Apparent reduction of early relapses with perioperative NSAID suggests transient systemic inflammation post surgery precipitates metastatic activity in breast and other cancers

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Reference: MW Retsky, R Demicheli, WJM Hrushesky, P Forget, M DeKock, I Gukas, RA Rogers, M Baum, V Sukhatme and JS Vaidya. Reduction of breast cancer relapses with perioperative non-steroidal anti-inflammatory drugs: new findings and a review; *Current Medicinal Chemistry*, 2013, 20, 4163-76. PubMed PMID: 23992307. http://www.eurekaselect.com/114602/article

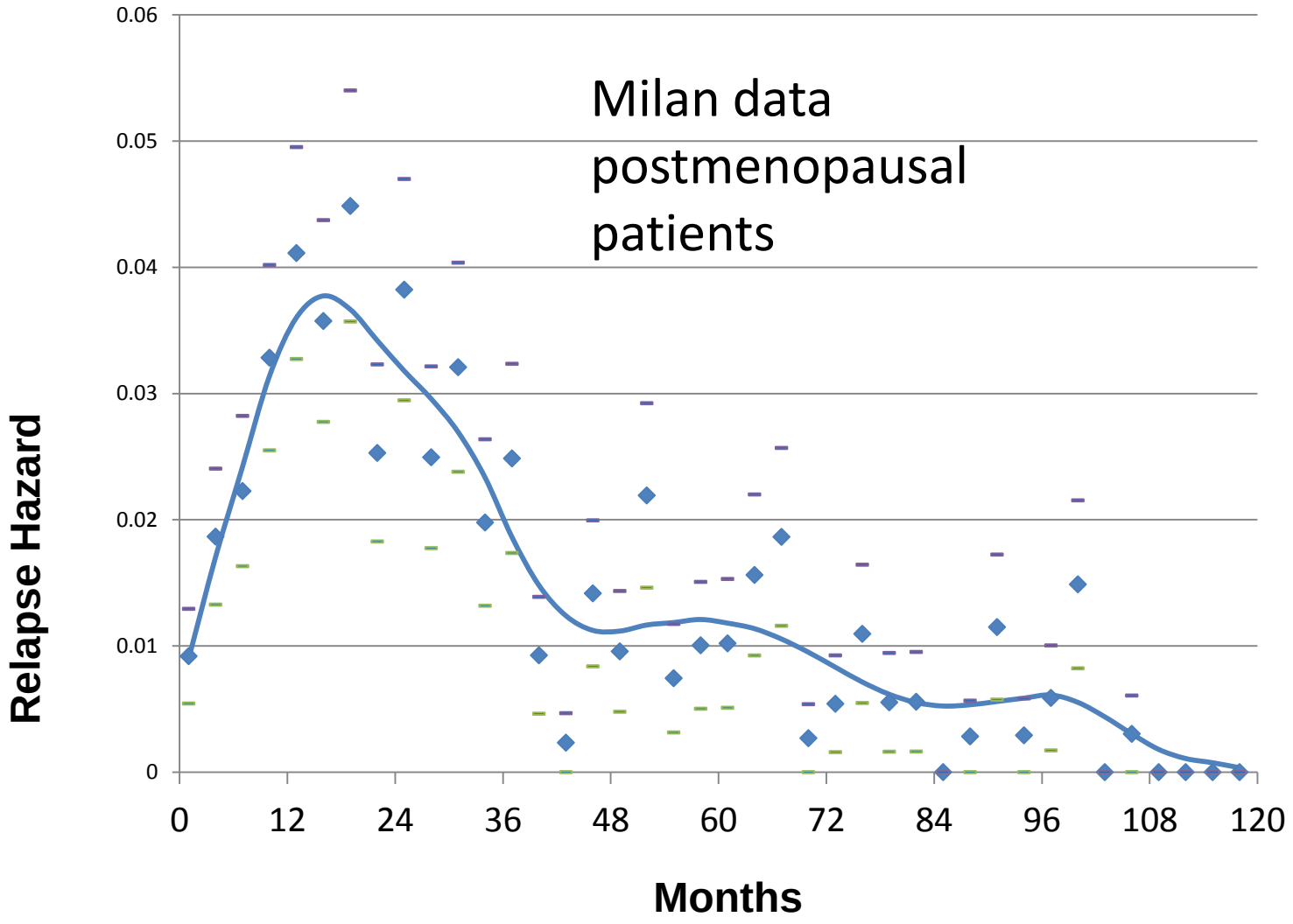
Disclosure: Funded by Susan G Komen 100484. Michael Retsky has patents pending on treatment of early stage cancer and method to prevent surgical site infections. Also on the Board of Directors of the Colon Cancer Alliance (www.ccalliance.org). No other COI to report.

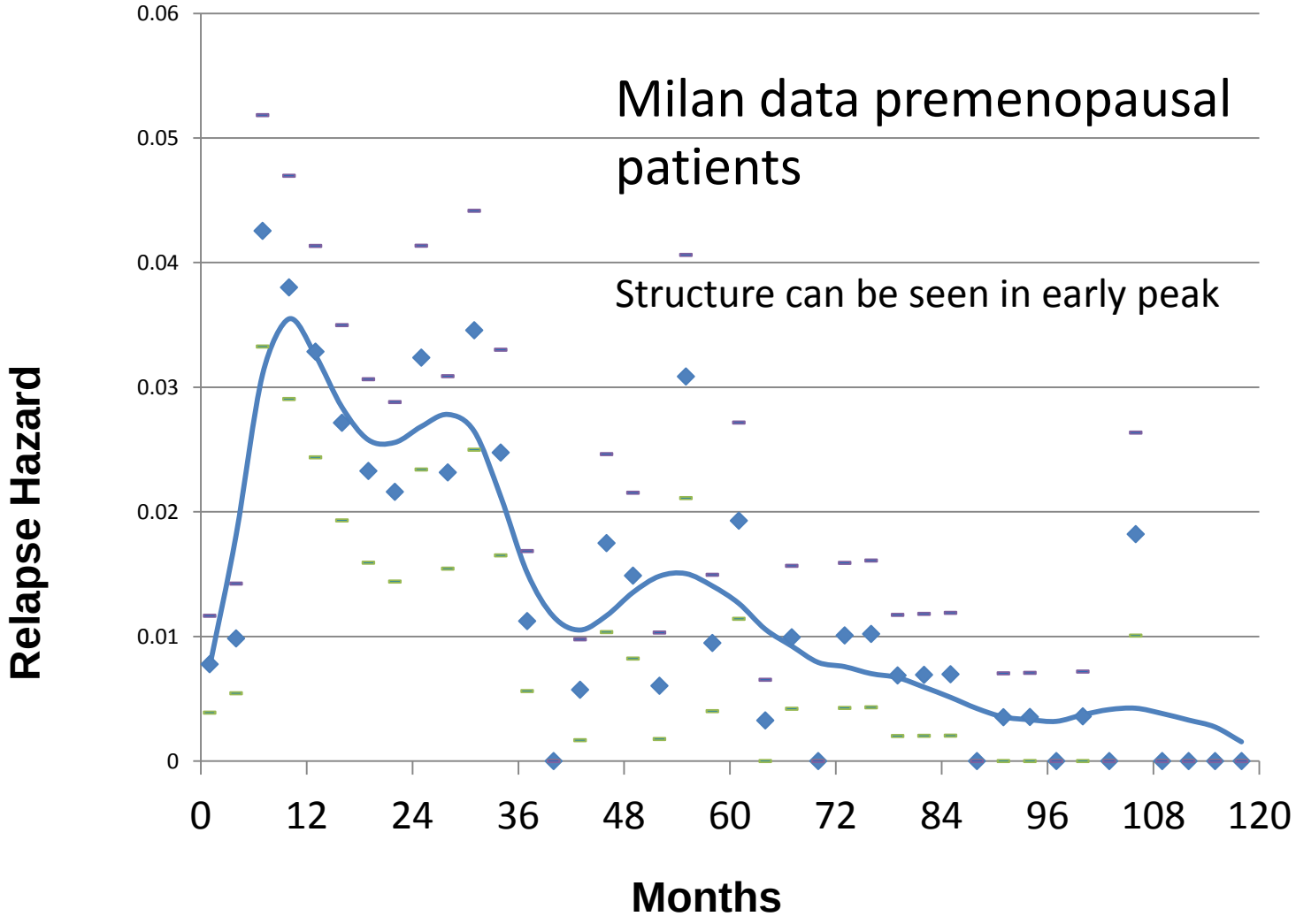
Data presented in 1993 showing bimodal relapse patterns in breast cancer databases from Italy and UK
(Demicheli et al, BCR&T1996, Baum et al, Eur J Cancer 1999)

Milan data: 1173 early stage breast cancer patients with 16-20 year follow-up (mastectomy only).

Sharp peak at 18 months
Nadir at 50 months
Broad peak at 60 -70 months with a long tail extending to 15-20 years.

Now identified in 21 databases from US, Europe and Asia.


Milan data
postmenopausal
patients
Relapse Hazard
0.06
0.05
0.04
0.03
0.02
0.01
0
0
12
24
36
48
60
72
84
96
108
120
Months


Milan data premenopausal patients
Structure can be seen in early peak
Relapse Hazard
0.06
0.05
0.04
0.03
0.02
0.01
0
0
12
24
36
48
60
72
84
96
108
120
Months

Milan data in Disease-Free Survival format



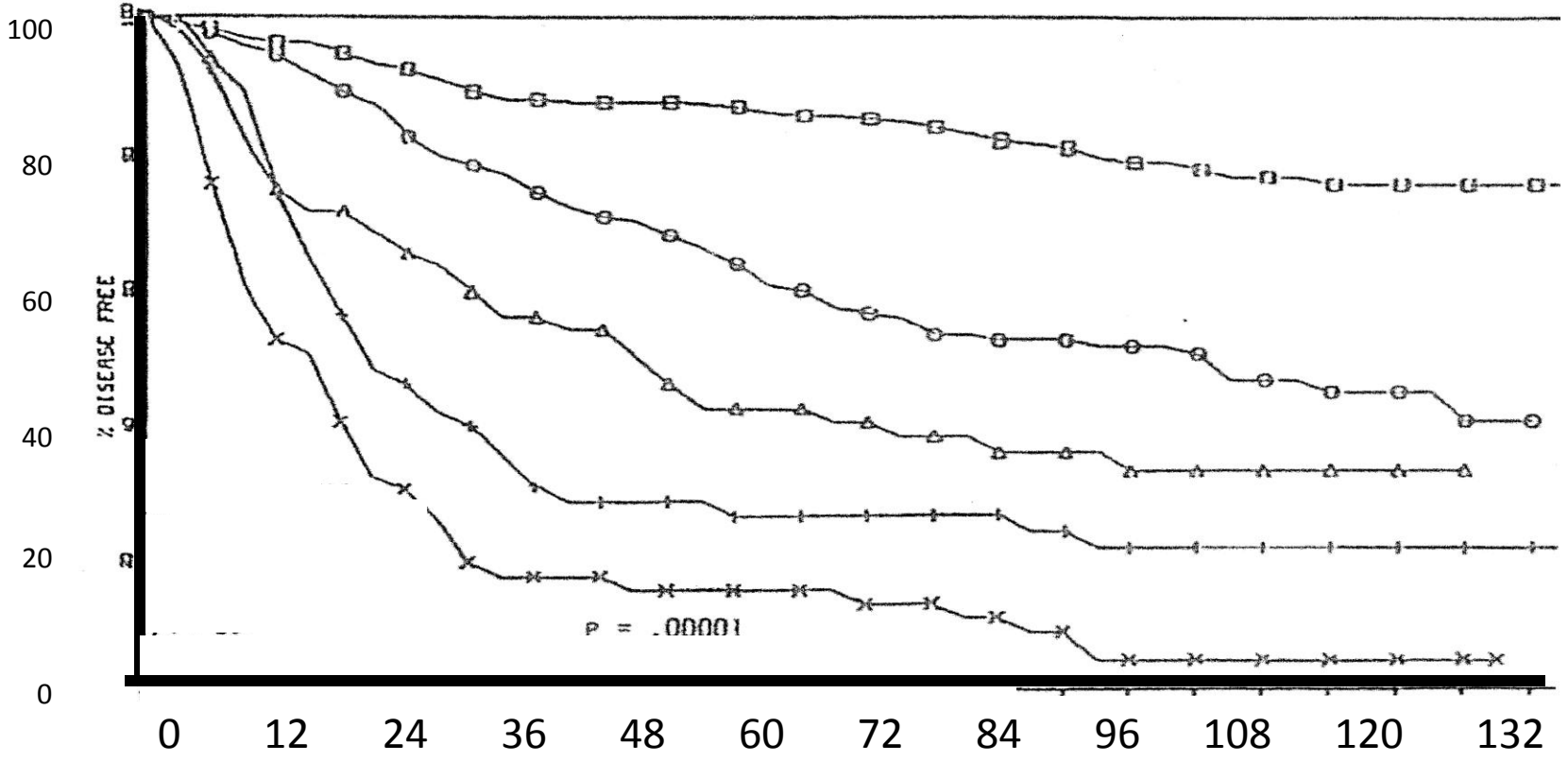
Bonadonna, Valagussa et al. NEJM 1995

Other data from Europe, Asia and US that show a possible bimodal relapse pattern:

* authors cite bimodal pattern

Fisher et al. Cancer 1984.
Bedwinek. Cancer 1984
**Sant et al, Eur J Cancer. 1991*
de la Rochefordiere et al. Lancet 1993.
Veronesi et al. JNCI 1995.
Saphner et al. JCO 1996.
**Holmberg & Baum. Nature Med 1996.*
**Fortin et al. JCO 1999.*
**Karrison, et al, J Natl Cancer Inst 1999. (mortality data)*
**Yakovlev, et al Cancer 1999.*
**Gasparini et al. Breast Cancer Res & Treat 2001*
**Ripley et al. Stat Med 2004*
**Jatoi et al. Breast Ca Res & Treat 2005*
**Jerez et al. Breast Ca Res & Treat 2005*
**Anderson et al. Breast Ca Res & Treat 2006*
**Stearns et al. Brit J Surg, 2007*
**Gao et al. Breast Cancer Res 2007*
**Kimura et al. BCR&T 2007*
**Zhang et al BMC Genomics 2007 (different gene patterns)*
**Yin et al BCR&T 2009*
**Ribelles et al BCR 2013*

Relapse-free survival for patients treated only with surgery. Grouped by nodal count. From top, nodes = 0, 1-3, 4-6, 7-12, >12. Bimodal pattern may be seen.



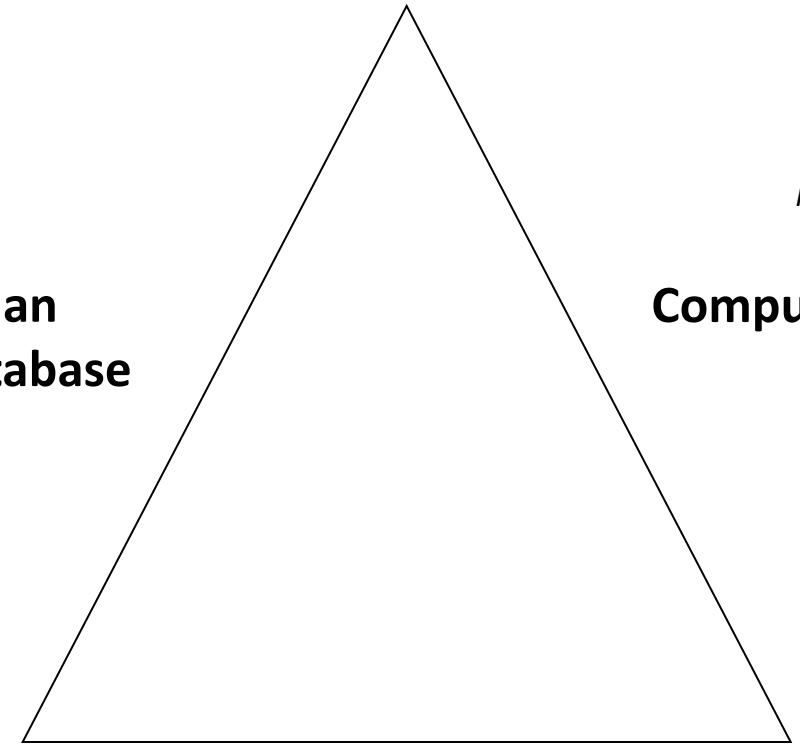
Fisher et al. Cancer 1984.

This was not explainable with the continuous growth model that has guided breast cancer early detection and therapy for many years.

Retsky M, Metronomic Chemotherapy was Originally Designed and first used in 1994 for Early Stage Cancer - why is it Taking so Long to Proceed? Journal of Bioequivalence and Bioavailability, May 2011, Editorial
http://www.omicsonline.org/0975-0851/JBB-Editorial6.pdf

MW Retsky; How long should adjuvant chemotherapy be given in early stage colon cancer? Clinical and Experimental Pathology. 3:1 2013. http://www.omicsonline.org/2161-0681/2161-0681-3-136.digital/2161-0681-3-136.html

Fitting a simple growth model to Milan data



Retsky et al BCR&T 1997

Milan database

Computer simulation

Bonadonna, Valagussa et al. NEJM 1995

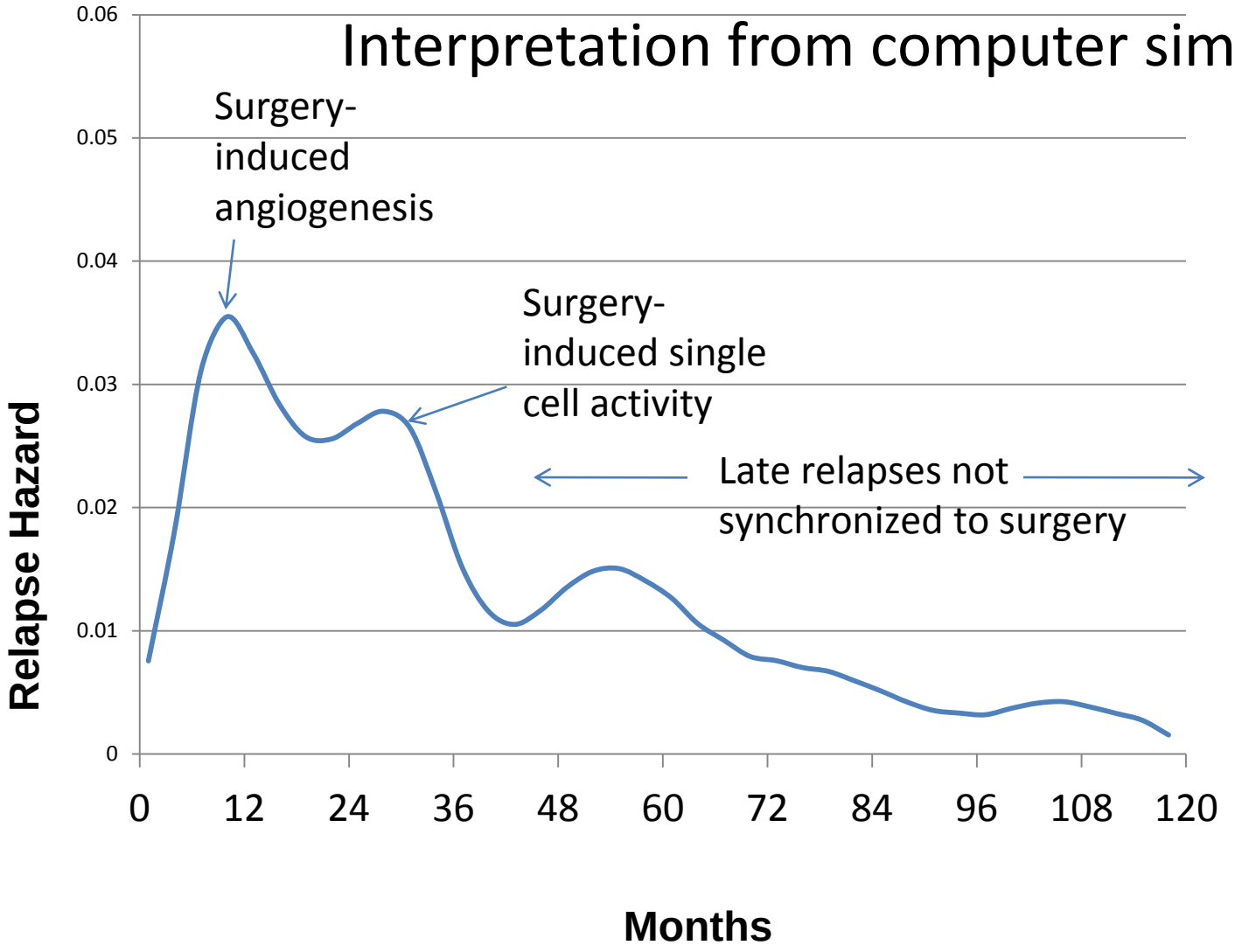
Growth model

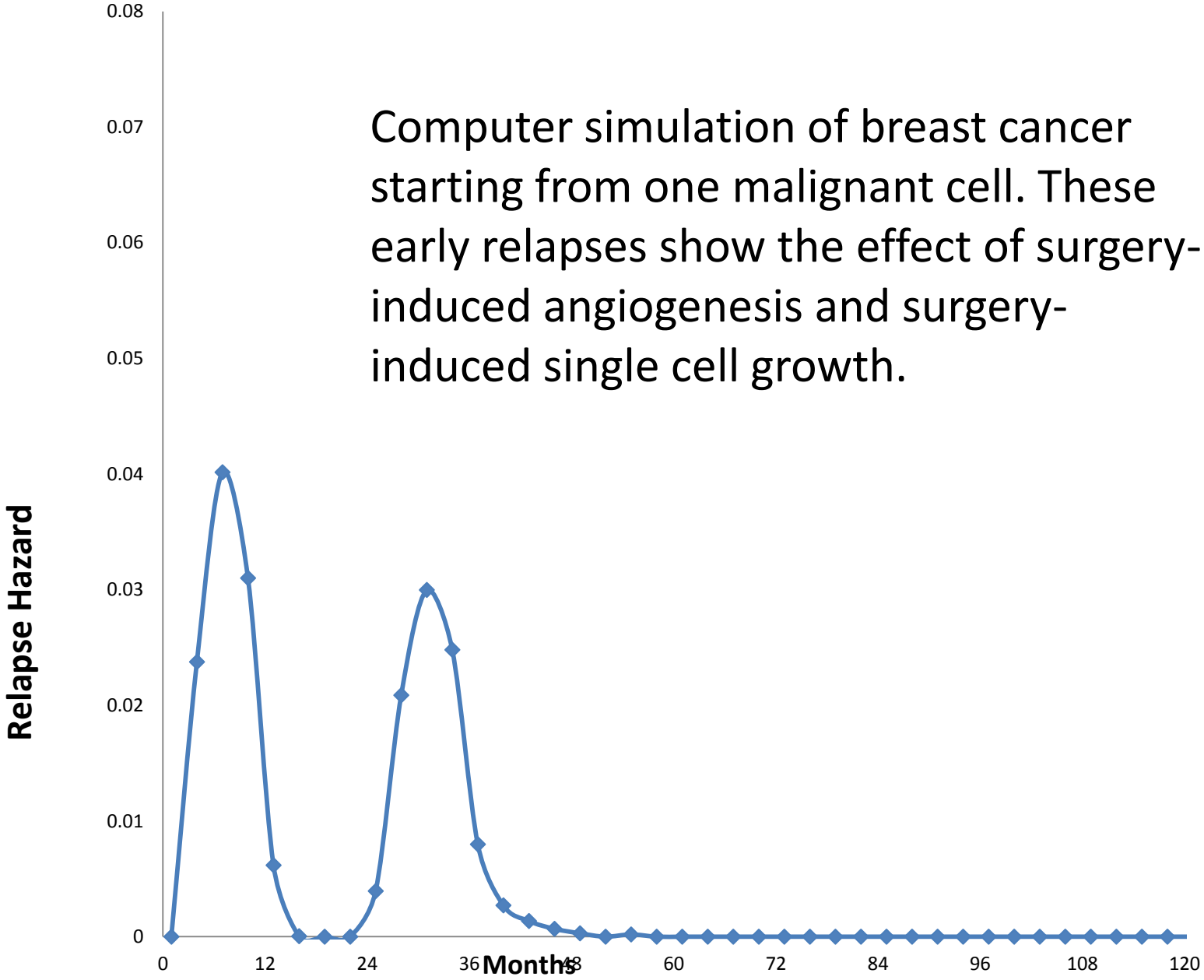
Demicheli et al. Ann Onc 1997

single cell ⇨ avascular micrometastases ⇨ growing lesion

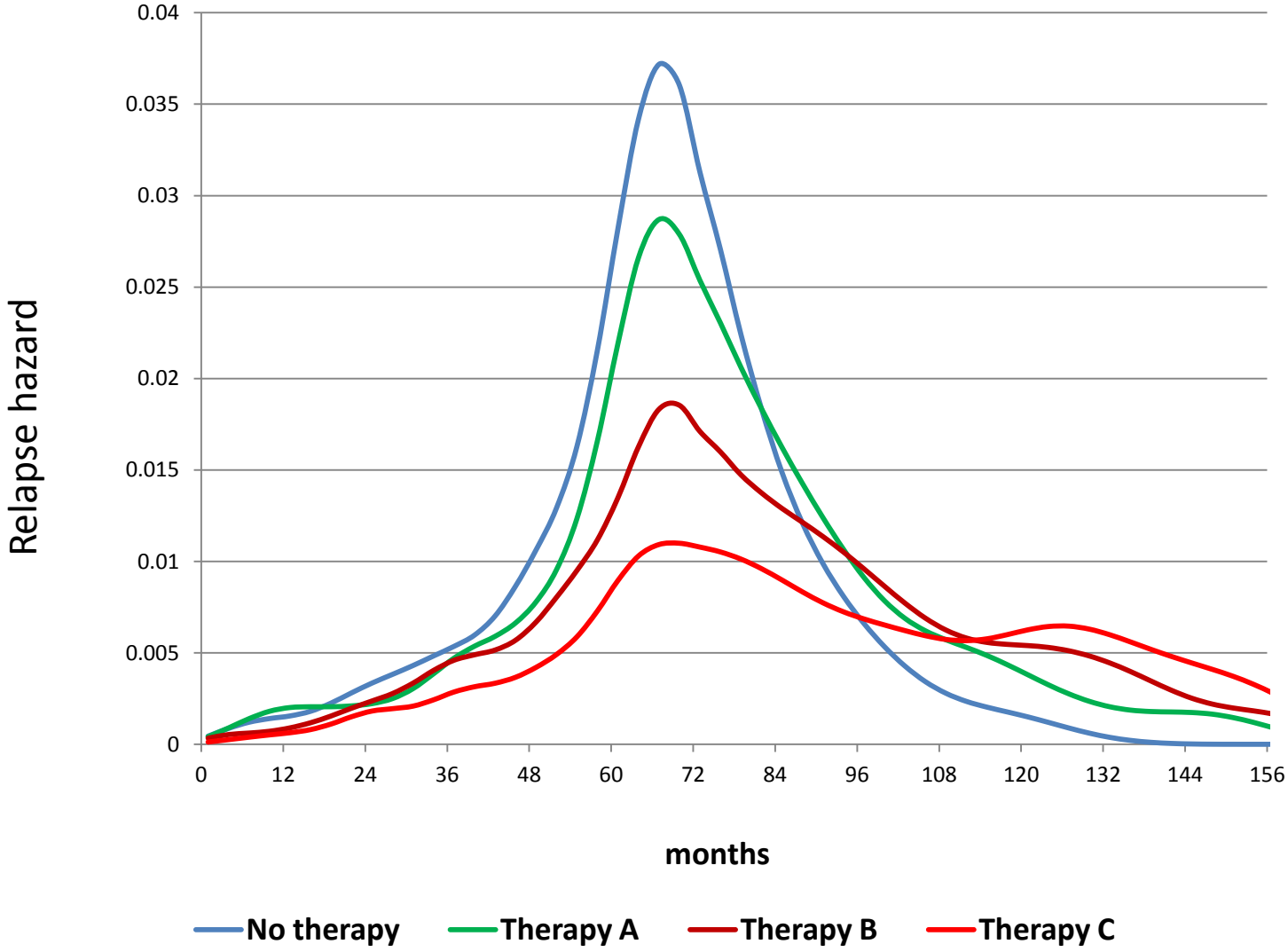
possible dormancy *possible dormancy*

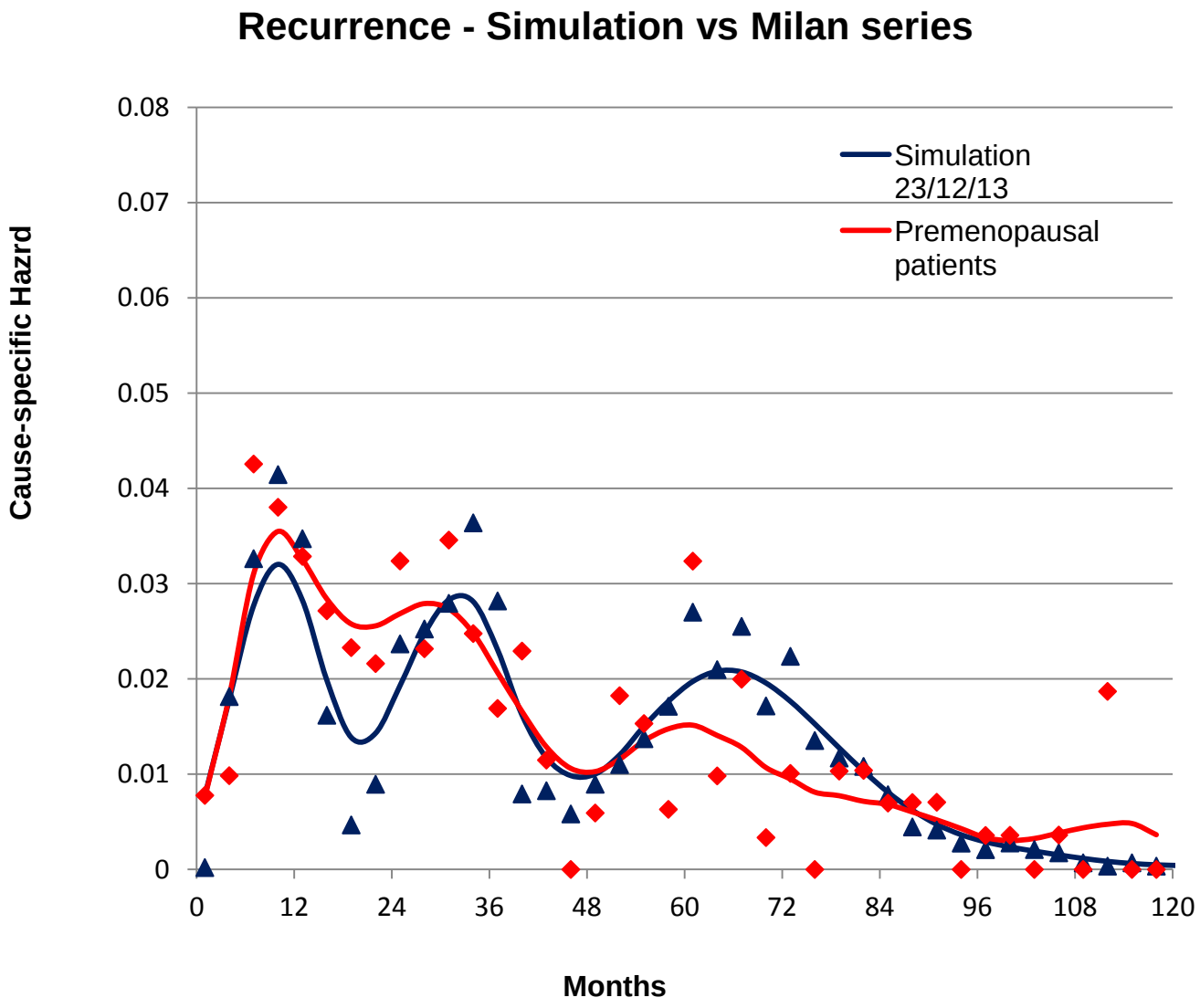
Milan data premenopausal patients
Interpretation from computer simulation




Computer simulation of breast cancer starting from one malignant cell. These early relapses show the effect of surgery-induced angiogenesis and surgery-induced single cell growth.
Relapse Hazard
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
12
24
36
48
60
72
84
96
108
120
Months

Computer simulation of late relapse events. Results of long-term antiangiogenic therapy on late relapses.




Recurrence - Simulation vs Milan series
Cause-specific Hazrd
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
12
24
36
48
60
72
84
96
108
120
Months
Simulation 23/12/13
Premenopausal patients

Results of computer simulation

Early (dominant) peak composed of two previously unreported surgery-induced relapse modes.

Avascular micrometastases induced to vascularize (10 mo.)

20% of premenopausal node-positive patients. Sharp.

5:1 node-positive to node-negative, 2:1 pre- compared to postmenopausal.

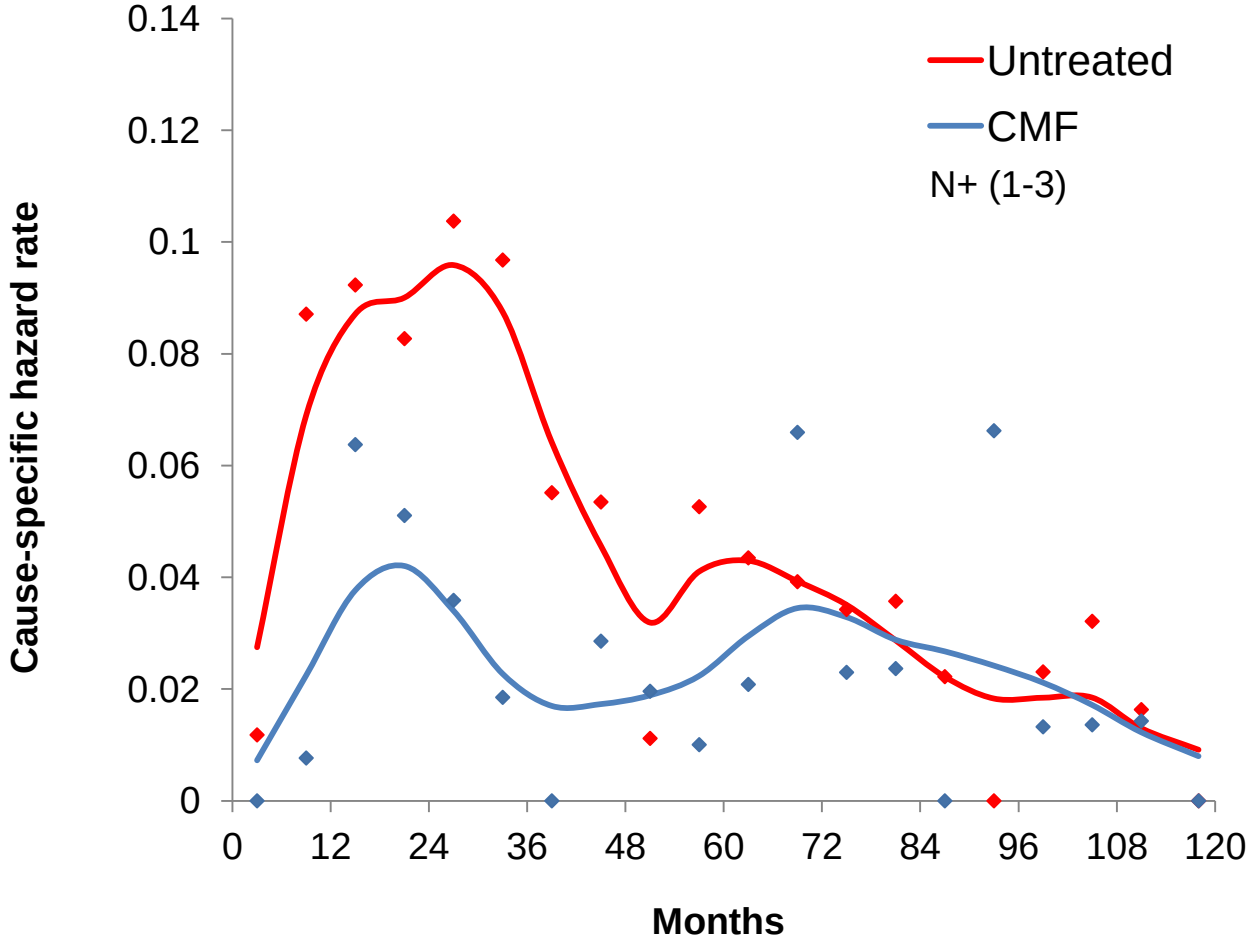
Previously inactive single cells induced to divide and then stochastically vascularize (30 mo. peak).

50% to 80% of relapses (depending on tumor size and nodes pos)

Late peak (50-200 mo) is the “natural history” of breast cancer.

Effect of adjuvant chemotherapy on relapse hazard

Main effect is on early relapses, little effect on late relapses.



Milan data - Premenopausal plus postmenopausal patients

Similar relapse patterns seen in other cancer sites

Pancreatic - Deylgat B, et al. Postsurgery activation of dormant liver micrometastasis: a case report and review of literature. J Gastrointest Cancer. 2011 Mar;42(1):1-4. Review. PubMed PMID:20602181.

Melanoma – Tseng, et al. Giant cutaneous melanomas: evidence for primary tumour induced dormancy in metastatic sites? *BMJ Case Reports* 2009; doi:10.1136/bcr.07.2009.2073

NSCLC – Demicheli et al. Jour Thorac Onc 2012

Prostate – Hanin and Zaider. Cancers 2011
Weckermann et al JCO 2009

Osteosarcoma - Smithers DW. Clin. Radiol. 19: 113, 1968.
Tsunemi T et al Clin Orthop Relat Res 2003 Feb;(407):159-66

Did we rediscover something that was known 2,000 years ago?

Aulus Cornelius Celsus (30 BC - 38 AD)

First there is the cacoethes, then carcinoma without ulceration, then the fungating ulcer. (staging of cancer)

None of these can be removed but the cacoethes: the rest are irritated by every method of cure. The more violent the operations the more angry they grow.

After excision it recurs, bringing with it the cause of death, whereas at the same time by using no extirpation protract lives, notwithstanding the disorder, to an extreme old age.

Galen of Pergamum (131-203 AD)

(Galen introduced the concept of “humors” being responsible for cancer, a theory that dominated medicine for over 1000 years. Cancer was due to an excess of black bile (humor). Galen coined the term “crab” to describe cancer.)

We have often cured this disease in the early stages, but after it has grown to a noticeable size no one has cured it with surgery.

Ariel, I. A historical review of breast cancer treatment. In *Breast Cancer: Controversies in Management; Leslie, W., Houston, J., Eds.; Futura Publishing Co.: Armonk, NY, USA, 1994.*

Can this explain important clinical observations in breast cancer?

Adjuvant chemotherapy works particularly well for premenopausal N+ patients

Retsky, Bonadonna, Folkman et al 2004

Mammography apparently works better for women age 50-59 than age 40-49

Retsky et al 2001, 2003, 2005, 2008, 2012
Demicheli et al 2004,
Baum et al 2005

Racial disparity in outcome

Retsky et al 2007
Demicheli et al 2007
Gukas et al 2009

Most important finding

Something happens at or around the time of primary surgery to precipitate the early wave of relapses that account for over half of all breast cancer relapses.

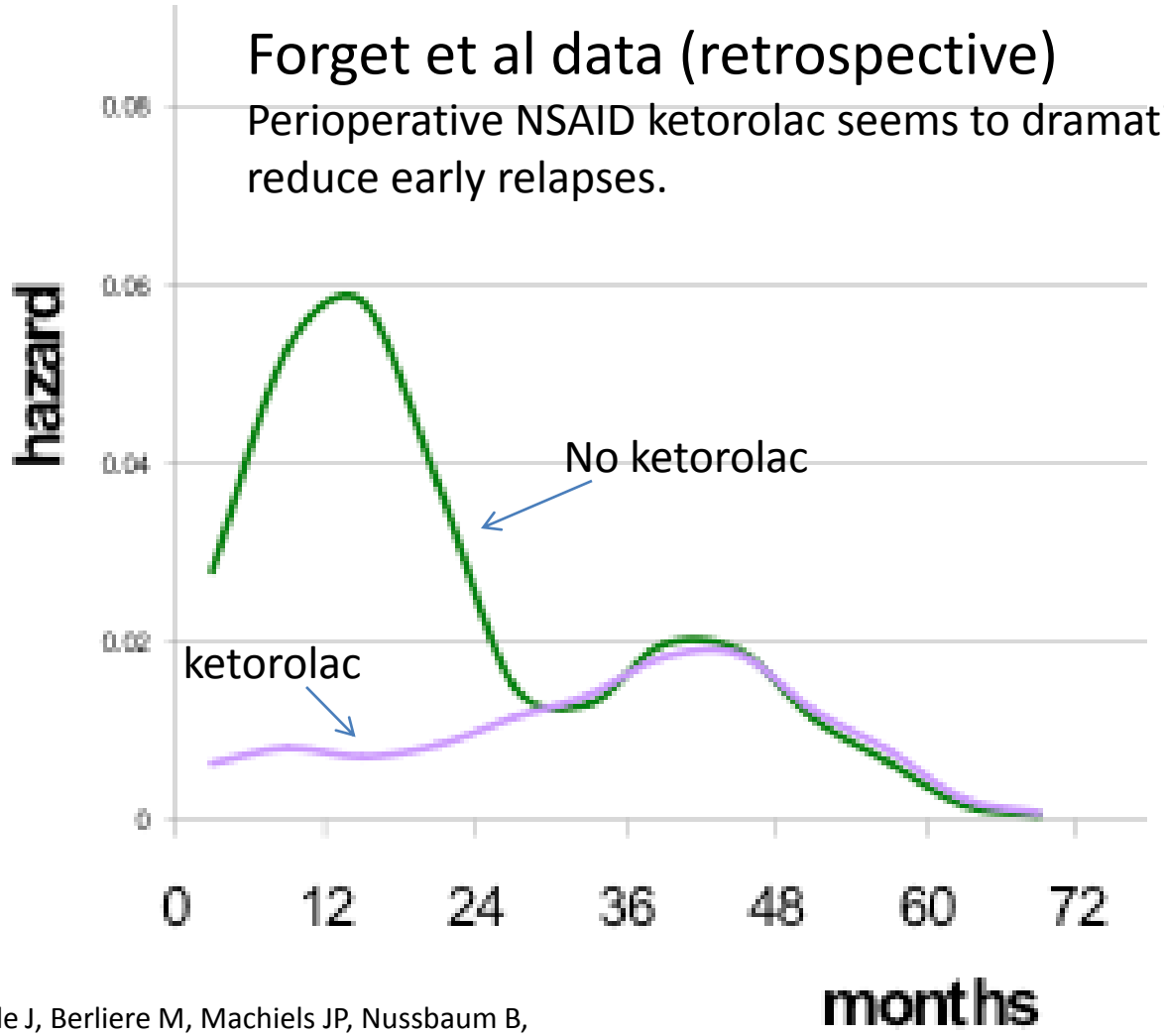
Surgery apparently induces angiogenesis of dormant avascular micrometastases and starts growth from single cancer cells.

This may be a general effect.

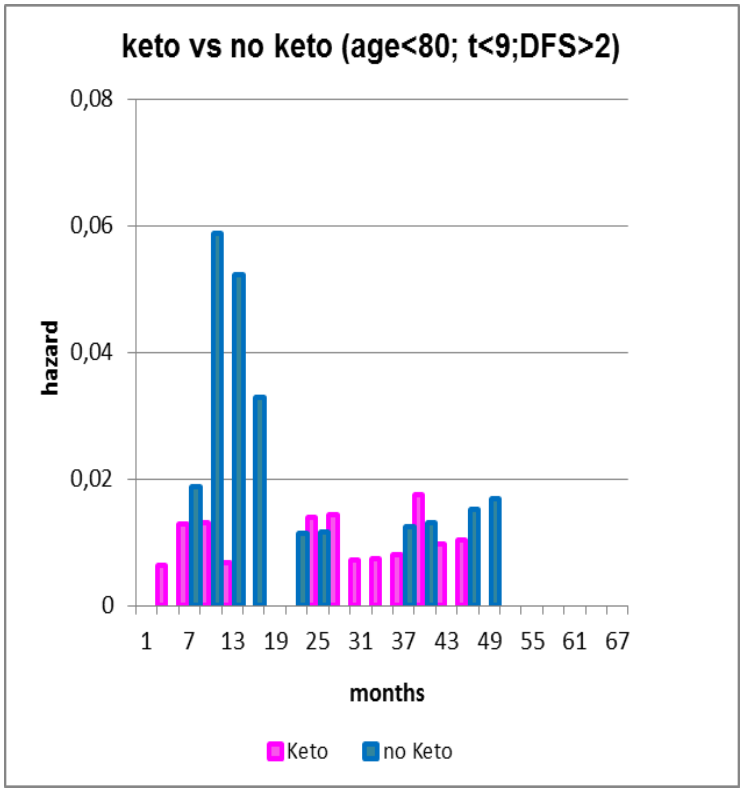
June 2010 – an unexpected and dramatic report

Forget et al data (retrospective)

Perioperative NSAID ketorolac seems to dramatically reduce early relapses.



Forget P, Vandenhende J, Berliere M, Machiels JP, Nussbaum B, Legrand C, De Kock M; Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. Anesth Analg. 2010 Jun 1;110(6):1630-5.



Months	0	6	12	18	24	30	36	42	48
Patients at risk	316	302	283	266	260	252	223	183	150
Keto group	175	168	162	157	155	151	140	115	99
No-Keto group	141	134	121	109	105	101	83	68	51

Forget et al data updated September 2011 by Sarah Amar and analyzed by Romano Demicheli

Five-fold reduction in relapses months 9-18. Three vs. 15 events.

We knew that some intervention at time of surgery would be needed to stop early relapses but what mechanism could explain Forget et al data?

Explore relationship among

Inflammation
Cancer surgery
NSAIDS
Angiogenesis
tumor growth
circulating tumor cells (CTC)
CTC released during surgery



Our attention is drawn to inflammation

El Saghir et al Trauma-associated growth of suspected dormant micrometastasis. BioMedCentral Cancer 2005.

Background: Cancer patients may harbor micrometastases that remain dormant, clinically undetectable during a variable period of time. A traumatic event or surgery may trigger the balance towards tumor growth as a result of associated angiogenesis, cytokine and growth factors release.
Case presentation: We describe a patient with non-small cell lung cancer who had a rapid tumor growth and recurrence at a minor trauma site of his skull bone.
Conclusion: This case is an illustration of the phenomenon of tumor growth after trauma or surgery and its associated cellular mechanisms. This phenomenon deserves further investigation and study.

44 yo smoker with inoperable nsclc . 15 months later bumps head and tumor rapidly grows there (7 cm diam in 30 days).

Retsky comments BMC Cancer 2005. (input from Taturo Udagawa)



Figure 1
Photograph of the patient showing the described 7 cm mass at the site of the trauma at the right lateral side of his head.

Retsky M. What would explain the sudden growth of lung cancer after minor trauma reported by El Saghir et al? BioMedCentral Cancer 2005
http://www.biomedcentral.com/1471-2407/5/94/comments

"... El Saghir et al ... circulating cancer cells were entrapped at the trauma site is probably close to the truth. ...

The unusual isolated and exaggerated situation allowed El Saghir et al to observe what may be a new and possibly important hematologic metastatic pathway: inflammation as a facilitating precursor to tumor.

Metastasis is a very inefficient process. (many) cancer cells might be found in a patient's blood but only a few metastases occur. The inflammation sequence discussed by Martins-Green et al would certainly increase metastatic efficiency since it bypasses extravasation through an intact vessel wall and it provides growth factors in the microenvironment."

*Martins-Green et al 1994 - Avian Rous Sarcoma virus in circulation. Tumor grows at any site of wounding and is positively correlated with inflammation.

*Virchow 1863 – chronic inflammation leads to tumor growth

* Balkwill et al 2001 - if genetic damage is the “match that lights the fire” of cancer then inflammation is the “fuel that feeds the flames”.

*Pascual et al. 2011 - inflammatory response after resection for colonic cancer. Inflammatory marker (IL- 6) in serum about 1/300 that of peritoneal fluid and decay to baseline in approximately 1 week

*Perez-Rivas et al 2012 – inflammatory markers in serum after mastectomy

*The inflammatory response is initiated by tissue damage and can be intensified by mast cells which release histamine, which then markedly increases the permeability of adjacent capillaries.

*Blood speed in capillaries is 0.05cm/sec (compared to 40-50 cm/sec in large arteries) which would make leaky capillary venules a very efficient way for CTC to enter tissue.

*Jones and Rous 1914 - “The localization of secondary tumors at points of injury has been so often remarked upon that it is unnecessary to cite specific instances. The cause for the phenomenon is unknown.”

*Walter et al 2011 two squamous cell carcinoma of the lung case reports metastatic tumor outgrowth after recent physical trauma - termed "Inflammatory oncotaxis"

* Karhade et al 2014 - Well established that cancer patients have CTC and correlates with early relapse.

*Pachmann 2010 - Peak in CTC after mastectomy but 3-7 days later

* Weinberg 2005- Cancer usurps wound healing process.

*Dvorak 1986 – description of cancer as wound healing gone awry

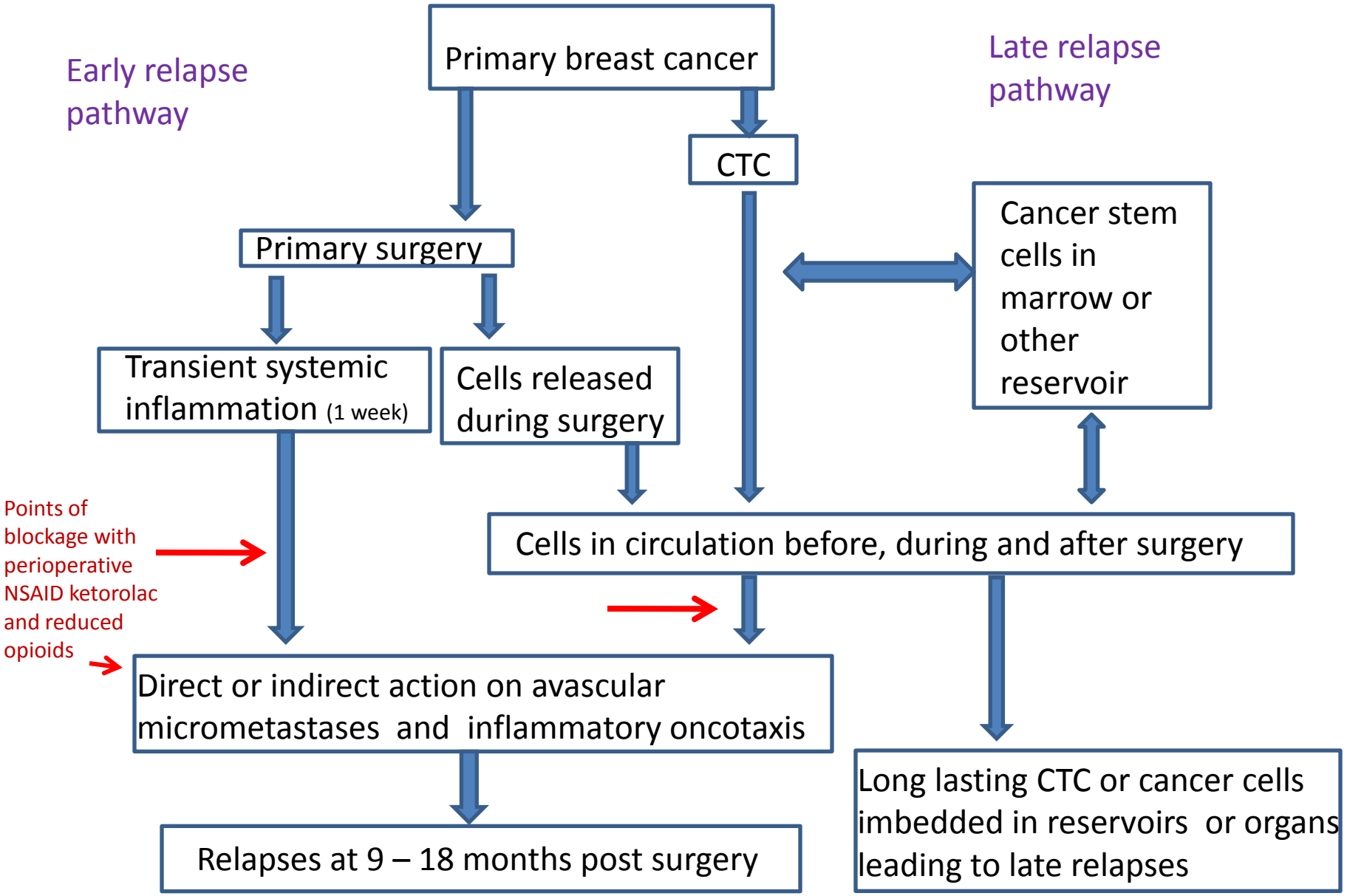
*D'Amato et al 2008 – NSAIDs reduce capillary leakage and are antiangiogenic

*Klement et al – platelets actively sequester angiogenesis regulators (and degranulate with inflammation) Blood 2009. (10% dip in platelets post surgery)

*Burke 1996 - Perioperative NSAID ketorolac results in reduced use of opioids – considered to be proangiogenic.

*Montovani 2008, Rothwell 2012 – NSAIDs reduce risk and mortality of breast and colon cancer after 2 years of use

Proposed explanation why perioperative NSAID ketorolac prevents early relapses



Conclusions

1. Early relapses in breast cancer which comprise the majority of relapses consist of surges of angiogenesis and single cell activation. These events are triggered by primary surgery. Late relapses are not.

2. Forget et al retrospective data suggest perioperative NSAID ketorolac reduces early relapses 5-fold. This may reduce breast cancer mortality by 25 to 50% at low cost and toxicity. (Clinical trials: Phase II underway in Brussels and Phase III scheduled to start in Seoul.)

3. These data suggest transient systemic inflammation (identified after colon and breast cancer surgery) is the precipitating factor.

4. CTC and cells released via surgery (including cancer stem cells released from marrow) in the presence of transient systemic inflammation could account for the single cell activation that was prevented by perioperative NSAID.

5. There are a number of mechanisms that could explain how perioperative NSAID prevents surgery induced angiogenesis.

6. The relapses avoided in Forget et al data will likely not appear later.

7. Breast cancer runs its course in over a decade but most of the events leading to relapse seem to occur in the week or two after surgery.

8. This suggests metastatic progression is accelerated 100 fold during the 1-2 weeks post primary surgery.

9. This is a host response and theoretically independent of the cancer cell phenotype.

Phase III clinical trial scheduled to begin in 2014 in Seoul

http://clinicaltrials.gov/ct2/show/NCT02141139?term=breast+ketorolac&rank=2

International Collaborators



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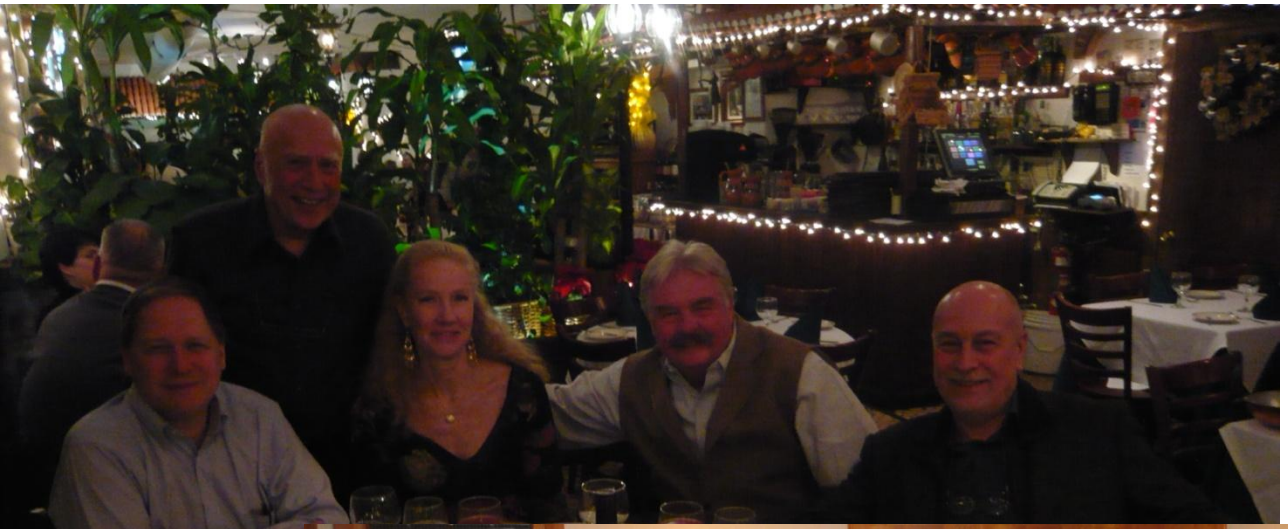


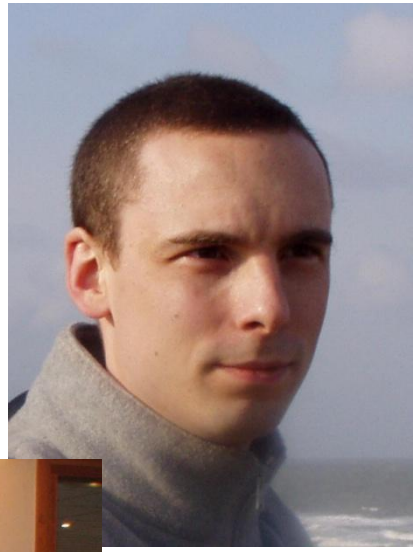
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