CAMPUS Cuore SUMMIT

Napoli, 1-2 ottobre 2021
Hotel Excelsior

Asa nella riduzione degli eventi cardioncologici

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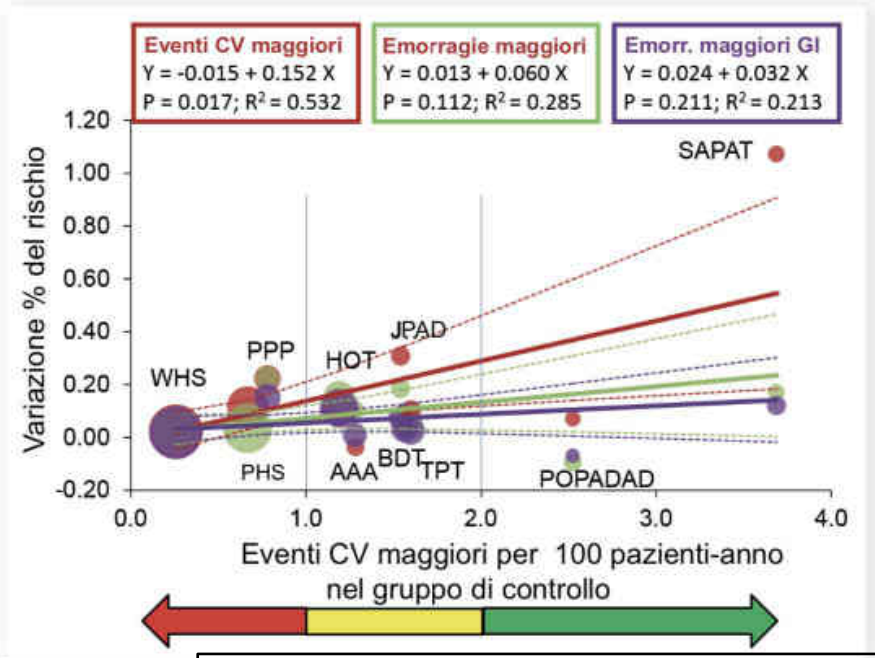
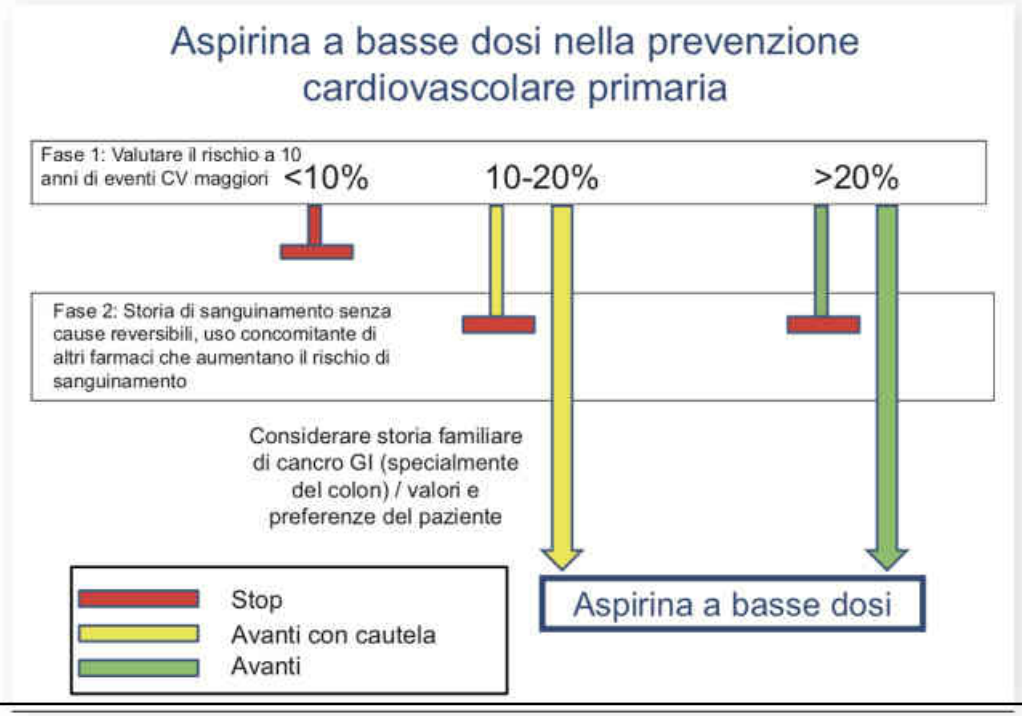
Joseph Buchner -1828

La terapia con aspirina nella prevenzione cardiovascolare primaria. Documento di consenso intersocietario italiano

Massimo Volpe[1], Maurizio Giuseppe Abrignani[2], Claudio Borghi[3], Sergio Coccheri[4], Paolo Gresele[5], Giuseppe Patti[6], Bruno Trimarco[7], Raffaele De Caterina[8]





Review > Lancet. 2007 May 12;369(9573):1603-13. doi: 10.1016/S0140-6736(07)60747-8.

Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies

Enrico Flossmann [1], Peter M Rothwell, British Doctors Aspirin Trial and the UK-TIA Aspirin Trial

Affiliations + expand

PMID: 17499602 DOI: 10.1016/S0140-6736(07)60747-8

Meta-Analysis > Lancet. 2011 Jan 1;377(9759):31-41. doi: 10.1016/S0140-6736(10)62110-1. Epub 2010 Dec 6.

Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials

Peter M Rothwell [1], F Gerald R Fowkes, Jill F F Belch, Hisao Ogawa, Charles P Warlow, Tom W Meade

Affiliations + expand

PMID: 21144578 DOI: 10.1016/S0140-6736(10)62110-1

The effects of platelets on cancer

Recent evidence suggests that platelets have a direct effect in each step of cancer cell proliferation. When activated, platelets recruited to the tumor microenvironment can locally regulate tumor cell behavior and promote proliferation not only through paracrine signaling but also through direct contact with tumor cells

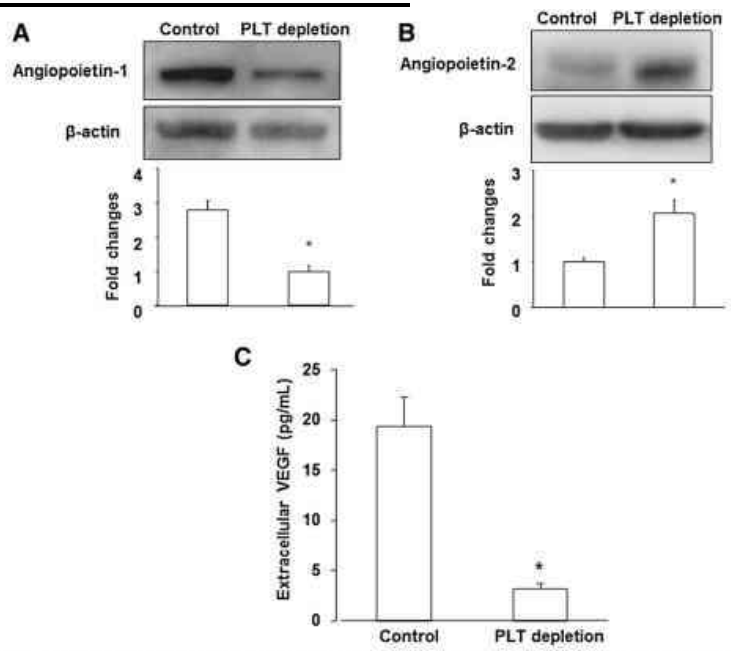


Figure 5 Platelets changed intratumoral levels of angiogenic factors. (A), (B) Western blot analysis of Angiopoietin-1, 2 expression in tumors from control and PLT-depleted mice. Quantification of western blot analysis for each protein (normalized to β-actin). **(C)** Microdialysis was used to sample extracellular proteins in vivo. Extracellular VEGF level was measured by ELISA as described in *Materials and Methods*. The results are expressed as the mean ± SEM. * $p < 0.05$, ($n = 6$ for each group).

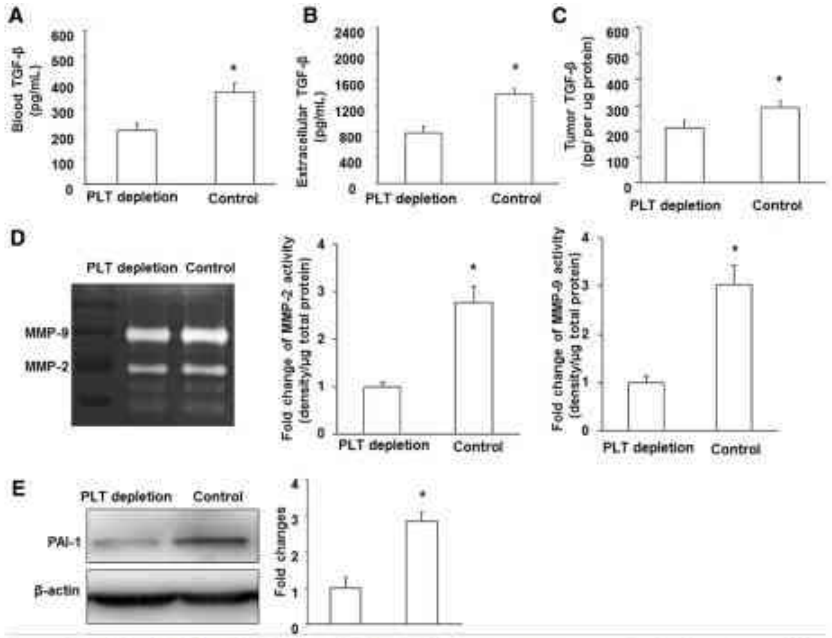
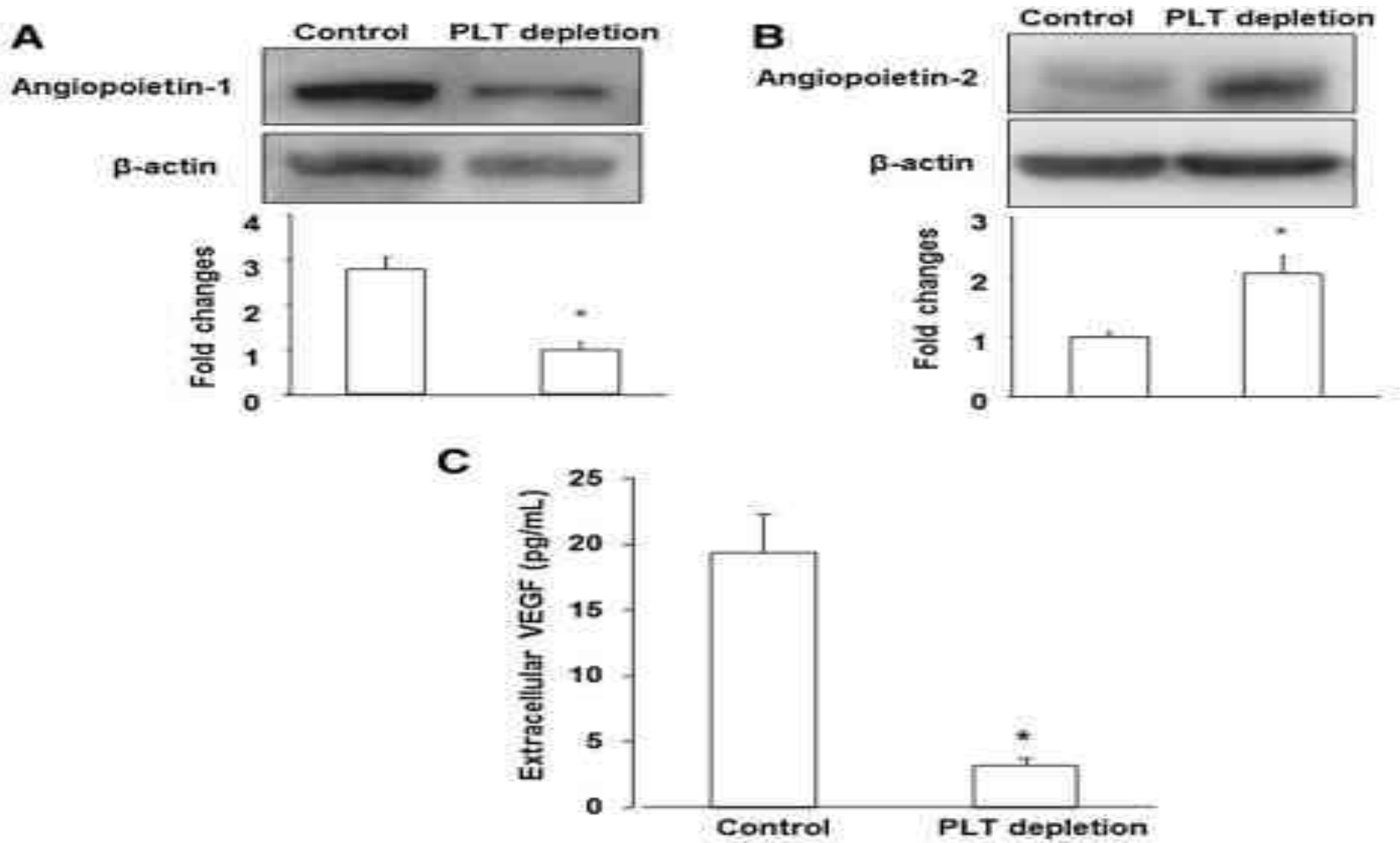


Figure 6 Platelets changed levels of TGF-β1, MMP-2,9, and PAI-1. TGF-β1 levels were measured by ELISA in plasma **(A)**, microdialysates **(B)**, and tumor hemogenates **(C)** as described in *Materials and Methods*. **(D)** Gel zymography analysis of MMP-2, 9 from microdialysates in tumors from PLT-depleted, control mice. **(E)** Western blot analysis of PAI-1 expression in tumors from PLT-depleted, control mice (normalized to β-actin). The results are expressed as the mean ± SEM. * $p < 0.05$.

Li R, et al. *BMC Cancer*. 2014;14:167.

The effects of platelets on cancer



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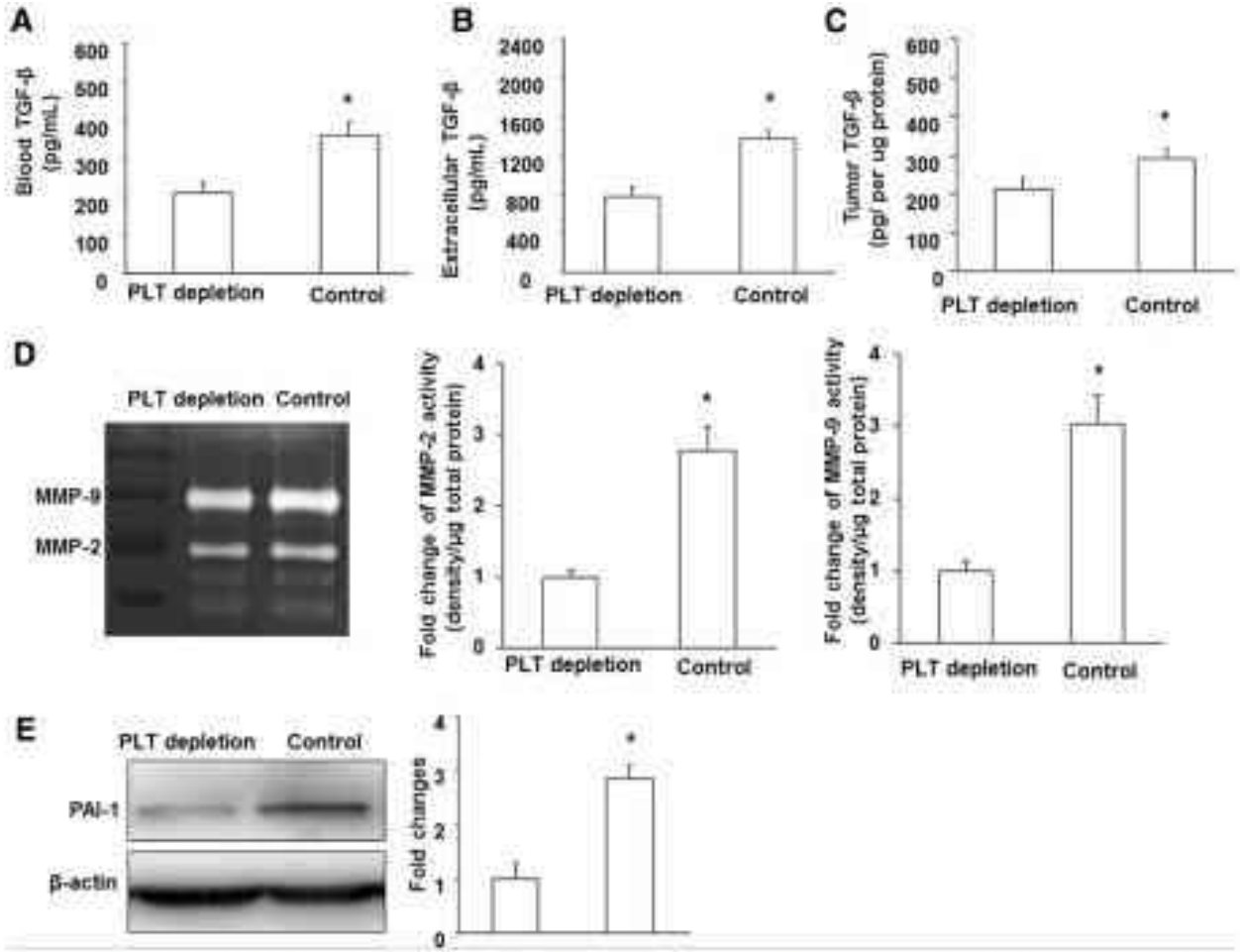

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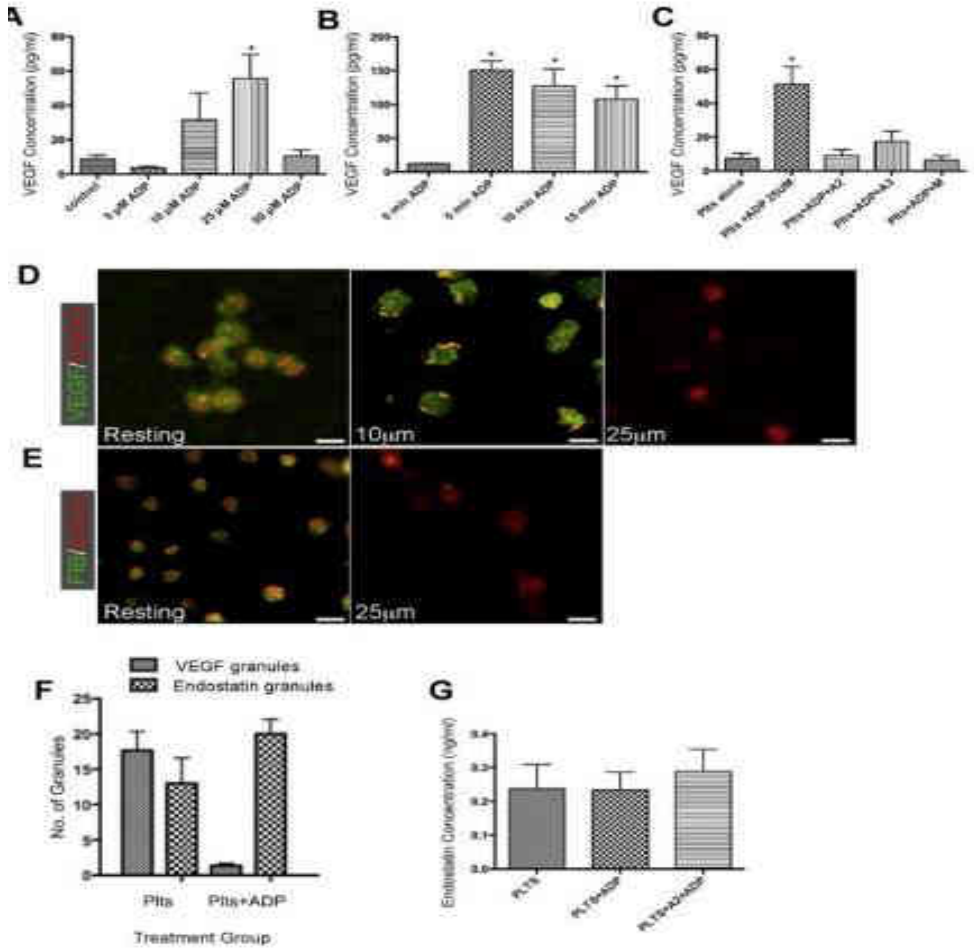
Li R, et al. *BMC Cancer*. 2014;14:167.

The effects of platelets on cancer

- platelets could theoretically <u>stimulate or inhibit angiogenesis;</u>
- however, in most studies, the pro-angiogenic effects prevail over the anti-angiogenic effects.
- These proangiogenic factors induce formation of tumor-infiltrating blood vessels and may promote proliferation/differentiation of cancer

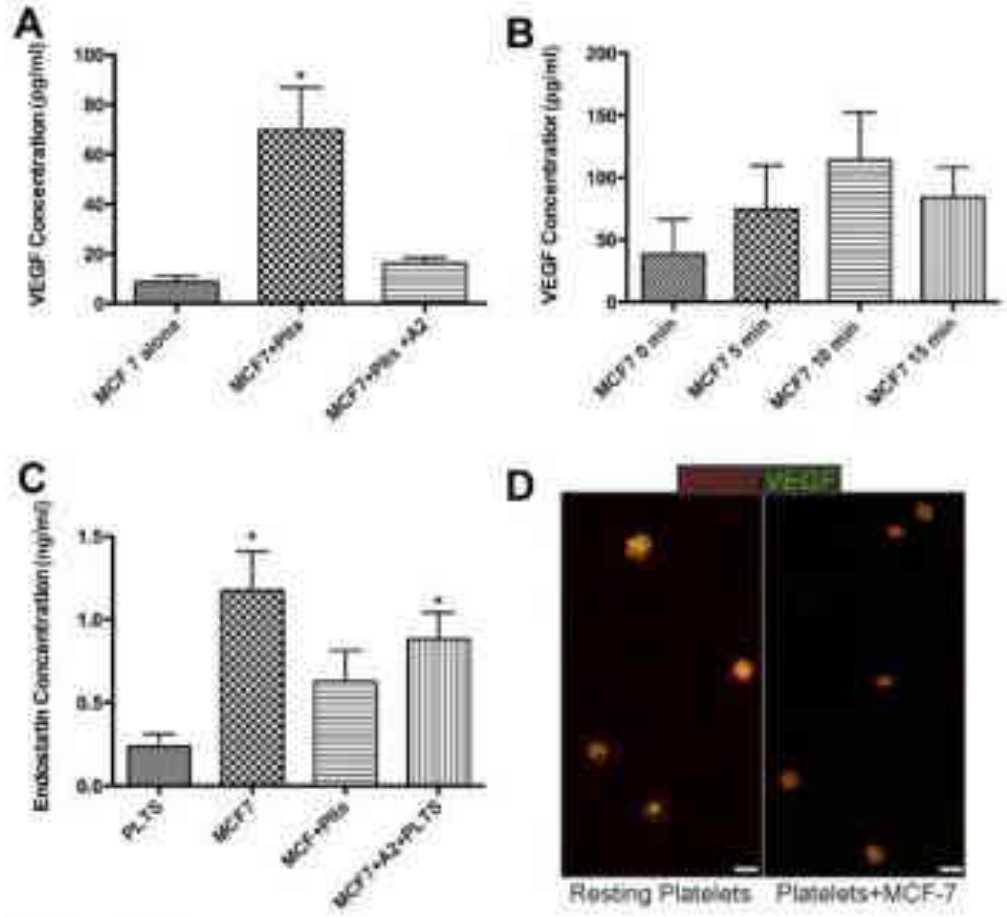


Battinelli EM et al *Blood*. 2011;118:1359-1369.

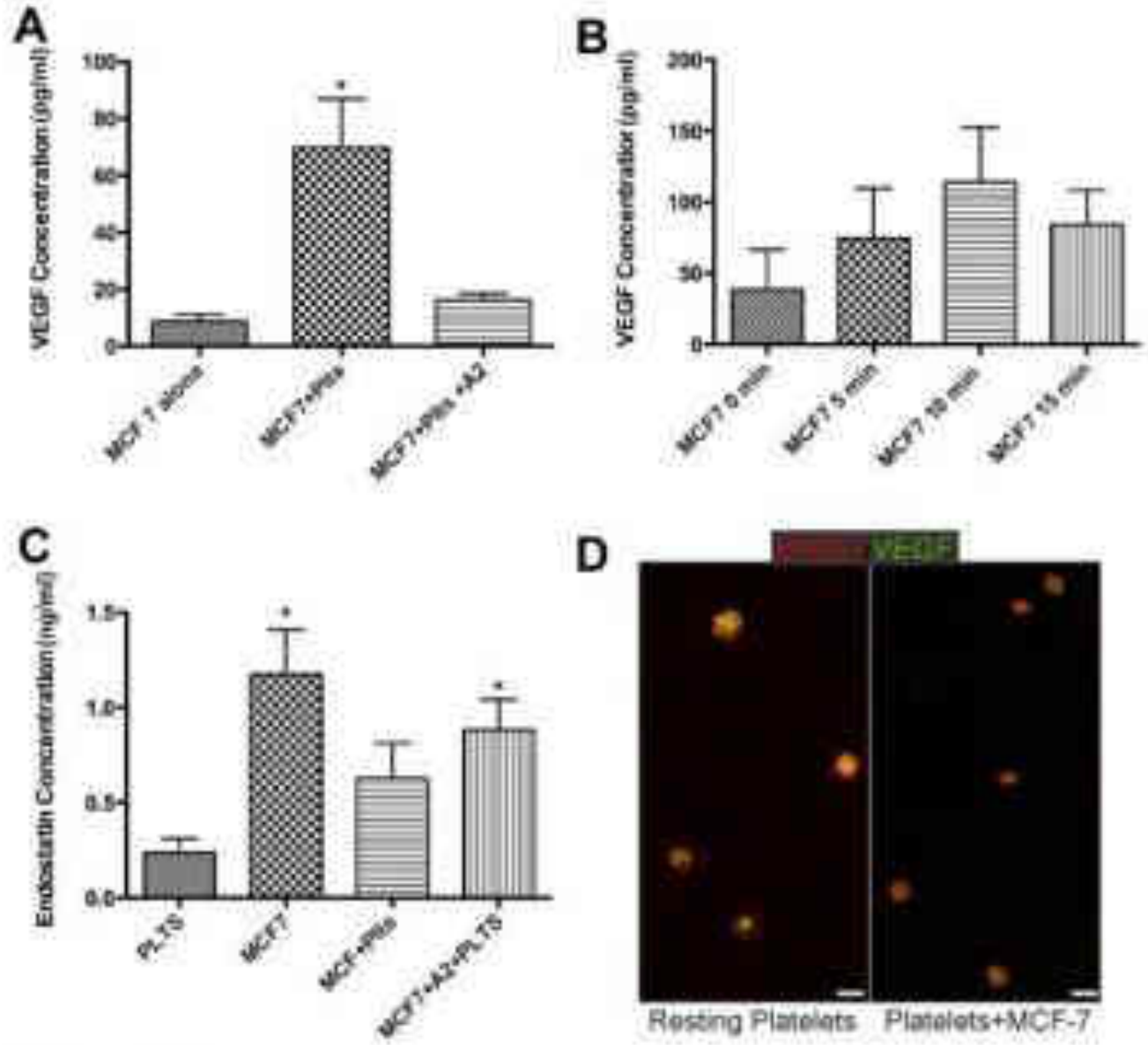
The effects of cancer on platelets

MCF-7 breast cancer cells induce the preferential release of VEGF from platelets.

- The exposure to the tumor cell line, MCF-7, led to differential release of VEGF from platelet granules, thus providing a mechanism to create a pro-angiogenic microenvironment for tumor growth.



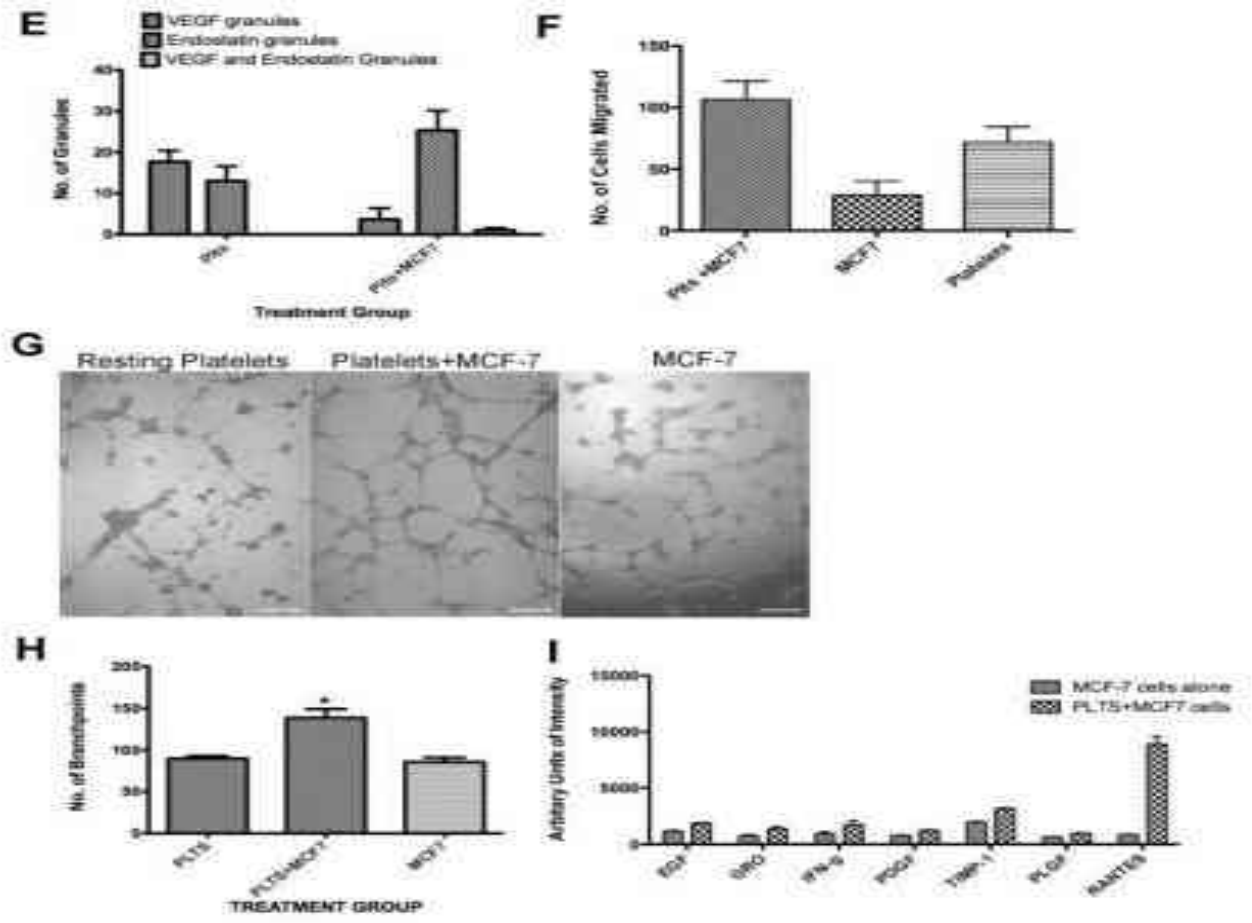
Battinelli EM et al *Blood*. 2011;118:1359-1369.


A
VEGF Concentration (pg/ml)
100
80
60
40
20
0
MCF 7 alone
MCF7+Plts
MCF7+Plts +A2
B
VEGF Concentration (pg/ml)
200
150
100
50
0
MCF7 0 min
MCF7 5 min
MCF7 10 min
MCF7 15 min
C
Endostatin Concentration (ng/ml)
1.5
1.0
0.5
0.0
PLTS
MCF7
MCF+Plts
MCF7+A2+PLTS
D
VEGF
Resting Platelets
Platelets+MCF-7

The effects of cancer on platelts

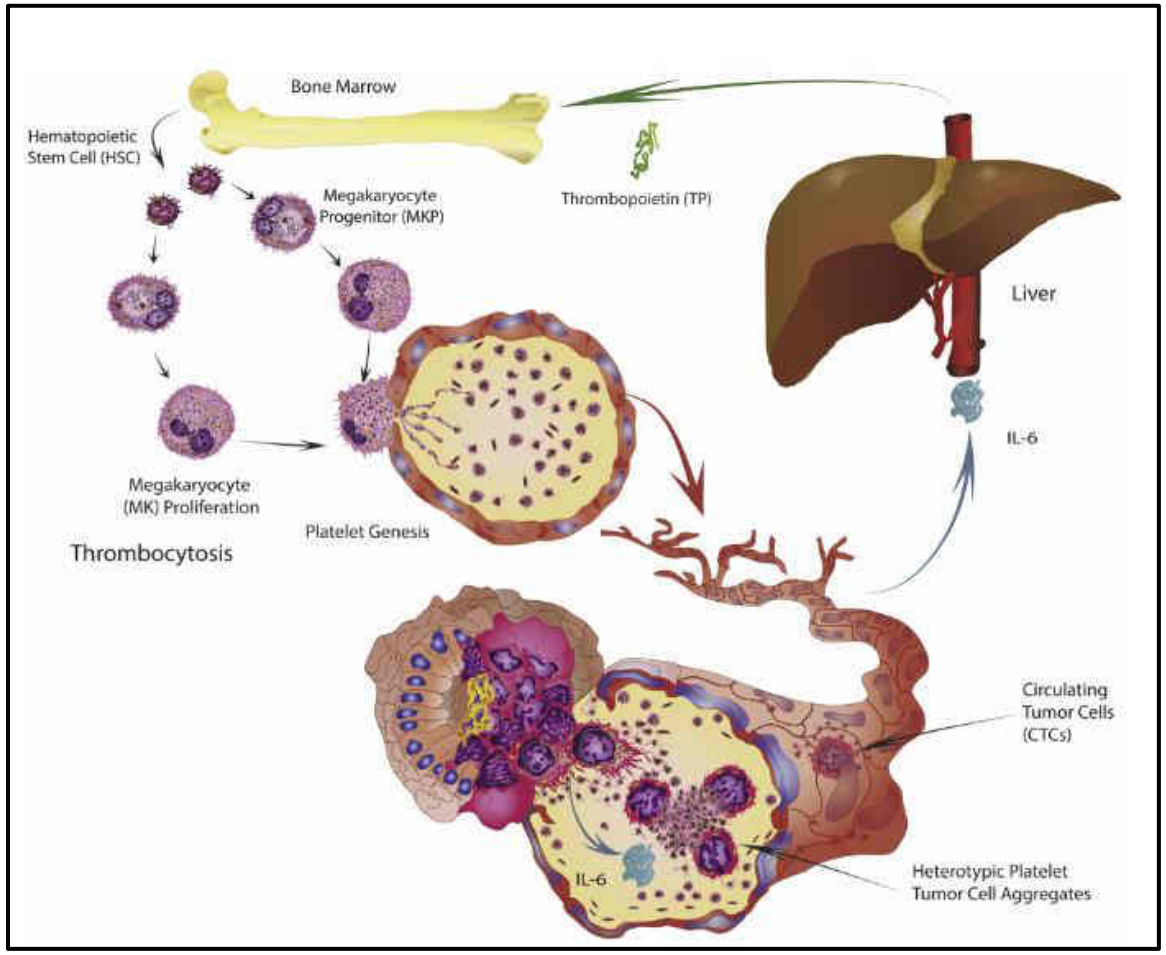
MCF-7 breast cancer cells induce the preferential release of VEGF from platelets.

- the release from MCF-7–stimulated platelets demonstrated an increased angiogenic potential. Interestingly, there is also an increase in the number of pro-angiogenic proteins present in the releasate, but many of the proteins are not the same as the pro-angiogenic proteins released during the process of activation with the platelet agonist ADP.



Battinelli EM et al *Blood*. 2011;118:1359-1369.

Mechanisms of Trousseau's Syndrome



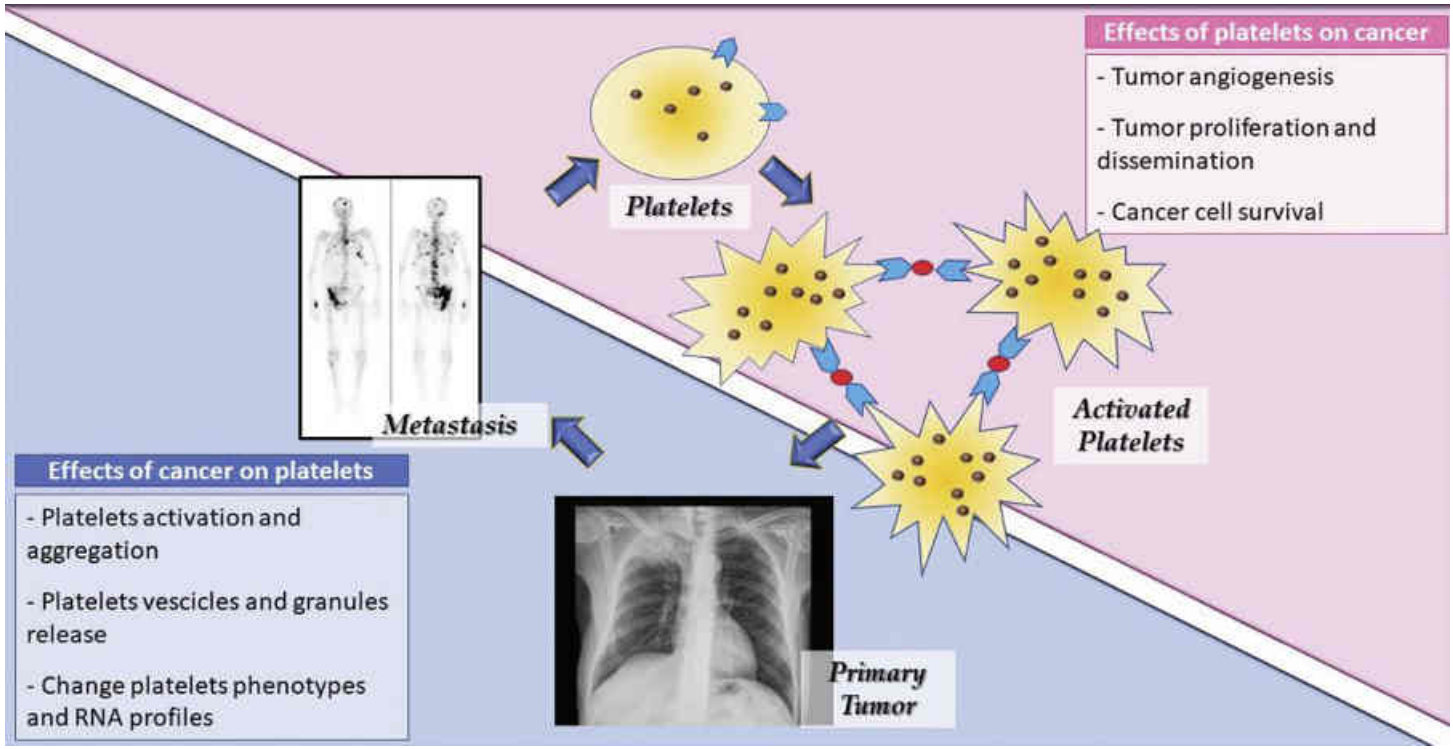
Paracrine secretion of interleukin-6 (IL-6) from tumor cells stimulates the production of thrombopoietin (TP) by the liver. In turn, this fuels megakaryopoiesis and platelet genesis. The combination of these events contributes to thrombocytosis and hypercoagulability in cancer patients known as Trousseau's syndrome.

Haemmerle M *Cancer Cell*. 2018;33(6):965-983

Crosstalk between cancer and platelets

Platelet can contribute to metastasis by shielding tumor cells from immune host system, triggering epithelial-mesenchymal transition (EMT), mediating tumor/vascular wall interaction and due to various mechanisms helping extravasation of tumor cells from host vasculature.

They are also able to mediate tumor cell survival and growth at distant sites by guiding establishment of metastatic niches



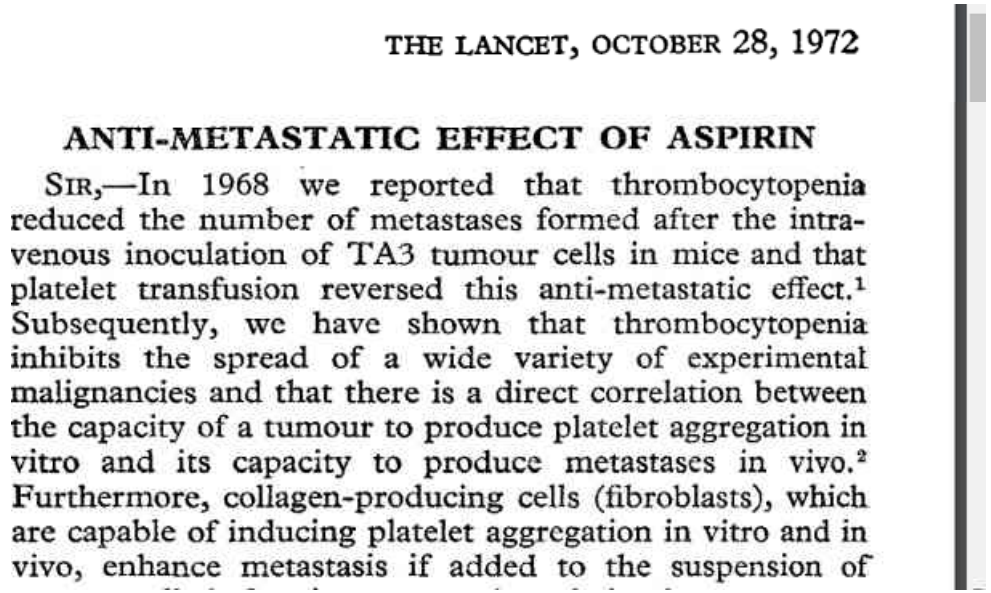
Santoro C, et al. *Semin Thromb Hemost*.

Anti metastatic effect of aspirin

The idea that aspirin could be of benefit against cancer arose from initial observations that tumor metastases are reduced in rats with thrombocytopenia

Many mechanisms have been suggested for how aspirin can impact malignancy including:

1. inhibition of cyclooxygenase
2. promotion of apoptosis
3. DNA mismatch repair
4. Inhibition of tumor cell proliferation by blockade of mitochondrial calcium uptake.



THE LANCET, OCTOBER 28, 1972

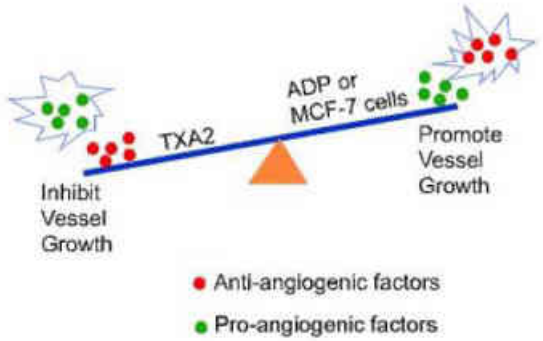
ANTI-METASTATIC EFFECT OF ASPIRIN

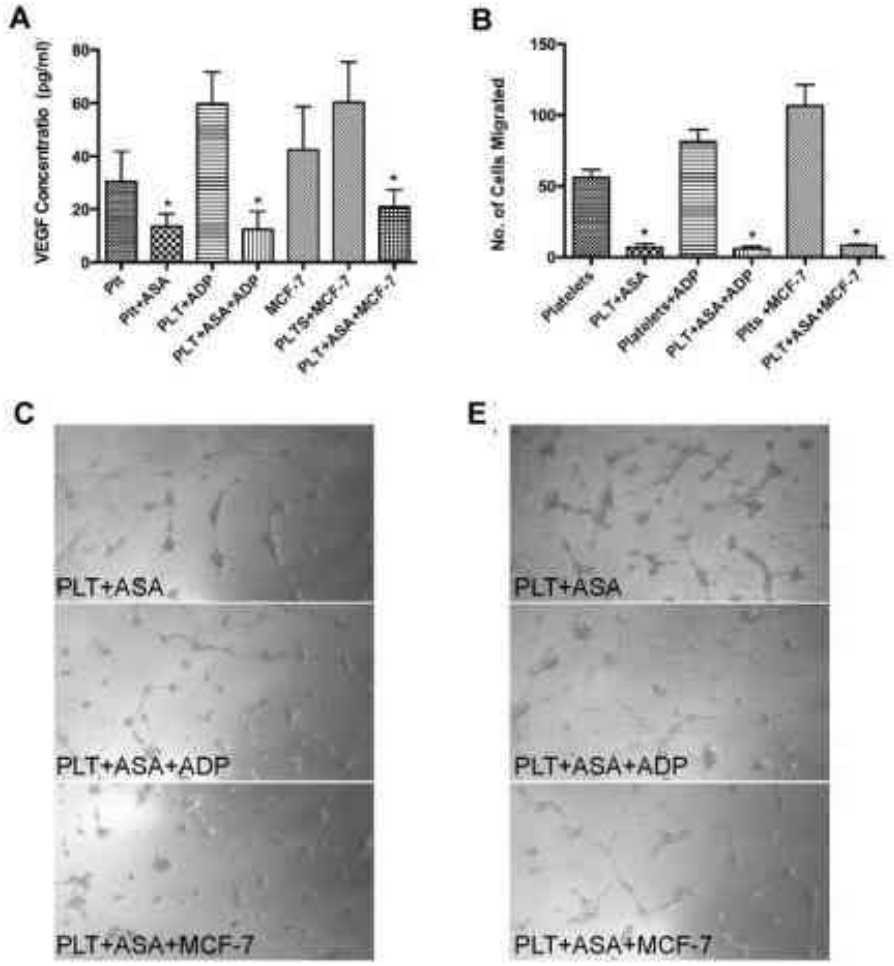
SIR,—In 1968 we reported that thrombocytopenia reduced the number of metastases formed after the intravenous inoculation of TA3 tumour cells in mice and that platelet transfusion reversed this anti-metastatic effect.[1] Subsequently, we have shown that thrombocytopenia inhibits the spread of a wide variety of experimental malignancies and that there is a direct correlation between the capacity of a tumour to produce platelet aggregation in vitro and its capacity to produce metastases in vivo.[2] Furthermore, collagen-producing cells (fibroblasts), which are capable of inducing platelet aggregation in vitro and in vivo, enhance metastasis if added to the suspension of

Aspirin inhibits VEGF release and angiogenesis mediated by ADP or MCF-7 cell exposure

Another mechanism by which aspirin could modulate cancer is as an irreversible inhibitor of platelet activation with subsequent decrease in VEGF release and decrease in angiogenic potential

These anti-metastatic effects are not limited to aspirin as other antiplatelet agents such as P2Y12 and GPII/IIIa antagonists

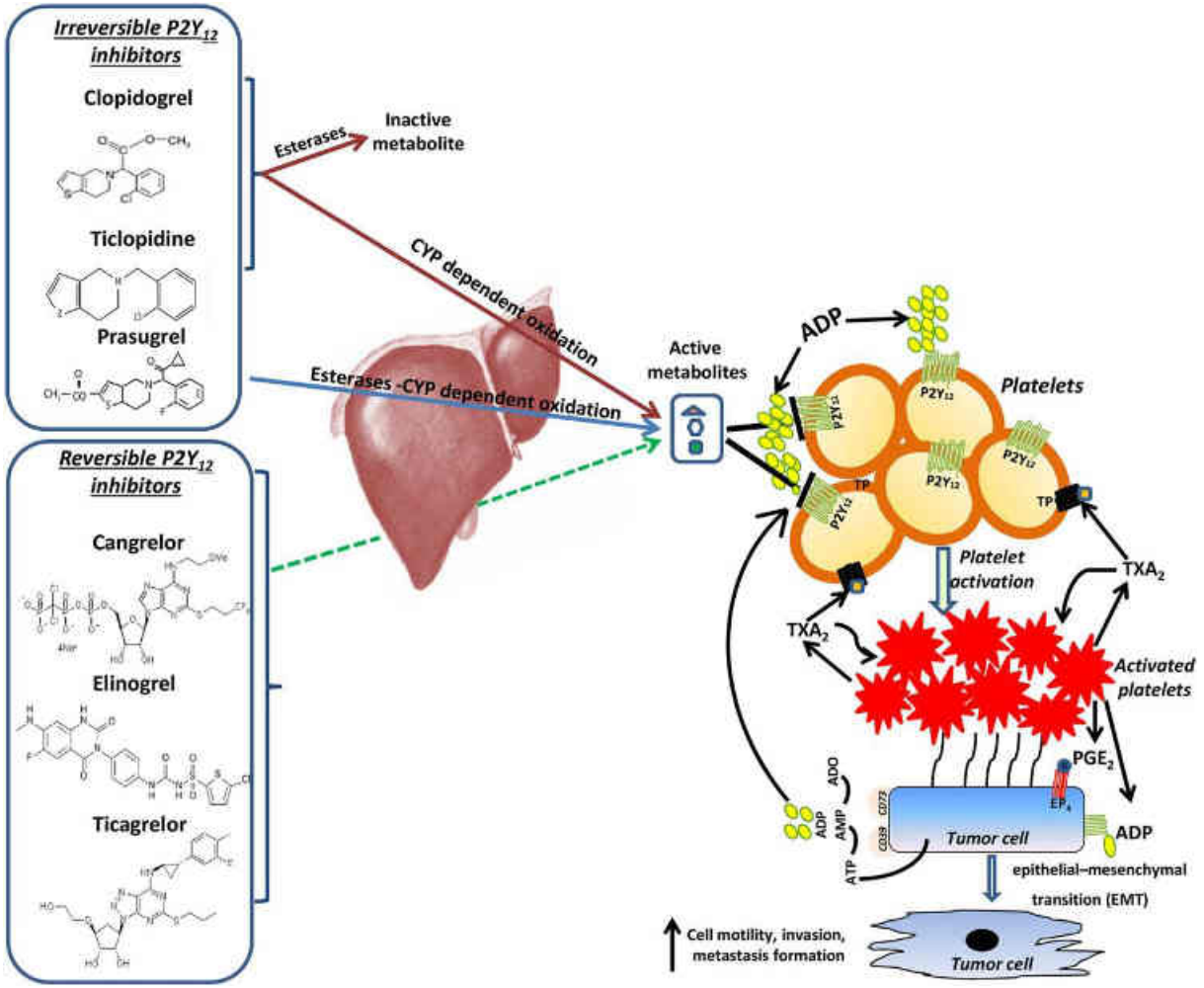




Battinelli EM et al *Blood*. 2011;118:1359-1369.

The potential contribution of P2Y12 receptor in cancer and metastasis.

Recently, the relationship between P2Y12 and cancer was reviewed by Ballerini et al. indicating the important role of P2Y12 in malignant cells.



Ballerini P,. *Front Pharmacol*. 2018;9:66.

Carcinogenesis vol.18 no.5 pp.1001–1006, 1997

Chemopreventive efficacies of aspirin and sulindac against lung tumorigenesis in A/J mice

- In A/J mice, a strain highly susceptible to carcinogen-induced tumors, aspirin (294 mg/kg in drinking water for 7 weeks) was proven to reduce the onset of lung tumors induced by a tobacco-specific nitrosamine (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)

Table I. Effects of feeding NSAIDs on lung tumorigenesis induced by NNK in A/J mice[a]

Group No.	Treatment with NSAIDs	No. of surviving mice/no. of initial mice	Total dose of NNK (mg/mouse)[b]	Dose of NSAIDs mg/kg diet (mg/kg body weight)	Body weight (g/mouse)[c]	Lung tumor multiplicity[d]	Incidence of mice with tumor
1	None	10/10	None	None	31.2±0.9	0.2 ±0.13	2/10
2	None	24/25	9.13±0.03	None	25.3±1.0*	9.92±1.97	23/24
3	Sulindac	25/25	9.12±0.01	123 (15)	24.4±1.3*	4.72±1.44**	25/25
4	ASA	15/15	9.14±0.03	294 (35)	27.7±0.7*	3.93±0.62**	14/15
5	Non-buffered Aspirin®	14/15	9.12±0.01	294 (32)	26.2±0.5*	3.71±1.10**	14/14
6	Buffered Aspirin®	15/15	9.12±0.02	294 (32)	28.0±2.5	8.07±2.21	15/15

[a]Six- to 7-week-old mice were given NNK in drinking water between week 0 and week 7. NSAIDs were given between weeks –2 to +23.
[b]Mean ± SD (n = 14–25).
[c]Mean ± SD (at week +23). Statistically different from group 1 (*$P < 0.005$, Student's t-test).
[d]Mean ± SE. Lung tumors larger than 1mm were counted. Statistically different from group 2 (**$P < 0.05$, Student's t-test).

ASA and non-buffered Aspirin® were the most effective inhibitors and reduced the incidence of lung multiplicities by 60 and 62%, respectively

Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial

John Burn, Harsh Sheth, Faye Elliott*, Lynn Reed, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Möslein, Fiona E McRonald, Lucio Bertario, D Gareth Evans, Anne-Marie Gerdes, Judy W C Ho, Annika Lindblom, Patrick J Morrison, Jem Rashbass, Raj Ramesar, Toni Seppälä, Huw J W Thomas, Kirsi Pylvänäinen, Gillian M Borthwick, John C Mathers, D Timothy Bishop, on behalf of the CAPP2 Investigators*

Summary

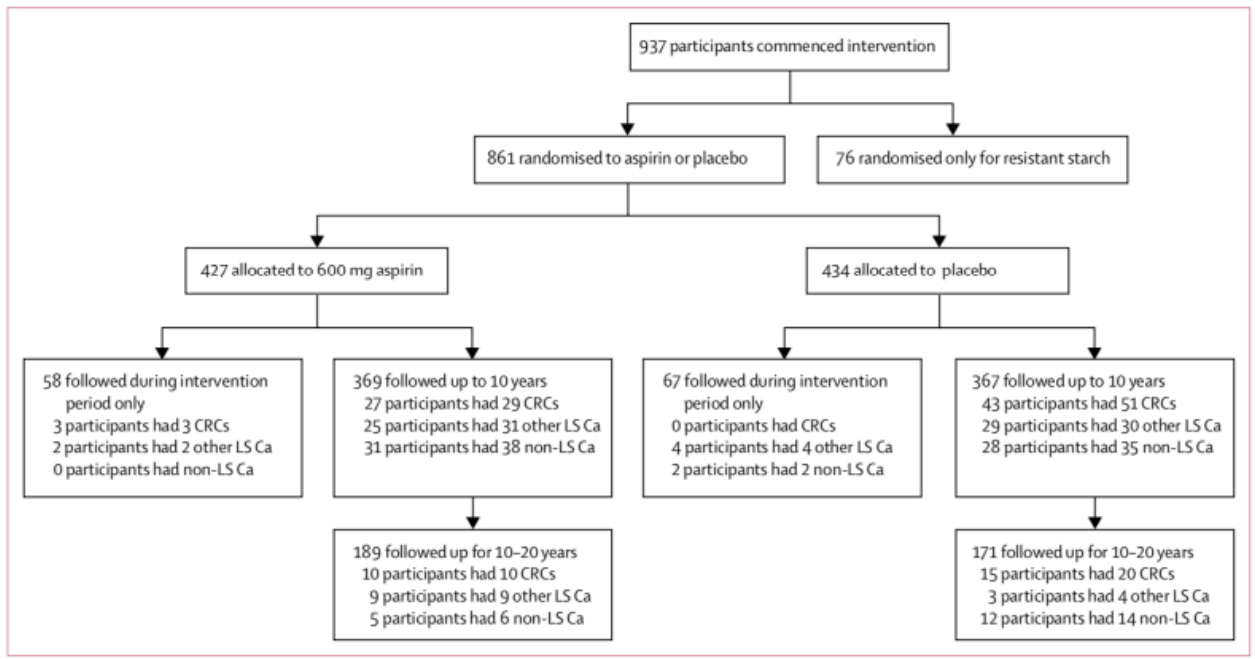


Figure 1: **Trial profile**
CRC=colorectal cancer. LS Ca=Lynch syndrome associated cancers.

www.thelancet.com Vol 395 June 13, 2020

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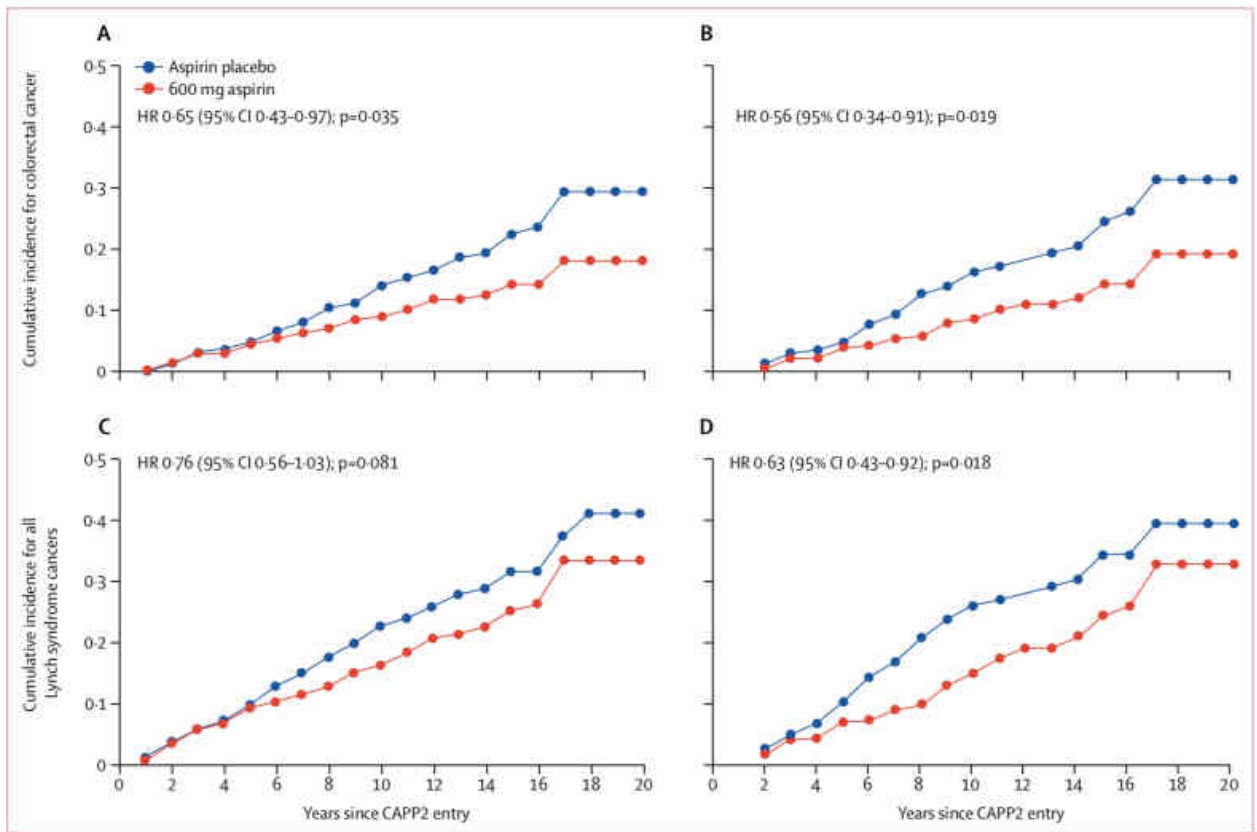
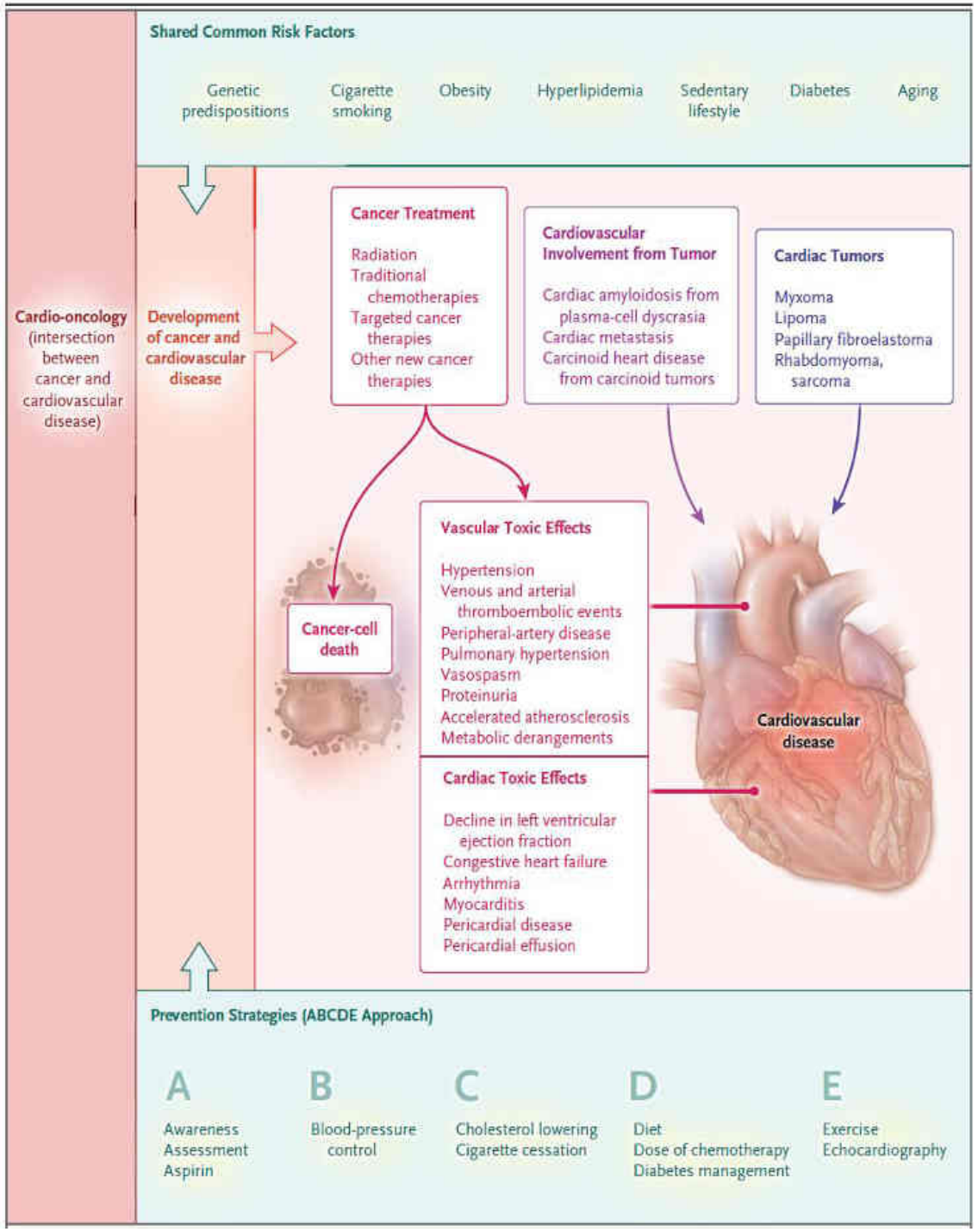


Figure 2: Time to first colorectal cancer and time to any Lynch syndrome cancer in all CAPP2 study participants followed up for 10 years and for 20 years in England, Finland, and Wales

www.thelancet.com Vol 395 June 13, 2020



The World of Cardio-oncology

Where Cancer and CV Disease Meet

- **Cardio-oncology has evolved because of the explosion of cancer treatments and related cardiovascular toxicity.**
- **Common genetic and traditional risk factors may predispose patients to both cancer and cardiovascular and metabolic diseases.**
- **The intersection between cancer and cardiovascular disease extends beyond toxicology**

Moslehi JJ. N Engl J Med. 2016;375:1457-1467.

Conclusion

- **Targeting platelet-cancer cell interaction is a potential strategy to reduce both cancer metastasis and cancer-associated thrombosis.**
- **Clinical studies reported positive results about the potential benefit of long-term aspirin to prevent several cancer types, particularly affecting the gastrointestinal tract.**
- **Several pharmacologic approaches have been tested, and very promising results have been obtained with some of them, but mostly in vitro or in preclinical models.**
- **Clinical evidence of a beneficial effect of other anti-platelet agents, such as P2Y12 inhibitors, in cancer is still largely deficient. This is of crucial importance when considering the recent approaches suggesting P2Y12 inhibitor monotherapy with aspirin withdrawal.**