

Theories on Metastasis:  
Innovative Thinking  
An Advocacy Perspective

Project LEAD Workshop  
NBCC Annual Advocacy Conference 2011

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# *The Big Question*

If we want to end death from breast cancer, shouldn't we be studying metastasis?



# *But we already do study metastasis!*

- Aren't *all* of our new drugs developed by studying their effects in women with metastatic breast cancer (MBC)?
- What about all the metastatic patients in clinical trials?
- But...are these therapies really designed for them?
- Could the lack of research focusing *specifically* on metastatic processes have something to do with the limited, incremental benefit of the treatments we use?

# *Why does metastasis matter?*

- Metastasis or its treatment is the cause of virtually all breast cancer deaths, *not* primary breast cancer
- After \$ billions of breast cancer research, 40,000 US women (and men) still die of breast cancer every year, and there are over half a million annual breast cancer deaths worldwide (WHO)
- “Despite advances in the treatment of breast cancer, approximately 30% of women initially diagnosed with earlier stages of breast cancer eventually develop recurrent advanced or metastatic disease.”\*
- Last two decades, >20 new drugs FDA approved for MBC, yet the median length of survival has only minimally increased to about 3 years

\* O’Shaughnessy, *Oncologist* 2005;10(suppl 3):20–29

# *We don't study metastasis: Epidemiology*

US Population (registry-based NCI SEER data)

*What we know:*

- Number of deaths from breast cancer
- Mortality rates (overall, by race/ethnicity, state)
- Length of survival from *initial* diagnosis

*What we don't know:*

- Prevalence (how many are living with MBC)
- Recurrence rates, timing of recurrence
- Survival (how long women live with MBC, overall and by tumor subtype, treatment, etc)

*What we don't count, we can't plan for!*

# *We don't study metastasis:*

## *Basic science and translational research*

Why do we know so little about metastasis?

- Most research has focused on tumorigenesis (how tumors are formed), using *primary* breast cancer tissue
- Most metastatic breast cancers are not biopsied—biopsy considered too invasive and unnecessary
- Most women with MBC are treated on the basis of primary tumor biomarkers (HER2, ER/PR)—little metastatic tissue has been available for research
- But recent research suggests that re-biopsy may be important for treatment planning, due to changes in ER/PR and HER2 status

Steeg, Theodorescu, [Metastasis: A Therapeutic Target for Cancer](#),  
*Nat Clin Pract Oncol.* 2008

# *We don't study metastasis: Clinical trials*

- Although they enroll MBC patients, most clinical trials use tumor-growth endpoints in patients with widely disseminated metastatic disease (Response rates: CR, or complete response, and PR, or partial response)
- Adjuvant (metastasis prevention) trials take many years, require thousands of patients, and are *very* expensive
- Shouldn't we consider other trial designs and/or other endpoints more directly related to the metastatic process? (arresting tumor growth, prevention of outgrowth of micrometastases)

# *We don't study metastasis: Advocacy*

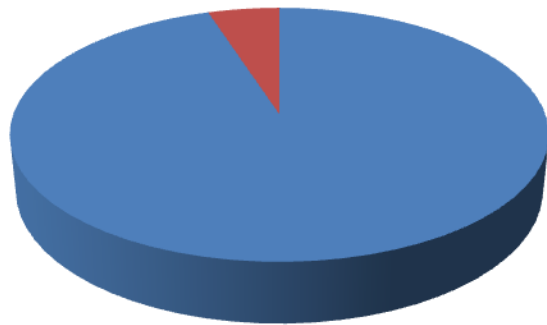
Very few advocates focus on MBC--*WHY?*

- Avoidance: Vast majority of advocates are primary breast cancer survivors at risk of recurrence

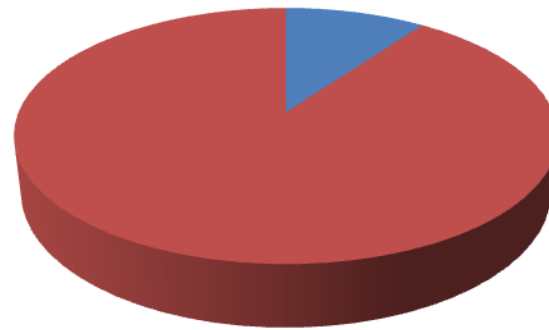
*“We are what the pink crowd wants to forget because we are the painful reminders of what can happen.”*

- Expertise required: Lack of knowledge about complex MBC treatments and the different issues that women with MBC face
- Lack of data: Incidence and prevalence of MBC unknown, so basic tools for advocacy are missing
- Screening and early detection still a primary focus
- Naïvete and fatalism both play a role

## Only 5 Percent of Cancer Research Funds Are Spent on Metastases, Yet It Kills 90 Percent of All Cancer Patients



**Cancer Research Funding**



**Cause of Cancer Deaths**

 **Metastasis**

*ScienceDaily (June 1, 2010)* — On average, about five percent of total cancer research funding is spent on investigating metastases (the spread of cancer cells around the body) in Europe, yet metastatic disease is the direct or indirect cause of 90 percent of all cancer deaths, according to an editorial in the *European Journal of Cancer* (EJC).

**Table 1 – Examples of funding for metastasis research as a percentage of total cancer research funding.**

Organisation/country	Period	Cancer research funding	Metastasis research <sup>***</sup>	% Devoted to metastasis
Deutsche Krebshilfe (German Cancer Aid) <sup>a</sup>	2007	73,150,000 EUR	3,191,000 EUR	4.3
National Cancer Research Institute Partners, UK <sup>b</sup>	2002	£ 257,000,000	£ 74,000,000	2.9
National Cancer Research Institute Partners, UK <sup>b</sup>	2006	£ 391,000,000	£ 200,000,000	5.1
Oncosuisse, Swiss Cancer League and Foundation Cancer Research, Switzerland <sup>c</sup>	2006–2008	43,943,750 CHF	5,094,400 CHF	11.6
European Union (FP6) <sup>d</sup>	2002–2006	485,000,000 EUR	24,205,137 EUR	5.0
American Cancer Society, USA <sup>e</sup>	2009	485,000,000 \$	11,000,000 \$	2.3
Canadian Cancer Research, Alliance <sup>f</sup>	2006	390,200,000 CAD	25,200,000 CAD	6.5

\* Keywords: Metastasis; Dissemination; Invasion; Progression.

<sup>a</sup> Deutsche Krebshilfe Annual Report 2008, <<http://www.krebshilfe.de/ueber-uns0.html>>.

<sup>b</sup> NCRI web site: <<http://www.ncri.org.uk/default.asp?s-1&p-3&ss-2>>.

<sup>c</sup> ‘Cancer Research in Switzerland, a Publication of Oncosuisse, Swiss Cancer League and Foundation Cancer Research, Switzerland on their funded research projects 2006–2008’ Edition 2009; <<http://www.swisscancer.ch/research>>.

<sup>d</sup> Jungbluth S, Kelm O, van de Loo JW, Manoussaki E, Vidal M, Hallen M, Trias OQ. *Mol Oncol* 2007;1:14–18. <[http://www.lifecompetence.eu/index.php/kb\\_317/kb.html](http://www.lifecompetence.eu/index.php/kb_317/kb.html)>.

<sup>e</sup> ACS website: <[http://www.cancer.org/docroot/RES/RES\\_3.asp?sitearea=RES&level=1](http://www.cancer.org/docroot/RES/RES_3.asp?sitearea=RES&level=1)>.

<sup>f</sup> Cancer Research Investment in Canada 2006, report published by CCRA ([http://www.ccra-acrc.ca/default\\_en.htm](http://www.ccra-acrc.ca/default_en.htm)).

“Although there is considerable variation, the median spent on metastasis research is around **5%** of total cancer research funding. Is this sufficient?”

Jonathan Sleeman, Patricia S. Steeg, “[Cancer metastasis as a therapeutic target](#),” *European Journal of Cancer* 46 ( 2010 ) 1177–1180 (free full text)

# *Are metastases different from primary tumors?*

- Put another way, are mechanisms involved with tumorigenesis different from mechanisms involved with metastasis?
- We treat metastases like primary tumors, largely with the same tools, yet some treatments (anti-angiogenic drugs) may actually promote more disease!
- Different gene expression
  - Example: tumor suppressor genes
- Different organ microenvironments
  - Example: bisphosphonate interaction with bone homeostasis
- **“Understand(ing) the mechanism and process of metastasis (is) a pre-requisite for effective rational design of novel therapies.”** (Sleeman, Steeg, 2010)

# *The vision: Metastasis prevention*

- Could primary breast cancers be **cured** by treatments derived from an understanding of metastasis pathways and interactions with microenvironment?
- Could clinical trials be done to look at the potential of such treatments to **suppress** further metastatic outgrowth in patients in the early stages of MBC?
- Could distant metastatic disease be **stabilized** by such treatments, allowing for control as a truly chronic disease?



**National Breast Cancer Coalition**

The  
**Breast  
Cancer  
Deadline**

**2020**

“We will come together to look at preventing metastasis—  
making certain that no more lives are taken.”

Fran Visco, President  
National Breast Cancer  
Coalition

[breastcancerdeadline2020.org](http://breastcancerdeadline2020.org)