# Breast Cancer & Physical Activity

Allen Tran
Exercise and Disease
Fall 2010

# The Breast

- The Breast is made up of:
  - Milk Ducts
  - Lobes
    - Supplies the ducts with milk
- Two main types of breast cancer
  - Ductal carcinoma
  - Lobular carcinoma
  - Inflammatory Breast Cancer


National Cancer Institute

Why is this important?

# Statistics

- 2nd most common cancer in women (worldwide & U.S.)
- 1 in 8 (12%) chance of developing invasive breast cancer some time in a woman's life
- 2nd leading cause of cancer death in women (1st=lung cancer)
  - 1 in 35 chance of BC responsible for woman's death
- Currently there are over 2.5 million breast cancer survivors in U.S.
- *Males: <1% of all BC cases, usually found in men 60-70 y.o.*

American Cancer Society

# Risk Factors

- Older age.
- Menstruating at an early age.
- Later menopause.
- Older age at first birth or never having given birth.
- A personal history of breast cancer or benign (noncancer) breast disease.
- A mother or sister with breast cancer.
- Previous high-dose exposure radiation to the breast/chest.
- Breast tissue that is dense on a mammogram.
- Taking hormones such as estrogen and progesterone.
- Caucasian ethnicity.

National Cancer Institute

# Genetic Factors: BRCA genes

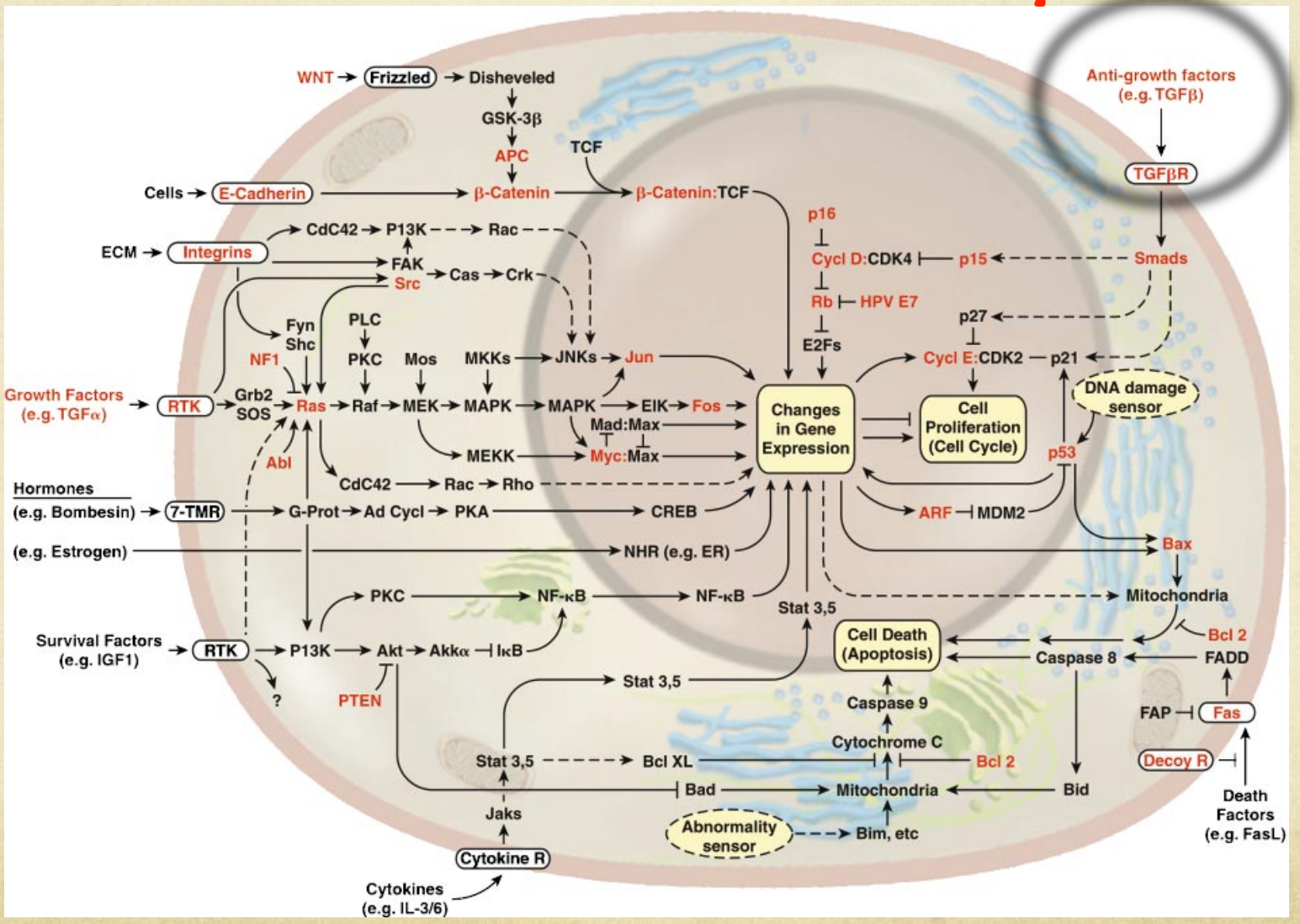



Figure 2. The Emergent Integrated Circuit of the Cell

Hanahan and Weinberg, 2000

# Genetic Factors: BRCA genes

- BRCA1 and BRCA2 help prevent cancer by making proteins that help keep the cells from growing abnormally
- An inherited mutated copy of either gene from a parent

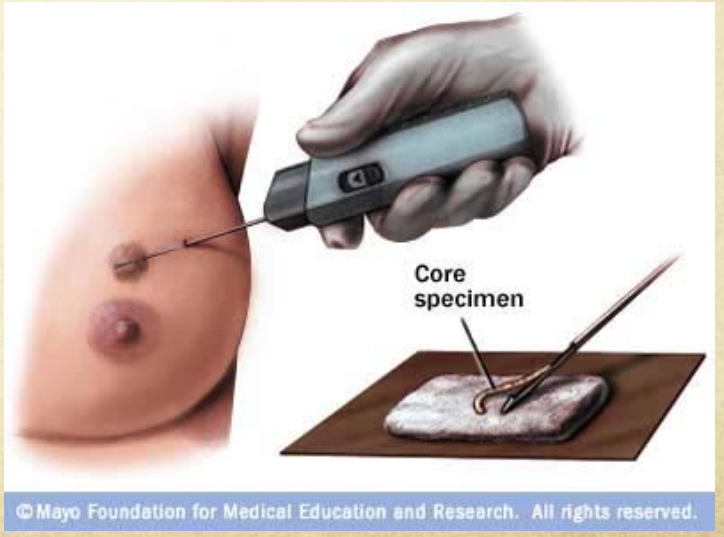
→ high risk of developing breast cancer during lifetime (up to 80%).

National Cancer Institute

# Detecting/Diagnosing Breast Cancer

- Self-Exam
- Mammogram (X-ray of the breast)

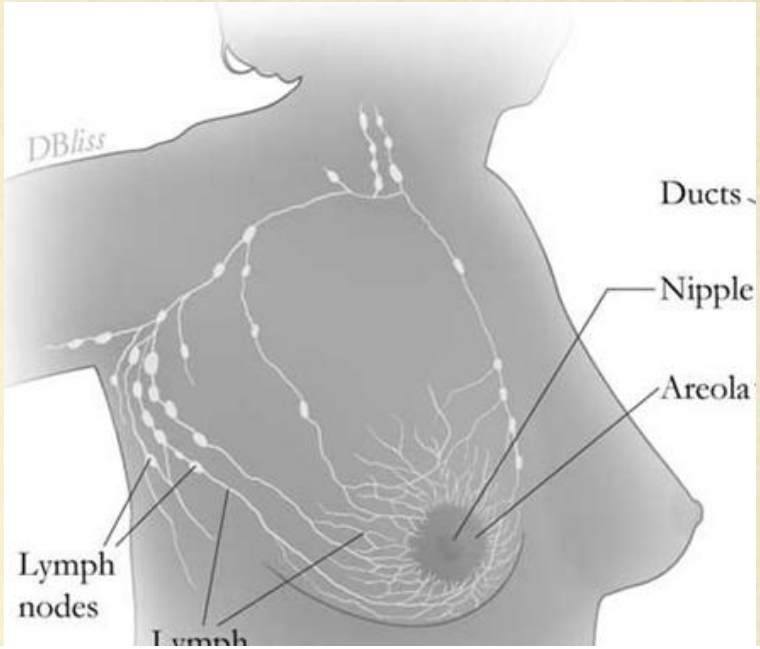
- MRI
- Biopsy
  - Removal of entire lump, part of lump, or sample with needle
  - Testing for cancer
    - <u>Estrogen & Progesterone receptors</u>
      - Receptor +, Receptor -
    - HER2 growth factor




National Cancer Institute

# Staging

- Stage 0- **In Situ**
- Stage I - <2cm, lymph nodes negative
- Stage II
  - <2 cm, nodes –
  - 2-5 cm, nodes + or –
  - >5cm, nodes –

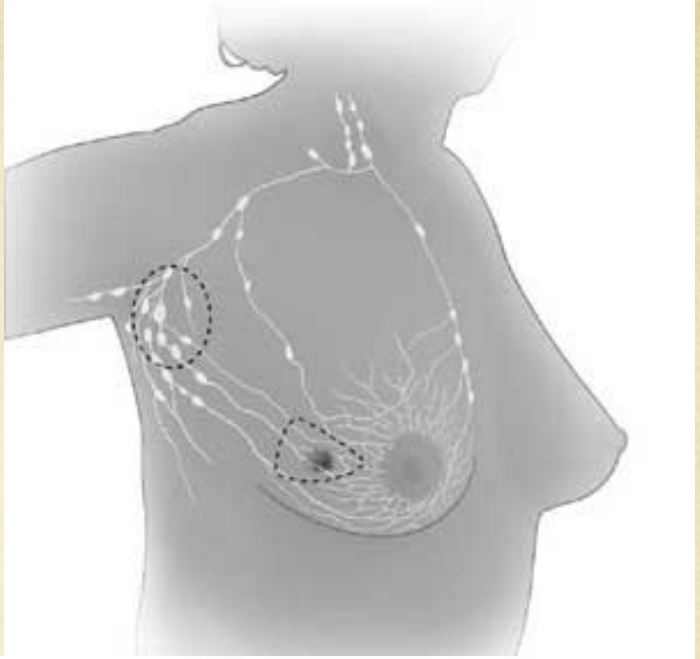


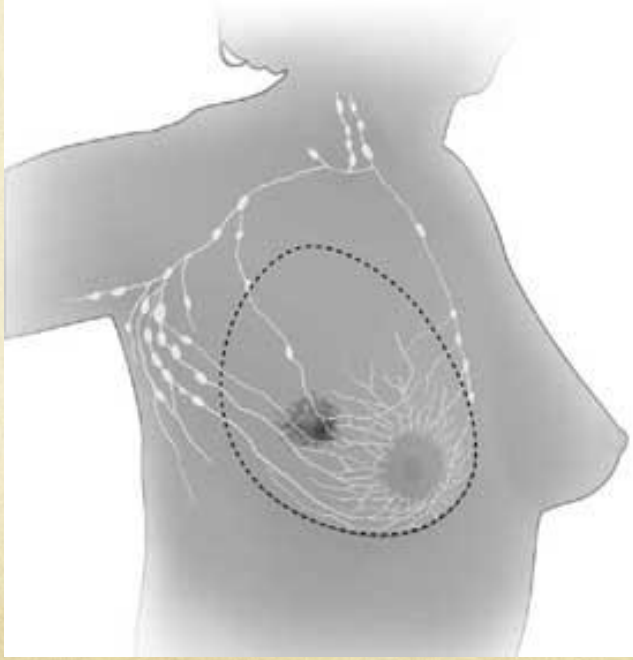

# Treatment

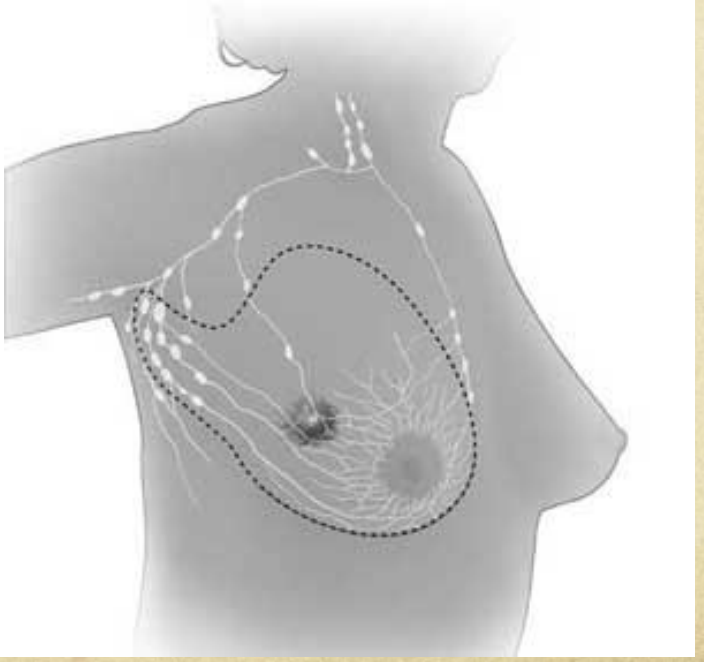
- Five types:
  - Surgery
  - Radiation Therapy
  - Chemotherapy
  - Hormone Therapy
  - Target Therapy

# Treatment

- Surgery
  - Lumpectomy
  - Mastectomy
    - Reconstruction







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# Treatment

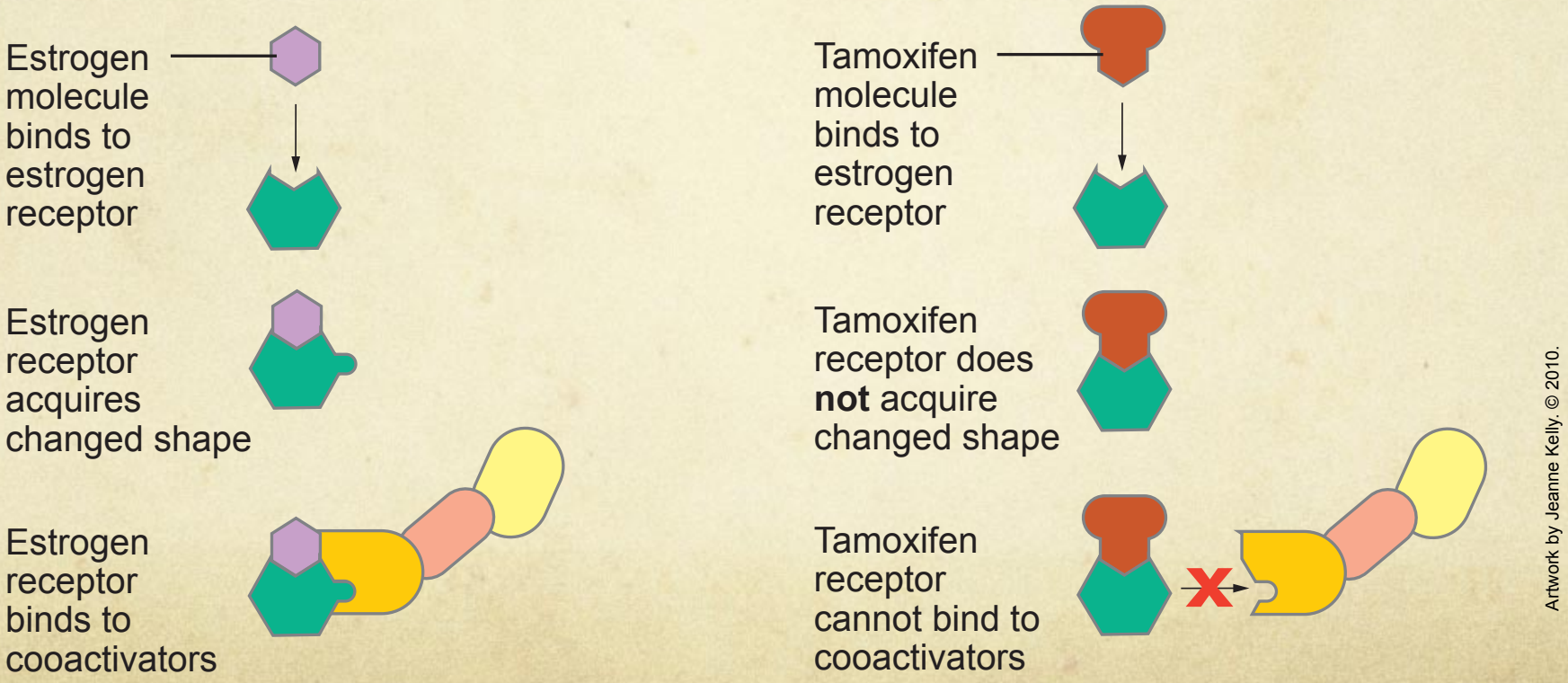
- Radiation Therapy
  - Kills cancer cells or prevents further growth

- Chemotherapy
  - Drugs taken by mouth or through IV to kill cancer cells or prevent further growth
  - Systemic chemotherapy

National Cancer Institute

# Treatment

- Hormone Therapy- <u>specific for receptor + cancer</u>
  - Tamoxifen
  - Aromatase Inhibitors



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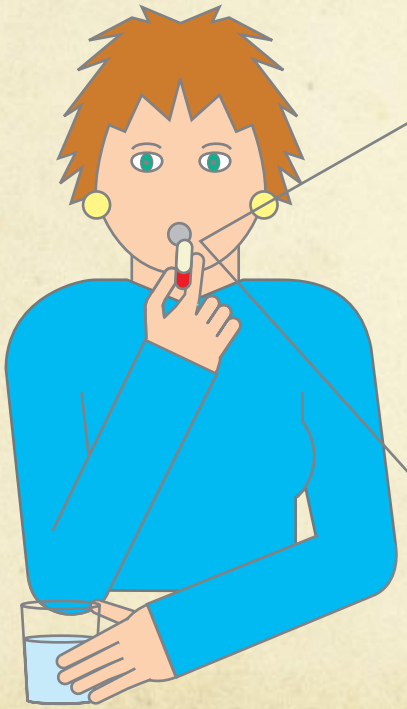

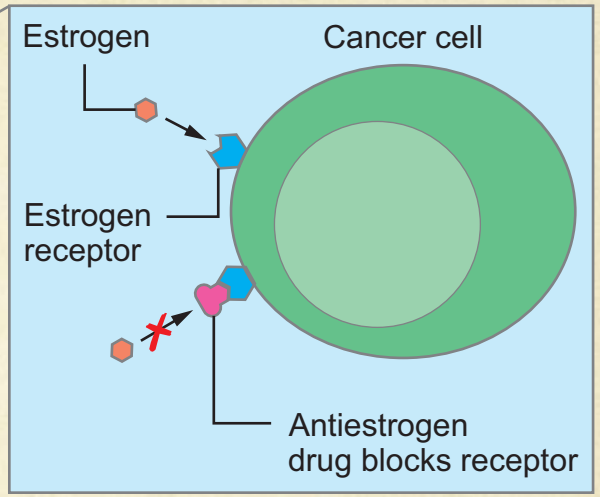


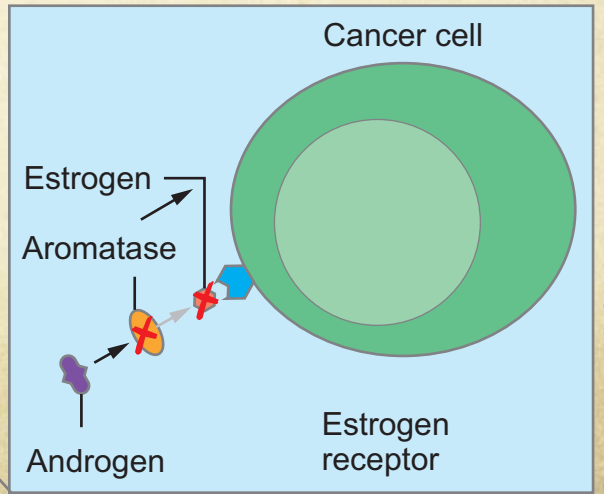


Artwork by Jeanne Kelly. © 2010.

National Cancer Institute

# Treatment

- Targeted Therapy
  - Monoclonal antibody therapy (HER2 protein)

# What is the role of physical activity in breast cancer?

# Proposed mechanisms

- reduction in circulating levels of and cumulative exposure to sex steroid hormones
- changes to insulin-related factors and adipocytokines
- modulation of inflammation and the immune system
- hormonal and cellular metabolism pathways

Friedenreich and Cust, 2010

# Proposed mechanisms

- reduction in circulating levels of and cumulative exposure to sex steroid hormones
  - Breast cancer is related with lifetime exposure to endogenous sex hormones
  - Reduced adipose tissue may have a stronger effect on postmenopausal women
    - Non-active ovaries
    - Conversion of androgens to estrogens in adipose
- changes to insulin-related factors and adipocytokines
- modulation of inflammation and the immune system
- hormonal and cellular metabolism pathways

Friedenreich and Cust, 2010

# Proposed mechanisms

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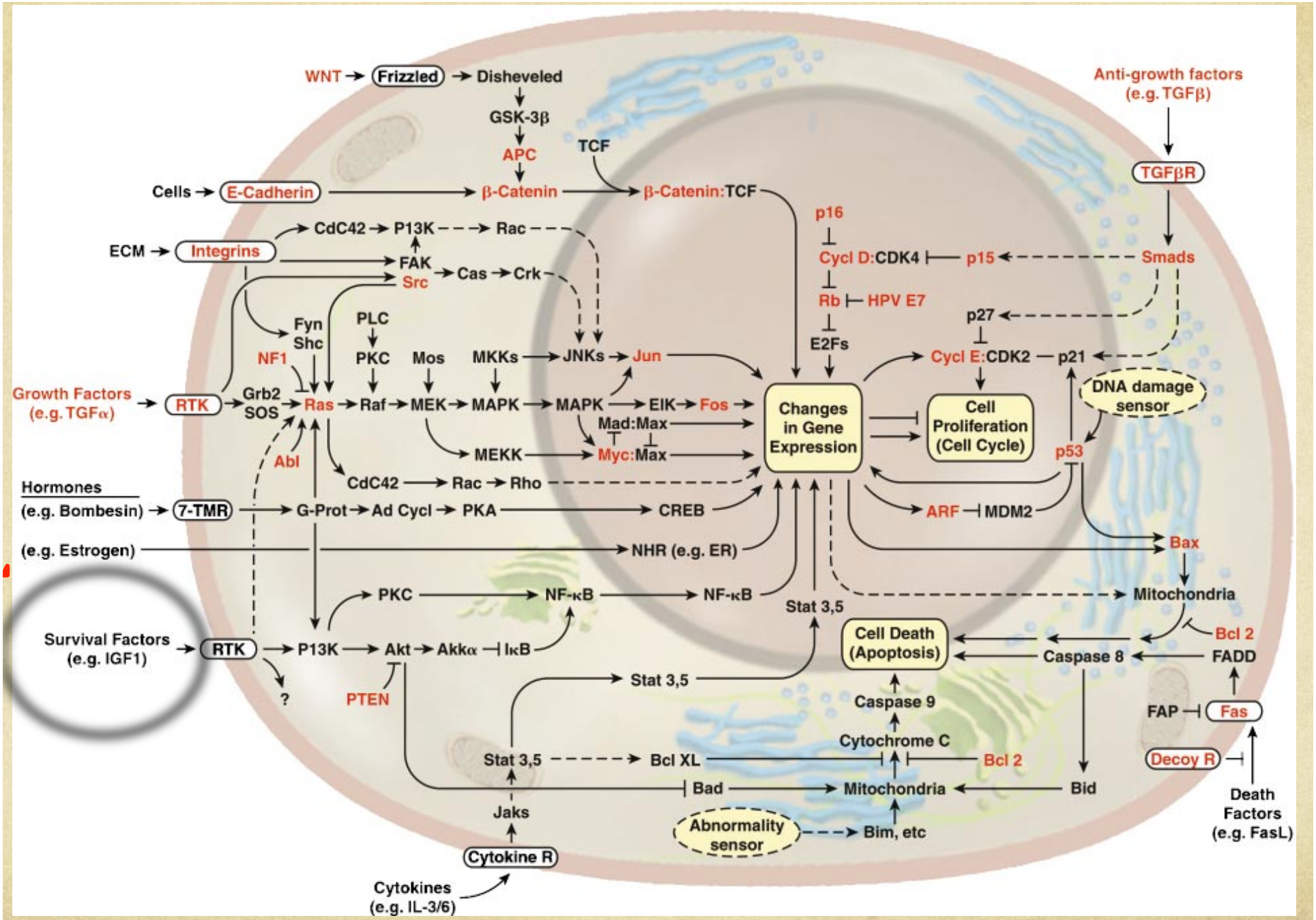


Figure 2. The Emergent Integrated Circuit of the Cell

Hanahan and Weinberg, 2000

# Proposed mechanisms

- reduction in circulating levels of and cumulative exposure to sex steroid hormones
- changes to insulin-related factors and adipocytokines
  - Physical activity is associated with:
    - Improved insulin sensitivity
    - Increased levels of *globulin* (binds to/deactivates sex hormones)
    - Increased levels of IGF-*binding protein*
- modulation of inflammation and the immune system
- hormonal and cellular metabolism pathways

Friedenreich and Cust, 2010

# Proposed mechanisms

- reduction in circulating levels of and cumulative exposure to sex steroid hormones
- changes to insulin-related factors and adipocytokines
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Friedenreich and Cust, 2010

# Proposed mechanisms

- reduction in circulating levels of and cumulative exposure to sex steroid hormones
- changes to insulin-related factors and adipocytokines
- modulation of inflammation and the immune system
- hormonal and cellular metabolism pathways
  - Activating several pathways related to breast cancer development

Friedenreich and Cust, 2010

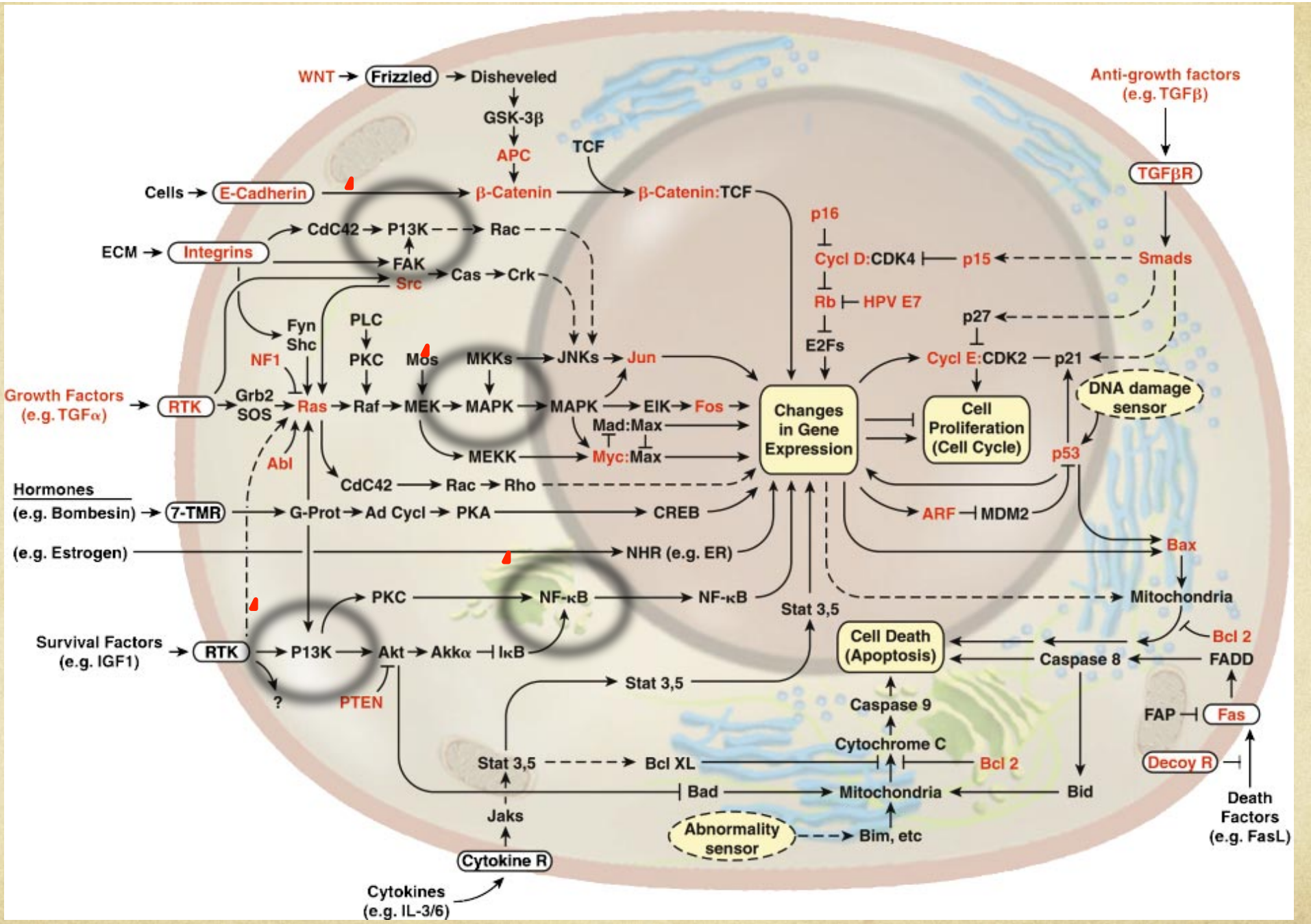


Figure 2. The Emergent Integrated Circuit of the Cell

Hanahan and Weinberg, 2000

# What is the role of PA?

Decrease risk of acquiring breast cancer

CANCER

Extend survival and prevent reoccurence


Improve quality of life

# Effects of PA

1. Reduce the risk of acquiring cancer
2. Extend survival following treatment
3. Improve quality of life

# Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects

C M Friedenreich,[1] A E Cust[2]

- Review of the epidemiological literature on PA and risk of breast cancer
- 34 case-control studies
- 28 cohort studies

Friedenreich and Cust, 2008

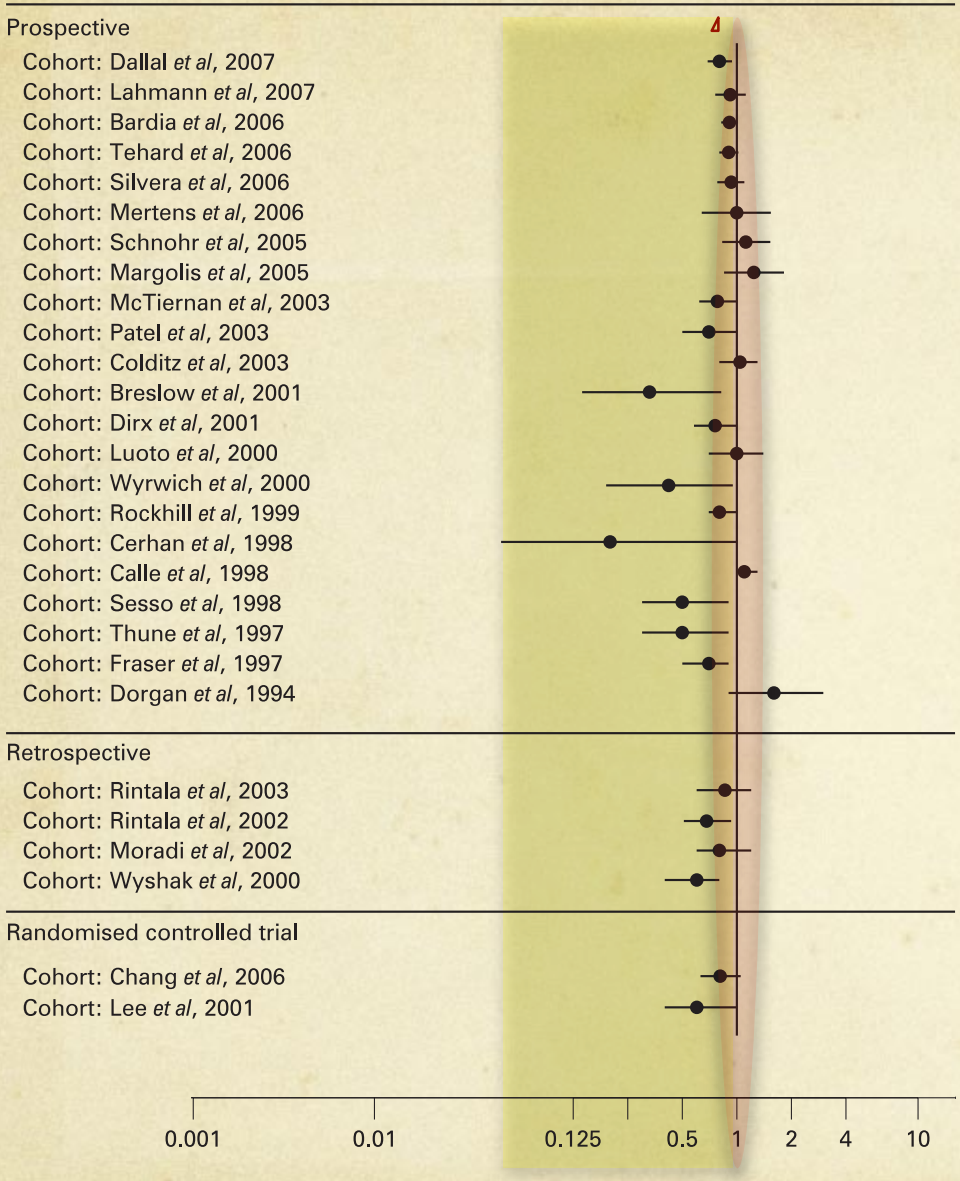


**Figure 1** Cohort studies of physical activity and breast cancer risk.

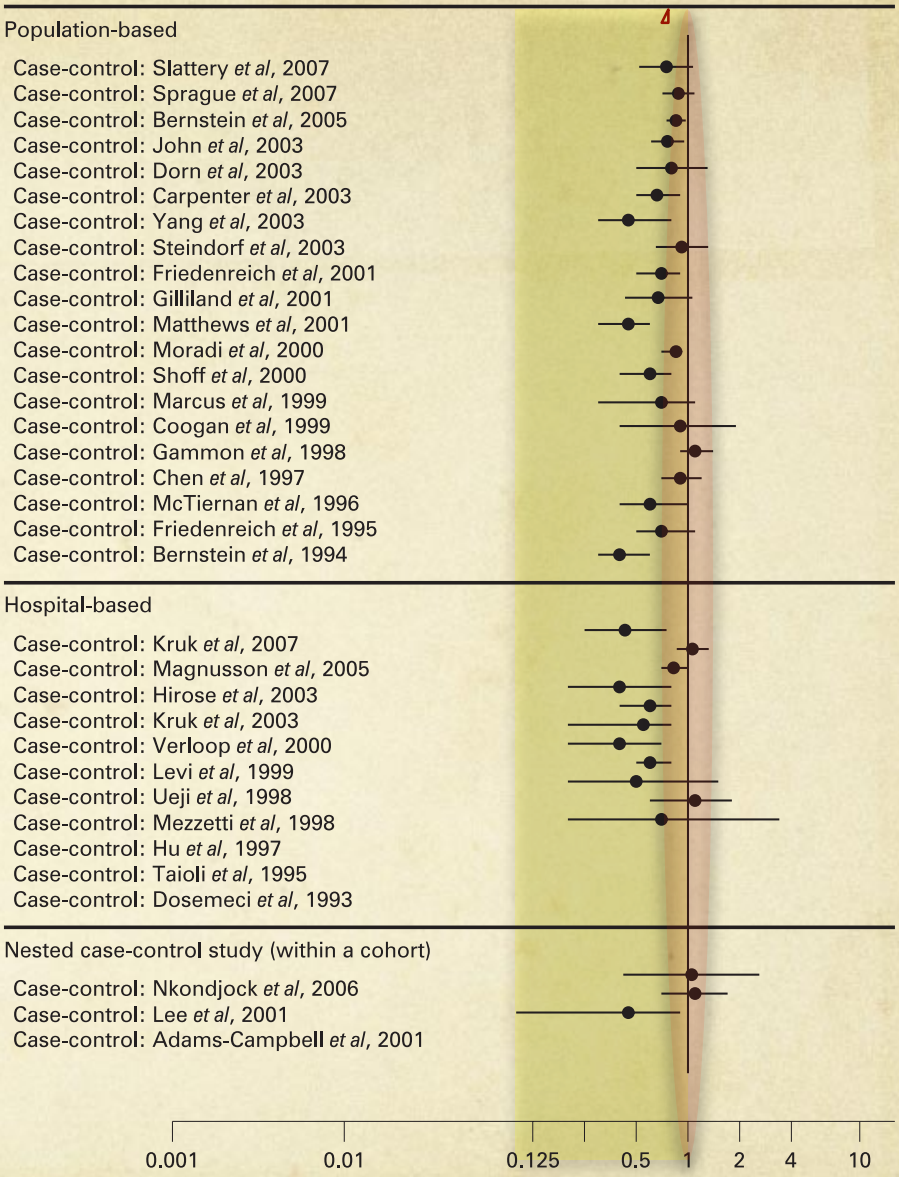


**Figure 2** Case-control studies of physical activity and breast cancer risk.

Friedenreich and Cust, 2008

# Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects

C M Friedenreich,[1] A E Cust[2]

- Evidence of a risk reduction associated with PA was found in 47 (76%) of 62 total studies
  - Average risk decrease: 25-30%
- Stronger decreases in risk for:
  - Recreational activity
  - Lifetime or later life activity
  - Vigorous activity
    - However "both moderate and vigorous intensity activity conferred a nearly equal benefit for a decrease in breast cancer risk" (22% vs 26%)
  - Among postmenopausal women
  - Those with hormone receptor **negative** tumors

Friedenreich and Cust, 2008

# Beyond Recreational Physical Activity: Examining Occupational and Household Activity, Transportation Activity, and Sedentary Behavior in Relation to Postmenopausal Breast Cancer Risk

Stephanie M. George, PhD, MPH, MA, Melinda L. Irwin, PhD, MPH, Charles E. Matthews, PhD, Susan T. Mayne, PhD, Mitchell H. Gail, MD, PhD, Steven C. Moore, PhD, Demetrius Albanes, MD, Rachel Ballard-Barbash, MD, MPH, Albert R. Hollenbeck, PhD, Arthur Schatzkin, MD, DrPH, and Michael F. Leitzmann, MD

- Prospectively examined non-recreational physical activity and sedentary behavior in relation to breast cancer risk
- 97039 postmenopausal women in the National Institutes of Health–AARP Diet and Health Study

George et al, 2010

**TABLE 3—Occupational and Household Activity, Transportation Activity, and Sedentary Behavior in Relation to Invasive Breast Cancer Incidence Among Postmenopausal Women: National Institutes of Health–AARP Diet and Health Study, 1996–2003**

| | No. Person-Years | No. Cases | Age-Adjusted RR (95% CI) | $P_{trend}$ | Multivariate 1 RR (95% CI)[a] | $P_{trend}$ | Multivariate 2 RR (95% CI)[b] | $P_{trend}$ |
|---|---|---|---|---|---|---|---|---|
| **Occupational and Household Activity** | | | | | | | | |
| Routine activity during the day | | | | .003 | | .024 | | .092 |
| Sitting all day | 49 144 | 258 | 1.00 | | 1.00 | | 1.00 | |
| Sitting and a little walking | 206 859 | 933 | 0.84 (0.73, 0.96) | | 0.84 (0.73, 0.97) | | 0.86 (0.75, 0.99) | |
| Standing or walking, no lifting | 251 087 | 1132 | 0.81 (0.71, 0.93) | | 0.83 (0.72, 0.95) | | 0.86 (0.74, 0.98) | |
| Lifting or carrying light loads, or climbing stairs often | 115 128 | 514 | 0.80 (0.69, 0.93) | | 0.83 (0.71, 0.96) | | 0.86 (0.74, 1.00) | |
| Heavy lifting or carrying | 9 775 | 29 | 0.55 (0.38, 0.81) | | 0.62 (0.42, 0.91) | | 0.64 (0.43, 0.94) | |
| **Transportation Activity** | | | | | | | | |
| Years walked or biked to work | | | | .051 | | .081 | | .084 |
| <1 | 555 972 | 2540 | 1.00 | | 1.00 | | 1.00 | |
| 1–2 | 24 197 | 110 | 1.00 (0.83, 1.21) | | 0.99 (0.82, 1.20) | | 0.99 (0.82, 1.20) | |
| 3–5 | 25 376 | 120 | 1.03 (0.86, 1.23) | | 1.03 (0.86, 1.24) | | 1.03 (0.86, 1.24) | |
| 6–9 | 10 357 | 33 | 0.69 (0.49, 0.97) | | 0.69 (0.49, 0.98) | | 0.70 (0.50, 0.98) | |
| ≥10 | 16 090 | 63 | 0.84 (0.65, 1.08) | | 0.86 (0.67, 1.11) | | 0.86 (0.67, 1.11) | |

- 38% risk reduction for heavy lifting or heavy carrying during day at work or home
- Caveat: self-reported activity questionnaire

George et al, 2010

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ORIGINAL INVESTIGATION

# Physical Activity and Risk of Breast Cancer Among Postmenopausal Women

*A. Heather Eliassen, ScD; Susan E. Hankinson, RN, ScD; Bernard Rosner, PhD; Michelle D. Holmes, MD, DrPH; Walter C. Willett, MD, DrPH*

- Prospective study within the Nurses' Health Study
  - Examined postmenopausal women
- Assessed associations of specific and total activity (measured in MET-h) since menopause
  - Reported average time per week in various activities (ie, walking running, bicycling, swimming, etc.) and intensity (mph)
- Follow-up every 2-4 years from 1986-2006
  - 4782 documented invasive breast cancer cases

Eliassen et al, 2010

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*A. Heather Eliassen, ScD; Susan E. Hankinson, RN, ScD; Bernard Rosner, PhD; Michelle D. Holmes, MD, DrPH; Walter C. Willett, MD, DrPH*

- Results
  - Only brisk walking (3.0 - 3.9 mph) was associated *significantly* with lower cancer risk
  - Compared with less than 3 MET-h/wk (<1 h/wk walking), women engaged in higher amounts of recent total physical activity were at lower breast cancer risk (<27 MET-h/wk) [approximately 1 h/d of brisk walking]
    - Hazard ratio: 0.85
  - Association between total activity and breast cancer did not differ between receptor +/- tumors

Eliassen et al, 2010

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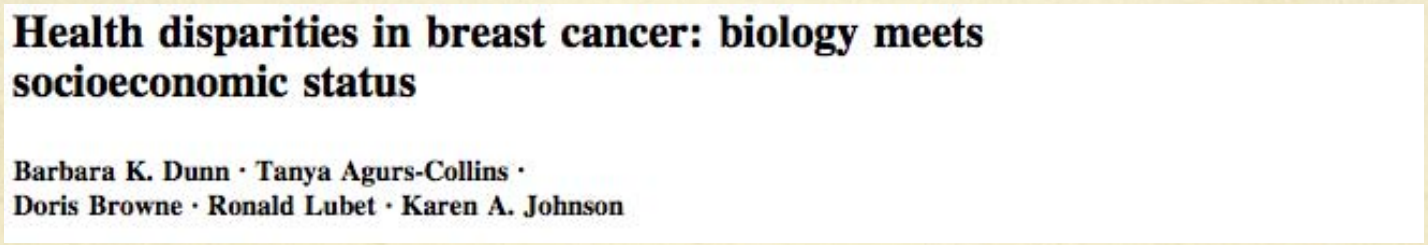
Friedenreich and Cust, 2008

# Hormone Receptor Negative Tumors

- Hormone receptor-negative tumors fail to respond to current established targeted therapies
  - Worse prognoses than receptor-positive BC's
  - Lack of obvious molecular targets (HER2 protein, E receptor)



**Health disparities in breast cancer: biology meets socioeconomic status**

Barbara K. Dunn · Tanya Agurs-Collins · Doris Browne · Ronald Lubet · Karen A. Johnson

- Women of African descent tend to have more aggressive breast cancers that present more frequently as estrogen receptor negative tumors.

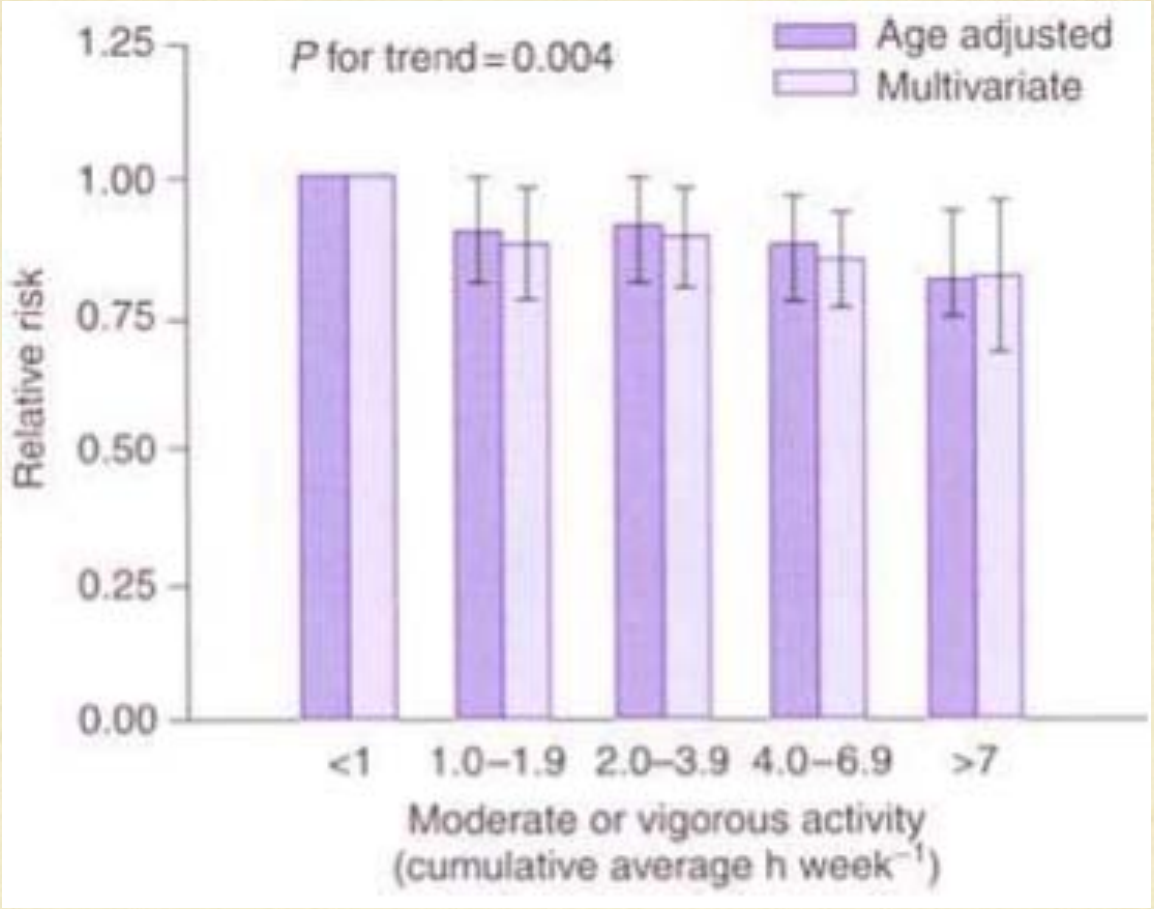
Dunn et al, 2010

# Hormone Receptor Negative Tumors

- Some evidence for greater risk reductions in women with:
  - ER–/PR– tumors (27% reduction) vs ER+/PR+ tumors (14%)

Friedenreich and Cust, 2008

# Any effects for pre-menopausual women?




Relative risk for breast cancer according to level of physical activity between 1980 and 1994 among women who were aged 30–55 in 1976

Rockhill et al, 1999

# Effects of PA

1. Reduce the risk of acquiring cancer
2. Extend survival following treatment
3. Improve quality of life


- Prospective observational study
- Nurses' Health Study
  - 2987 nurses diagnosed with stage I, II, or III breast cancer between 1984 and 1998 (follow up until 2002)

Holmes et al, 2005

**Table 2.** Age-Adjusted and Multivariable-Adjusted Relative Risks According to Physical Activity Category After Breast Cancer Diagnosis

| | Total (N = 2987) | Physical Activity After Diagnosis, MET-h/wk | | | | | *P* for Trend |
|---|---|---|---|---|---|---|---|
| | | <3 (n = 959) | 3-8.9 (n = 862) | 9-14.9 (n = 335) | 15-23.9 (n = 428) | ≥24 (n = 403) | |
| Total deaths | 463 | 188 | 126 | 38 | 51 | 60 | |
| Age-adjusted RR (95% CI) | | 1.00 | 0.69 (0.55-0.87) | 0.53 (0.37-0.75) | 0.56 (0.41-0.77) | 0.67 (0.50-0.90) | .004 |
| Multivariable-adjusted RR (95% CI)* | | 1.00 | 0.71 (0.56-0.89) | 0.59 (0.41-0.84) | 0.56 (0.41-0.77) | 0.65 (0.48-0.88) | .003 |
| Breast cancer deaths | 280 | 110 | 84 | 20 | 32 | 34 | |
| Age-adjusted RR (95% CI) | | 1.00 | 0.79 (0.60-1.06) | 0.47 (0.29-0.76) | 0.60 (0.41-0.89) | 0.64 (0.44-0.94) | .01 |
| Multivariable-adjusted RR (95% CI)* | | 1.00 | 0.80 (0.60-1.06) | 0.50 (0.31-0.82) | 0.56 (0.38-0.84) | 0.60 (0.40-0.89) | .004 |
| Recurrence | 370 | 137 | 108 | 29 | 45 | 51 | |
| Age-adjusted RR (95% CI) | | 1.00 | 0.82 (0.64-1.06) | 0.53 (0.35-0.79) | 0.66 (0.47-0.93) | 0.76 (0.55-1.04) | .05 |
| Multivariable-adjusted RR (95% CI)* | | 1.00 | 0.83 (0.64-1.08) | 0.57 (0.38-0.85) | 0.66 (0.47-0.93) | 0.74 (0.53-1.04) | .05 |

- 3 MET/hrs = walking at an average pace (2-3 mph) for 1 hour
- Greatest benefit seen in women who performed the equivalent of walking 3-5 hours/week at an average pace
  - Little evidence of correlation between increased benefit & greater intensity

Holmes et al, 2005

# Effects of PA

1. Reduce the risk of acquiring cancer
2. Extend survival following treatment
3. Improve quality of life

# Quality of Life

The aim of physical training in cancer patients is the positive effect on:

- Fitness
- Muscle strength
- Physical well-being
- Anxiety
- Depression
- Quality of life in the widest sense

Pedersen and Saltin, 2006

**Improvement in self-reported physical health predicts longer survival among women with a history of breast cancer**

**Ruth E. Patterson · Nazmus Saquib · Loki Natarajan · Cheryl L. Rock · Barbara A. Parker · Cynthia A. Thomson · John P. Pierce**

- Women's Healthy Eating and Living (WHEL) Study
  - 2343 breast cancer survivors
- Assessment of physical health via "quality of life" (QoL)
  - RAND-36-item Health Survey
    - general health perceptions
    - physical functioning
    - bodily pain
    - role limitations due to physical health problems
- No association of change in physical health w/ additional breast cancer events or mortality in women diagnosed ≥2 yrs before study
- However, for women >2 yrs post-diagnosis
  - Hazard ratio= 0.38 for increased vs. decreased physical health

Patterson et al, 2010

# Randomized Trial of Exercise Therapy in Women Treated for Breast Cancer

*Amanda J. Daley, Helen Crank, John M. Saxton, Nanette Mutrie, Robert Coleman, and Andrea Roalfe*

- Intervention study
  - 108 women treated for breast cancer 1-3 years previously
  - Functional Assessment of Cancer Therapy (FACT) survey
    - Quality of Life Survey
  - Randomly assigned to 8-wk groups:
    - Aerobic exercise therapy (50 min, moderate intensity, 3x/wk)
    - Exercise-placebo (light intensity flexibility & passive stretching)
    - Usual Care
- Significant differences favoring aerobic exercise therapy relative to usual care for the Quality of Life survey
  - Not attributable to attention (no effect in exercise placebo)

Daley et al, 2007

# Limitations of the current science

- Difficulty of assessing physical activity
- Limited number of controlled exercise intervention trials examining underlying biological mechanisms
- Lack of randomized controlled trials of exercise for cancer prevention

Friedenreich, Neilson, and Lynch, 2010

# Summary

- The current evidence demonstrates that the beneficial effect of physical activity is too strong to overlook
- Vigorous exercise is great for reducing risk, but moderate intensity is adequate
- PA may be one of the most effective interventions available for hormone-negative cancers
- There is a need to move from:

  observational studies → intervention trials → clinical practice

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