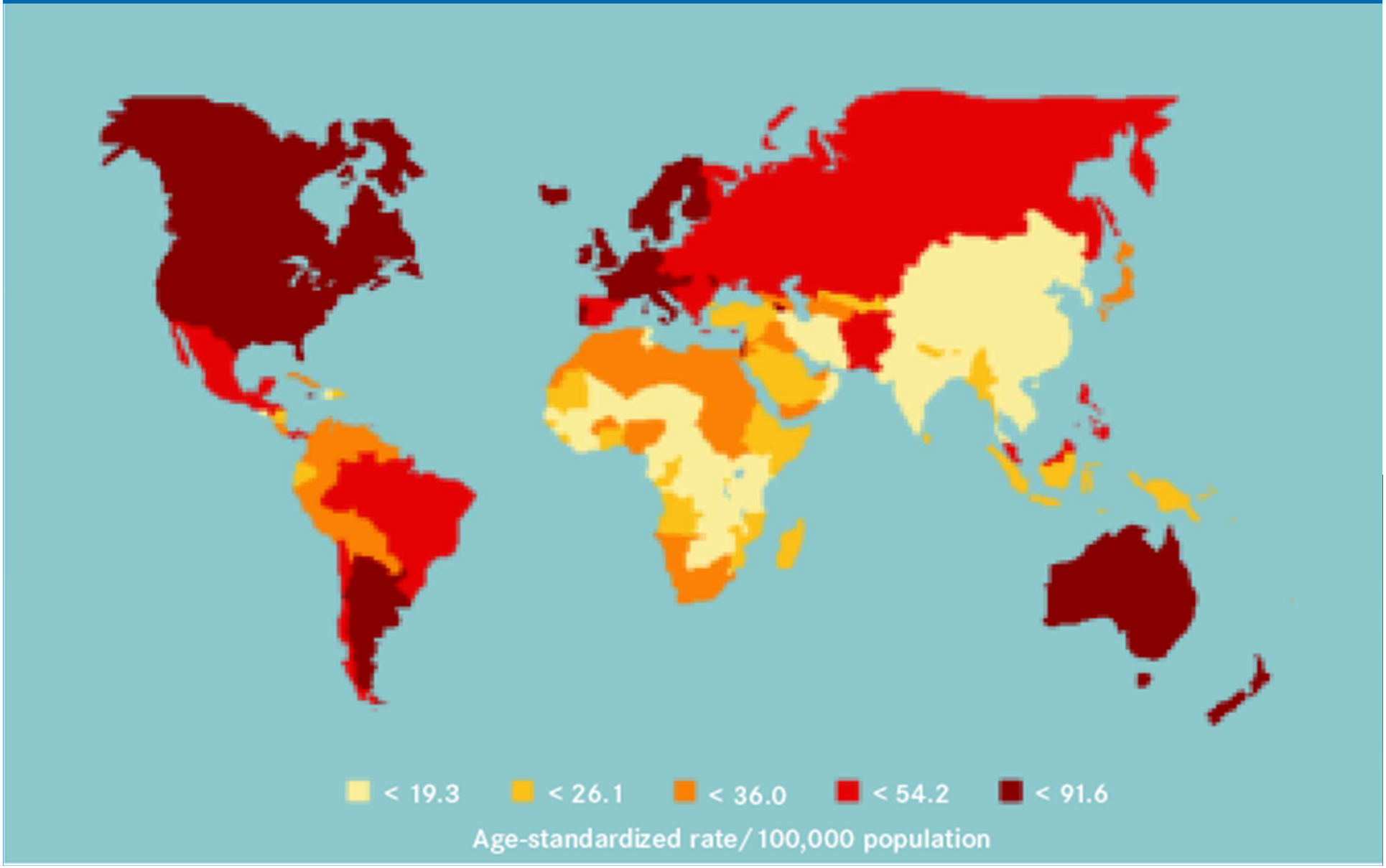
Breast Cancer : An Overview

Prof. P.K.Sur
Dept. of Radiotherapy
Medical College, Kolkata
&
Chairman, ICRO

Global Burden of Breast Cancer



Epidemiology of Breast Cancer

- Commonest cancer of women worldwide, with more than one million cases annually
- Considerable geographic, ethnic and racial variation in incidence of breast cancer
- Affluent populations carry greatest risks, with >80 cases/ 100,000 populations in a year
- Incidence of invasive breast cancer now seems to leveling off in western countries, but increasing in developing nations, due to more urbanization and lifestyle factors

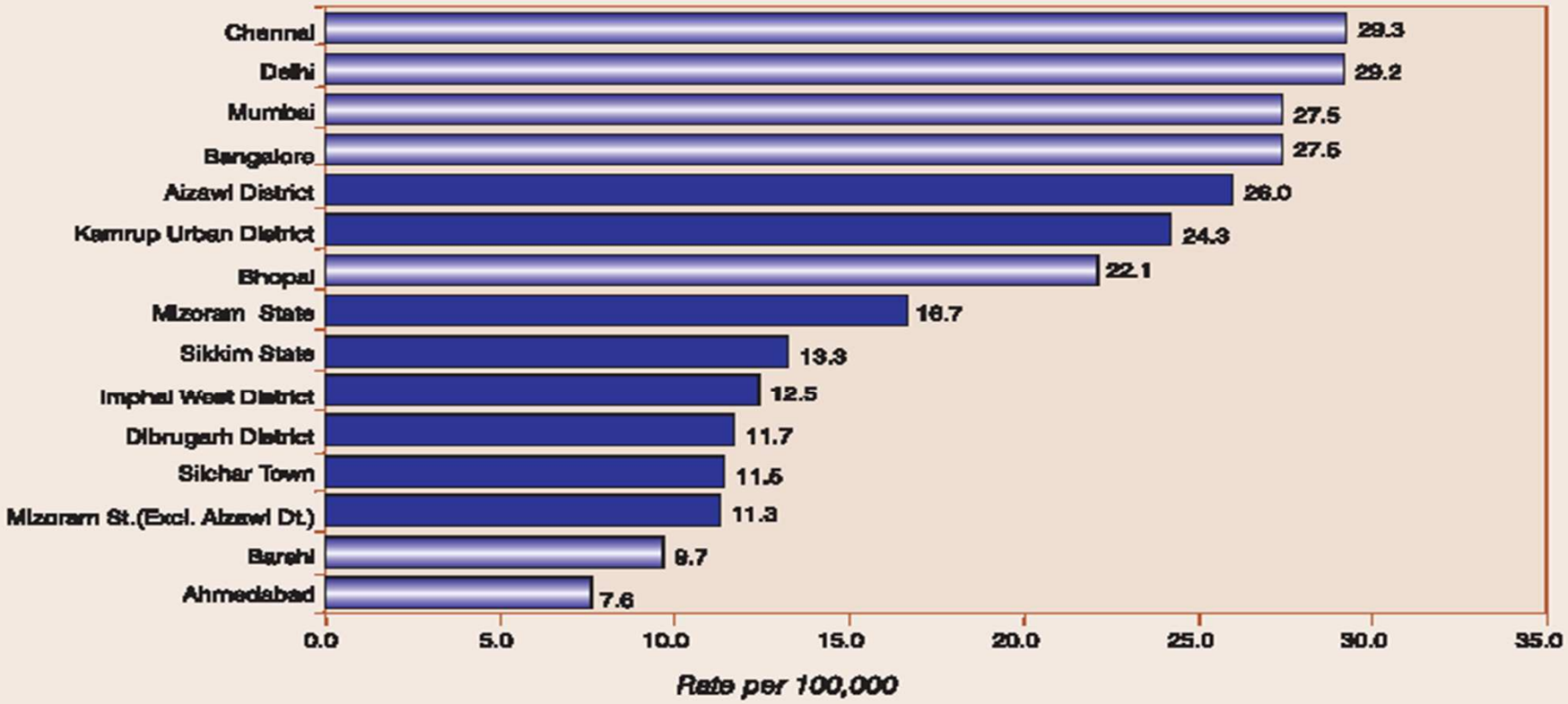
Epidemiology

- Since 1990, age-adjusted mortality from breast cancer coming down, at 2.3% per year
- Decline in mortality due to *early detection, increased awareness and tremendous advances in the multimodal treatment strategy*
- In India, age-adjusted incidence much lower compared to western countries, but an increasing trend visible in large metros and age of onset also appears to be younger

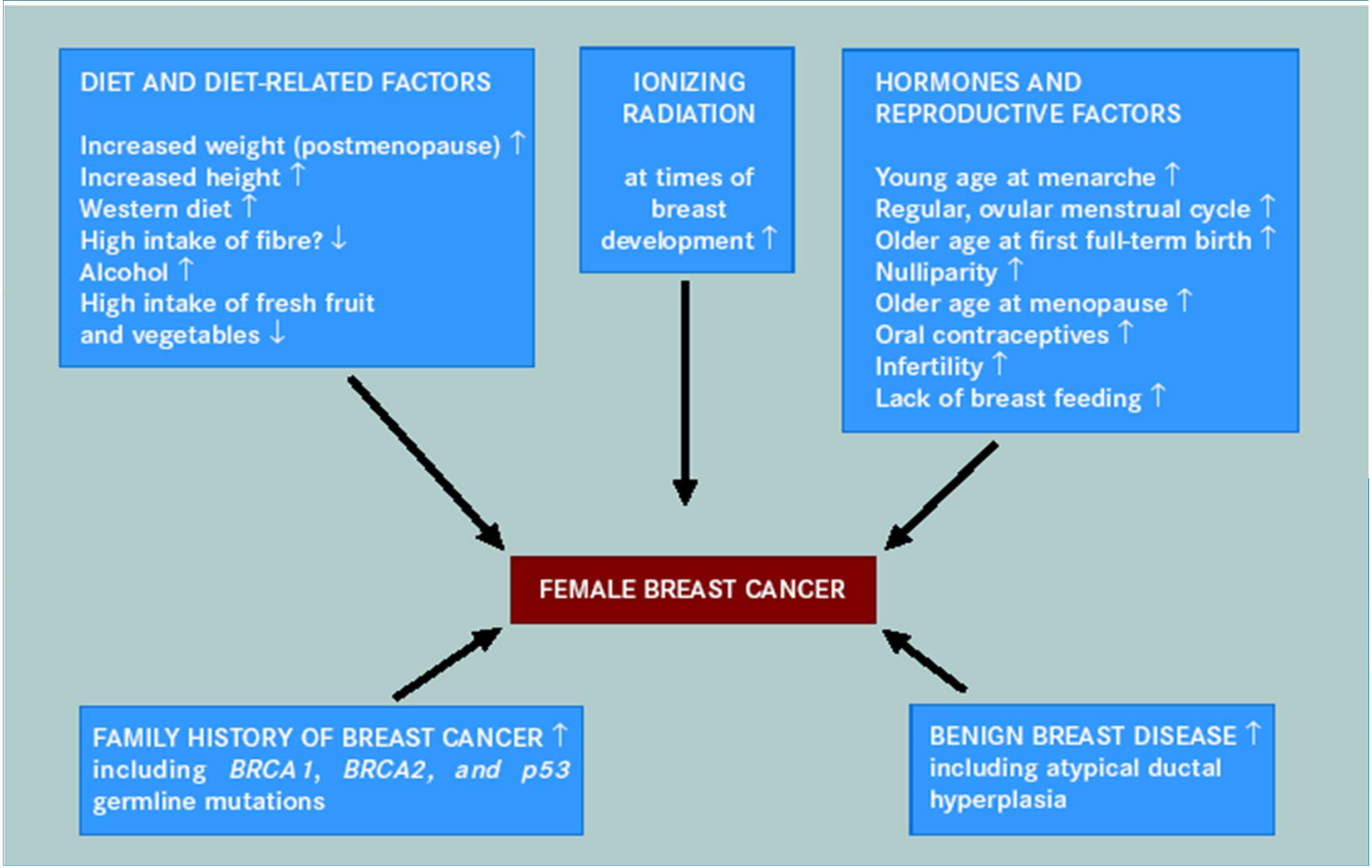
Incidence of Breast cancer in India

Fig. 6.14 : Comparison of Age Adjusted Incidence Rates (AARs) Across All PBCRs

BREAST (C50) - FEMALES



Established Risk Factors



Gail's Model for risk prediction

- A model for predicting an individual's annual and lifetime risks of breast cancer
- Based on patient's age , no. of first degree relatives with Ca breast, age at first childbirth, age at menarche, no. of breast biopsies and h/o atypical ductal hyperplasia
- Use of exogenous hormones and many other risk factors ***not*** incorporated in this model

Prevention of Breast Cancer

A) **NSABP-P1 Trial**: Tamoxifen vs Placebo

1) 5 yrs of Tamoxifen use reduces risk by 50%
2) Benefit in all age groups
3) Women with LCIS had 56% reduction of risk
4) Selectively reduced ER+ve tumours
5) Major toxicities Endometrial Ca and TE events

B) **STAR Trial (1999-05)**: Tamoxi vs Raloxifene

Risk reduction similar, but less toxicity with Raloxifene, and restricted to women > 50 yrs

C) **Prophylactic Bilateral Mastectomy**: 90% risk reduction in women with family history

D) **Prophylactic Bilateral Oophrectomy:** Reduces risk of both Ca Breast and Ovary in women with BRCA1 and BRCA2 mutations

Genetic Screening

- Only 5-10% of breast cancer patients have germline mutations, showing an autosomal dominant inheritance pattern in familial cancer
- BRCA1, BRCA2 and p53 genes are affected mainly, of which the first two matter mostly
- In women with BRCA1 and BRCA2 mutation, lifetime risk of breast cancer 65-75 %
- No definite screening recommendations in those with proved germline mutations
- ASCO advises Annual Mammography,Clinical and Self breast exam starting at 25-35 yrs

Diagnosis and Work-up

- History and Physical Examination
- FNAC/ Biopsy (guided by PE/ USG/Mammo)
- Radiologic Studies: Chest X-ray
  Bilateral Mammogram
  Ultrasound/CT abdomen
  (In advanced cases)
  Bone Scan (st II onwards)
- Laboratory studies: CBC, LFT etc
- Pathological studies: ER/PR/HER2 neu status
  BRCA in selected cases

Imaging in Breast Cancer Diagnosis and Work-up

Mammography:

- Most critical component in imaging of breast cancer
- Bilateral Mammograms a routine work-up procedure
- Typically seen as an ill-defined mass with spiculated margins with or without micro-calcifications
- Useful both as diagnostic and screening procedure
- Average sensitivity 90% and specificity 94%
- Positive predictive value about 10-14% for screened pts, but significantly higher for symptomatic pts
- After mammography guided FNAC/Biopsy, detection rate of malignancy about 30 %

Other Imaging tools in Breast Cancer

A) **Ultrasound**:

1) Useful tool to complement mammography in diagnosis and treatment
2) As a guide for interventional procedures
3) Evaluation of lumpectomy cavity site for planning RT boost

B) **MRI of Breast**:

1) Not used routinely
2) Supplements mammography and ultrasound in diagnosis of doubtful lesions
3) Assessment of response after Neo-adjuvant CT

Imaging in Breast Cancer

C) **CT Scan**: 1) No role in routine work-up and staging
2) May be done in advanced and node positive cases as a supplement

D) **Bone Scan**:

1) Limited value in stage I and II and should be reserved for those with bone pain only
2) Routine procedure in advanced cases however

E) **Pet Scan**

1) No established role in early stage disease
2) Increasing role in locally advanced, recurrent and metastatic cancers

Breast Conservation Strategy in the Management of Breast Cancer

Why Breast Conservation?

↓

Because the patients want it

Conservative Surgery + RT vs Mastectomy

Ref.	Comparison	No.	Recurrence	Surv.
Veronesi et (QUART)	Halstead vs quadrant	701	No difference	No diff.
Sarrazin et al	MRM vs WLE + RT	179	No Diff	No Diff
Fisher et al (NSABP)	MRM vs Lumpectomy	1843	in cases with-out RT	No Diff
Donegan et al (EORTC)	MRM vs WE + RT	903	No Difference	No Diff
Lichter et al (NCI)	MRM vs WE + RT	237	NR	No Diff

Trials of Cons. Surgery with and without Radiotherapy

Ref.	Study		Recurrence	Surv.
Veronesi 93 (MILAN III)	Quadrant + RT vs Quadrantectomy only	↑	without RT	No Diff.
Upsala 90 (Sweeden)	Segmental Resection + RT vs SR Only	↑	without RT	No Diff
Stewart 89 (Scottish Trial)	Lumpectomy + RT vs Lumpectomy only	↑	without RT	No Diff
NSABP 06	Lumpectomy + RT vs Lumpectomy only	↑	without RT	No Diff

Conclusions from Randomized Trials

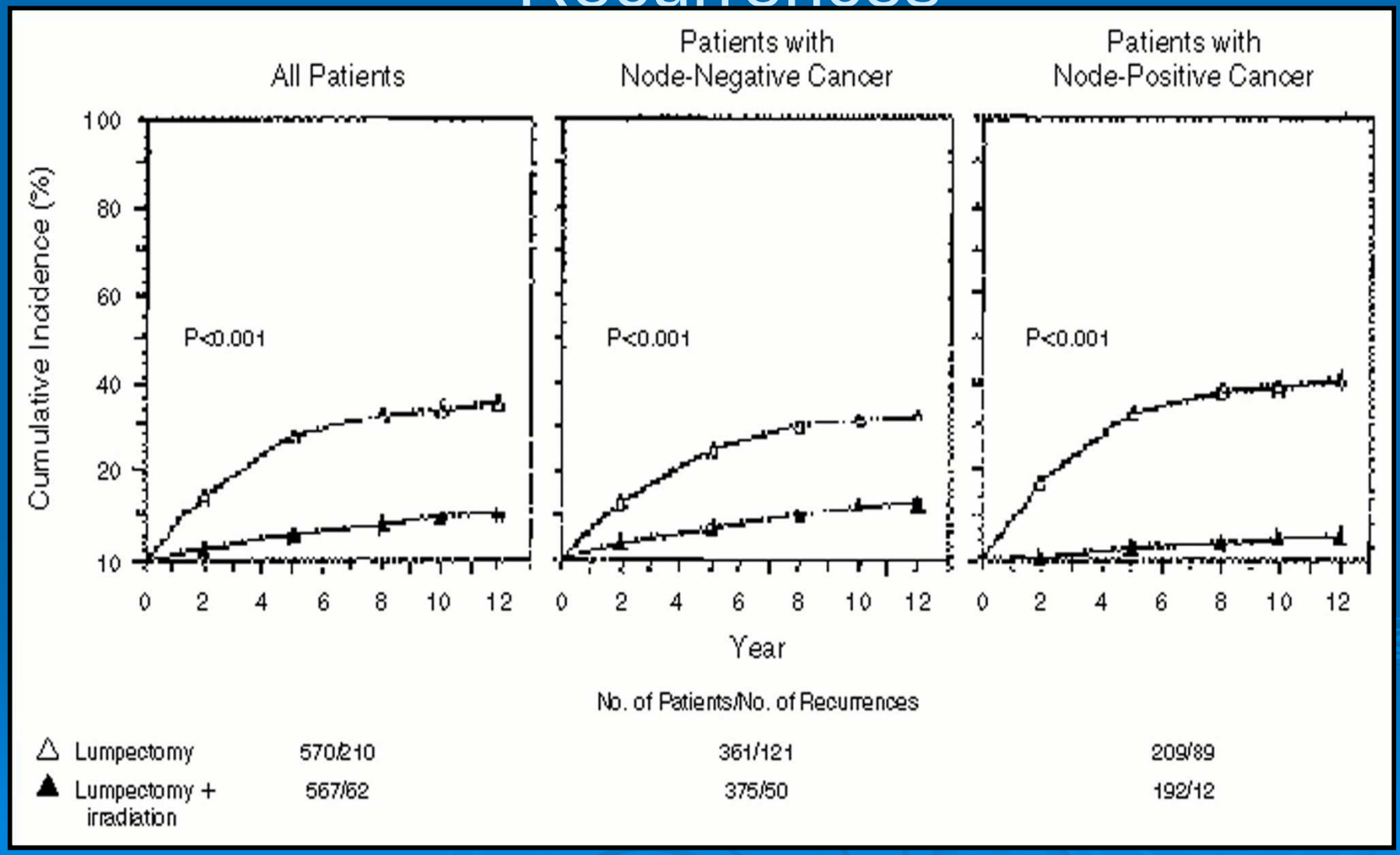
- Conservative surgery produces equivalent results as Mastectomy

- Local control will definitely be less if radiotherapy is not added, but survival not influenced

↓

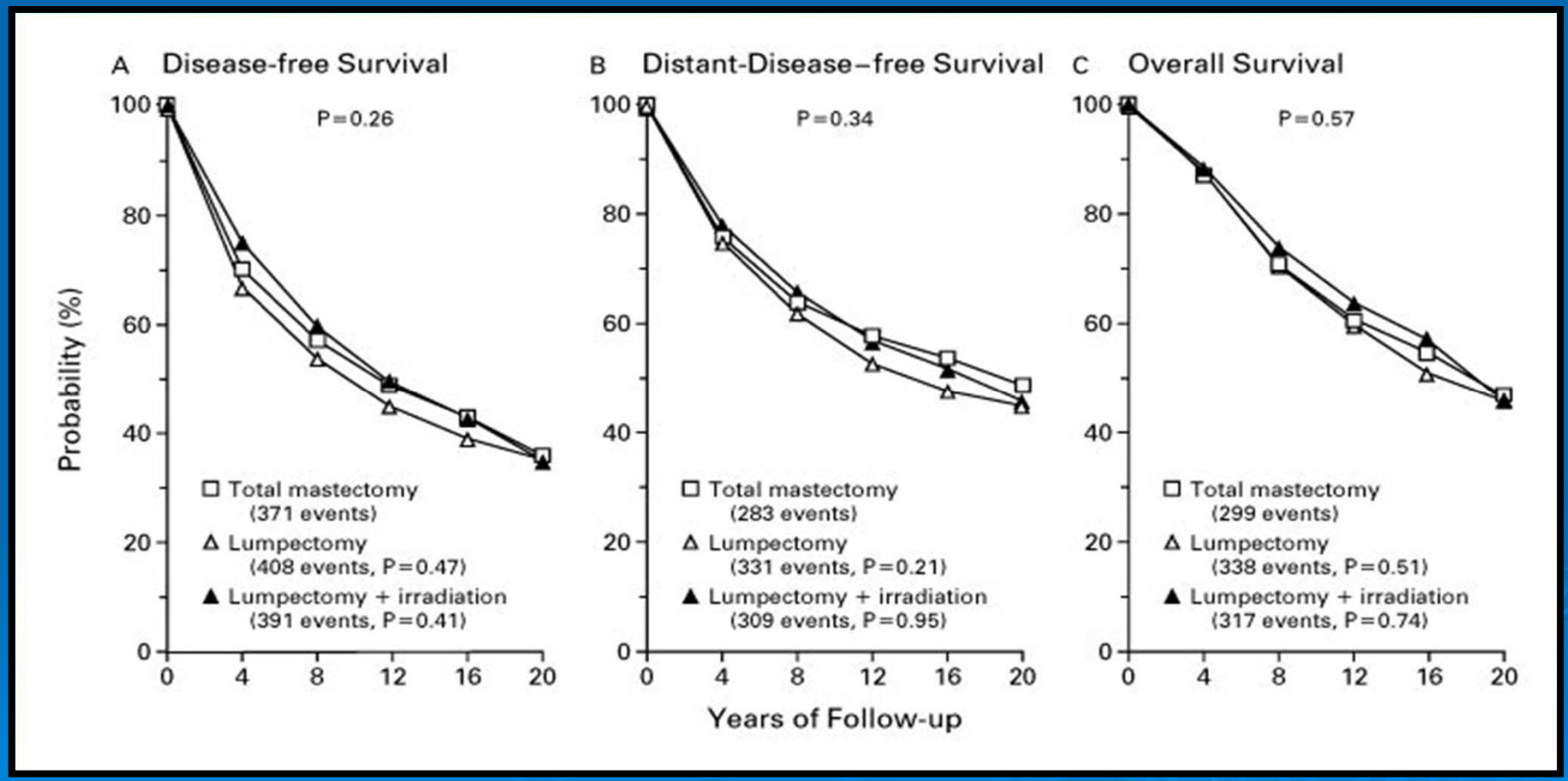
NSABP long term follow-up results prove the point

NSABP-06 12 Year Follow up: Recurrences



N Engl J Med. 1995 Nov 30;333(22):1456-61

National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 Study 20 Yr Follow up in 2002



Is RT required in all patients after lumpectomy?

N Engl J Med. 2002 Oct 17;347(16):1233-41

Better Local Control Vs Survival

- The improved local control resulting from adjuvant RT after BCS did not translate into improved survival at 20 years
- The probable reason is long term cardiotoxicity caused by irradiation of the heart in left sided breast cancers
- Subset analysis of Right versus Left sided breast cancers show left sided RT compromising long term survival at 20 Years

Local Control vs Survival

Oxford Meta-analysis and Danish Trials infuse fresh data

↓

Firmly establishes the role of loco-regional treatment

To enhance the survival as well

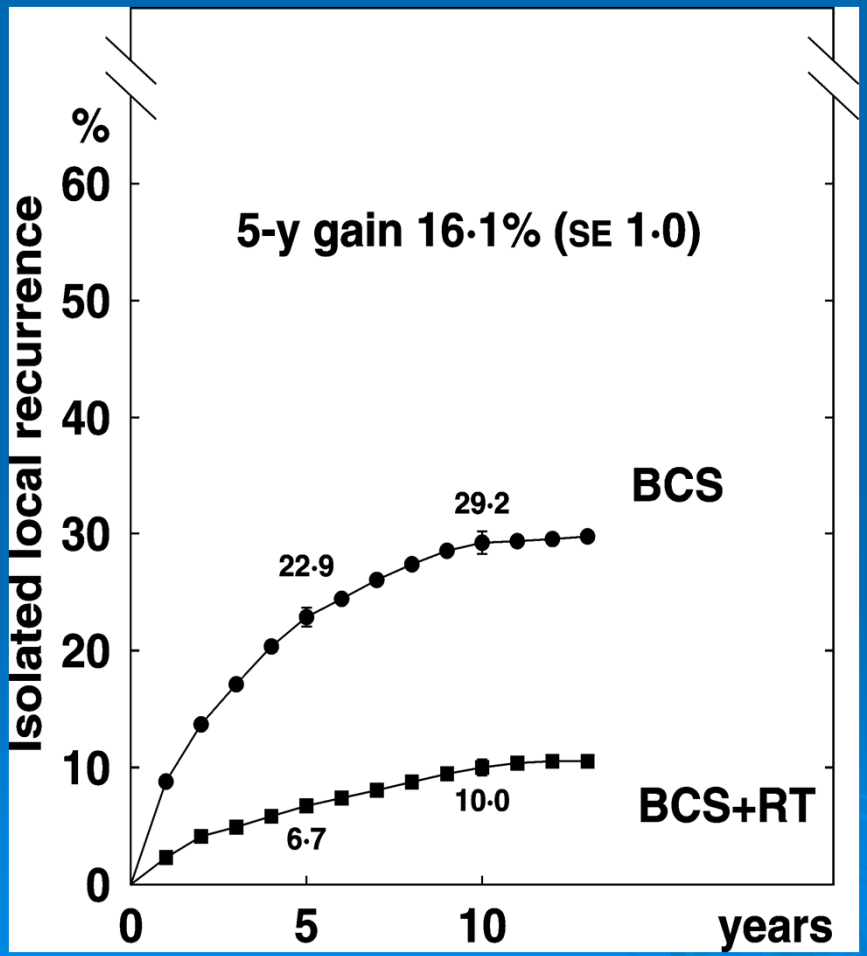
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

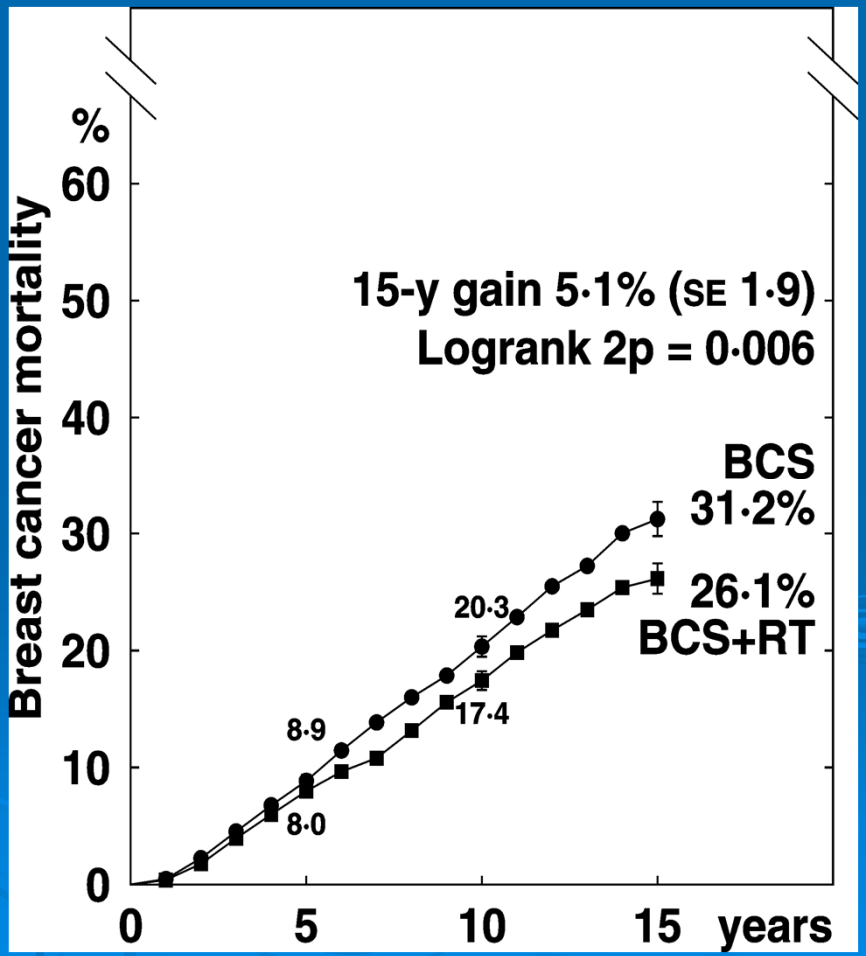
Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

EBCTCG Lancet 2005; 366: 2087-2106

Effect of radiotherapy after breast-conserving surgery (10 trials of BCS ± RT) on local recurrence and on breast cancer mortality

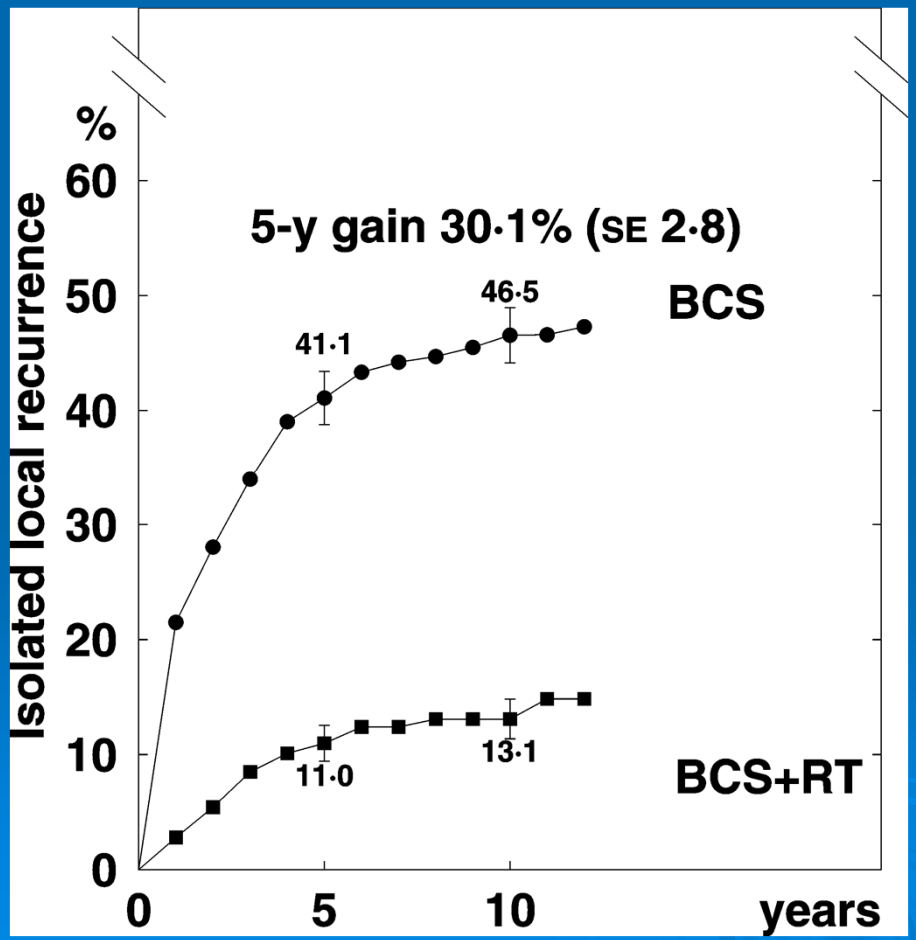
6097 women with node-negative disease

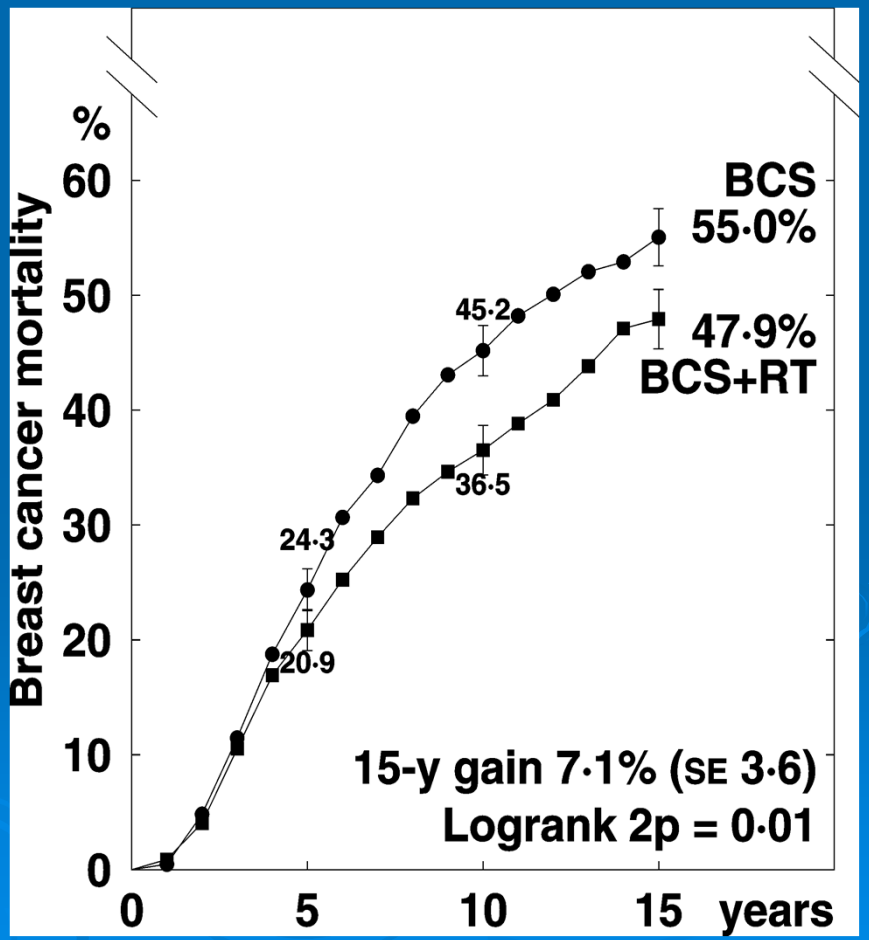




Effect of radiotherapy after breast-conserving surgery (10 trials of BCS ± RT) on local recurrence and on breast cancer mortality

1214 women with node-positive disease





Conclusions

- In early breast cancer, local treatments have little impact on breast cancer mortality during the first few years, but have definite, although moderate, effects by 15 years

- avoidance of local recurrence in a conserved breast and elsewhere are of comparable relevance to 15 year breast cancer mortality.

- *about one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided.*

Further development: APBI

Accelerated Partial Breast Irradiation

(APBI)

RT to the Tumour bearing area or the affected Quadrant instead of whole breast

As the recurrences occur mostly in the vicinity of the primary tumour

Early results are encouraging

Current Indications for APBI
ABS 2002

- be appropriate candidates for standard BCT
- be ≥ 45 years old
- have invasive ductal carcinoma, unifocal
- have tumour size </= 3 cm
- have negative microscopic surgical margins
- be axillary node-negative by axillary dissection (Level I–II) or sentinel lymph node evaluation

Evolution of Adjuvant Drug Therapy in Breast Cancer:

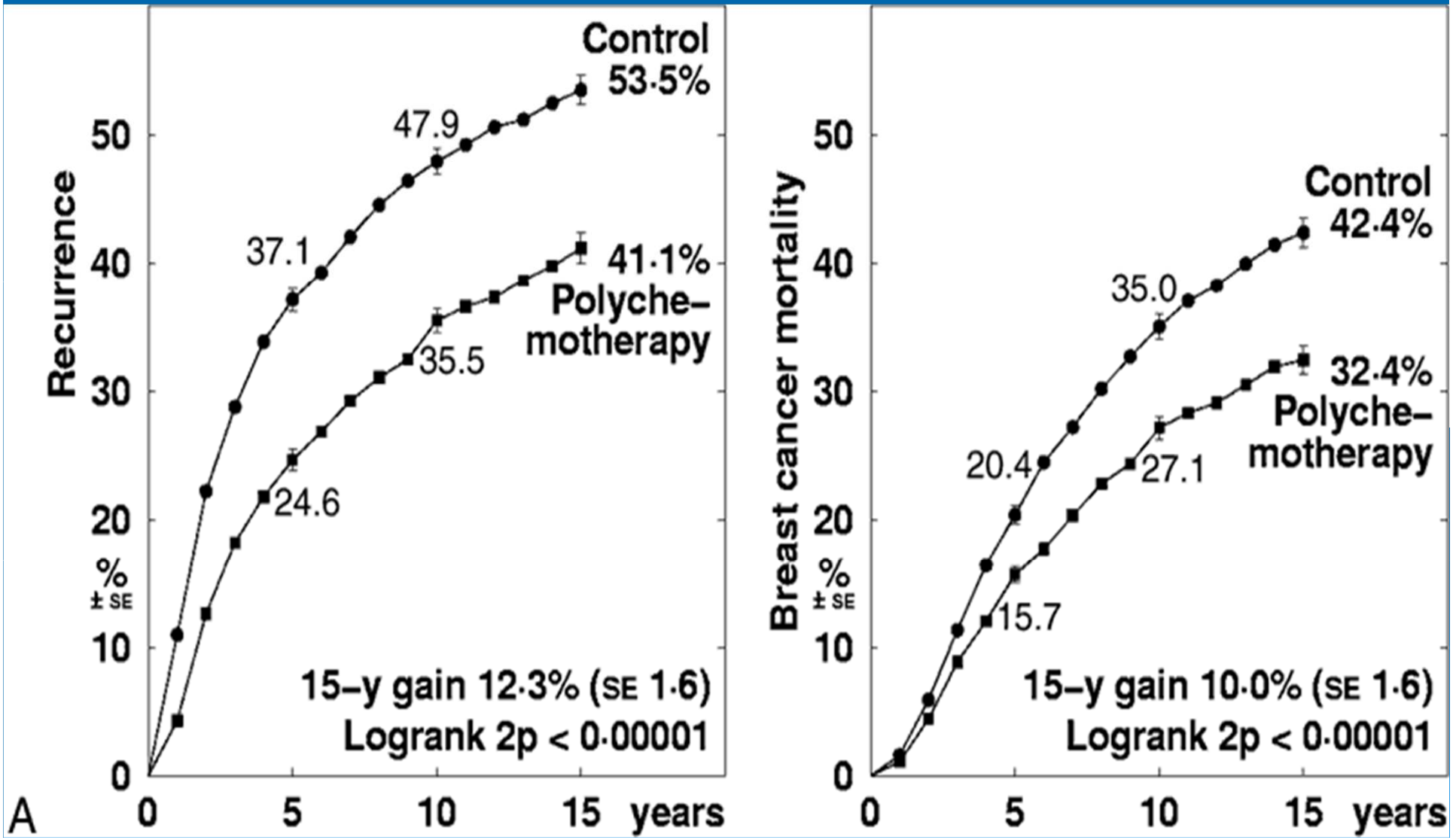
Started with the trial of Ovarian ablation (Cole 1970)

Followed by NSABP and Historic Milan Trial By CMF

Guided our policy of Adjuvant Therapy till the publication

of Meta- analysis few years back

Results of Oxford Meta-analysis



NIH Consensus on Adjuvant drug therapy

- Adjuvant polychemotherapy should be given to majority of women with localised breast cancer >1 cm.size , regardless of nodal, menopausal or hormone receptor status.
- For women with node negative breast cancer <1 cm.,decision to use chemotherapy should be individualised.
- Anthracycline based chemotherapy significantly more effective than CMF (small benefit).

Newer Developments: Role of Taxanes in Adjuvant Treatment

- Both RFS and OS improved significantly with addition or substitution with Paclitaxel or Docetaxel (CALGB 9344, BCIRG)
- Several other studies showed increased RFS only whereas OS improvement not significant (NSABP B28, MDACC 2002)
- Stongest support is for 4 AC → 4 T (CALGB) Or 6 cycles of TAC (BCIRG)
- Support use of taxanes in Node positive women, but effect independent of ER Status

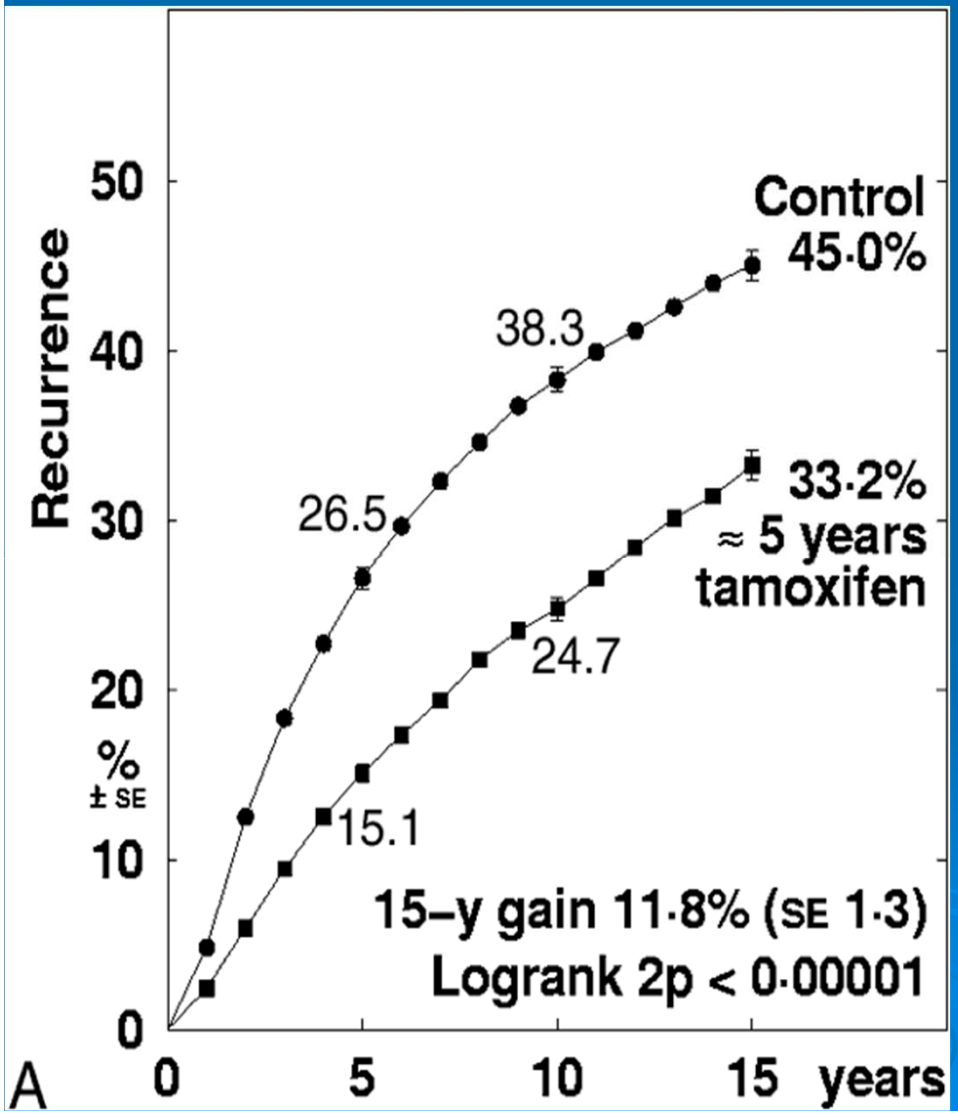
Use of Taxanes: Ongoing debate

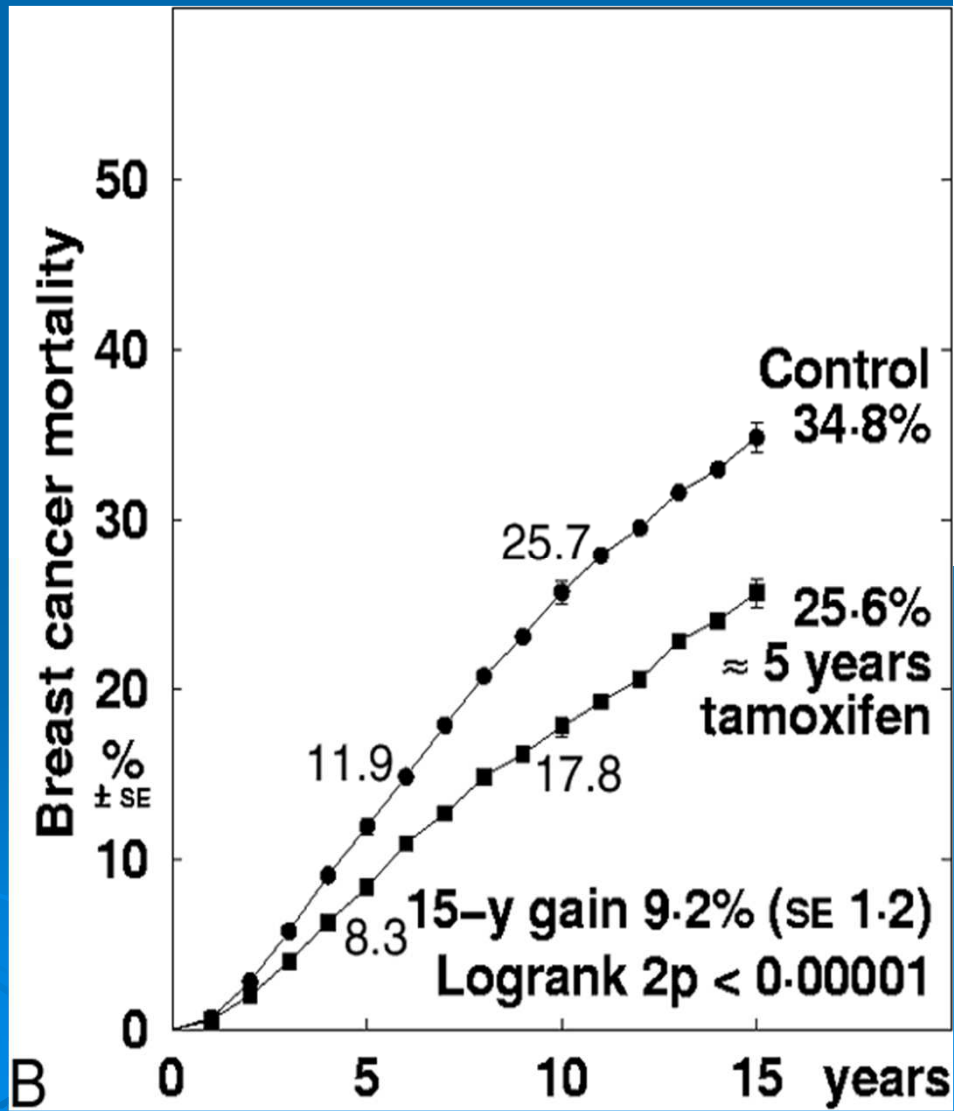
New data presented at ASCO 2008:

Summary of Recent pooled analysis of 22903 women participating in 13 adjuvant Taxane studies:

- Overall benefits with taxane containing regimes
- Absolute 5 yr risk reduction 5% for DFS and 3% OS
- Not affected by type of Taxane (Pacli or Docetaxel)
- Not affected by Nodal Status (1-3 vs >=4 nodes)
- Independent of ER Status
- Several unresolved issues (cost-benefit analysis and quality of life issues not reported)
- Next Oxford Meta-analysis to provide further insights

Benefits of Endocrine Therapy as Adjuvant Treatment





Advances in Endocrine Therapy

The 3rd generation Aromatase Inhibitors are an exciting new development in the endocrine therapy of ER +Breast Cancer in post-menopausal women

- Anastrozole superior to Tamoxifen in reducing the risk of relapse, Survival not affected significantly
- *In advanced breast cancer* in post-menopausal women,Letrozole clearly better, and Anastrozole as good as Tamoxifen.
- No sig. difference in mortality with 5 yrs vs 10 yrs of tamoxifen but recurrence significantly lower in long arm (ATLAS Study)

Targeted Therapy in Breast Cancer

- Transtuzumab (Herceptin), the new symbol of success after Tamoxifen in HER-2 +ve (IHC3 or Fish+) tumours
- Benefits pts with HER2+ve metastatic breast cancers, when combined with chemotherapy or Hormones
- As adjuvant treatment highly consistent results showing improvements in DFS and even OS (HERA, BCIRG and 3 other randomized trials)

Advances in targeted therapy

- Herceptin given for 1 year following completion of primary treatment is a new standard in HER2 overexpressing tumours
- Lapatinib (a dual kinase inhibitor) and Bevacizumab (targeting VEGF) are new promising molecules under clinical evaluation
- Cost-effectiveness analysis needs to be done in our setting,as the absolute benefit (in reducing recurrence) after 1 yr of adjuvant therapy is only 5.5%

Thank You