RECENT ADVANCES
BREAST CANCER THERAPY

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Brief overview



- Introduction
- Etiology
- Pathogenesis
- Symptoms
- Staging and classification
- Treatments available at present
- Advanced pharmacotherapy
- Summary

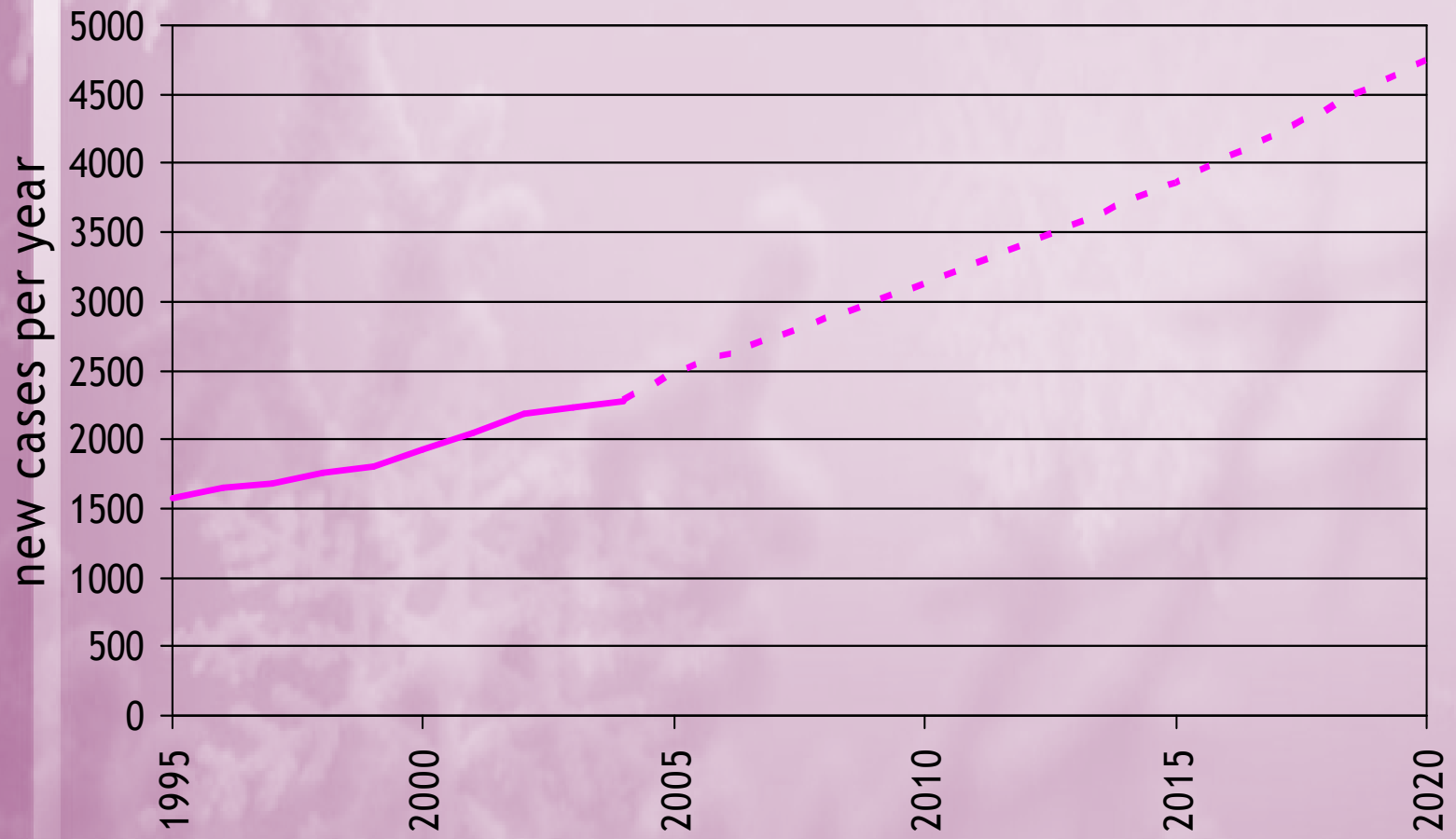
Introduction



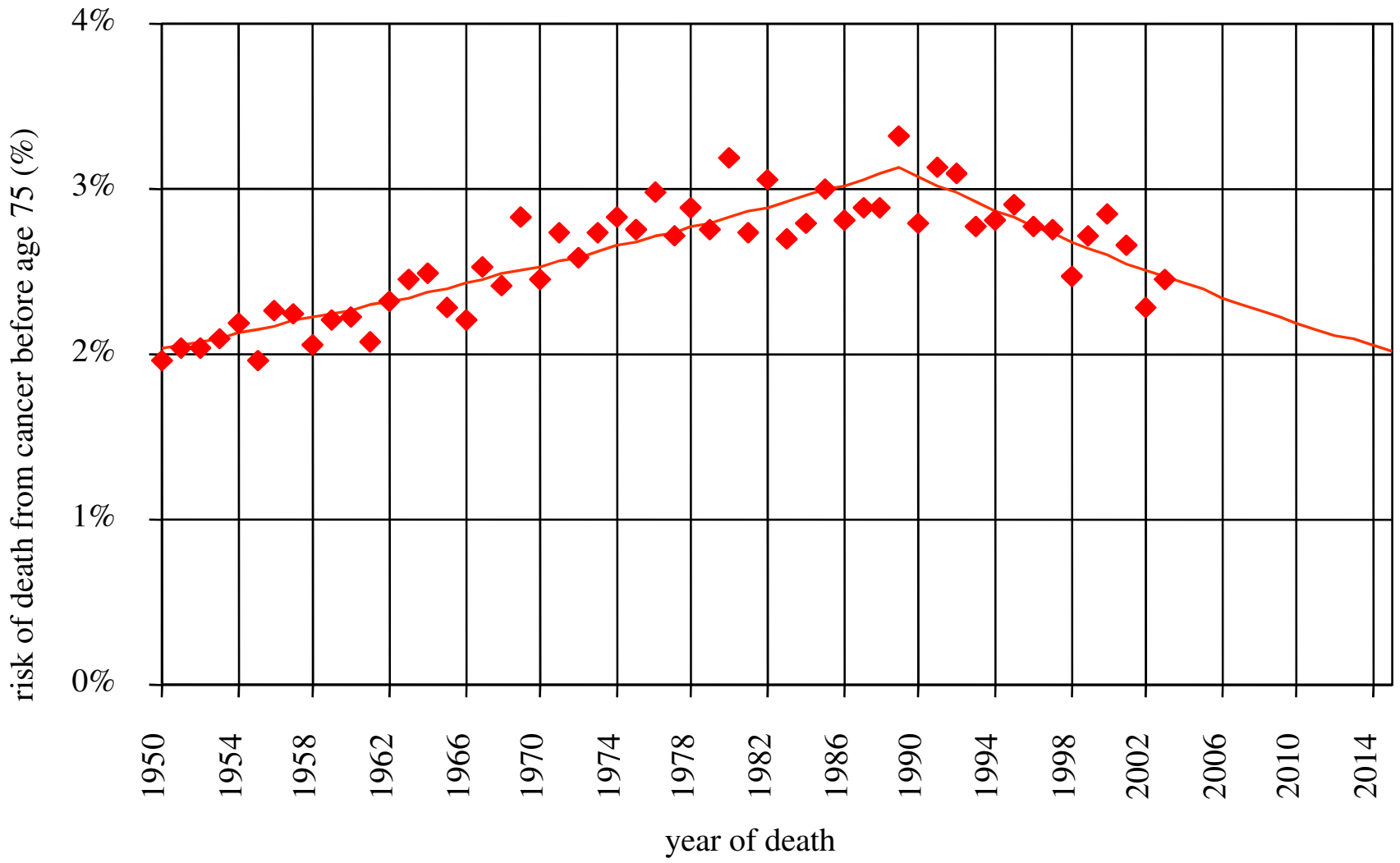
- The estimated number of new cancers in India per year is about 7 lakhs and over 3.5 lakhs people die of cancer each year.
- In Karnataka there would be about 1.5 lakhs cancer cases at any given time and about 35,000 new cancer cases are added to this pool each year.

- **2nd** leading cause of death
- **2nd** most common cancer
- **All** women are at risk
- Incidence increases with age

Projected number of Breast Cancers to 2020



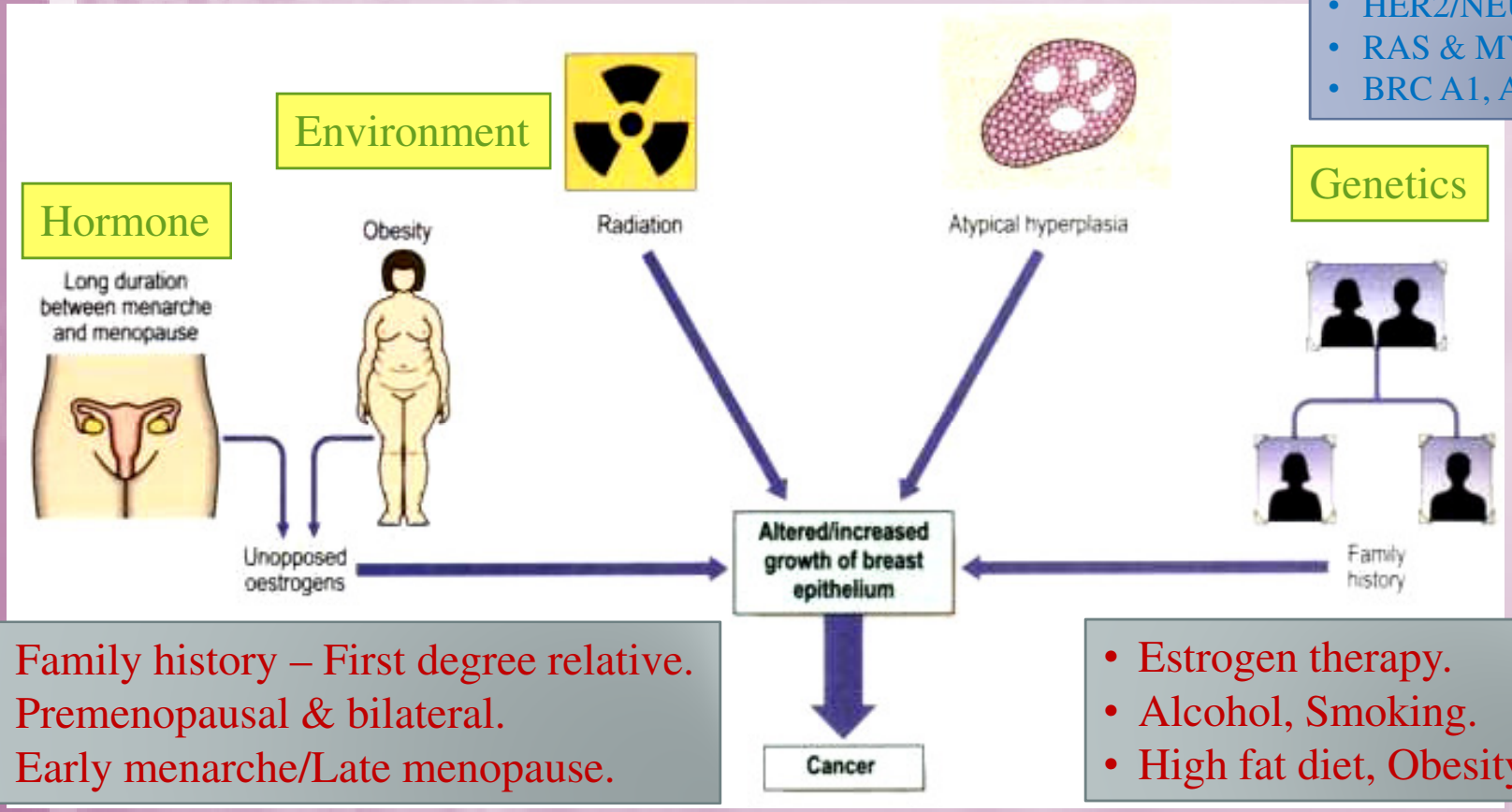
Deaths from Breast Cancer 1950-2014



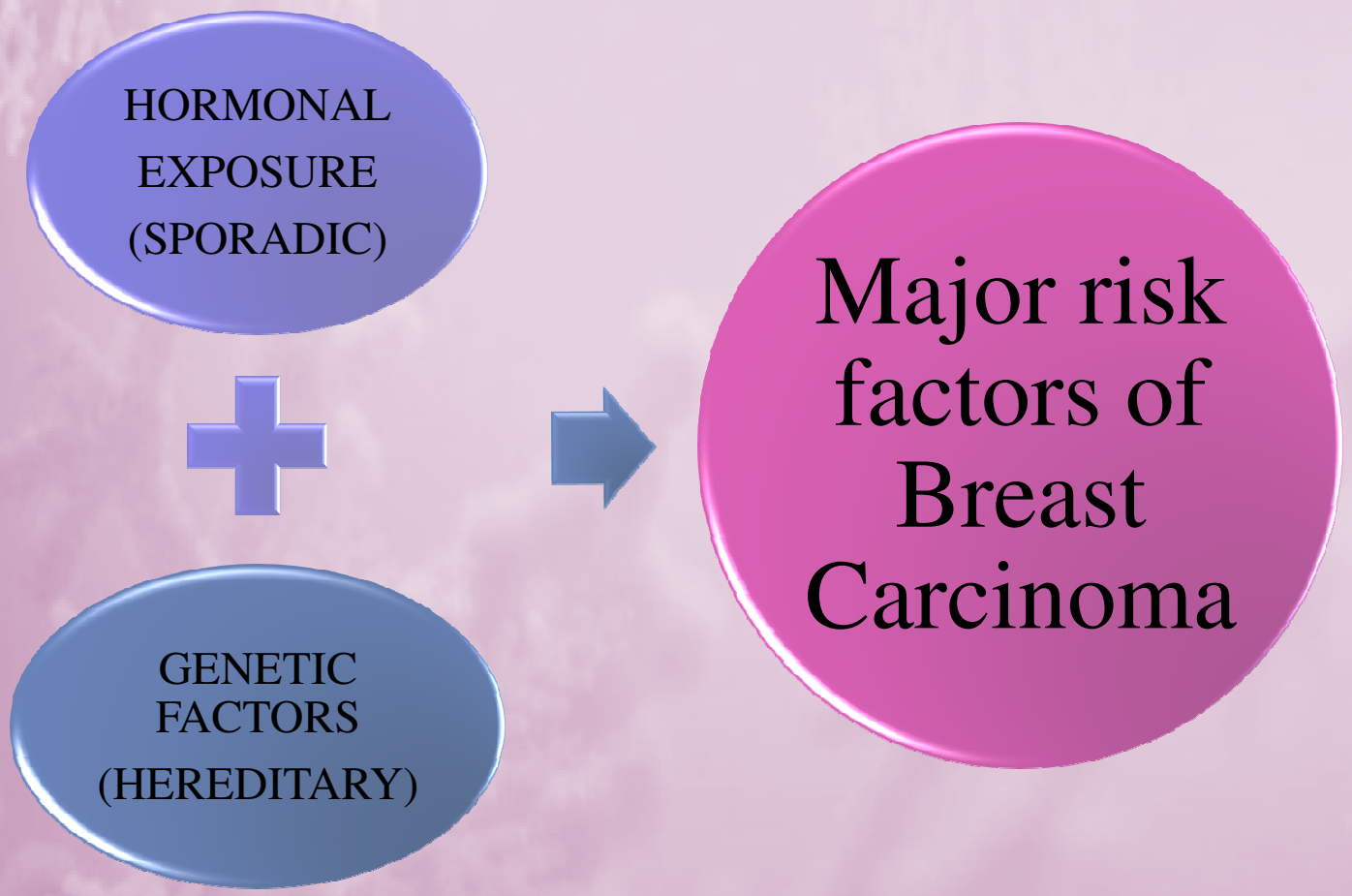
Why?

- Incidence is increasing
  - Mammographic screening
  - Environmental Factors
- Mortality is decreasing
  - Early Detection
  - Better Treatment Options

Etiology of Breast Carcinoma:



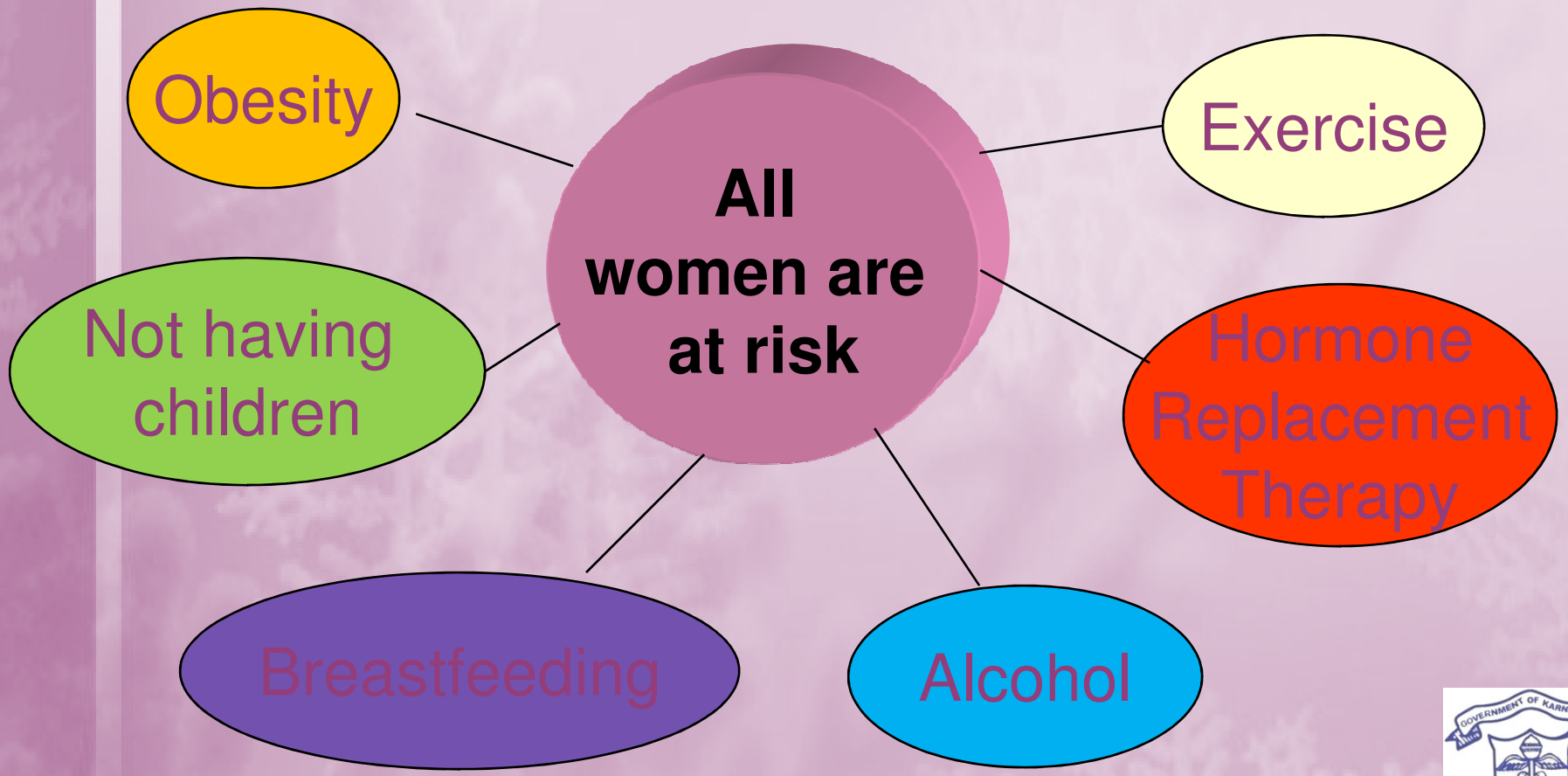
- Overexposure to oestrogens and underexposure to progesterone
- No definite relationship to oral contraceptives
- Some tumours contain hormone receptors and respond to hormone manipulation
- No good evidence for viral involvement


HORMONAL EXPOSURE (SPORADIC)
GENETIC FACTORS (HEREDITARY)
Major risk factors of Breast Carcinoma

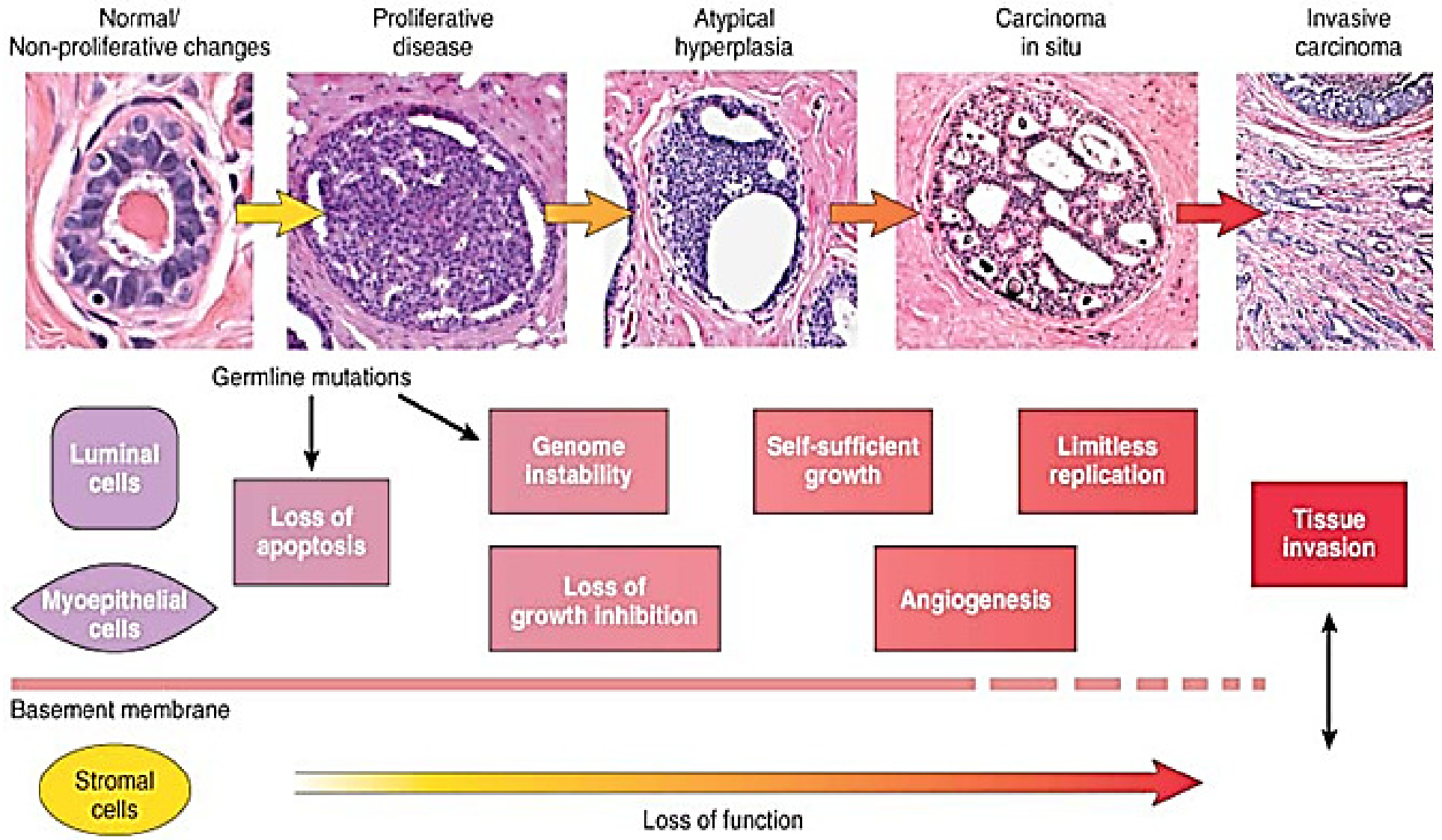
PREVENTION

Breast Cancer Risk Factors

that can be *controlled*



Pathogenesis:



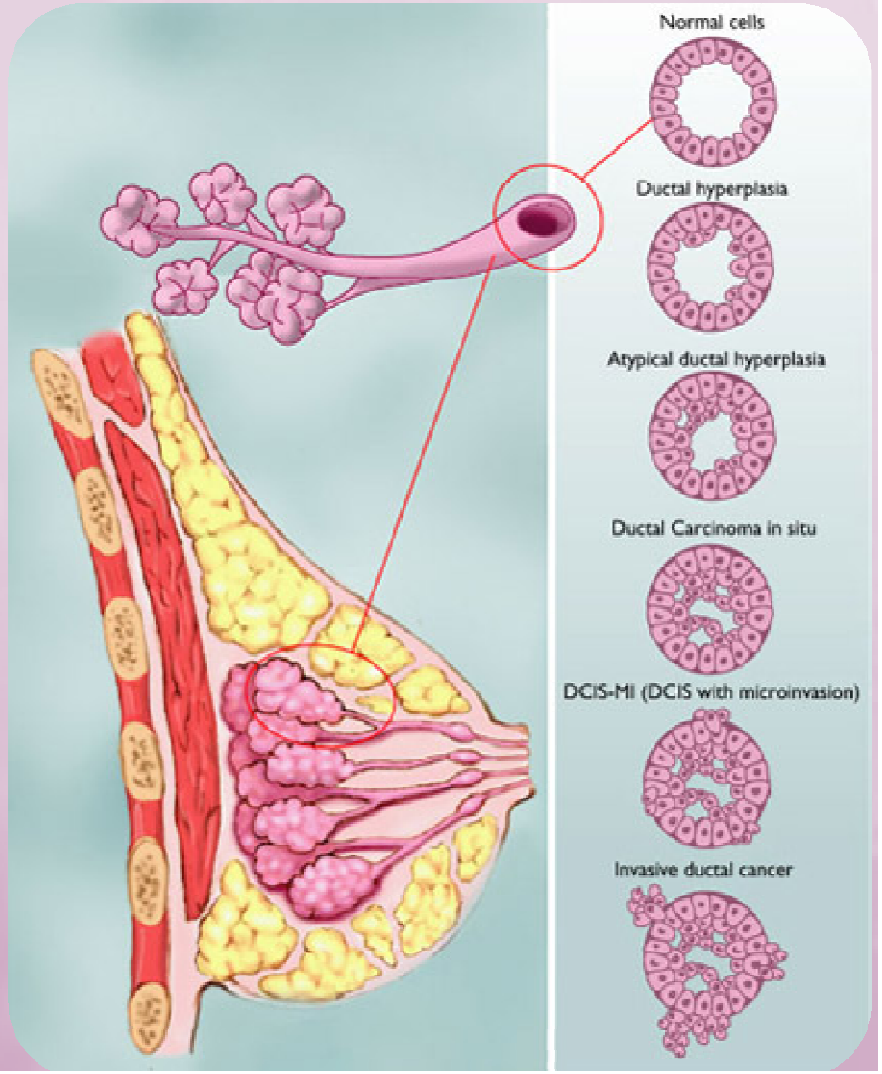
BREAST CARCINOMA - CLASSIFICATION

> 95 % breast malignancies → ADENOCARCINOMAS

BREAST CARCINOMA

IN SITU
Neoplastic cells – limited within the ducts,lobules by BM.

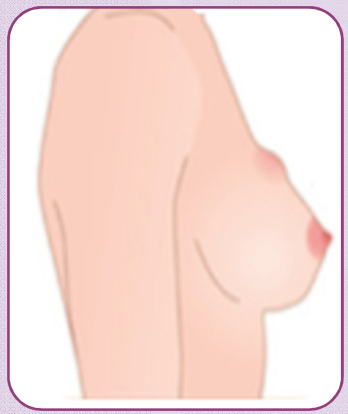
INVASIVE
Penetrated through the BM into the stroma.



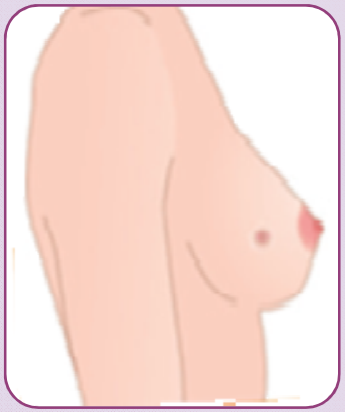
CLASSIFICATION – BREAST CARCINOMA

- ***NON-INVASIVE/IN SITU CARCINOMA***
  - Intraductal carcinoma
  - Lobular carcinoma in situ
- ***INVASIVE CARCINOMA***
  - Infiltrating (invasive) duct carcinoma – NOS
  - Infiltrating (invasive) lobular carcinoma
  - Medullary carcinoma
  - Colloid (mucinous) carcinoma
  - Papillary carcinoma
  - Tubular carcinoma
  - Adenoid cystic carcinoma
  - Secretory carcinoma
  - Inflammatory carcinoma
  - Carcinoma with metaplasia
- ***PAGET'S DISEASE OF THE NIPPLE***

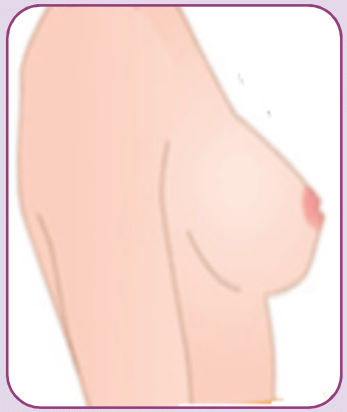
SYMPTOMS OF BREAST CANCER



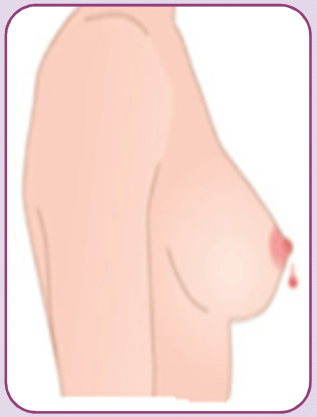
A persistent lump of thickening in the breast or armpit area.



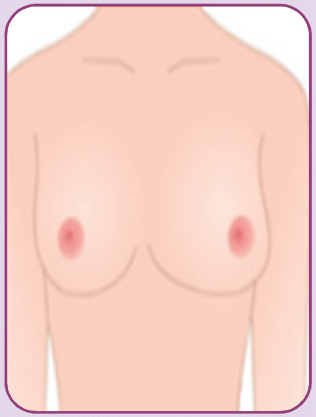
Changes in the colour or skin of the breast, areola or nipple(e.g. dimpling, puckering or scaling)



A newly retracted /inverted (pulled in nipple)



Blood or discharge from the nipple.



A change in the size or shape of the breast.

SCREENING FOR BREAST CANCER

A Good Breast Health Plan

A

Self Awareness (Monthly Self Exams) (BSE)

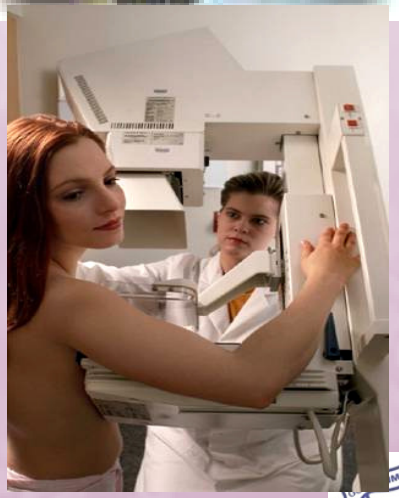
B

Clinical Breast Examination (CBE)

C

Mammograms





Staging Breast Cancer



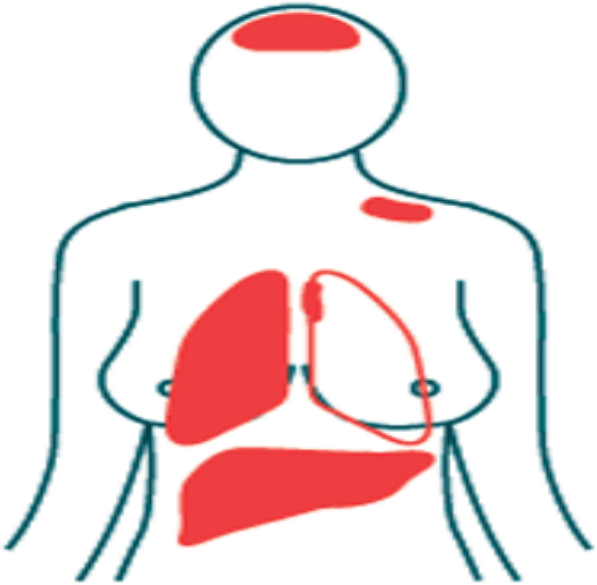
Stage 1
Early disease: tumour confined to the breast (node-negative)



Stage 2
Early disease: tumour spread to movable ipsilateral axillary node(s) (node-positive)



Stage 3
Locally advanced disease: tumour spread to the superficial structures of the chest wall; involvement of ipsilateral internal mammary lymph nodes



Stage 4
Advanced (or metastatic) disease: metastases present at distant sites, such as bone, liver, lungs and brain and including supraclavicular lymph node involvement

Stage	T: Primary Cancer	Lymph Nodes (LNs)	M: Distant Metastasis	5-Year Survival (%)
0	DCIS or LCIS	No metastases	Absent	92
I	Invasive carcinoma ≤2 cm	No metastases	Absent	87
II	Invasive carcinoma >2 cm	No metastases	Absent	75
	Invasive carcinoma <5 cm	1 to 3 positive LNs	Absent	
III	Invasive carcinoma >5 cm	1 to 3 positive LNs	Absent	46
	Any size invasive carcinoma	≥4 positive LNs	Absent	
	Invasive carcinoma with skin or chest wall involvement or inflammatory carcinoma	0 to >10 positive LNs.	Absent	
IV	Any size invasive carcinoma	Negative or positive lymph nodes	Present	13

TREATMENT FOR BREAST CANCER

- Surgery
- Radiation Therapy
- Chemotherapy
- Hormonal Therapy





STAGE	MEDICAL THERAPY	COMMENTS
I (<1cm) Hormone receptor–positive Hormone receptor–negative HER-2–positive	Endocrine therapy ± chemotherapy Consider chemotherapy Strongly consider trastuzumab based chemotherapy	Consider genomic testing
I (>1cm) Hormone receptor–positive Hormone receptor–negative HER-2–positive	Endocrine therapy ± chemotherapy Chemotherapy Trastuzumab based chemotherapy	Consider genomic testing
II (LN negative) Hormone receptor–positive Hormone receptor–negative HER-2–positive	Endocrine therapy ± chemotherapy Chemotherapy Trastuzumab-based chemotherapy	Consider genomic testing

II (LN positive), III Hormone receptor–positive Hormone receptor–negative HER-2–positive	Chemotherapy* + endocrine therapy Chemotherapy Trastuzumab based chemotherapy	*Consider tumor grade; extent of disease; % HRpositive; markers of proliferation (Ki67); patient health

Non–Trastuzumab-Based Regimens

- AC (doxorubicin, cyclophosphamide)
- TC (docetaxel, cyclophosphamide)
- TAC (docetaxel, doxorubicin, cyclophosphamide)
- Dose-dense chemotherapy: AC followed by paclitaxel, administration every 2 wk
- AC followed by paclitaxel administered weekly
- AC followed by docetaxel
- FAC (5-fluorouracil, doxorubicin, cyclophosphamide)
- FEC (5-fluorouracil, epirubicin, cyclophosphamide)
- CMF(cyclophosphamide, methotrexate, 5-fluorouracil)
- FAC or FEC followed by paclitaxel weekly or docetaxel

Trastuzumab-Based Regimens

- AC followed by paclitaxel weekly + trastuzumab → trastuzumab maintenance
- AC followed by docetaxel + trastuzumab → trastuzumab maintenance
- TCH(docetaxel, carboplatin, trastuzumab) → trastuzumab maintenance
- Chemotherapy followed by trastuzumab maintenance

Neoadjuvant Therapy

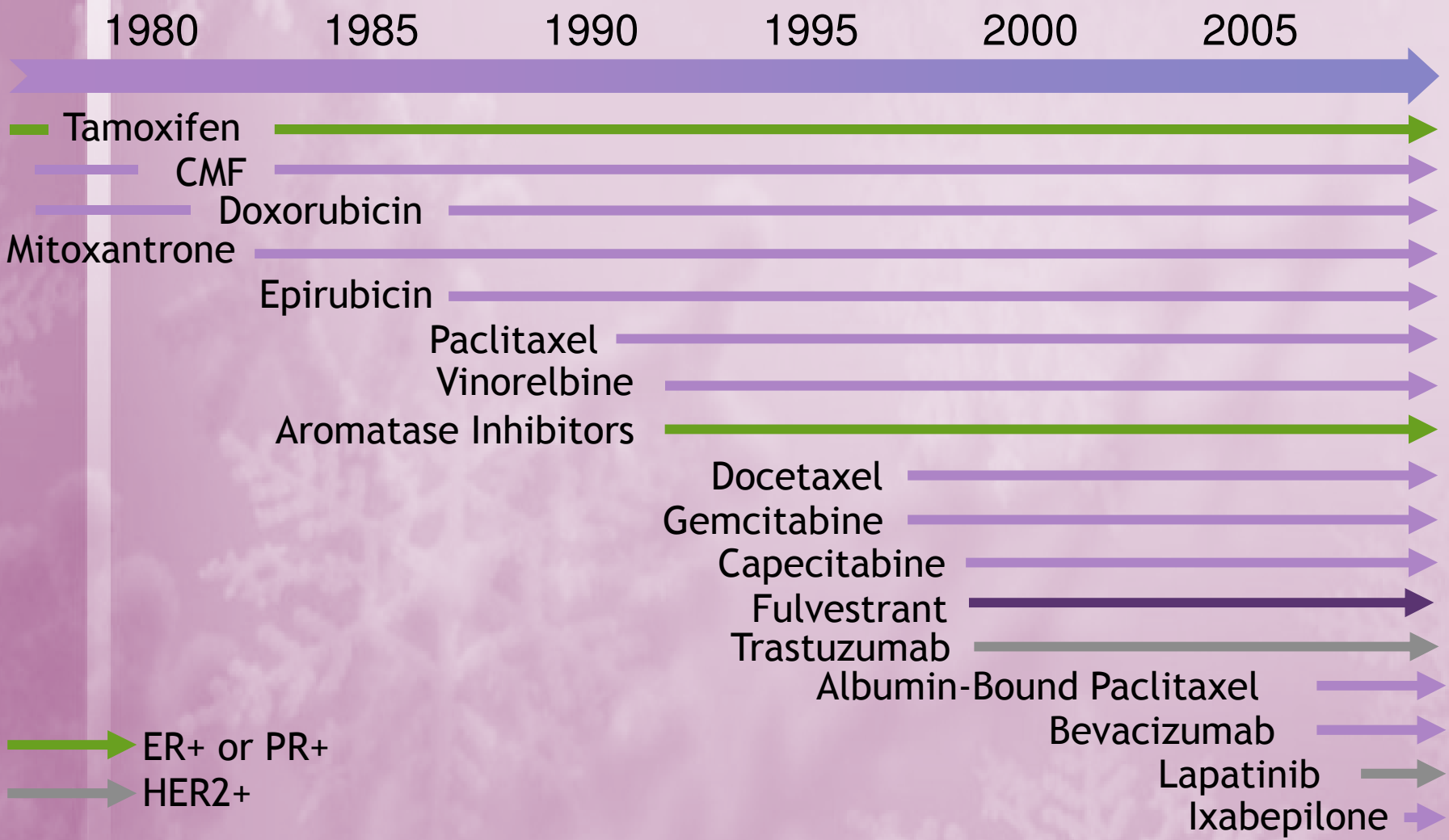
- Paclitaxel weekly + trastuzumab followed by FEC + trastuzumab

class	drugs	Mechanism of action
anthracyclines	doxorubicin, epirubicin	topoisomerase II inhibitor and antimetabolite
taxanes	paclitaxel, docetaxel	microtubule inhibitors
Alkylating agents	cyclophosphamide	Alkylation of DNA or RNA
Antimetabolites	Methotrexate, flurouracil	Folic acid and pyrimidine analogues
Antibiotics	Mitomycin, doxorubicin*, mitoxantrone	Intercalation of DNA basepairs and breaking of DNA, *also by inhibiton of topoisomerase II
Monoclonal antibodies	Transtuzumab	Targets HER2
estrogen receptor modulators	Tamoxifen, raloxifen	Binds to ERs, of estrogen sensitive tumors
ovarian ablation or suppression	Goserelin, leuprolein	LHRH analogues

Advanced pharmacotherapy

- The first prospective trials of systemic treatment combined oophorectomy, to deprive patients of estrogens, with radical mastectomy. Since these early trials, hundreds of prospective studies have involved thousands of women

Advances in Treatment



Hormone therapy

- For ER+ metastatic disease, hormone treatment is recommended as first line therapy, in the absence of life threatening visceral disease.
- The choice of hormone therapy depends on previous treatments and menopausal status.
- About 80% of breast cancers are ER positive. For these cancers, Tamoxifen remains the standard of care for premenopausal women
- five years of adjuvant tamoxifen,, reduces the relative risk of relapse by 41% and death from breast cancer by 31%.
- For postmenopausal women, aromatase inhibitors like letrozole, anastrozole and exemestane are superior to tamoxifen addition of a bisphosphonate or denosumab in those with osteoporosis.

- Women who are premenopausal at diagnosis but later become postmenopausal (naturally or as a result of chemotherapy), benefit from switching to an aromatase inhibitor after two to three years of tamoxifen.

- Pooled data from the ATLAS and ATTom trials confirm that, compared with no endocrine therapy, 10 years of adjuvant tamoxifen reduces death , by one third in the first 10 years of follow-up, with a continued benefit beyond 10 years.

- Fulvestrant, an antiestrogen and selective estrogen downregulator, had significant improvement in survival rates in postmenopausal women with ER-positive MBC

- The combination of everolimus, an inhibitor of mTOR, with the hormone therapy exemestane controls disease for substantially longer than exemestane and placebo

Biological therapy

- About 15% of breast cancers have amplification of the HER2 gene, and these cancers have an intrinsically worse prognosis
- Trastuzumab is a monoclonal antibody against the extracellular domain of the HER2 receptor, and given every three weeks for a year improves disease-free survival
- 1yr of adjuvant trastuzumab for all eligible patients with HER2+ early-stage breast cancer had favorable outcomes.
- All patients derived benefit from adjuvant trastuzumab with chemotherapy
- Pertuzumab HER2 dimerization inhibitor, trastuzumab and docetaxel are a new standard for the first-line treatment of HER2+ metast breast cancer

- ado-trastuzumab emtansine, antibody-drug conjugate consisting of the monoclonal antibody trastuzumab linked to
the cytotoxic agent mertansine (DM1) for use as a single agent for the treatment of patients with HER2-positive, metastatic breast cancer improved survival by 5.8 months

- Adjuvant Bevacizumab which inhibits vascular endothelial growth factor A (VEGF-A) in Triple-Negative Breast was not much successful

- The inhibition of many other pathways similar to mTOR using targeted therapies is being investigated in phase I-III clinical trials.

- antiangiogenic agents - Angiogenesis central role in tumor growth and distant metastasis. Drugs belonging to protease inhibitors, recombinant antibody to vascular endothelial growth factor (VEGF), endothelial toxins and naturally occurring agents are under trials.

Drug	Action	Treatment	status	Year	Phase
irosustat	steroid sulfatase inhibitor	**early breast cancer**	ER +, post menopausal	2012	2
nivolumab	IgG4 monoclonal antibody	Advanced breast cancer		2013	1/2
ipilimumab	CTLA-4 inhibitor	Advanced breast cancer		2013	1/2
AZD4547	FGFR inhibitor		ER+, FGFR1+	2010	2
AZD5363	Akt inhibitor	Advanced breast cancer	ER+	2013	1/2
buparlisib	PI3K inhibitor	Advanced cancer	ER+, HER-	2013	3
saracatinib	inhibitor of Src and Abl	**advanced breast cancer**	ER+	2012	2
GDC0941	PI3K inhibitor		ER+	2012	2

Drug	Action	Treatment	status	Year	Phase
lapatinib,	tyrosine kinase inhibitor	Advanced breast cancer	Post menopausal, HER 2 +	2011	3
niraparib	PARP, inhibitor	Advanced breast cancer	BRCA, HER2-	2014	3
panobinostat	HDAC inhibitor	Advanced breast cancer	HER 2+	2008	1/2
TKI258	FGFR3 inhibitor	Advanced breast cancer	HER 2-	2010	2
Panitumumab	EGFR inhibitor	Triple negative breast cancer		2013	2

Chemotherapy

- Chemotherapy is used for hormone resistant cancer, hormone receptor negative disease, and rapidly progressive disease, as well as most HER2 positive cancers irrespective of oestrogen receptor status.
- The choice of which chemotherapy to use depends on patient factors, tumour factors and duration and response to previous chemotherapy.
- It is often given for a fixed number of cycles, especially with regimens that incur toxicity
- There is no consensus on the optimal duration of chemotherapy.

Chemotherapy

- Combination adjuvant chemotherapy reduces the relative risk of death from breast cancer by about a third with the absolute risk reduction depending on the risk of relapse.

- Neoadjuvant therapy and locally advanced breast cancer

- Patients not suitable for conservative surgery can be treated with preoperative chemotherapy, HER2 targeted therapy, or endocrine therapy to downstage the tumour

- Patients who achieve a complete pathological response to chemotherapy, especially those with oestrogen receptor negative breast cancer, have a good prognosis.

- Intense Dose-Dense Chemotherapy High-Risk Patients with ≥4 Positive LNs, Both 10-yr relapse-free survival and overall survival were significantly improved in the dose-dense arm
- Eribulin a mitotic inhibitor, is effective after A/T early in MBC treatment. Efficacy in TNBC promising and First-line eribulin is safe and active
- Platinum based chemotherapy has activity in mTNBC and some first-line patients can have very durable response
- Ixabepilone, is an analog of epothilone B plus capecitabine demonstrates superior efficacy to capecitabine alone in metastatic breast cancer resistant to anthracyclines and taxanes
- nab-Paclitaxel as First-Line Therapy for MBC with Poor Prognostic Factors

- The best chemotherapy agent to partner with lapatinib remains capecitabine, pyrimidine antagonist.
- Trastuzumab-emtansine is an antibody-drug conjugate that specifically targets chemotherapy to HER2 positive breast cancer cells.
- CDK Inhibitor PD 0332991 for Advanced Breast Cancer increased the survival rates

Drug	Action	Treatment	status	Year	Phase
Eribulin	mitotic inhibitor	**advanced breast cancer**		2013	4
Vinflunine	Microtubuli n inhibitor	Advanced breast cancer		2010	3
neratinib	Tyrosine kinase inhibitor	**advanced breast cancer**	HER2+	2013	3
Rucaparib	PARP inhibitor	**Advanced solid tumor**	BRCA1/2	2011	1/2
BAL101553	microtubule inhibitor	triple negative breast cancer		2011	1/2
Everolimus +	mTOR inhibitors		ER+, HER-	2014	2
nab-paclitaxel + gemcitabine/car boplatin	Chemother apy	triple negative breast cancer	ER-, HER-	2014	2/3

Drug	Action	Treatment	status	Year	Phase
Erlotinib	Tyrosine kinase inhibitor	Stage I, II, III		2013	2
oxaliplatin	inhibition of DNA synthesis	Recurrent and MBC		2011	2
Liposomal Doxorubicin	topoisomerase II inhibitor and antimetabolite	Post surgical elderly patients		2012	3
Amrubicin	topoisomerase II inhibitor and antimetabolite	**Metastatic Breast Cancer**	**HER2-**	2009	1/ 2
Enzastaurin	inhibits protein kinase C beta			2008	2

Bisphosphonates

- A recent meta-analysis of 36 randomised controlled trials found that treatment with bisphosphonates is associated with a reduced risk of recurrence of breast cancer in postmenopausal women only.
- Zoledronic Acid Added to Standard Therapy - sufficient vitamin D levels predicted benefit for zoledronic acid
- Ibandronate for the Treatment of Bone Metastases was similar to zolendronic acid
- denosumab increases bone mass in patients at high risk for fracture receiving adjuvant aromatase inhibitor therapy

Vaccines and stem cell therapy

- Neuvax vaccine which is a extracellular component of HER2 receptor is in phase 3 trial
- Allogeneic GM-CSF-secreting Breast Tumor Vaccine for the Metastatic Breast Cancer intact tumor cells genetically modified to secrete the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF)
- Vaccination With Autologous Breast Cancer Cells Sialyl-Tn-keyhole limpet hemocyanin (STn-KLH) engineered to Secrete GM-CSF in Metastatic Breast Cancer had an effective immune response to vaccine immunotherapy with minimal side effects,

- CXCR1/2 signals via transactivation of HER2. inhibitors with existing chemotherapy and endocrine therapy agents may be more effective leading to improved outcomes in both the adjuvant and advanced settings.

Others

- Fluvastatin had measurable biologic changes by reducing tumor proliferation and increasing apoptotic activity in high-grade, stage 0/1 breast cancer
- Aspirin may slow breast cancer recurrence and death
- Polyphenon E (Green Tea Extract) has potential mechanistic actions of tea polyphenols in growth factor signalling, angiogenesis and lipid metabolism.
- Aprotinin, uPA inhibitor which is a key regulator of the remodeling of recently formed blood clots in advanced breast cancer
- Curcumin may reduce inflammation in breast tissue and fat which may affect the risk of developing breast cancer.
- Metformin and Atorvastatin in Newly Diagnosed Operable Breast Cancer

Conclusions

Key advances in the management of breast cancer have been made in the last few years

- Adjuvant treatment is individualized to possibly include chemotherapy, hormone therapy and trastuzumab
- New treatments are intensive and may result in long-term health concerns
- Evidence-based, informative discussion to review risks and benefits for each patient is of critical importance
- We are on the brink of an era of diverse molecular stratification of breast cancer, and the development of increasingly personalised medicine.
- Through such approaches, the survival rates of patients with breast cancer are likely to continue to steadily improve.

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Thank you