Breast cancer (radio)biology: hormonal treatments and aromatase-inhibitors

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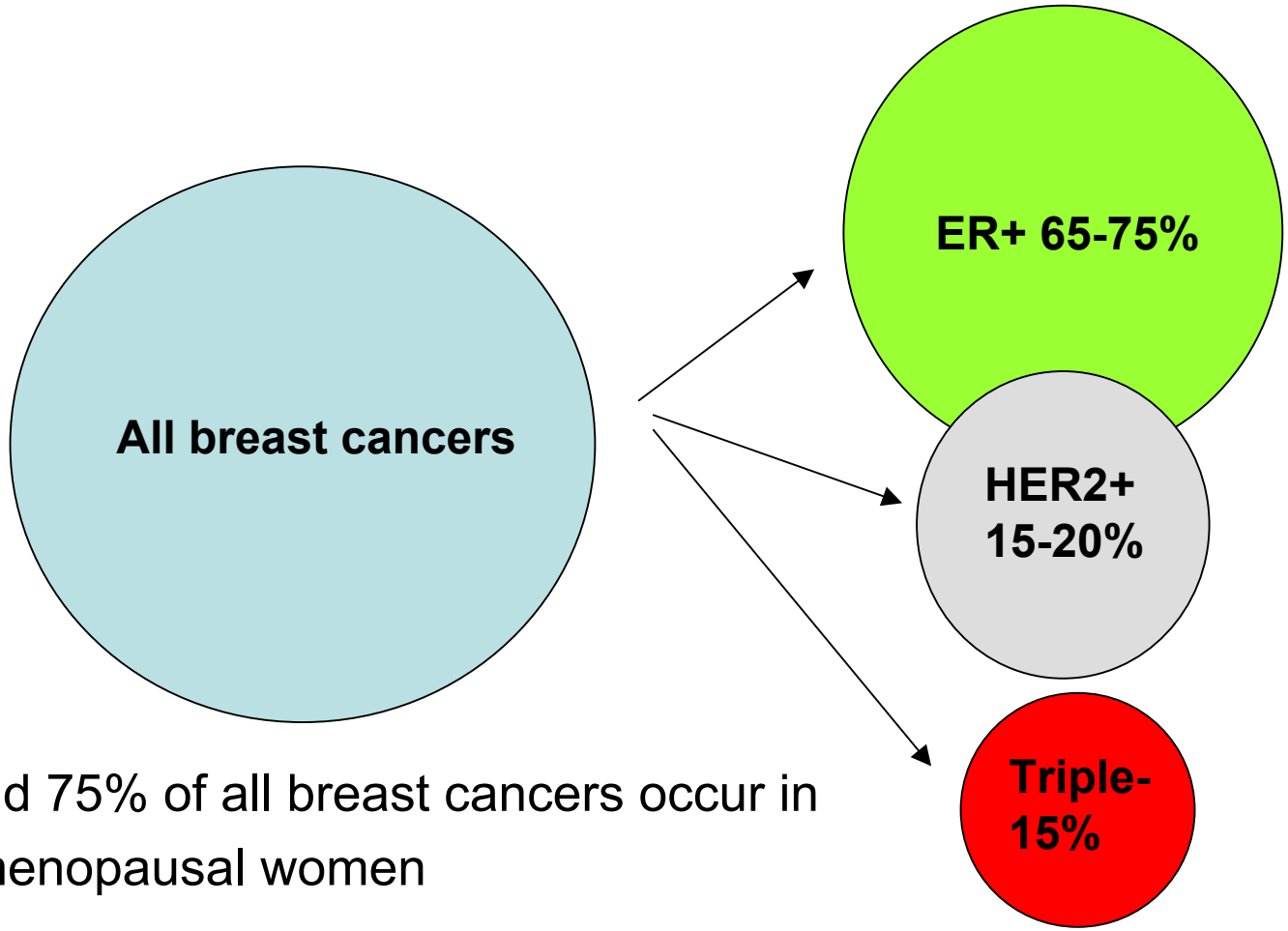
Clinical breast cancer subsets



- around 75% of all breast cancers occur in postmenopausal women

- of which around 80% are hormone receptor (ER) positive

Hormonal interventions in BC

Hormonal manipulation	Mechanism of hormonal effect	Eligible patients	Specific interventions
Ovarian suppression	Induces cessation of ovarian secretion of oestradiol	Premenopausal ER/PR-positive	Surgical ablation; ovarian irradiation; chronic ovarian stimulation using LHRH agonists (goserelin, leuprorelin) to induce desensitization
ER-binding drugs	Competitively inhibit binding of oestradiol to ER	All ER-positive	Tamoxifen, fulvestrant
Aromatase inhibitors	Blocks peripheral aromatization of androgens to oestrogens	Postmenopausal ER/PR-positive	Anastrozole, letrozole, exemestane
Adjuvant chemotherapy	Direct ovarian cytotoxicity leading to menses cessation (amenorrhoea)	Premenopausal Any ER status	Adjuvant protocols

10th St. Gallen Consensus Conference

Endocrine responsiveness categories

– Highly endocrine responsive:

the cells express steroid hormone receptors (diagnosed with proper immunohistological or biochemical method) and for which it is probable a response to endocrine therapy

– Incompletely endocrine responsive:

some expression of steroid receptors either quantitatively low or qualitatively insufficient to indicate a substantial chance for response

(<10% ER; no PgR, HER2 overexpression/amplification)

– Non responsive:

cells have no detectable expression of steroid receptors

Goldhirsch A. Ann. Oncol. 18:1133-44, 2007

10th St. Gallen Consensus Conference

	Highly endocrine responsive	Incompletely endocrine responsive	Endocrine non responsive
HER2 neg	ET	ET	CT
HER2 pos	CT + T + ET	CT + T + ET	CT + T

Goldhirsch A. Ann. Oncol. 18:1133-44, 2007

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The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial

Adjuvant Anastrozole

vs

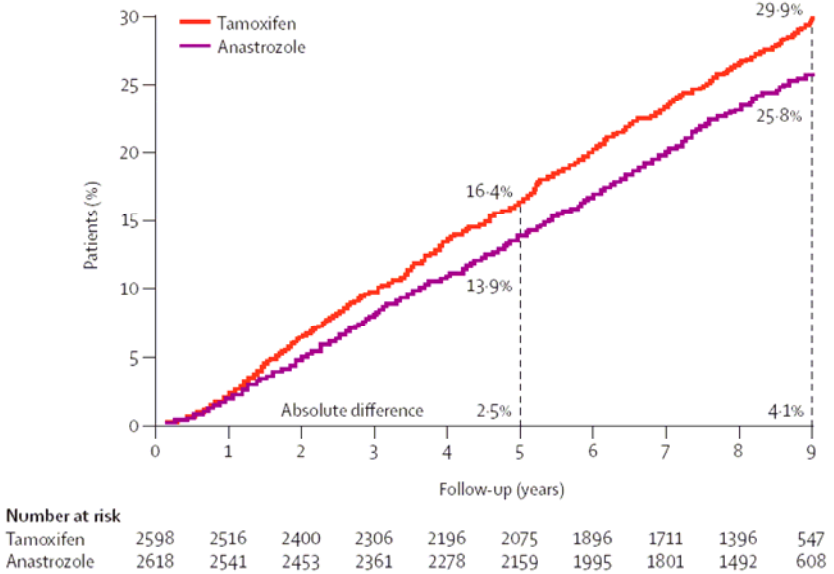
Tamoxifen

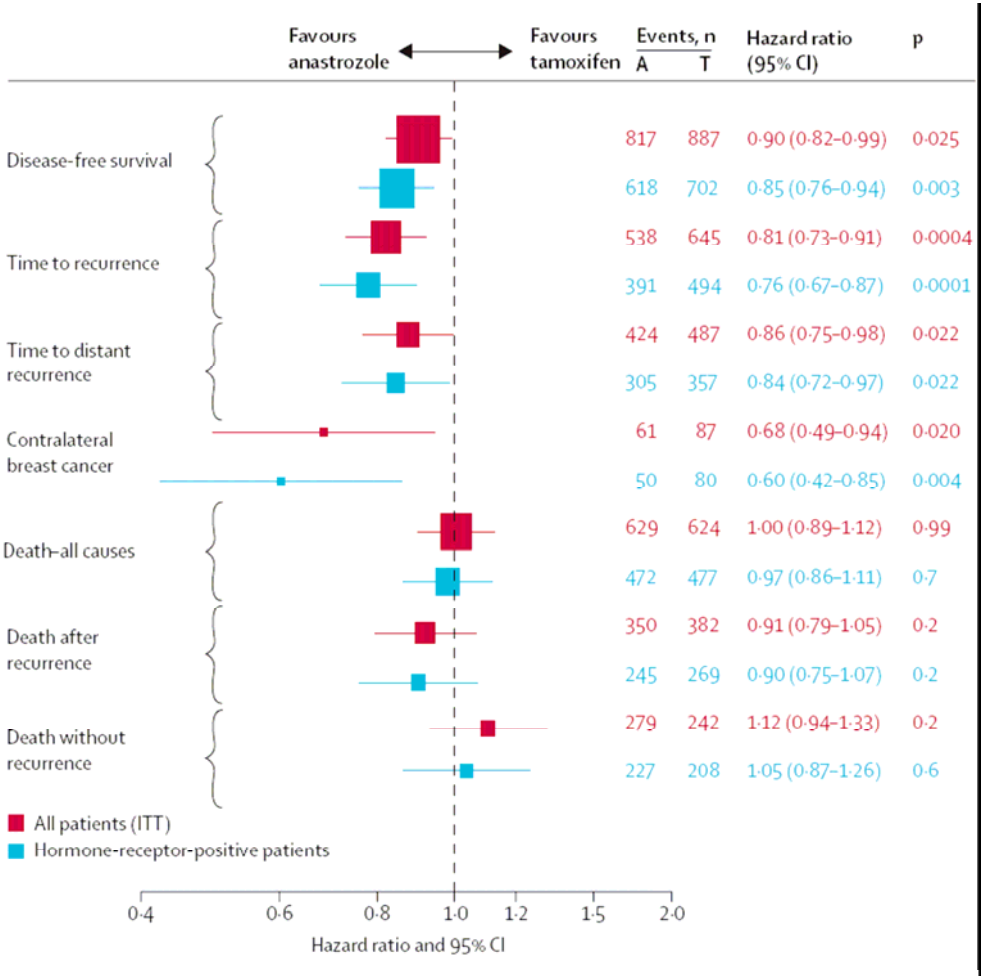
vs

Anastrozole + Tamoxifen

Superiority of AI vs TAM

(100-month analysis of the ATAC trial)





The ATAC Trialists' Group Lancet Oncol. 9:45-53, 2008

Effect of hormonal intervention in ER-poor (<10%) BC

- both LH-RH analogues and Aromatase Inhibitors have small but discrete benefit (5-10% response rate) also in ER-poor breast cancer

  - in the neoadjuvant setting
  - in the adjuvant setting
  - in the metastatic setting

Kaufmann M J Clin Oncol. 7:1113-19,1989

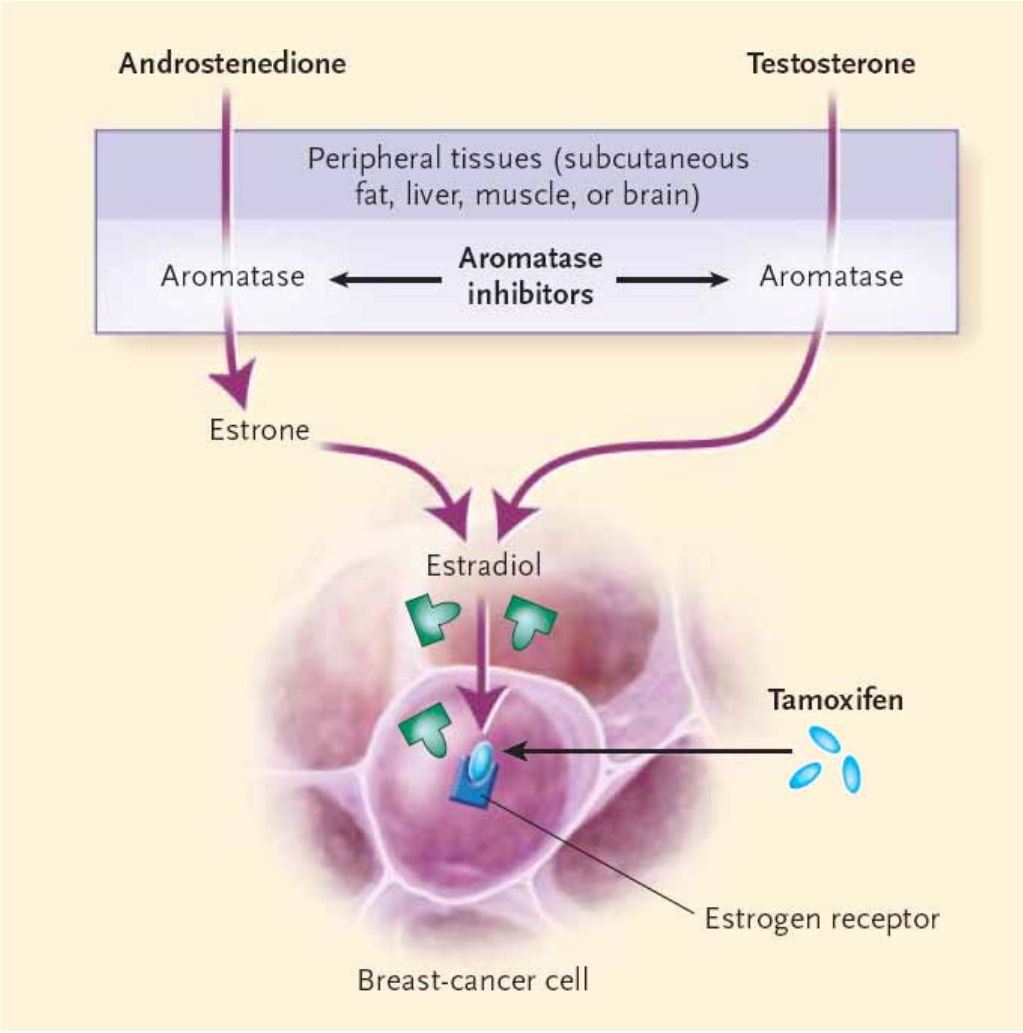
Moseson DL Cancer 41:797-802,1978

Klijn JD J Steroid Biochem 23:867-873,1985

Benefit of hormonal intervention in ER-poor breast cancer

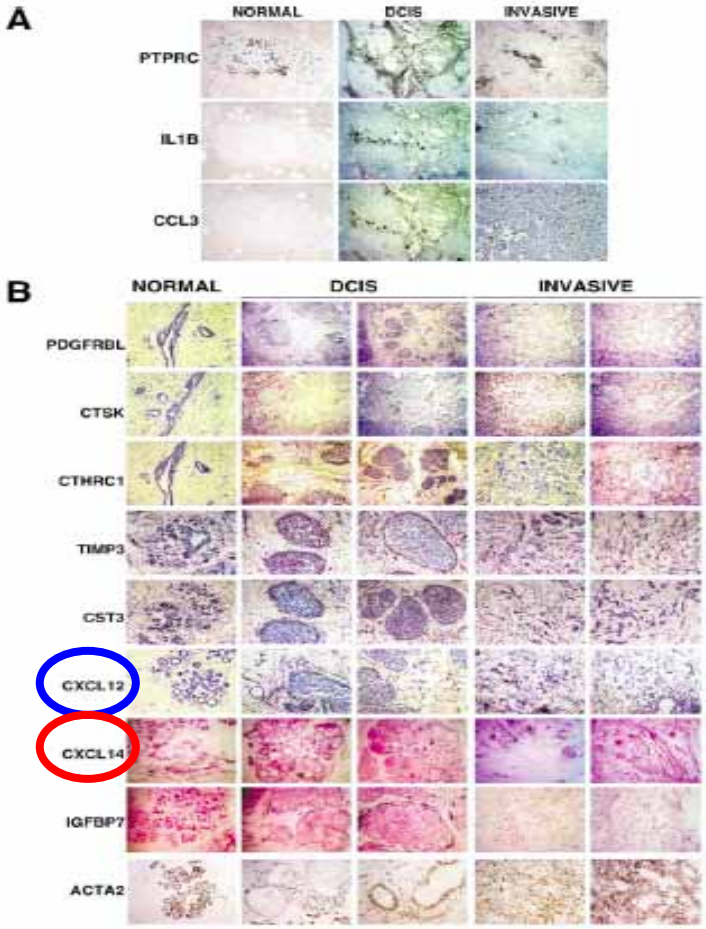
- not only ER-based
- but also tissue-based

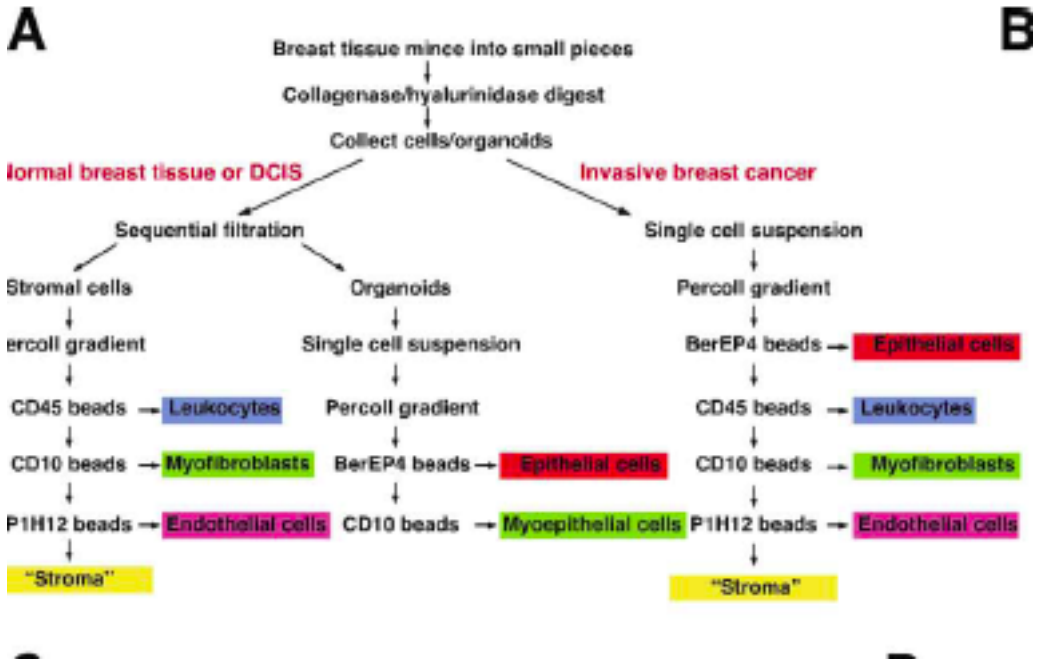
Aromatase expression in BC microenvironment



Smith IE NEJM 348:2431-2442,2003

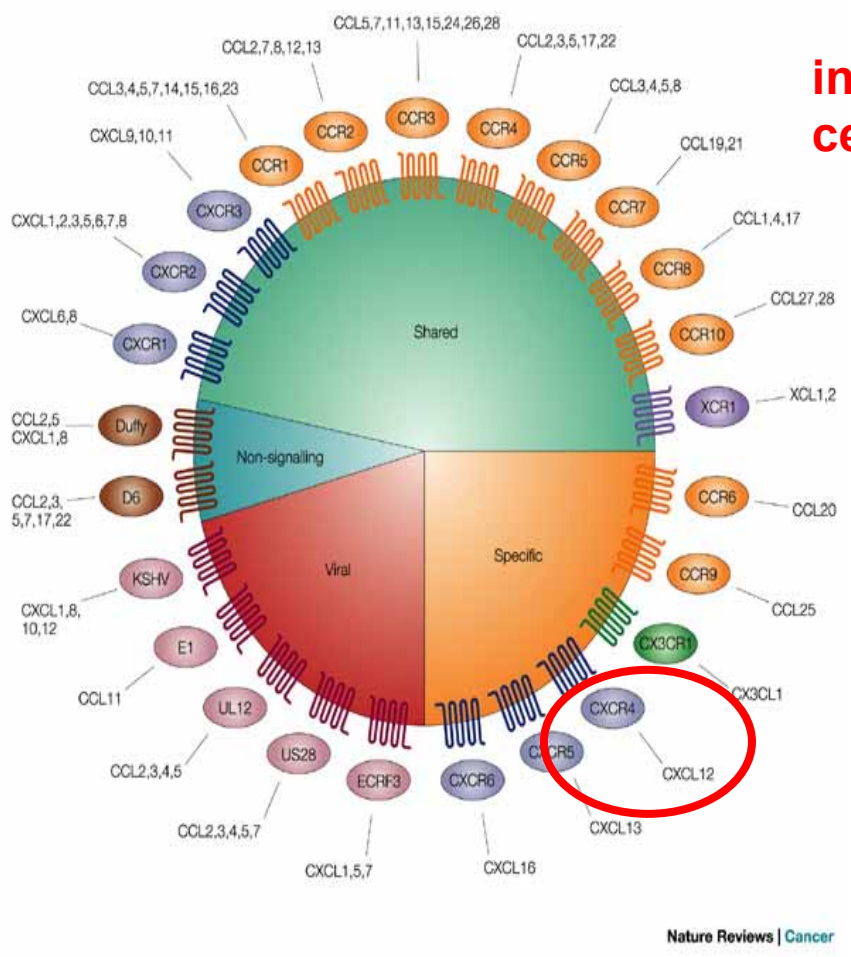
BC microenvironment





Allinen M et al. *Cancer Cell* 2004

Chemokines: chemoattractants cytokines



inducing chemotaxis of chemokine-responsive cells along chemical gradients

Chemokines are important in:

- **embryonal development**
- **organogenesis (brain, heart)**
- **immune response**
- **hematopoiesis**
- **tissue repair**

Balkwill, F et al *Nat Rev Cancer,* 2004

Chemokines in breast cancer: the CXCR4/SDF1 axis

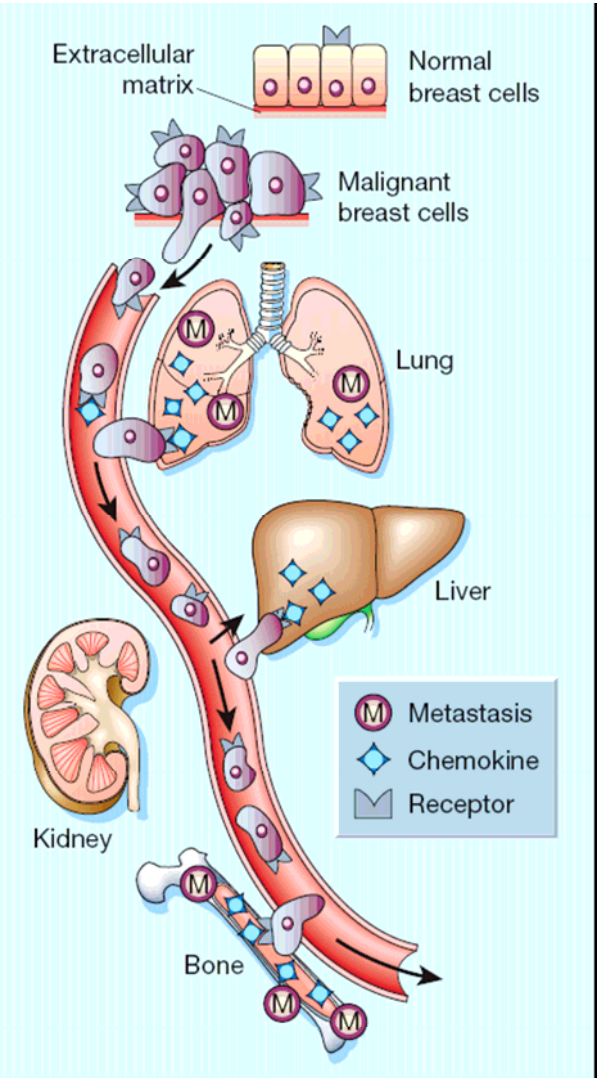
- The metastatization process is organ-specific and chemokine-mediated

- SDF1 transactivates HER2

- HER2 upregulates CXCR4

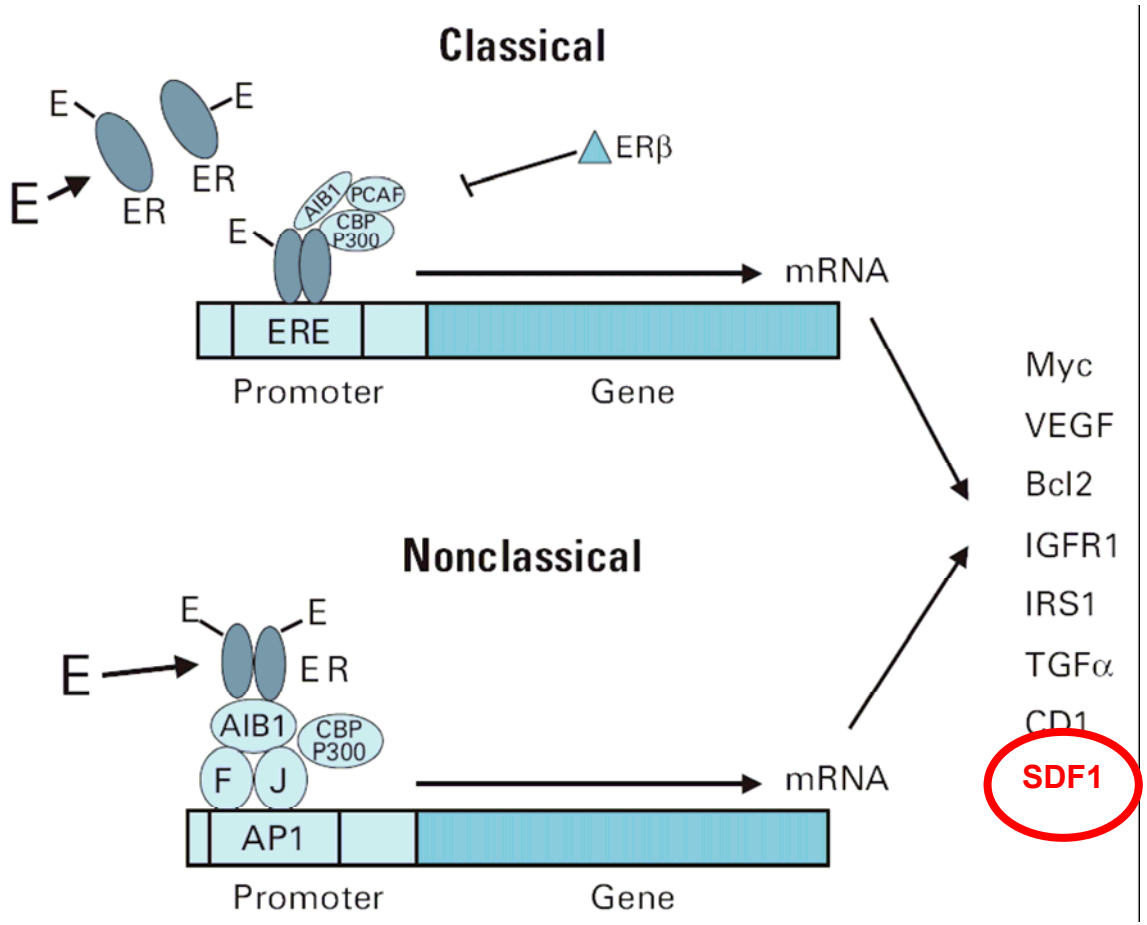
- VEGF induces CXCR4

- CXCR4 correlates with LN involvement and poor prognosis



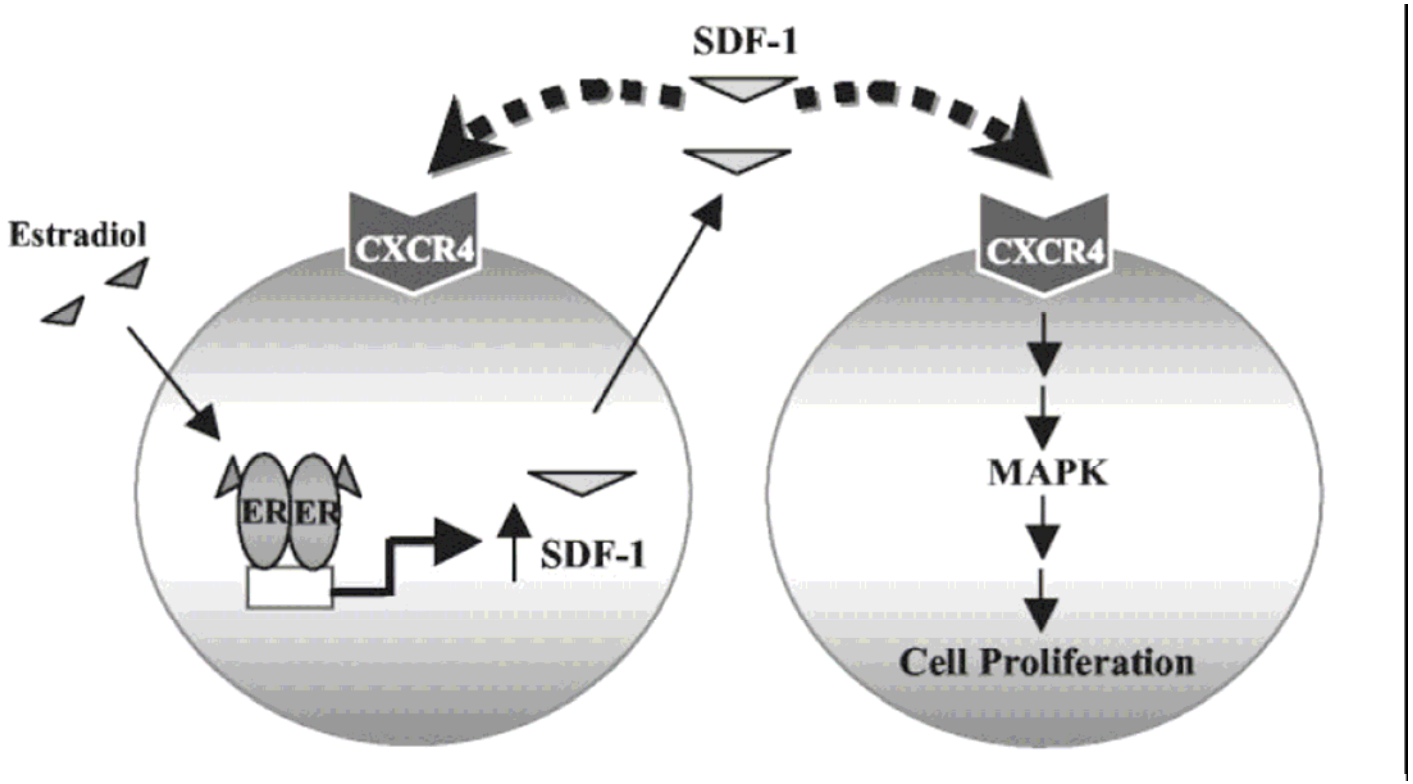
Muller et al. Nature 2001

Estrogen receptor biology



Osborne CK et al *J Clin Oncol*, 2005

Estradiol induces SDF1 and CXCR4-rich microenvironment



Hall JM et al *Molecular Endocrin,* 2003

Aim of the study

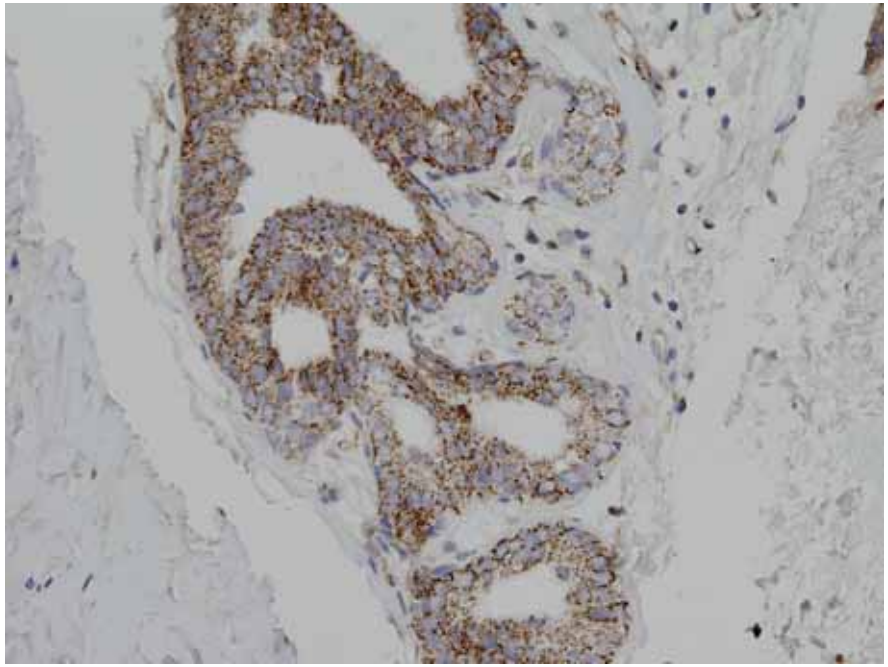
- to characterize early breast cancer (T1 N0 M0) in terms of:

  - SDF1 expression
  - CXCR4 expression
  - levels of circulating estrogens (E1 and E2)

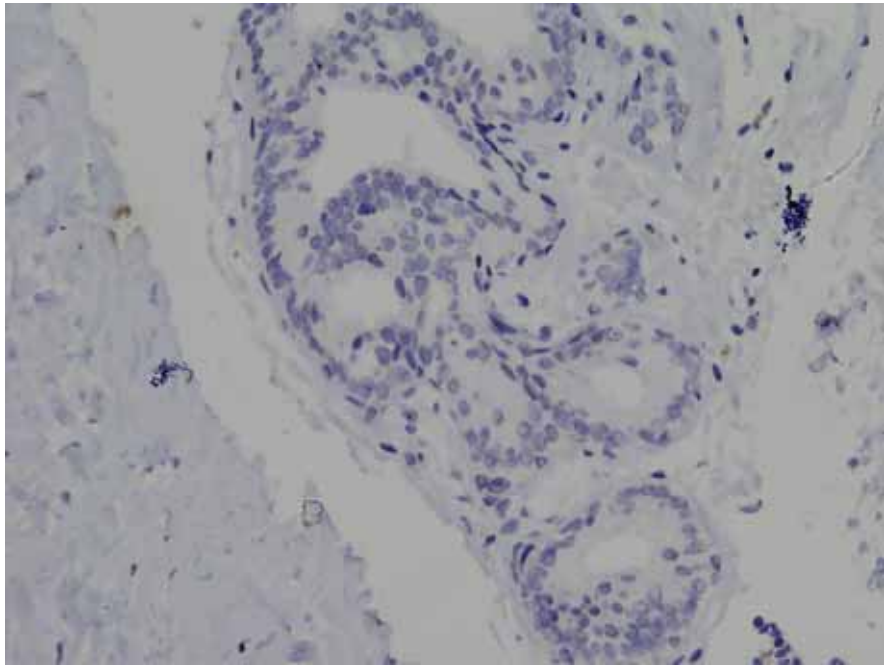
Results I

- CXCR4: nuclear and cytoplasmic staining in 15/71 (21%) pts

CXCR4 2+ ABC



CXCR4 1+ Envision



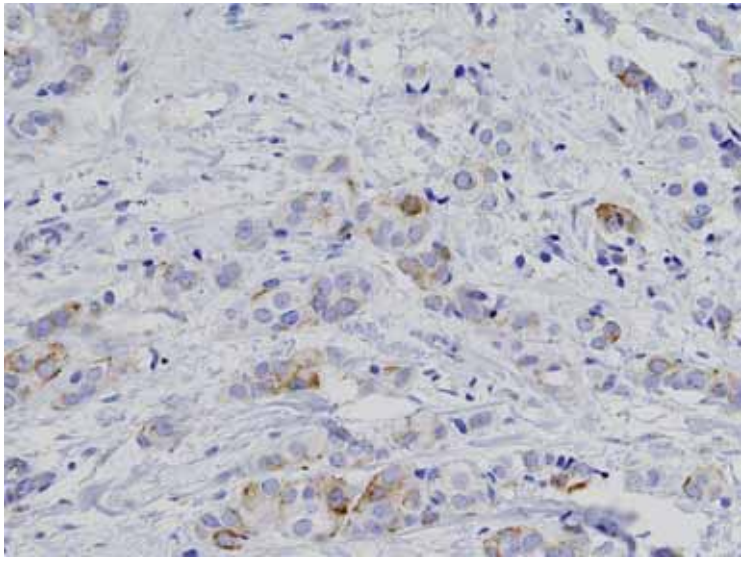
Grisanti S et al. *ASCO Meeting* 2007

Results II

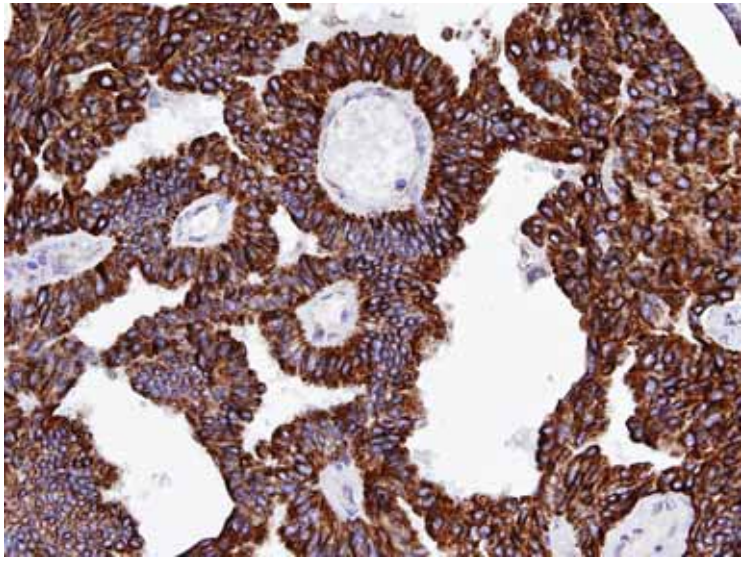
- SDF-1: strong membrane and peritumoral staining in:

3/71 (4%)	1+
20/71 (28%)	2+
48/71 (68%)	3+

SDF-1 1+



SDF-1 3+



Grisanti S et al. *ASCO Meeting* 2007

Results III

- after a median follow-up of 75 months 3/71 pts relapsed and died (both CXCR4+ and SDF1+)

- SDF1 was highly expressed in all ER-poor breast cancers

- no statistical significant correlations were found between CXCR4/SDF1 expression and either clinico-pathological variables or E1/E2 serum levels

Conclusions

• CXCR4 is expressed in about 20% of early breast cancers (T1) with no lymphnodal involvement (N0)

• SDF-1 is highly expressed (SDF1 3+) in 70% of all cases and in 13% of ER-poor cases

• the benefit from hormonal therapy with aromatase inhibitors is likely to be not only ER-based but also tissue-based

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