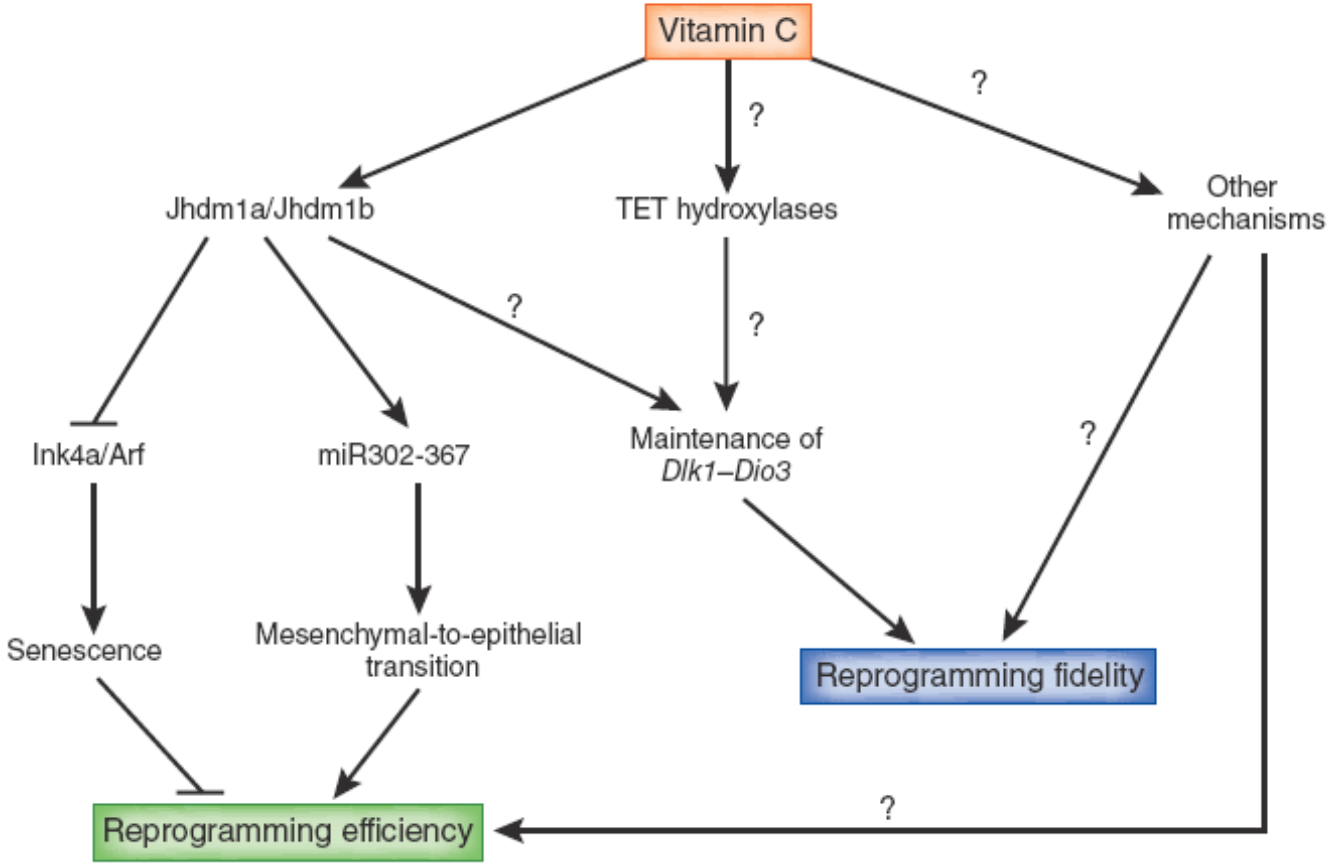

Control
Dox
Vit C
Dox + Vit C


b
ROS - DCFDA
% of control
250
200
150
100
50
0
*
#
Control
Dox
Vit C
Dox + Vit C


CK release (% of Control)
300
250
200
150
100
50
0
*
#
Control
Dox
Vit C
Dox + Vit C

Ascorbic acid prevents loss of *Dlk1-Dio3* imprinting and facilitates generation of all–iPS cell mice from terminally differentiated B cells

Matthias Stadtfeld[1–3,11,12], Effie Apostolou[1–3,12], Francesco Ferrari[4], Jiho Choi[1–3], Ryan M Walsh[1–3], Taiping Chen[6], Steen S K Ooi[7,8], Sang Yong Kim[9], Timothy H Bestor[8], Toshi Shioda[2], Peter J Park[4,5] & Konrad Hochedlinger[1–3,10]



Conclusioni

Dosi fisiologiche di vit C

- potebbero modulare la progressione neoplastica

- proteggono le cellule sane dallo stress ossidativo indotto dalle cure antitumorali

- sono in grado di correggere il deficit di vit C riscontrabile in molti pazienti oncologici

Dosi farmacologiche di vit C

- **hanno effetto anti-tumorale in modelli animali**
- **in pazienti selezionati, non sembrano indurre tossicità**
- **in case-reports si associano a prolungata sopravvivenza → mancano studi controllati**
- **potrebbero modulare l'effetto e la tossicità da chemioterapici ?**


Grazie!