Tumori ormono-dipendenti:
- Tumori della ghiandola mammaria
- Tumori della prostata

Genetic abnormalities common to breast and prostate cancer:
- Androgen receptor alterations
- BRCA1 and BRCA2 alterations
BRCA 1, BRCA 2 and DNA damage signaling

Germline mutations in BRCA1 and BRCA2 account for 50% of the families susceptible to breast cancer.

Germline mutations in BRCA1 and BRCA2 increase the risk of prostate cancer.

Gli steroidi sessuali ed i loro recettori:
- influenzano la proliferazione e la crescita dei tessuti bersaglio?
- inducono la cancerogenesi dei tessuti bersaglio?
- influenzano indirettamente l’azione di fattori di crescita?

Gli steroidi sessuali, estrogeni, progestinici ed androgeni, controllano lo sviluppo e la proliferazione di cellule di ghiandola mammaria e prostata.
Recettori steroidei: domini strutturali e funzionali

Meccanismo d'azione degli steroidi

Esempi di azioni trascrizionali degli steroidi sessuali

Estradiolo
- Induzione dell'espressione di PR

Androgeni
- Espressione di PSA

La presenza del recettore del progesterone in un tumore mammario umano indica, infatti, che ER è trascrizionalmente attivo in quel tumore.
L’antigene prostatico specifico (PSA) è considerato un marcatore in tumori prostatici umani

Esempi di attività non trascrizionale degli steroidi sessuali

Gli estrogeni inducono la traslocazione rapida di Erk-2 nel nucleo di cellule di carcinoma mammario umano

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<th>non trattate</th>
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Gli androgeni inducono modificazioni citoscheletriche in cellule di carcinoma prostatico

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<th>non trattate</th>
<th>androgeni</th>
<th>androgeni + EHT</th>
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scaricato da www.sunhope.it
Breast cancer is a common cancer, especially for women who started their periods early (before age 12) or reached menopause late (after age 55).

Breast cancer is more common among:
- women with no children
- women who delayed pregnancy until after age 30
- women who have used combination hormone therapy (estrogen plus progestin) for more than five years

What causes breast cancer?
Your genes and your hormones play a role in breast cancer but we don’t know exactly how. We know that estrogen (the major female hormone) and progestin (a synthetic form of progesterone, another female hormone) can cause breast tissue to grow faster than normal.
- Cancer usually appears in tissue that grows fast.

Overexpression of ER alpha is a prognostic and predictive factor in breast cancer patients

A large subset of breast cancers shows a single gene amplification of the ER alpha gene.
Typical treatments of breast cancers include surgery, radiation therapy, chemotherapy, hormone therapy, or a combination of these.

Hormone therapy works by blocking the effect of female hormones on the cancer. The most commonly used therapy is a female hormone blocker called tamoxifen. A newer therapy uses a pill (i.e., anastrozole, letrozole or exemestane) to prevent the body from making female hormones.
Possibili fenotipi di tumori mammari umani:

- ER+ / PR+
- ER+ / PR-
- ER- / PR+
- ER- / PR-

The role of AR in breast cancer

- AR is frequently expressed in metastatic breast cancers (Schippinger et al., 2006)
- Expression of functional AR defines a subset of ER/PR negative breast cancers (Doane et al., 2006)

Il 30% circa dei tumori mammari umani è caratterizzato da iper-espressione di EGF-R e neu/Erb B2
Association of Src with steroid receptors in human breast cancer cells

Src inactive conformation → Src active conformation

About 80 out of 100 (80%) of men who reach age 80 have prostate cancer. In most men, prostate cancer grows very slowly, but aggressive forms of the disease can spread quickly to other parts of the body, including bone.

- Androgen receptor is hallmark of prostate cancers
- Its modulation by chemical or surgical castration and antiandrogen treatment is used in prostate cancer therapy
PSA is a 30KDa serine protease
- serum PSA increases in patients with prostate cancer
- changes in serum PSA are associated with cancer metastasis, recurrence, response to treatment and survival

PSA is up-regulated by androgens, progestins and glucocorticoids in breast cancer cells

What about its physiological role in the breast?

ADT (androgen deprivation therapy) is mainly used to treat prostate cancer that has spread outside the prostate. It can cause a rapid loss of calcium and other minerals from your bones, making them weak and more likely to break (fracture).

MOST PROSTATE TUMORS REGROW AFTER 12-18 MONTHS OF ANDROGEN DEPRIVATION THERAPY
a) androgen deprivation strategies might incompletely suppress androgen levels
b) AR mutations or amplification
c) changes in AR and AR coregulator interactions
d) growth factor/kinase signaling pathways
Prostatic hormonal carcinogenesis is mediated by in situ estrogen production.

- The estradiol levels increase during aging in men and dogs.
- The incidence of prostate cancers is elevated in African Americans that have high levels of estradiol and androgens.
- Estradiol in combination with androgens induces prostate cancer in humans.

Prostate and prostate cancer cells express AR and ER and are targets of androgen and estradiol.

Modulation of ER with the antiestrogen Toremifene decreases early prostate cancer progression in humans (Price et al, J. Urol. 2006).
Src family kinases are overexpressed in prostate cancer and Src-activated pathways contribute to tumor progression.

The Src inhibitor, PP2, prevents the androgen- or estradiol-induced prostate cancer cell proliferation.

To date, 4 Src inhibitors, including Dasatinib, have reached clinical trials in patients with prostate cancer.
STROMAL AR PROMOTES PROSTATE TUMOR PROLIFERATION AND STIMULATES CANCER PROGRESSION

Niu et al., P.N.A.S 2008
Niu et al.,P.N.A.S 2008

Cytoplasmic filamin A correlates with invasiveness, metastasis and hormone-independence of human prostate cancers

(Bedolla et al., Clin. Cancer Res. 2009)

KEY POINTS

- ER may substitute for AR in activating signaling molecules that promote prostate cancer growth.
- AR may substitute for ER in activating signaling molecules that promote breast cancer growth.
- Steroid receptor interaction with signaling effectors or scaffolds may represent a novel therapeutic target in breast and prostate cancer.
Il 70% circa dei tumori prostatici umani metastatizza alle ossa


1) A rich venous plexus surrounds the prostate and connects to the venous drainage of the spine. Lumbosacral spinal metastases are common in advanced prostate cancer.

2) Prostate cancer cells express high levels of bone morphogenetic proteins (BMPs) and TGF-β. They become osteotropic.

3) The prostate cancer cells express high levels of integrin αvβ3.

4) Prostate cancer cells secrete high levels of vascular endothelial growth factor (VEGF) that promotes angiogenesis and activates the osteoblasts.

5) Cytokines and non-collagen proteins (BMPs, TGF-β, osteonectin, osteopontin, osteocalcin, and bone sialoprotein) expressed in the bone matrix may attract prostate cancer cells.

General mechanism of tumor cell metastasis to bone. Multiple steps are required for prostate cancer to metastasize to bone.
In cancer patients with bone metastases, tumor cells disrupt the normal process of bone resorption and bone formation, leading to increased bone destruction and/or aberrant bone formation.

Pathophysiology of osteolytic/osteoblastic metastatic bone disease in prostate cancer.

Levels of biochemical markers of bone metabolism in patients with osteolytic, osteoblastic, and mixed bone lesions.

- Bone is a common site of metastasis for prostate cancer
- Targeting bone resorption reduces osteolytic bone resorption and improves disease-free survival
- All steps in the metastatic process and the interaction with host cells are valid therapeutic targets for the treatment of bone metastasis and tumor progression