Cardiovascular Side Effects of Breast Cancer Therapies

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Theme Cancer

1/10/2019

Epidemiologi

Utredning

Behandling

- **Radioterapi/ Cytostatika/ Her2 blockad/ Immunterapi/ Anti-hormonell behandling**

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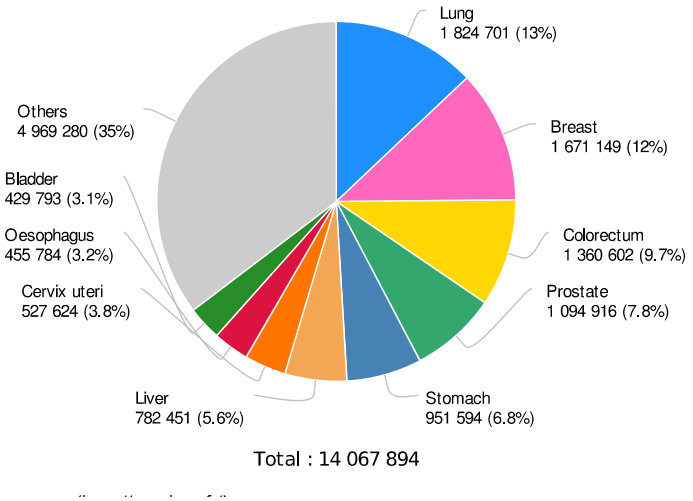
Bröstcancer

EPIDEMIOLOGI

Global cancer panorama

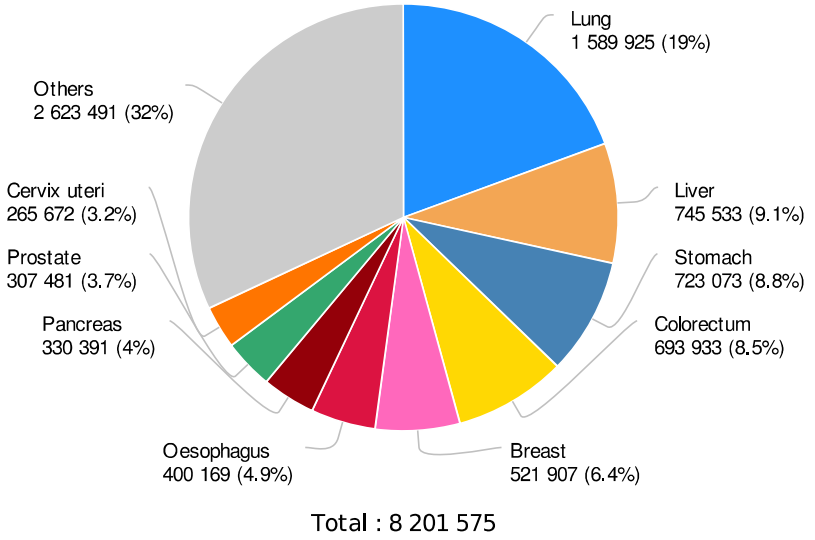
14,1 million cases

Estimated number of incident cases, both sexes, worldwide (top 10 cancer sites) in 2012



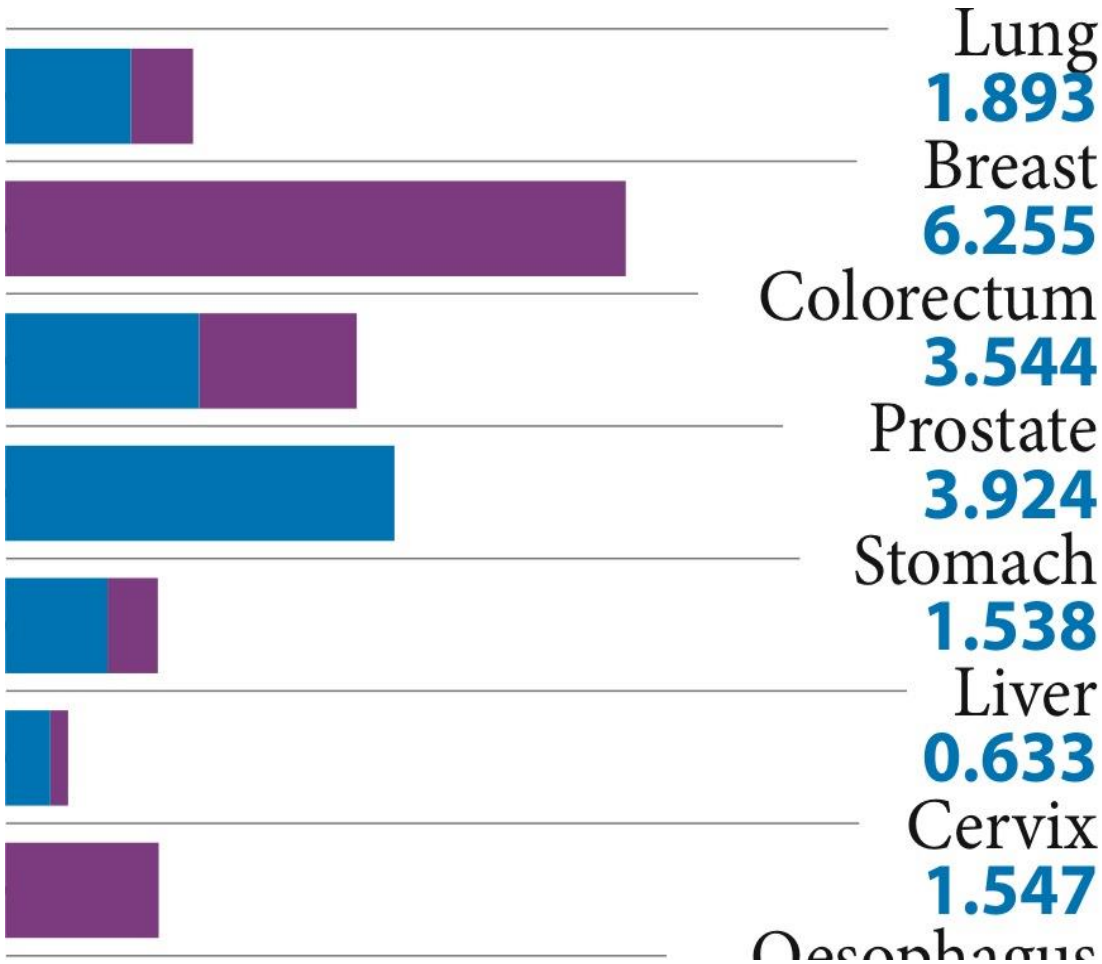
8,2 million deaths

Estimated number of deaths, both sexes, worldwide (top 10 cancer sites) in 201



GLOBOCAN 2012

Prevalence 32.5 million



Cancer research UK 2014

Förbättrad överlevnad

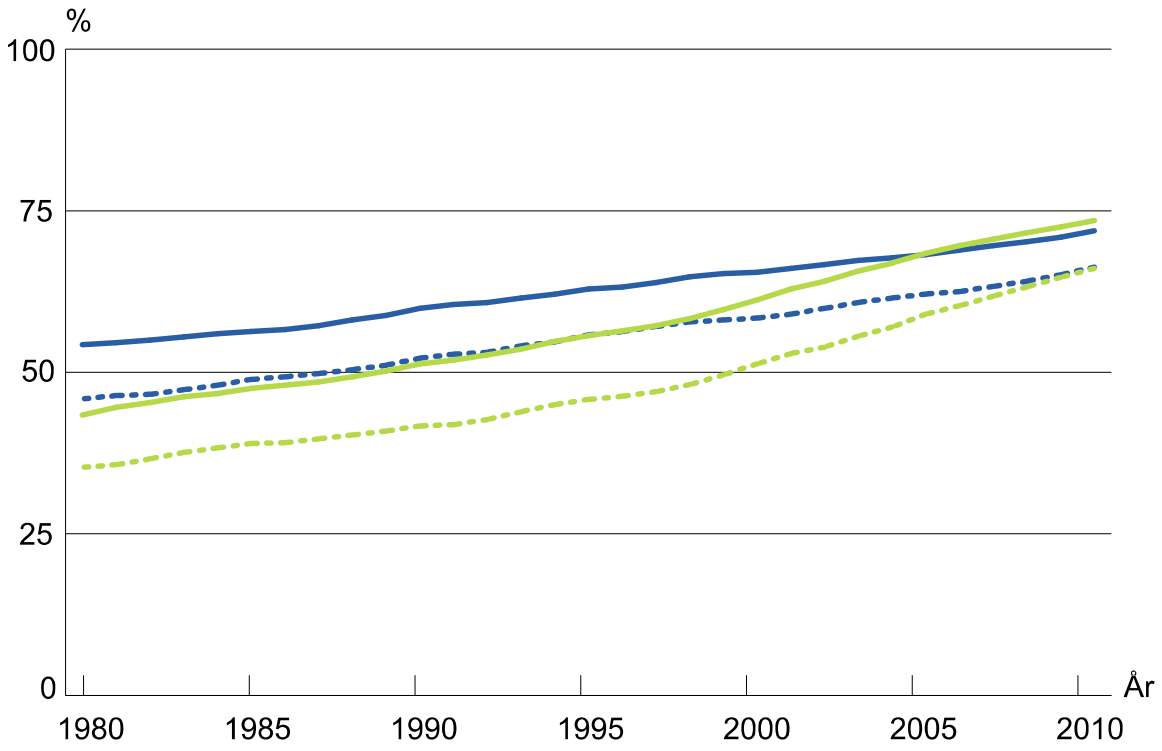
Relativ överlevnad

Totalsiffror för cancer, 1980-2010

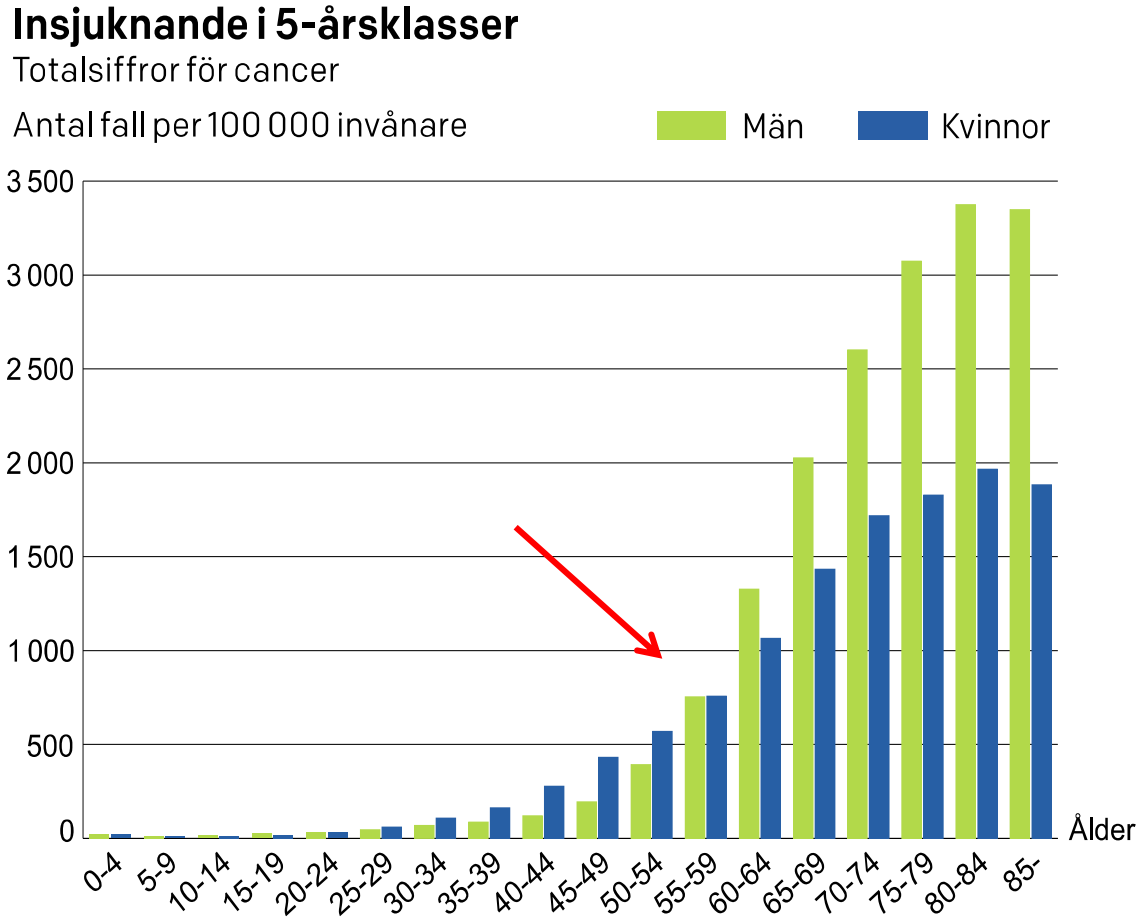
5-års relativ överlevnad — Män — Kvinnor

10-års relativ överlevnad — Män — Kvinnor

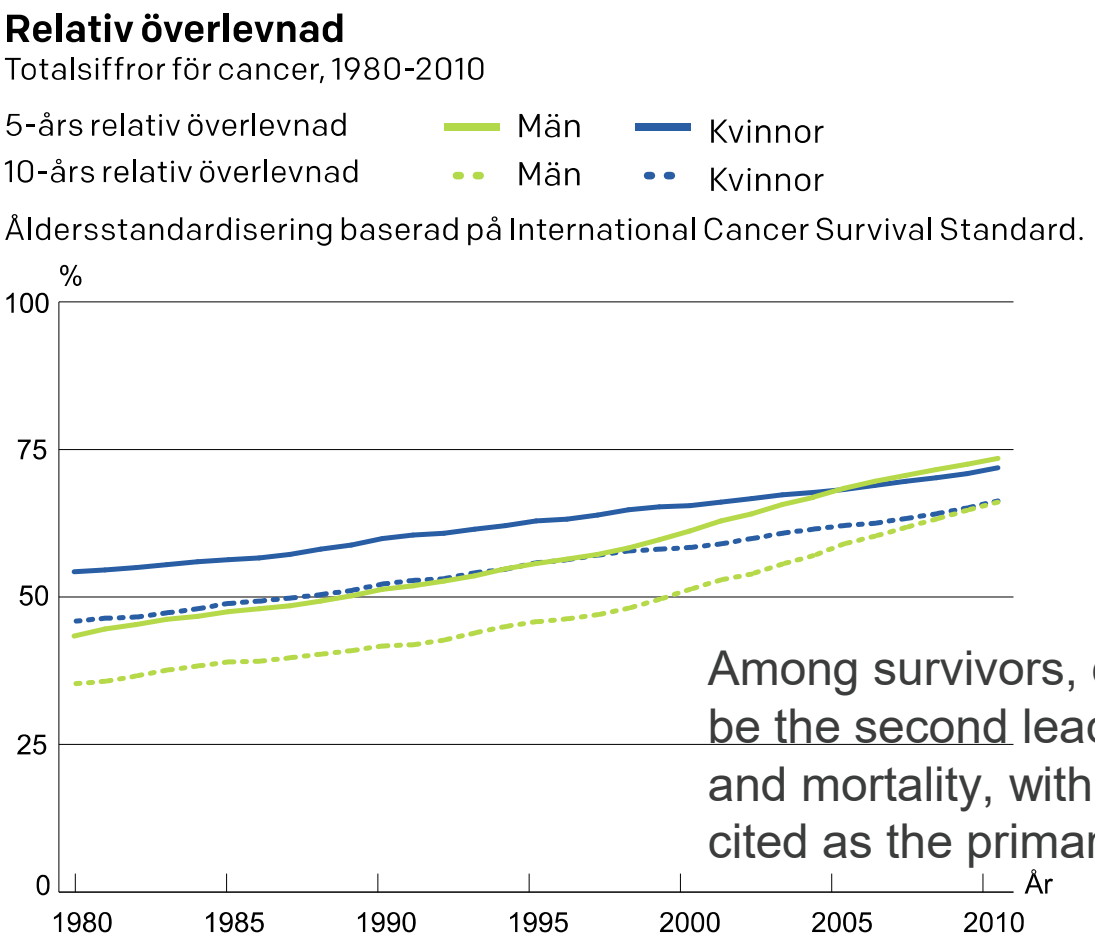
Åldersstandardisering baserad på International Cancer Survival Standard.



Många cancerpatienter har andra sjukdomar



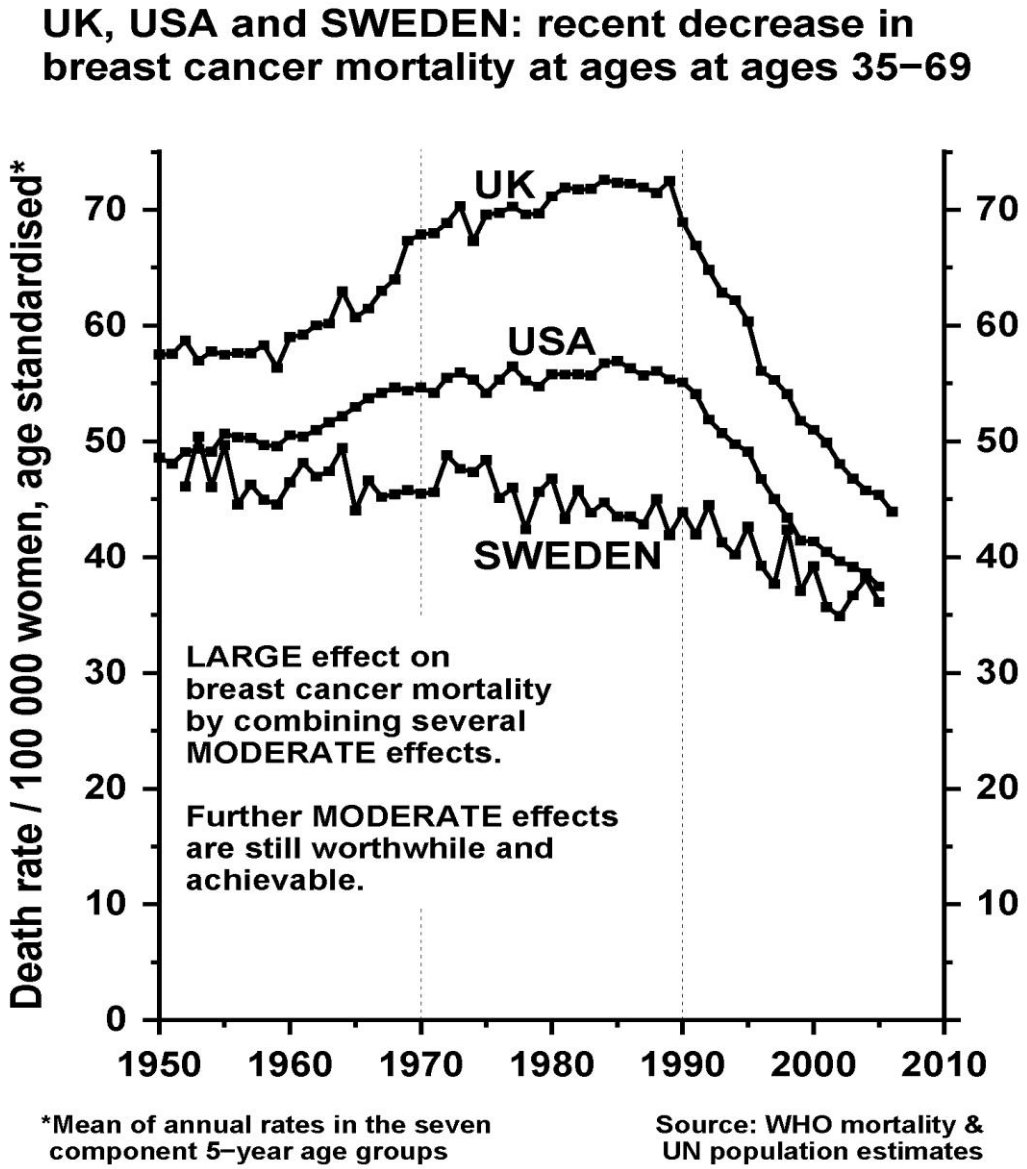
Cancer survival rates are improving



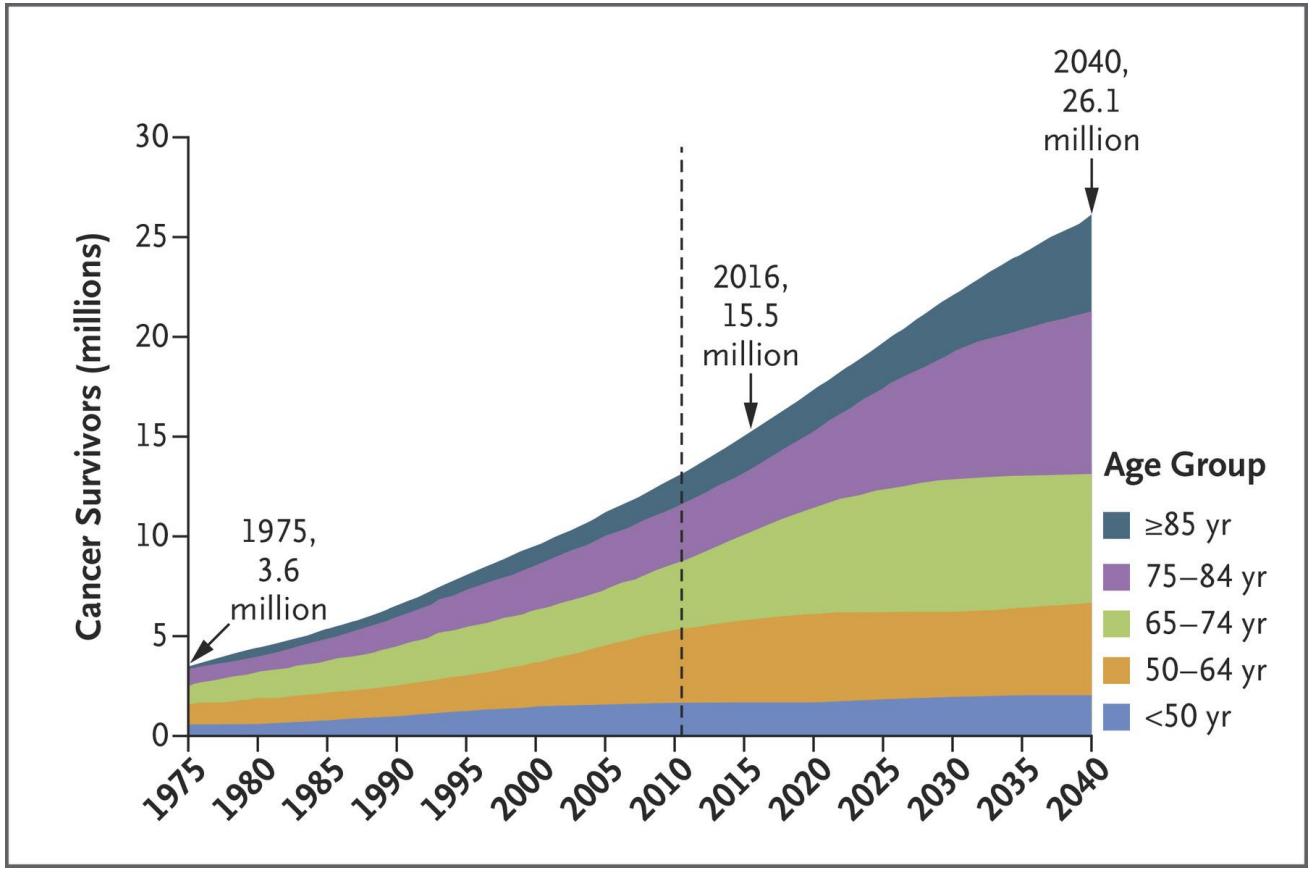
Among survivors, cardiotoxicity is reported to be the second leading cause of morbidity and mortality, with secondary malignancies cited as the primary cause of mortality.

Sulpher et al. J Oncol. 2015;2015:391848. doi: 10.1155/2015/391848.

Slide from Sir Richard Peto, Nobel Forum, KI 9/10 2008



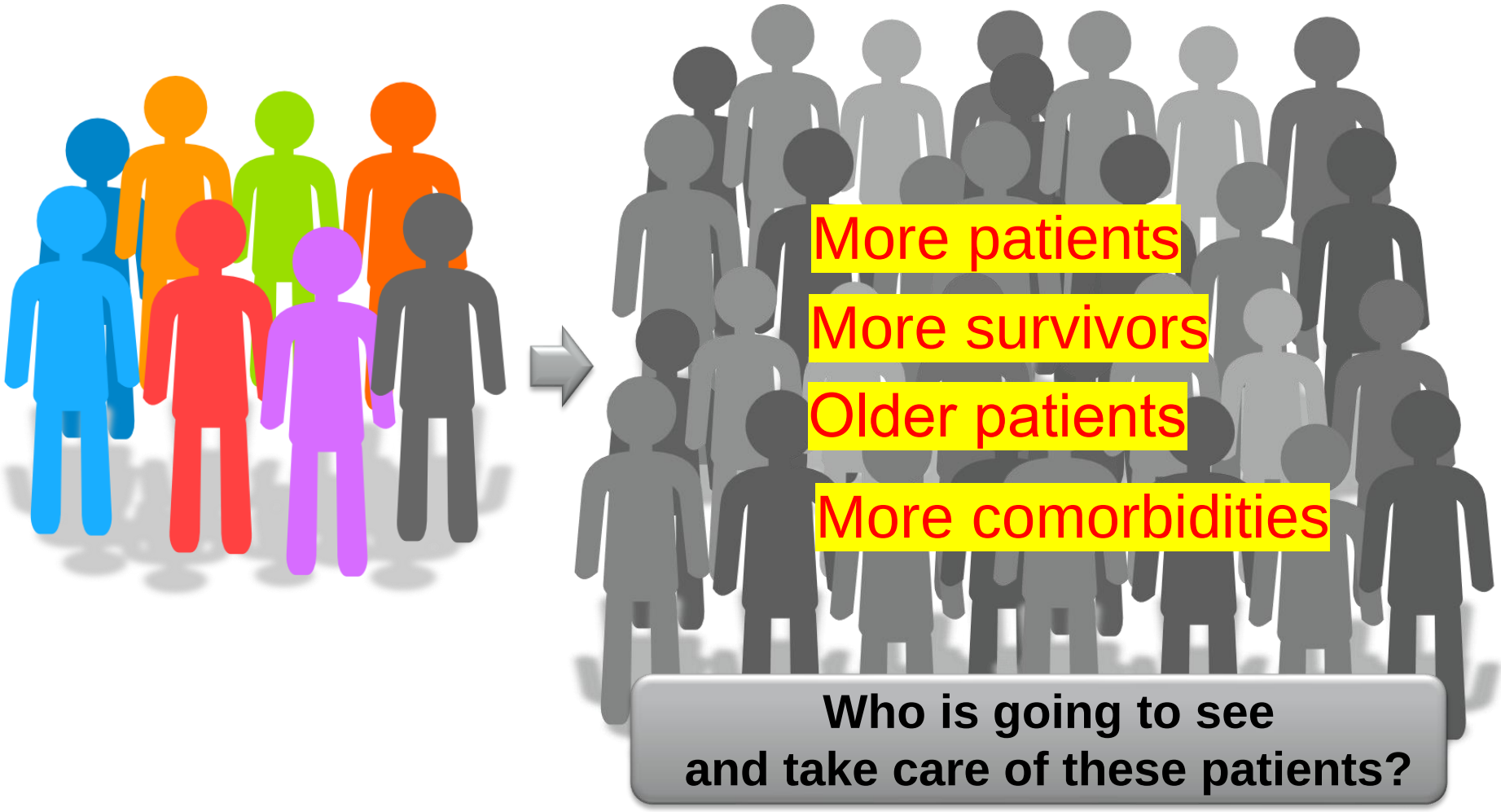
Cancer survivors are increasing. In 2040, the majority will be in their 60s, 70s, or 80s.



Shapiro CL, N Engl J Med. 2018

Cardio-Oncology

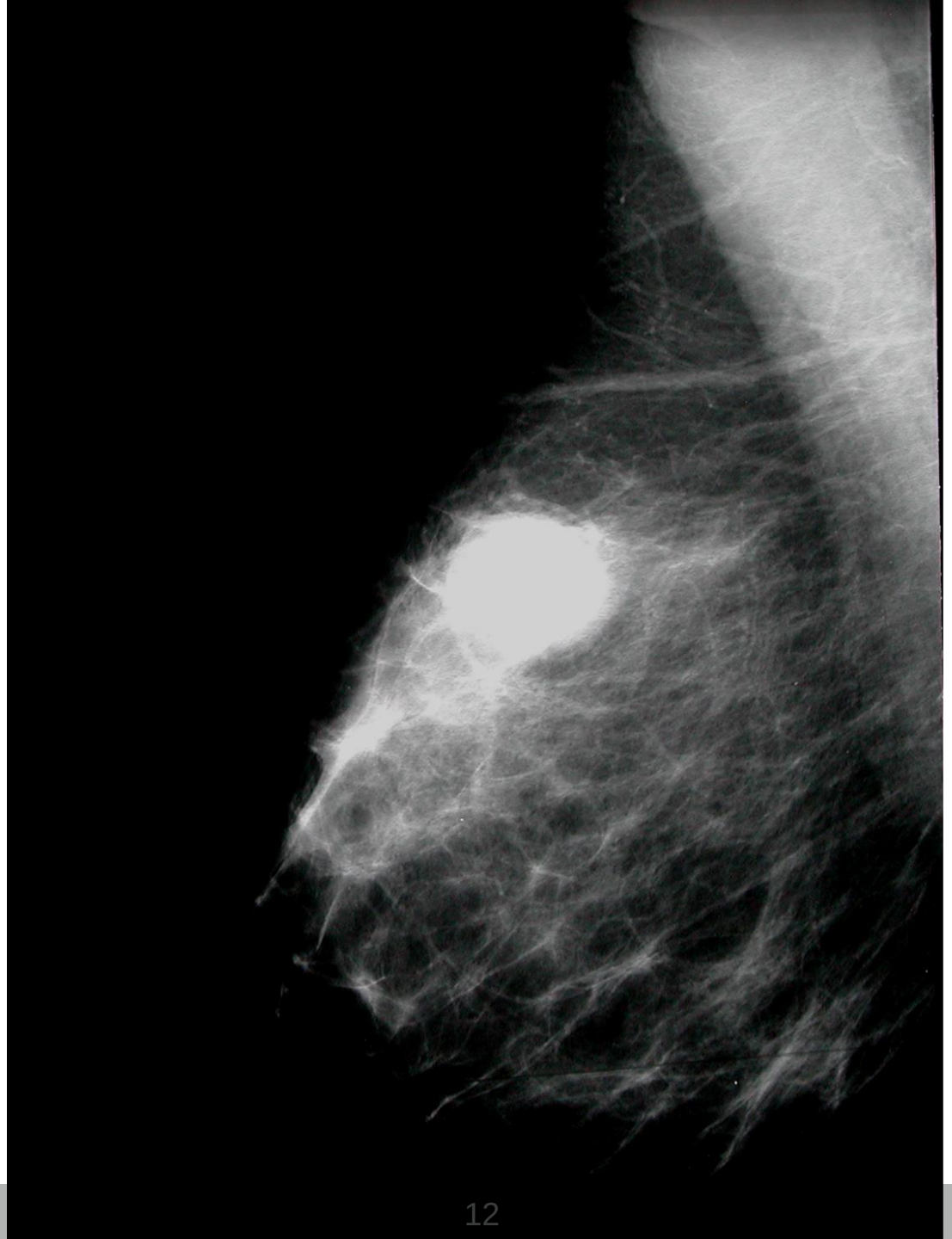
Changing Face of Cancer Care



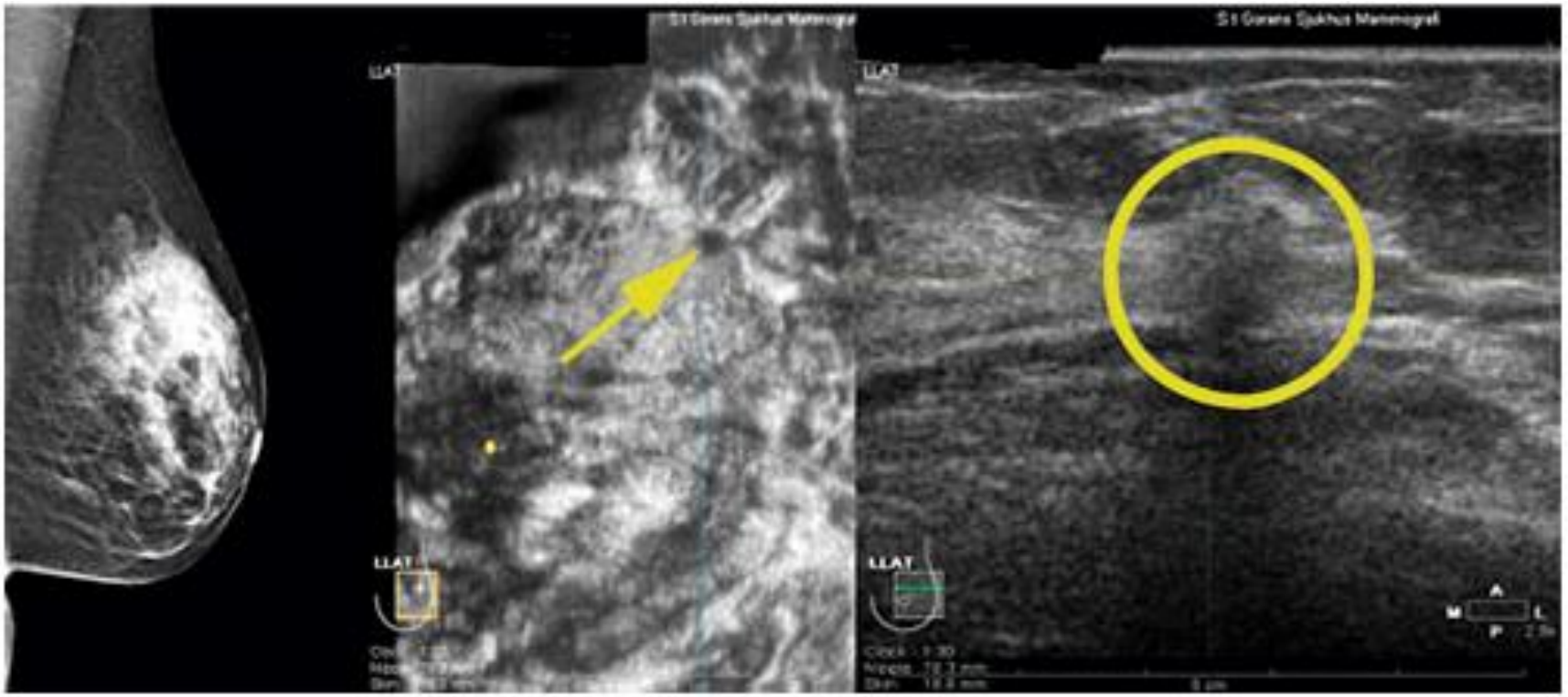
Bröstcancer

UTREDNING

Slides from assoc. Prof Edward Azavedo



B. 1956



Läkartidningen. 2017;114:EECU

Vad behöver vi veta?

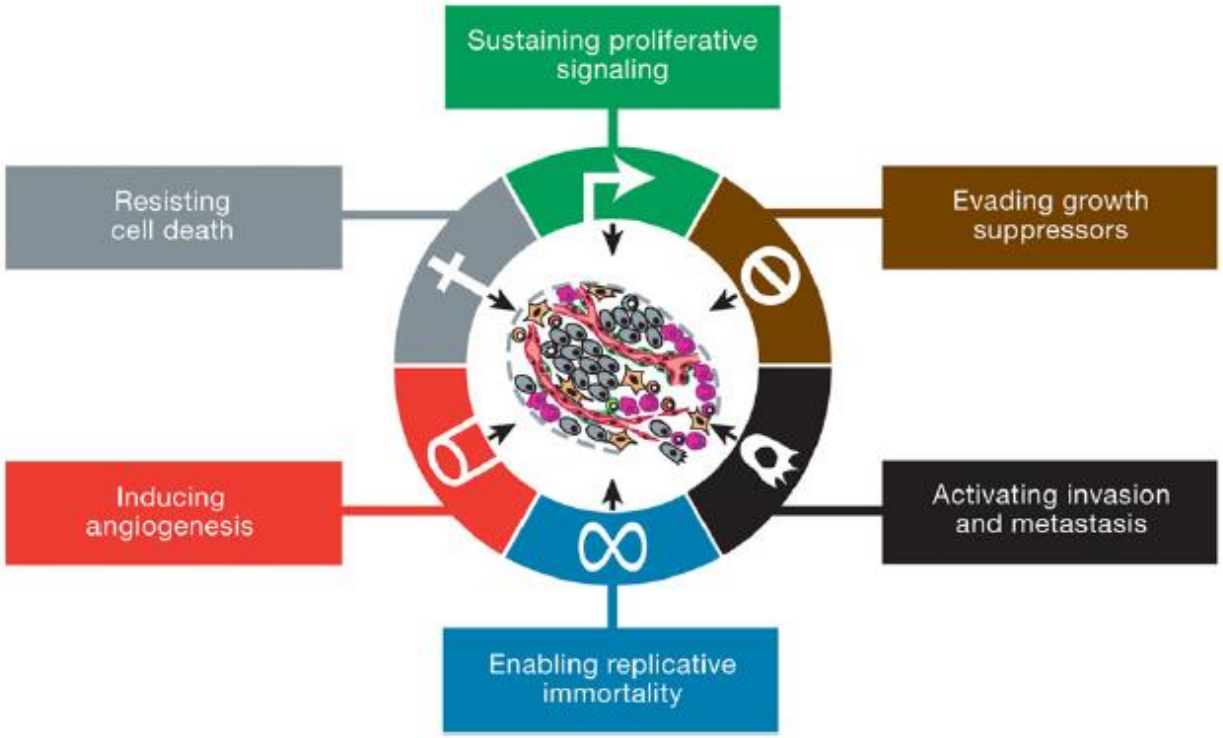
- Ålder
- Tumörens storlek
- Histologisk grad
- Receptor status
- HER-2/neu status
- Cellfördelningshastighet
- Lymfkörtel status

Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland



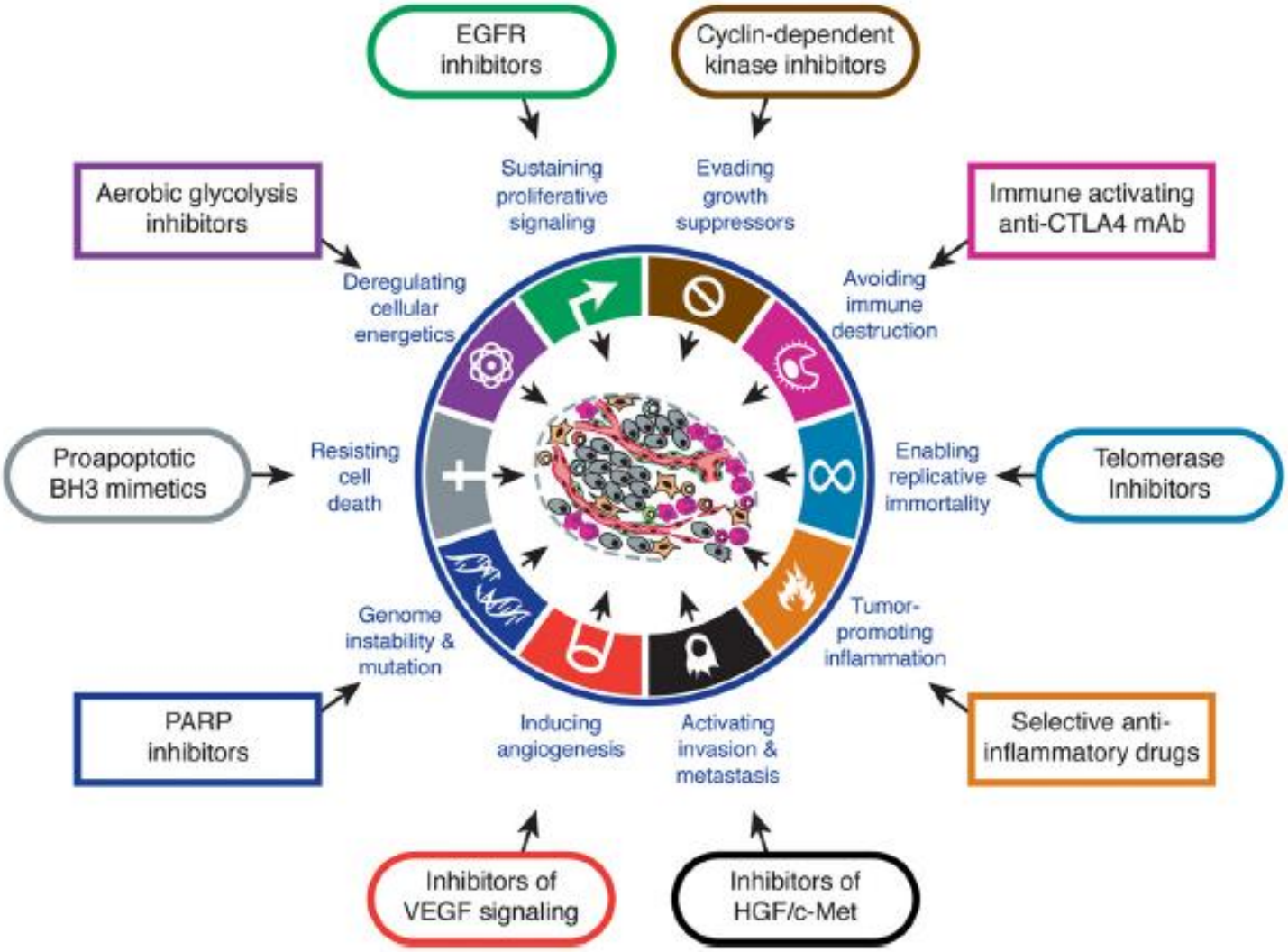


Figure 6. Therapeutic Targeting of the Hallmarks of Cancer

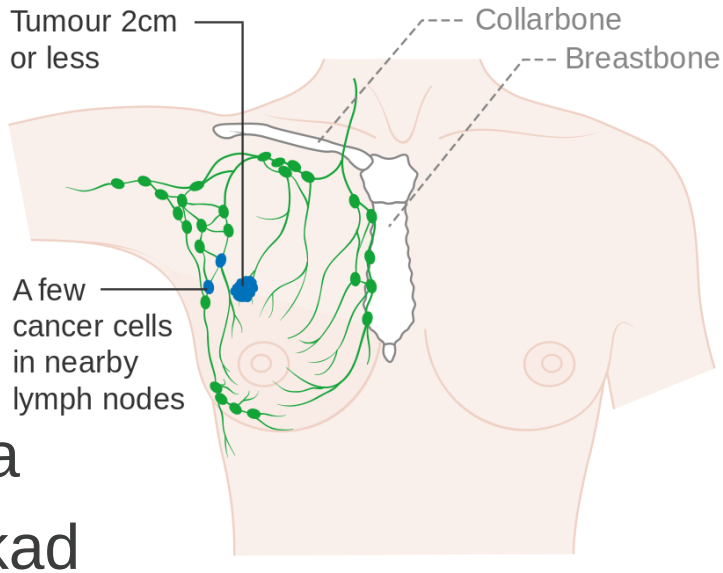
Drugs that interfere with each of the acquired capabilities necessary for tumor growth and progression have been developed and are in clinical trials or in some cases approved for clinical use in treating certain forms of human cancer. Additionally, the investigational drugs are being developed to target each of the enabling characteristics and emerging hallmarks depicted in Figure 3, which also hold promise as cancer therapeutics. The drugs listed are but illustrative examples; there is a deep pipeline of candidate drugs with different molecular targets and modes of action in development for most of these hallmarks.

Bröstcancer

BEHANDLING

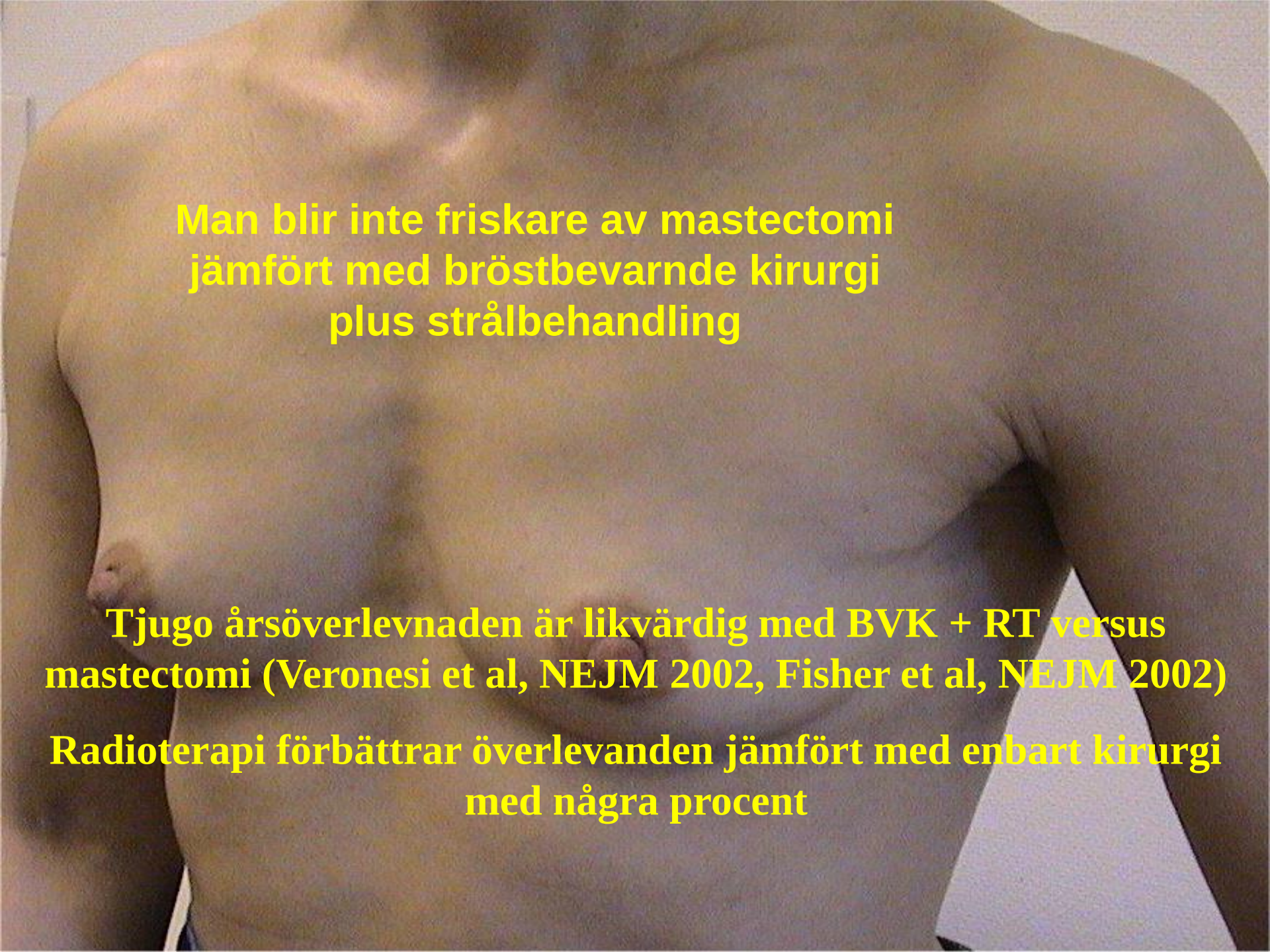
< 2cm + N0

1. Kirurgi
2. Adjuvant behandling
    1. Cytostatika
    2. Her 2blockad
    3. Radioterapi
    4. Anti-hormonell beh



>2cm eller N1<

1. Neoadjuvant
    1. Cytostatika
    2. Her 2blockad
2. Kirurgi
3. Adjuvant behandling
    1. Cytostatika
    2. Her 2blockad
    3. Radioterapi
    4. Anti-hormonell



Man blir inte friskare av mastectomi jämfört med bröstbevarnde kirurgi plus strålbehandling

Tjugo årsöverlevnaden är likvärdig med BVK + RT versus mastectomi (Veronesi et al, NEJM 2002, Fisher et al, NEJM 2002)

Radioterapi förbättrar överlevanden jämfört med enbart kirurgi med några procent

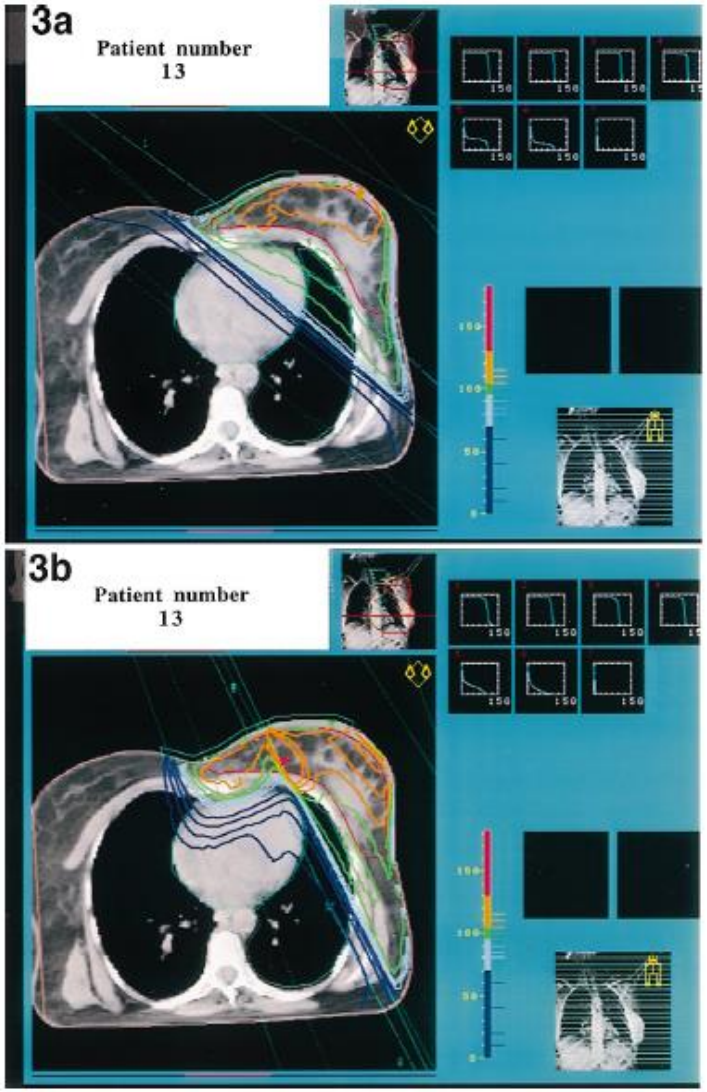


Fig. 3. Dose distributions in a section through the nipple for patient 13. Panel (a) shows the technique with 21 MV photons. Panel (b) shows the mixed electron–photon technique with 21 MV photons and 13 MeV electrons. The indicated isodose levels are 10, 20, 40 and 60% (dark blue), 80–90% (light blue), 95 and 100% (green) and 105, 110 and 115% (yellow).z

Jansson et al, Radiother & Oncology 1998

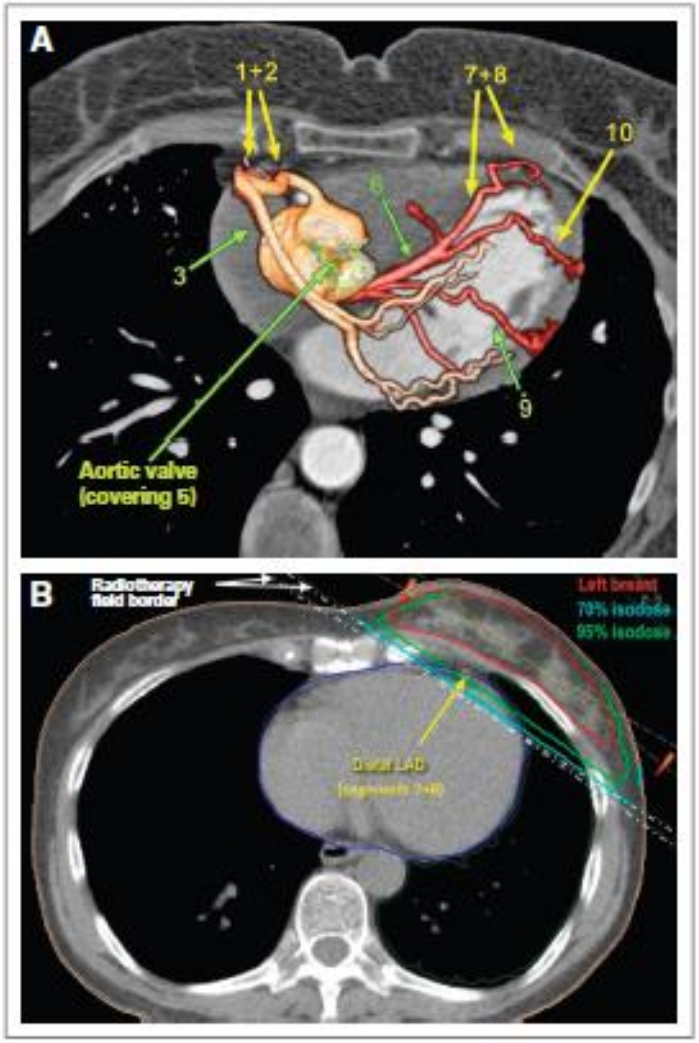
Postoperative RT to the breast parenchyma improves survival

EBCTCG, Lancet 2011

Postoperative RT to the regional nodes improves survival

EBCTCG, Lancet on Line 2014

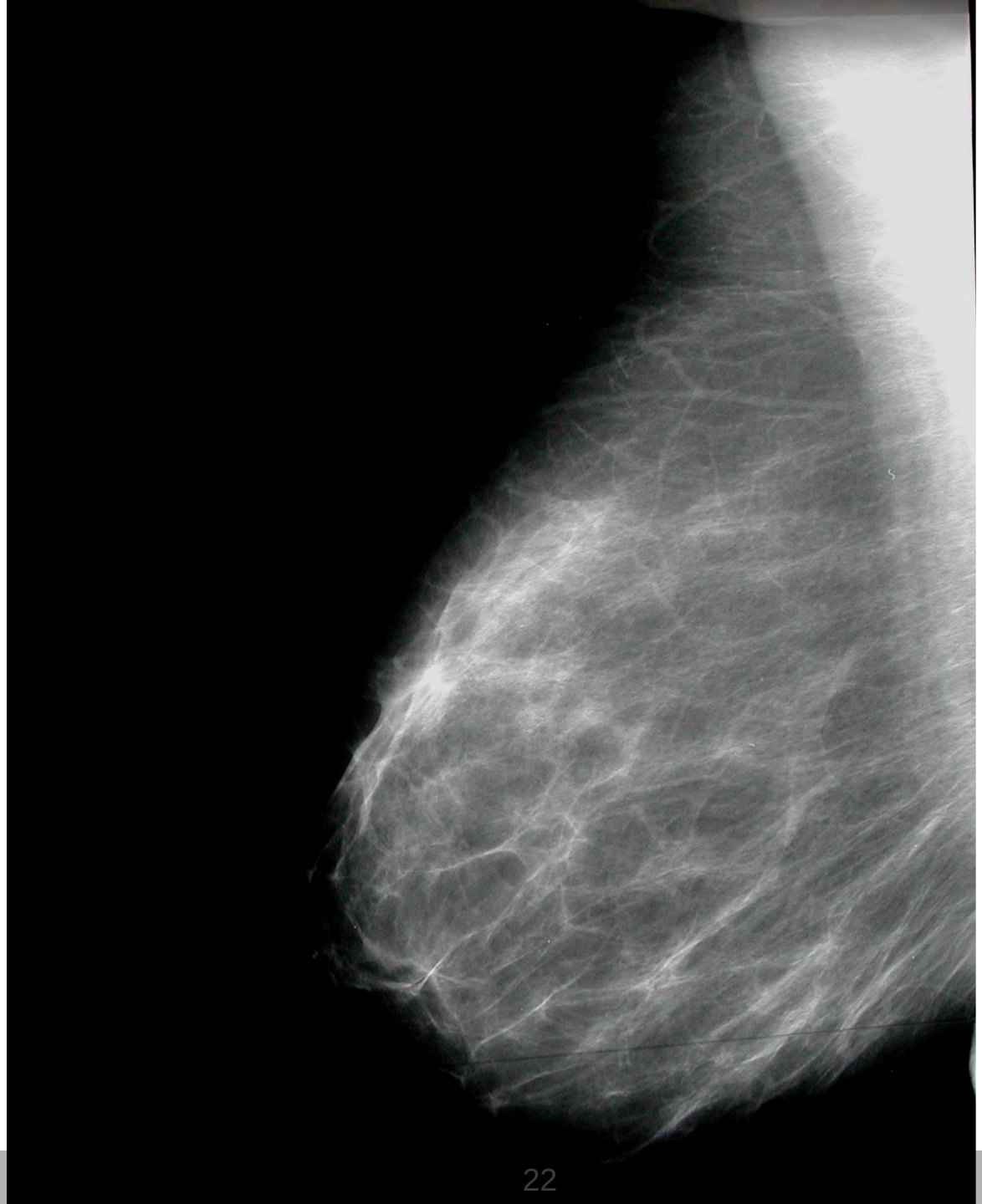
‘



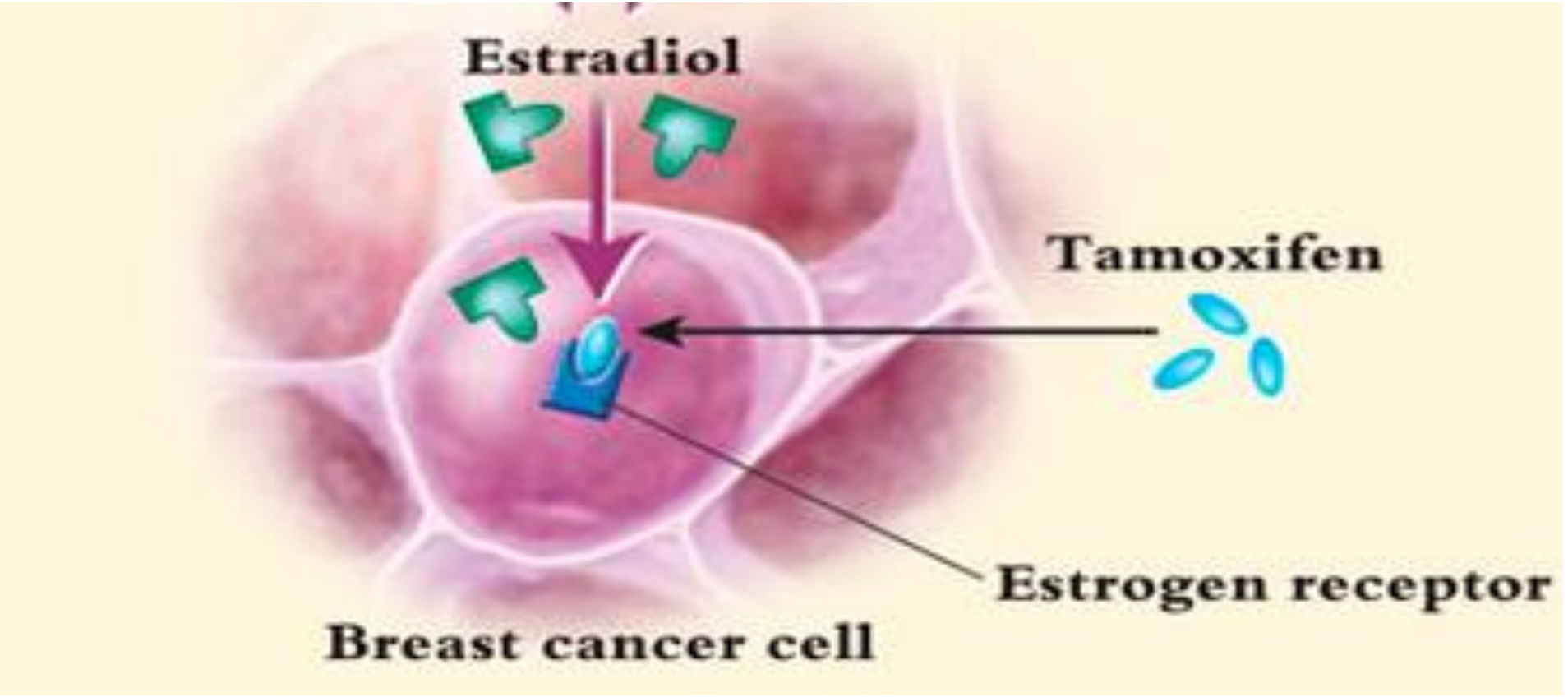
(A) Coronary angiogram superimposed on computed tomography (CT) of heart illustrating anatomy of coronary arteries with branches of right coronary artery artery (orange) and left circumflex and left anterior descending (LAD) arteries (red); numbered arrows indicate segments.

(B) CT dose-planned left tangential breast irridation showing distal LAD (yellow circle) and radiation fields.

Nilsson G et al, JCO 2012



After 4 courses of tFEC, sector resection Histological CR, both in breast & axillary nodes (29/1-02-conf. Rah)


Estradiol
Tamoxifen
Estrogen receptor
Breast cancer cell

Adjuvant systembehandling
Ger tydliga överlevnadseffekter

5 års överlevnad kring 90%
10 års överlvnad kring 80%

Mekanismen för kardiotoxicitet varierar mellan olika cancerbehandlingar

- Det första är direkt hjärtmuskelcellskada eller inflammation i hjärtmuskel och/eller hjärtsäck.
- Det andra är indirekt påverkan på koagulationssystemet med tromboembolier som kan leda till kardiovaskulära och cerebrovaskulära händelser.
- Det tredje är högt blodtryck som ofta ses vid behandling med antiangiogena läkemedel och kan ha akuta eller långsiktiga effekter på hjärtat med till exempel hypertrofi och med tiden utveckling av hjärtsvikt.
- Den fjärde mekanismen för hjärttoxicitet är genom förekomst av förmaksflimmer vilket i sig är vanligt hos äldre individer och kan förvärras av cancerbehandling.

Radiotherapy

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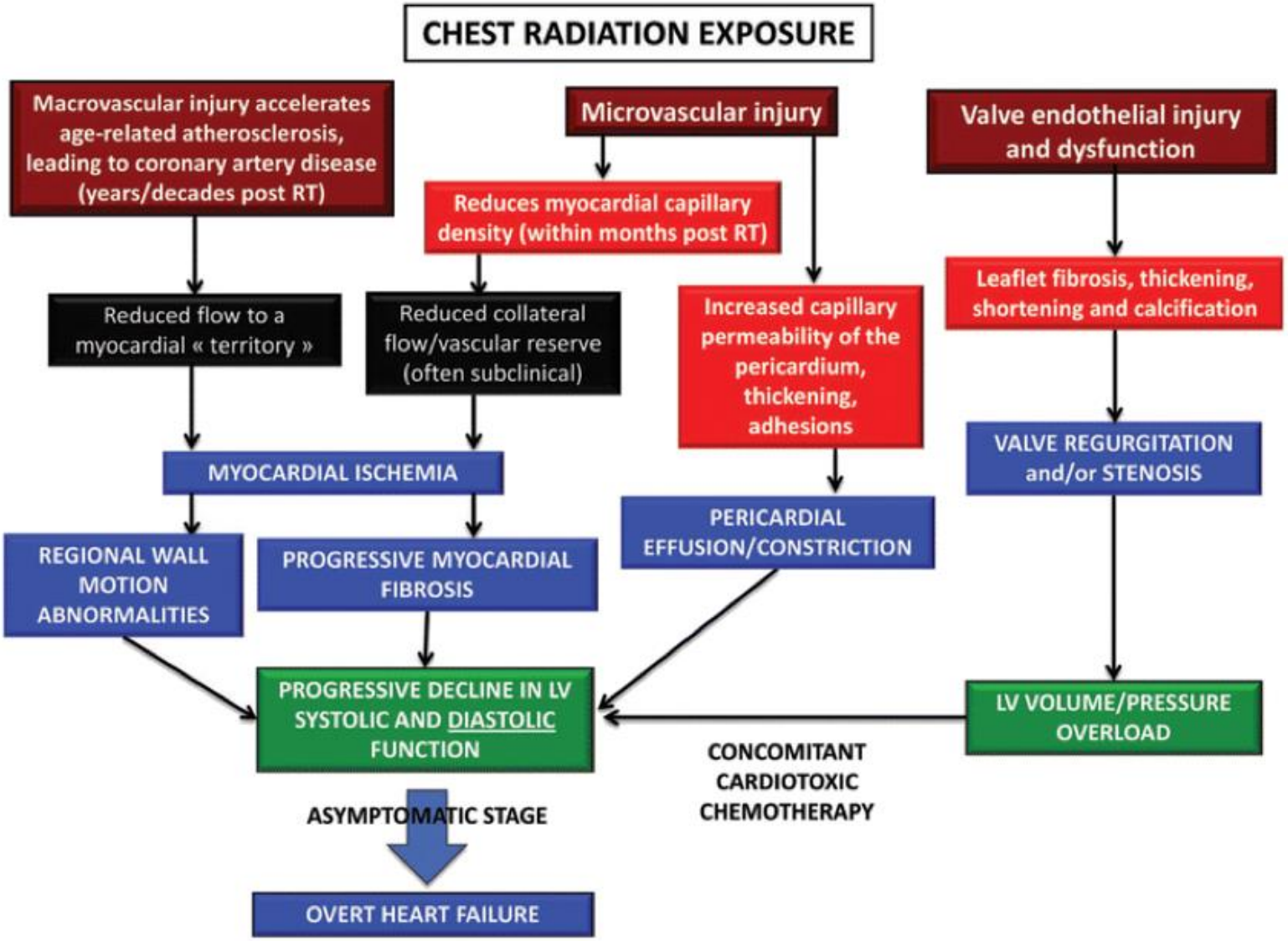


Chen-Scarabelli, C., McRee, C., Leesar, M.A. et al. J. Nucl. Cardiol. (2017) 24: 906. https://doi-org.proxy.kib.ki.se/10.1007/s12350-016-0535-y

10-year BC survivors treated with RT 1970-1986 had higher risk of CV toxicity

- 4414 BC survivors & Median FU of 18 years
- Compared to general population
- Radiotherapy (1970-1986) is associated with an increased risk of cardiovascular disease.
- Irradiated breast cancer patients should be advised to refrain from smoking to reduce their risk for cardiovascular disease.
- There is a linear relationship between cardiac dose and coronary artery disease without a clear threshold.

Hooning, M.J., et al., JNCI: Journal of the National Cancer Institute, 2007.
van den Bogaard VA,et al,. J Clin Oncol. 2017;35(11):1171–8. https://doi-org.proxy.kib.ki.se/10.1200/JCO.2016.69.8480.

Reduced CV toxicity due to new technology

- Advances in technology enabling highly focused radiotherapy delivery has reduced heart doses significantly in modern practice.
- Oncologists tailor radiotherapy planning to both the cancer recurrence and cardiac risk profile of individual patients and limit even low doses to the heart whenever possible.
- Proton therapy enables comprehensive target coverage while limiting the mean heart dose to < 1 Gy.

Mutter R et al, Pract Radiat Oncol. 2017;7(4):e243–e52. https://doi-org.proxy.kib.ki.se/10.1016/j.prro.2016.12.002.
MacDonald SM, et al.. Int J Radiat Oncol Biol Phys. 2013;86(3):484–90. https://doi-org.proxy.kib.ki.se/10.1016/j.ijrobp.2013.01.038..

Cytotoxic chematherapy

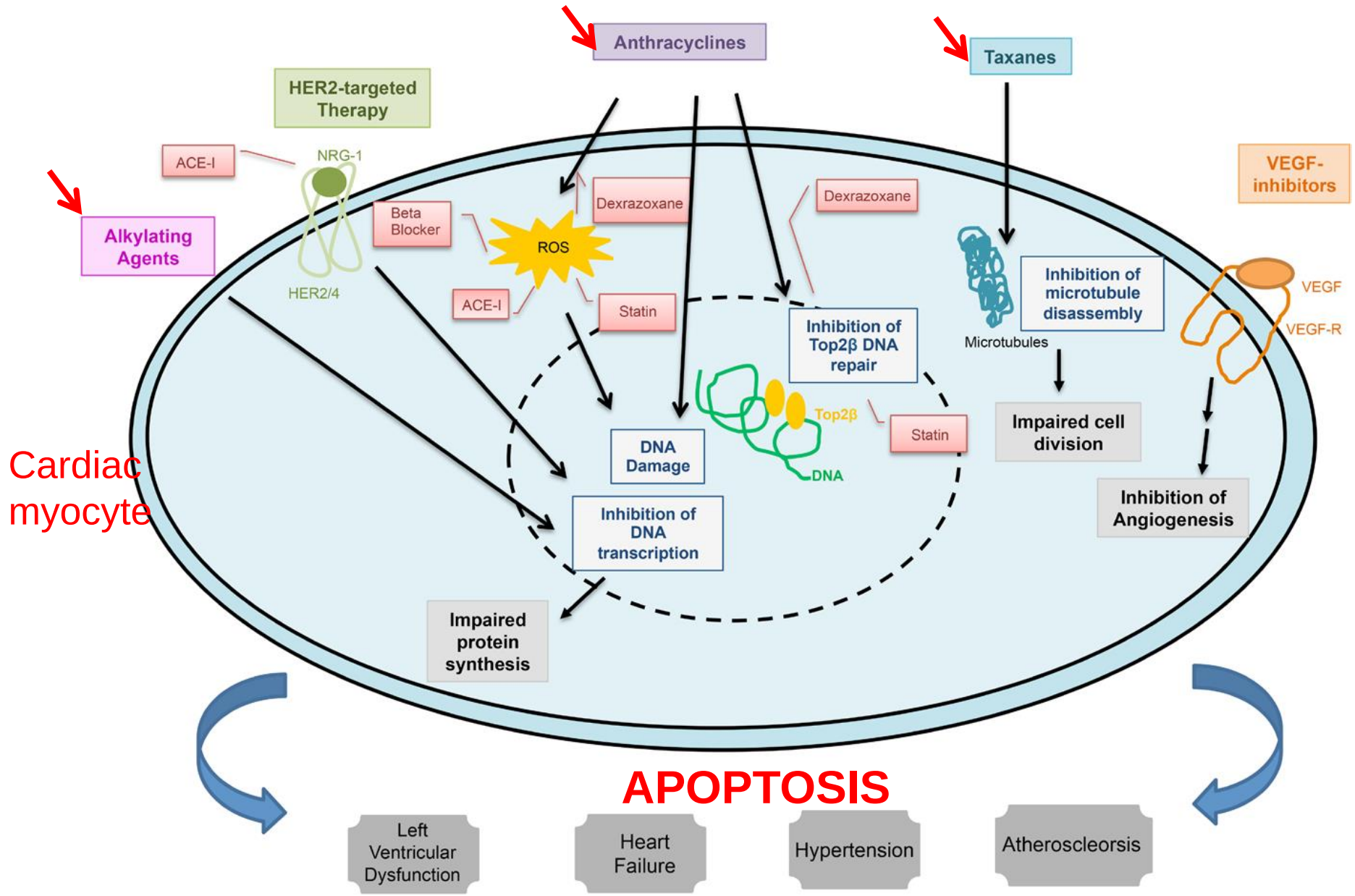
5-year survivors from the Childhood Cancer Survivor Study

- 14,359 survivors & Median FU of 24.5 years after diagnosis,
- 4,301 siblings
- cancer survivors had a significantly greater incidence of a severe, disabling, life-threatening, or fatal health condition, with risk increasing proportionally to age beyond 35 years.
- Heart was the most commonly affected organ among childhood cancer survivors ≥35 years old, with a hazard ratio of 7.9 [95% CI 5.4-11.6] for risk of cardiac involvement.
- HF [HR 11.4, 95% CI 4.7-27.3], stroke [HR 7.0, 95% CI 3.3-14.8], and myocardial infarction [HR 5.0, 95% CI 3.0-8.3] were the most common conditions,

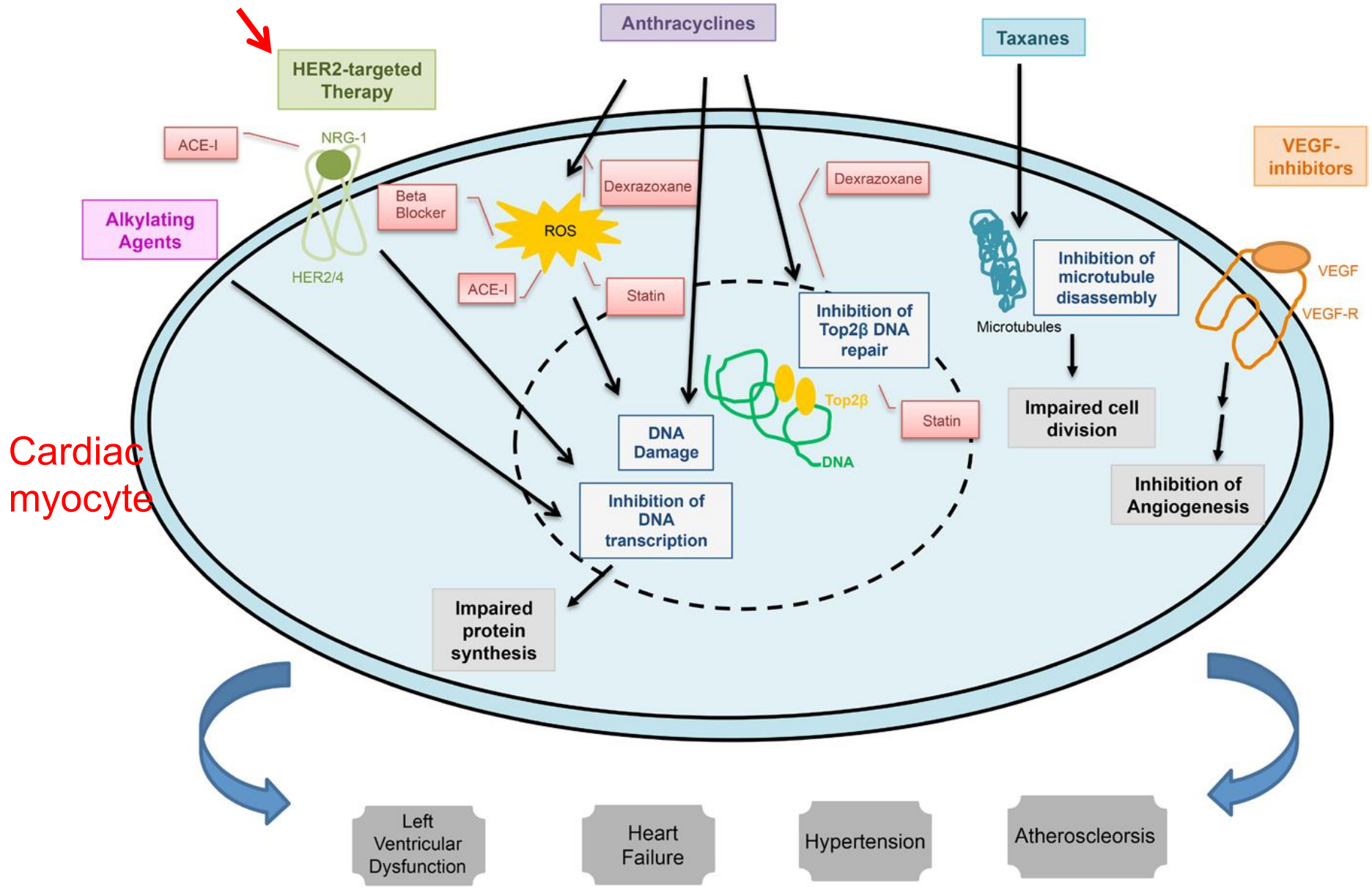
Armstrong et al, J Clin Oncol. 2014 Apr 20;32(12):1218-27. doi: 10.1200/JCO.2013.51.1055. Epub 2014 Mar 17.

Cytostatikainducerad toxicitet

- **Antracykliner**, som epirubicin eller doxorubicin, skadar direkt hjärtmuskelceller eller orsakar inflammation i hjärtmuskel och/eller hjärtsäck.
- **Antimetaboliter**, som capecitabin eller cytarabin, kan utveckla ischemi, perikardit och hjärtsvikt. I synnerhet kan kardiotoxicitet som framkallas av fluoropyrimidiner som 5-fluorouracil manifesteras i form av ischemisk hjärtsjukdom.
- **Antimikrotubulärt** medel, som paklitaxel eller vinkaalkaloider, kan orsaka sinusbradykardi, AV-block, ventrikeltakykardi, hypotension, hjärtsvikt och ischemi.
- **Alkylerande** medel, som cyklofosfamid, ifosfamid, eller mitomycin, kan orsaka mitralisinsufficiens och hjärtsvikt efter högdosbehandling.



Bloom et al; Circ Heart Fail. 2016



Bloom et al; Circ Heart Fail. 2016

Antracyklin-inducerad kardiomyopati

- Incidens och prevalens data saknas! [1]
- Kardiotoxiska effekter kan förekomma under eller efter behandling[2]

  → Tidig effekt är ovanligt.
- Kronisk, potentiell irreversibel doxorubicin-associerad myopati är allvarligt[3,4] och är relaterad till den kumulativa dosen.
  - Subkliniskskada börjar med första givna dosen, kliniskskada visar sig först efter 450 mg/m^2 (kumulativ dos) [5-7]

1. Cardinale D, et al. J Am Coll Cardiol.2000;36:517-522.
2. Bristow M, et al. Am J Med. 1978;65:823-832.
3. Lefrak E, et al. Cancer. 1973;32:302-314.
4. Minow R, et al. Cancer. 1977;39:1397-1402.
5. Valero V, et al. J Clin Oncol. 1999;17:1425-1434.
6. Swain SM, et al. Cancer 2003;97:2869-79.
7. Ewer MS, et al. Heart Fail Clin. 2011;7:363-372.

Antracyklin-inducerad kardiomyopati

- Svarar på hjärtsviktsbehandling, men skadan kvarstår och är irreversibel[1]
- Myokard-remodeling är en del av läkningsprocessen.
- Kardiomyopati kan förekomma flera år efter avslutad behandling
  - Sekventiell stress (trastuzumab, viral infektion) kan vara orsaken [2]

1.Haq M, et al. Cancer. 1985;56:1361-1365.
2. Ali M, et al. Cancer. 1994;74:182-188.

Anthracyclines:

- **Meta-analysis** 55 RCTs mostly in metastatic BC
  - Risk of CHF and LVEF reduction was, respectively, 5 and 6 time higher for an anthracycline-based regimen then for a non- anthracycline containing regimen
- BCIRG-001 adjuvant BC 6 **FAC** (5-FU, doxorubicin, and cyclo-phosphamide) or 6 **TAC** (docetaxel, doxorubicin, and cyclophosphamide)
  - Incidence of CHF was 0.7% and 1.6% in the FAC and TAC arms, respectively (p = 0.09)
- 2625 patients adj anthracycline. LVEF at baseline, every 3 months during treatment, 1 year following post-treatment, every 6 months for four subsequent years, and annually thereafter
  - 98% of observed LVEF decline occurred in the first 12 months of follow-up after chemotherapy

Risk factors:

- Therapy-related risk factors:
  - Accumulated dose of Anthracyclines (250 mg/m^2), Alkylating agents (125 mg/m^2)
  - Concomitant Anthra+taxanes, RT or HER 2 therapy
  - Bolus-injection
  - Prior treatment with anthracyclines
  - Formulation (liposomal doxorubicin)

- Patient related risk factors:
  - preexisting cardiac risk factors: hypertension, diabetes mellitus, smoking, increasing age, female gender, and postmenopausal status.
  - preexisting CV disease
  - metabolic abnormalities
  - hypersensitivity to the drugs
  - prior chemotherapy and/or radiation therapy.

Potential biomarkers might precede LVEF decline; Subclinical CV toxicity

- Troponin levels for asymptomatic anthracycline-induced cardiotoxicity
- Studies have shown that elevated troponin in this setting on echocardiogram and predicts future cardiac events
- Galectin-3, soluble ST-2 proteins, myeloperoxidase, and fibrocytes are also being studied as potential monitoring tools

Her 2 therapies

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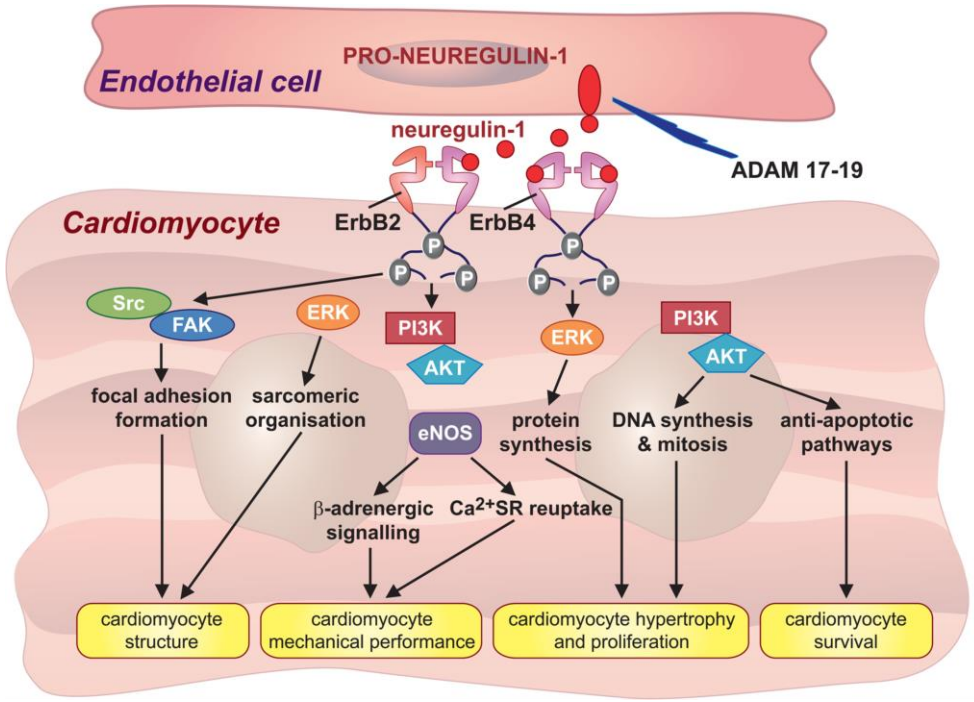
NRG-1/ErbB signalling in the cardiomyocyt

- Often reversible
- On-target effect
- Targets:
  - Trastuzumab: ErbB2
  - Pertuzumab: ErbB2/3 heterodimerization
  - Lapatinib: ATP binding site



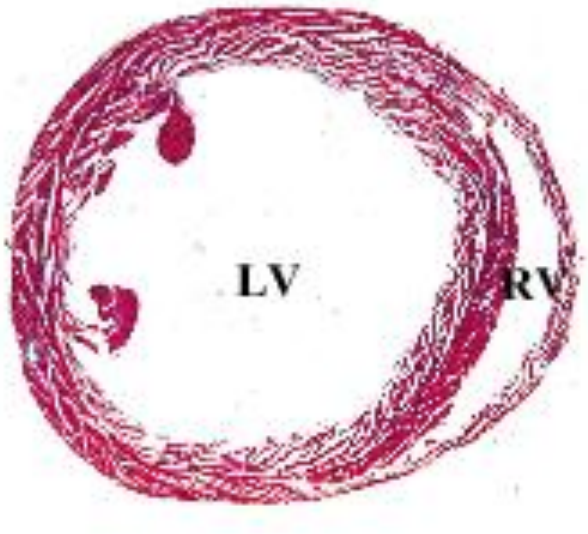
From: Cardiac endothelium–myocyte interaction: clinical opportunities for new heart failure therapies regardless of ejection fraction

Eur Heart J. 2015;36(31):2050-2060. doi:10.1093/eurheartj/ehv132

Phenotypic Analysis of erbB2 Knockout Mouse Myocardium

erbB2-floxed

erbB2-CKO



Abnormal cardiac development and dilation with erbB2 knockout

Crone SA, et al. Nat Med. 2002;8:459-465.

Trastuzumab CHF 0-28%

Table 3. Trastuzumab-associated cardiotoxicity in phase III clinical trials (Modified and updated from Ponde et al. [36]).

Author and year	Setting	Study design	Treatment arms	Number of patients	Any LVEF drop Number (%)	Any CHF Number (%)
Slamon D et al. [37]	MBC first line	Phase 3	AC + trastuzumab	143	Not reported	39 (27.2)
NEJM 2001			AC	135		11 (8.1)
			Paclitaxel + trastuzumab	91		12 (13.2)
			Paclitaxel	95		1 (1.1)
Von Minckwitz G et al. [38,39] JCO 2009 and Eur J Cancer 2011	MBC beyond first line	Phase 3	Capecitabine	78	0	0
			Capecitabine + trastuzumab	78	1 (1.28)	1 (1.28)
Kaufmann B et al. [40] (Tandem) JCO 2009	MBC first line	Phase 3	Anastrozole + trastuzumab	103	1 (0.97)	1 (0.97)
			Anastorozole	104	0	0
Gianni L et al. [41]	Neoadjuvant	Phase 3	A + paclitaxel + CMF + trastuzumab	117	30 (27)	2 (1.7)
The Lancet 2010			A + paclitaxel + CMF	217	33 (15)	0
Untch M et al. [42] (Gepar quattro) JCO 2010	Neoadjuvant	Phase 3	Chemotherapy + trastuzumab	445	4 (0.89)	1 (0.22)
			Chemotherapy	1050	0	2 (0.19)
Buzdar AU et al. [43] Lancet Oncol 2013	Neoadjuvant	Phase 3	FEC + paclitaxel + trastuzumab (concomitant)	142	35 (24.6)	1 (0.7)
			FEC + paclitaxel + trastuzumab (sequential)	138	21 (15.2)	0
Cameron D et al. [44]	Adjuvant	Phase 3	Chemotherapy + trastuzumab 1 year	1682	74 (4.4)	18 (1.1)
(HERA) The Lancet 2017			Chemotherapy + trastuzumab 2 year	1673	122 (7.3)	17 (1.0)
			Chemotherapy	1744	15 (0.9)	2 (0.1)
Romond EH et al. [45]	Adjuvant	Phase 3	AC + Paclitaxel	743	Not reported	9 (1.2)
(NSABP-B31) JCO 2012			AC + paclitaxel + trastuzumab	947	114 (12)	36 (3.8)
Advani PP et al. [2015] (N9831) JCO 2015	Adjuvant	Phase 3	AC + paclitaxel	664	64 (9.6)	6 (0.9)
			AC + paclitaxel + trastuzumab	710	119 (16.7)	19 (2.6)
			AC + paclitaxel/trastuzumab	570	136 (23.8)	20 (3.5)
Slamon D et al. [47,48] NEJM 2011 and SABCS 2015	Adjuvant	Phase 3	AC + docetaxel	1073	114 (11.2)	8 (0.8)
			AC + docetaxel + trastuzumab	1074	206 (19.1)	21 (2.0)
			Docetaxel + carboplatin + trastuzumab	1075	97 (9.4)	4 (0.4)
Spielman M et al. [49] JCO 2009	Adjuvant	Phase 3	FEC/ED	268	7 (2.6)	1 (0.37)
			EC/ED + trastuzumab	260	29 (11.1)	4 (1.5)
Joensuu H et al. [50] NEJM 2006	Adjuvant	Phase 3	Docetaxel/vinorelbine + FEC	116	0	2 (1.72)
			Docetaxel/vinorelbine + trastuzumab + FEC	115	0	1 (0.86)
Pivot X et al. [51] Eur. J. Cancer 1990	Adjuvant	Phase 3	Chemotherapy + trastuzumab 6 months	1690	45 (2.7)	9 (0.53)
			Chemotherapy + trastuzumab 1 year	1690	70 (4.1)	11 (0.65)

LVEF: left ventricular ejection fraction; CHF: congestive heart failure; MBC: metastatic breast cancer; AC: doxorubicin, cyclophosphamide; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; A: doxorubicin; CMF: cyclophosphamide, methotrexate, 5-fluorouracil; EC: epirubicin, cyclophosphamide; ED: epirubicin, docetaxel.

Double HER2 blockade is safe

Author and year	Setting	Study design	Treatment arms	Number of patients	LVEF drop (≥10 points and/or <50%) G2–G4 No. (%)	CHF No. (%)
Portera CC et al. [59] CCR 2008	MBC, beyond first-line	Phase II	Trastuzumab + pertuzumab	11	3 (27.3)	1 (9.1)
Gianni L et al. [60] JCO 2010	MBC, beyond first-line	Phase II	Pertuzumab	78	8 (10.3)	1 (1.3)
Baselga J et al. [61] JCO 2010	MBC, beyond first-line	Phase II	Trastuzumab + pertuzumab	66	3 (4.5)	0 (0.0)
Cortes J et al. [62] JCO 2012	MBC, beyond first-line	Phase II	Pertuzumab	29	3 (10.3)	0 (0.0)
Dang C et al. [63] JCO 2015	MBC, first-line	Phase II	Paclitaxel + trastuzumab + pertuzumab	69	1 (1.5)	0 (0.0)
Swain SM et al. [58] The Oncologist 2013	MBC, first-line	Phase III	Docetaxel + trastuzumab + placebo	406	25 (6.6)	7 (1.8)
			Docetaxel + trastuzumab + pertuzumab	402	15 (3.8)	4 (1.0)
Urruticoechea A et al. [64] ASCO 2016	MBC, beyond first-line	Phase III	Capecitabine + Trastuzumab	224	7 (3.1)	0 (0.0)
			Capecitabine + trastuzumab + pertuzumab	228	15 (6.6)	5 (2.2)
Gianni L et al. [65] Lancet Oncol 2012	Neoadjuvant setting	Phase II	Docetaxel + trastuzumab	107	1 (0.9)	0 (0.0)
			Docetaxel + trastuzumab + pertuzumab	107	3 (2.8)	0 (0.0)
			Trastuzumab + pertuzumab	107	1 (0.9)	1 (0.9)
			Docetaxel + pertuzumab	96	1 (1.0)	0 (0.0)
Schneeweiss A et al. [66] Ann Oncol 2013	Neoadjuvant setting	Phase II	FEC + trastuzumab + pertuzumab → docetaxel + trastuzumab + pertuzumab	72	4 (5.6)	0 (0.0)
			FEC → docetaxel + trastuzumab + pertuzumab	75	4 (5.3)	2 (2.7)
			TCH + pertuzumab	76	3 (3.9)	0 (0.0)
Rimawi MF et al. [67] SABCS 2016	Neoadjuvant setting	Phase III	TCH + pertuzumab	154	Not reported	Not reported
			TCH + pertuzumab + estrogen deprivation therapy	157	Not reported	Not reported
Von Minckwitz G et al. [68] NEJM 2017	Adjuvant setting	Phase III	Anthracycline → trastuzumab + pertuzumab	1,834	55 (3.0)	13 (0.7)
			Anthracycline → trastuzumab + placebo	1,894	60 (3.2)	5 (0.3)
			Non-anthracycline → trastuzumab + pertuzumab	528	9 (1.7)	2 (0.4)
			Non-anthracycline → trastuzumab + placebo	510	7 (1.4)	1 (0.2)

LVEF: left ventricular ejection fraction; CHF: congestive heart failure; MBC: metastatic breast cancer; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin, trastuzumab; Cotx: chemotherapy.

Risk factors:

- Therapy-related risk factors:
  - Concomitant Anthra+HER 2 therapy

- Patient related risk factors:
  - body mass index >25 kg/m^2, low LVEF prior to trastuzumab treatment, age

Immune checkpoint inhibitors

Karolinska Institutet

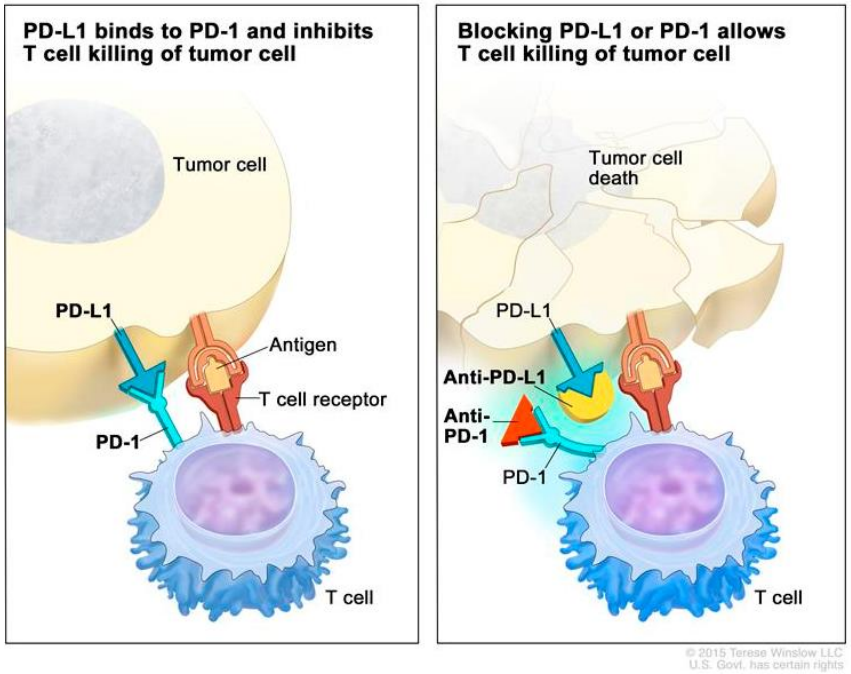
KAROLINSKA UNIVERSITETSSJUKHUSET

Immune-checkpoint blocking antibodies can induce tumor responses in various tumor types

Programmed cell death 1 (PD-1) inhibitors: Pembrolizumab, Nivolumab

PD-L1 inhibitors: Atezolizumab, Avelumab, Durvalumab

Cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor: Ipilimumab



A rare but serious complication!

Table 2. Published case reports of cardiotoxicity related to immune checkpoint inhibitors

References	Therapeutic agent	Number of cases	Cardiovascular adverse effects
Heinzerling et al. [9]	Ipilimumab, nivolumab or their combination, and pembrolizumab	8	Myocarditis, heart failure, cardiomyopathy, myocardial fibrosis, cardiac arrest
Johnson et al. [16••]	Nivolumab and ipilimumab combination	2	Myocarditis and myositis
Koelzer et al. [10]	Ipilimumab followed by nivolumab	1	Myocarditis and myocardial fibrosis
Laubli et al. [18]	Pembrolizumab	1	Myocarditis
Behling et al. [17]	Nivolumab	1	Complete heart block
Geisler et al. [19]	Ipilimumab	1	Cardiomyopathy with Takotsubo-like syndrome
Semper et al. [20]	Nivolumab	1	Myocarditis

Jain V et al Curr Treat Options Cardiovasc Med. 2017

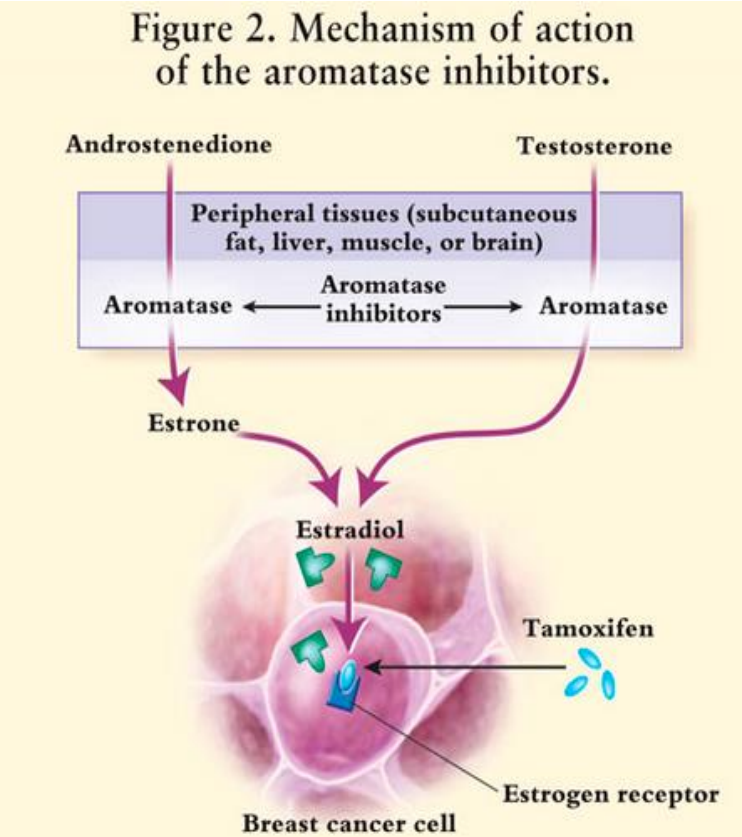
Potential risk factors:

- Patient related risk factors:
  - Pre-existent cardiac pathology or peripheral arterial disease
  - Patients who have already experienced one immune-related adverse event

Heinzerling L, Journal for ImmunoTherapy of Cancer2016

Aromatase Inhibitors

Estrogen synthesis is mediated by the enzyme aromatase



Source: Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med. *2003;348:2431-2442. Copyright © 2003 Massachusetts Medical Society. All rights reserved.*

Estrogens protect the cardiovascular system, by indirect and direct mechanisms

- Indirectly it regulates
  - serum lipid concentrations
  - coagulation and fibrinolytic systems
  - antioxidant systems.
- Directly it regulates
  - Production of vasoactive molecules, such as nitric oxide and prostaglandins
  - Increase vasodilation.

Adjuvant AI given in 4 ways:

- 5 years (up-front strategy)
- 2 to 3 years after 2 to 3 years of tamoxifen (switch strategy)
- Additional 5 years after 5 years of tamoxifen (extended strategy)
- 2-5 years in combination with ovarian function suppression

AI doesn't increase cardiovascular mortality

- MA.17: **5y Tamoxifen → 5y AI** OR **Placebo**: **No CVD**
- ATAC: **5y AI**, **Tamoxifen**, or **Switch**:
  - AI vs Tamoxifen: Hypercholesterolemia (9% vs. 3%; *P* < .0001) and hypertension (13% vs. 11%; *P* = .04). Cerebrovascular events (2% vs. 3%; *P* = .03) and thromboembolic events (3% vs. 5%; *P* = .004)
- BIG 1-98:**5y AI**, **Tamoxifen**, **Switch AI upfront** or **Tam upfront**
  - AI vs Tamoxifen: Hypercholesterolemia (Grade 1 in 35.1% and 17.3% patients, respectively) and Grade 3 to 5 cardiovascular events (2.4% vs. 1.4%; *P* = .001). Thromboembolic events (1.5% vs. 3.5%).
- TEAM: **5y AI** or **Switch Tam upfront**
  - AI vs Switch: all-grade cardiac failure (1% vs. <1%; *P* =.009), arrhythmia (4% vs. 3%; *P* =.038), hypertension (6% vs. 5%; *P* =.0003), hyperlipidemia (5% vs. <1%; P < .0001), and weight increase (7% vs. <1%)
- MA.17R: **5y AI → 5y AI** OR **Placebo**
  - AI vs Placebo: hypertension (16% vs. 15%; *P* =.48), hypercholesterolemia (21% vs. 19%; *P* =.31), and cardiovascular events (12% vs. 10%; *P* =.21)

Longer duration of AI treatment was associated with increased odds of developing CVD (OR, 1.26; 95% CI, 1.10-1.43; *P* < .001)

Table 4 Trials Included in Meta-Analysis to Evaluate Toxicity of AIs Compared With Tamoxifen[5]

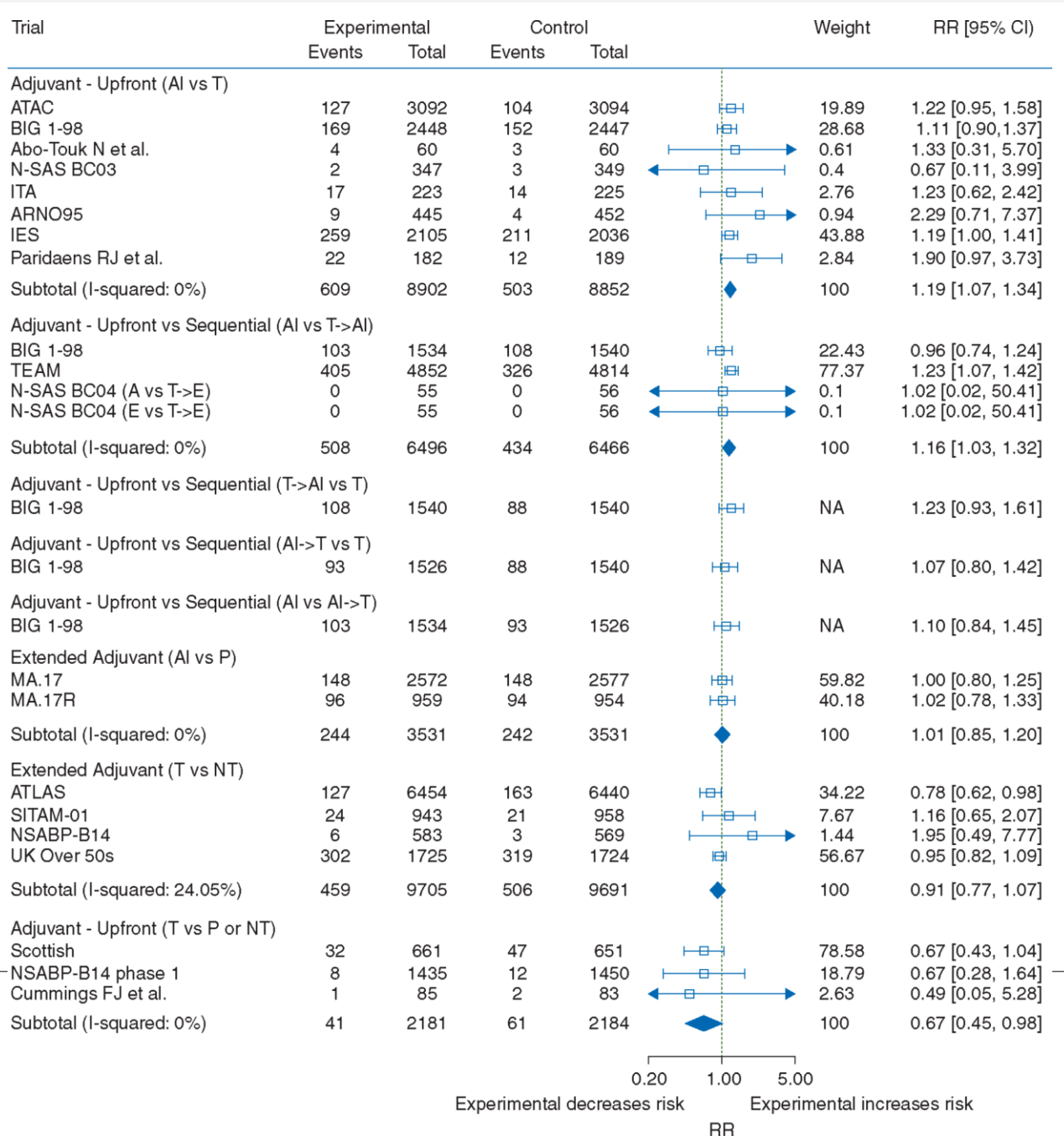
Study	Arm 1	Arm 2	Reference
ATAC	Ana 1 mg for 5 years	Tam 20 mg for 5 years	Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group et al[60]
BIG 01-98	Let 2.5 mg for 5 years	Tam 20 mg for 5 years	Coates et al[43]
IES	Tam 20 mg for 2-3 years → Exe 25 mg for 2-3 years	Tam 20 mg for 5 years	Coombes et al[57]
ABCSG8	Ana 1 mg for 2-3 years	Tam 20 mg for 2-3 years	Jakesz et al[61]
ARNO95	Tam 20-30 mg for 5 years	Tam 20-30 mg for 2 years → Ana 1 mg for 3 years	Jakesz et al[61]
ITA	Tam 20 mg for 2-3 years → Ana 1 mg for 2-3 years	Tam 20 mg for 5 years	Boccardo et al[62]
N-SAS BC03	Tam 20 mg for 5 years	Tam for 1-4 years → Ana 1 mg for 1-4 years	Aihara et al[63]
TEAM	Exe 25 mg for 5 years	Tam for 2.5 years followed by Exe for 2.5 years	van de Velde et al[11]

Amir E, et al. J Natl Cancer Inst 2011.

AI associated with 19% more cardiovascular events than tamoxifen.

No increased risk for adverse cardiovascular events with AI compared to placebo.

Protective effect of tamoxifen?



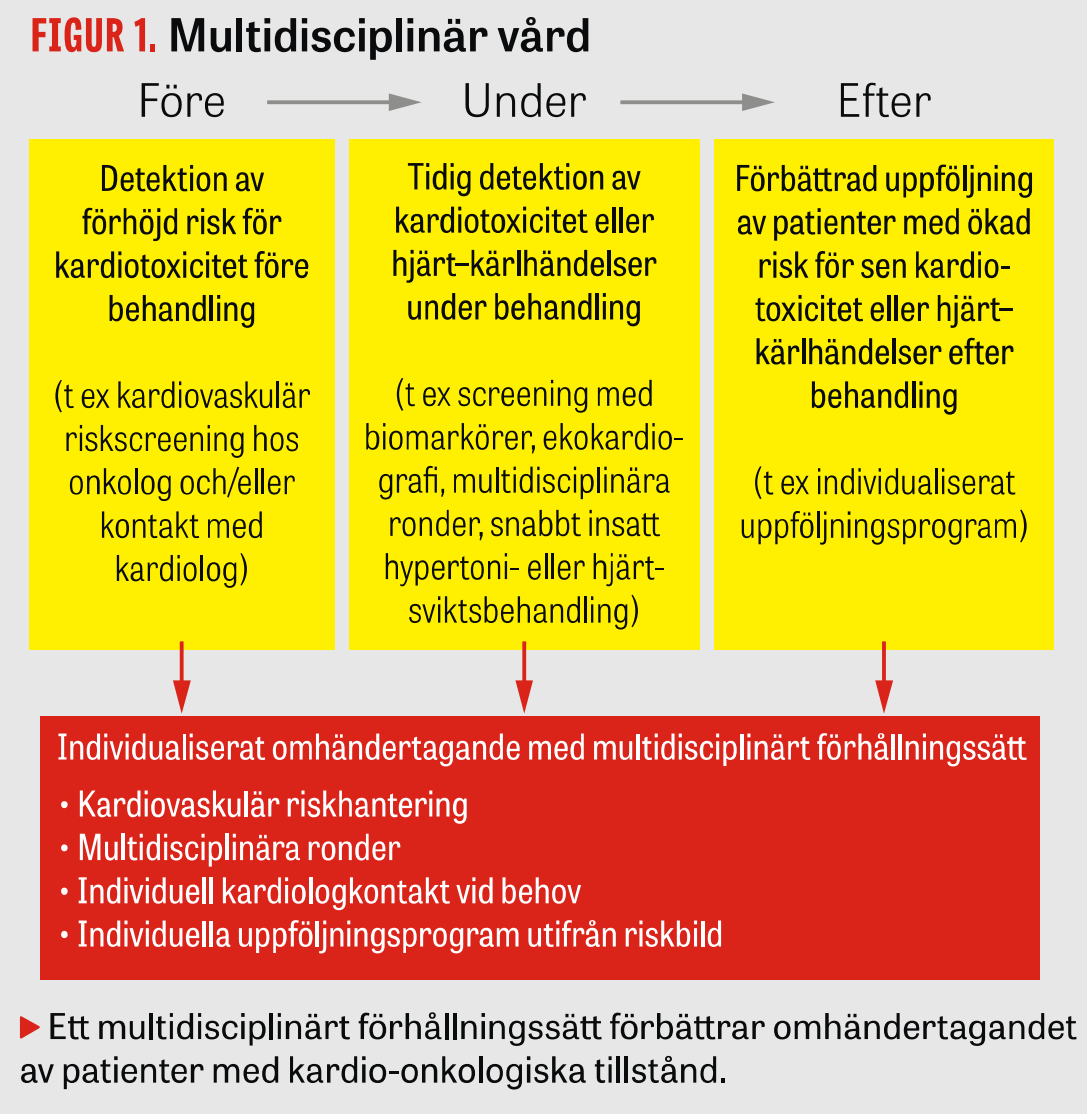
Trial	Experimental Events	Experimental Total	Control Events	Control Total	Weight	RR [95% CI]
Adjuvant - Upfront (AI vs T)						
ATAC	127	3092	104	3094	19.89	1.22 [0.95, 1.58]
BIG 1-98	169	2448	152	2447	28.68	1.11 [0.90,1.37]
Abo-Touk N et al.	4	60	3	60	0.61	1.33 [0.31, 5.70]
N-SAS BC03	2	347	3	349	0.4	0.67 [0.11, 3.99]
ITA	17	223	14	225	2.76	1.23 [0.62, 2.42]
ARNO95	9	445	4	452	0.94	2.29 [0.71, 7.37]
IES	259	2105	211	2036	43.88	1.19 [1.00, 1.41]
Paridaens RJ et al.	22	182	12	189	2.84	1.90 [0.97, 3.73]
Subtotal (I-squared: 0%)	609	8902	503	8852	100	1.19 [1.07, 1.34]
Adjuvant - Upfront vs Sequential (AI vs T->AI)						
BIG 1-98	103	1534	108	1540	22.43	0.96 [0.74, 1.24]
TEAM	405	4852	326	4814	77.37	1.23 [1.07, 1.42]
N-SAS BC04 (A vs T->E)	0	55	0	56	0.1	1.02 [0.02, 50.41]
N-SAS BC04 (E vs T->E)	0	55	0	56	0.1	1.02 [0.02, 50.41]
Subtotal (I-squared: 0%)	508	6496	434	6466	100	1.16 [1.03, 1.32]
Adjuvant - Upfront vs Sequential (T->AI vs T)						
BIG 1-98	108	1540	88	1540	NA	1.23 [0.93, 1.61]
Adjuvant - Upfront vs Sequential (AI->T vs T)						
BIG 1-98	93	1526	88	1540	NA	1.07 [0.80, 1.42]
Adjuvant - Upfront vs Sequential (AI vs AI->T)						
BIG 1-98	103	1534	93	1526	NA	1.10 [0.84, 1.45]
Extended Adjuvant (AI vs P)						
MA.17	148	2572	148	2577	59.82	1.00 [0.80, 1.25]
MA.17R	96	959	94	954	40.18	1.02 [0.78, 1.33]
Subtotal (I-squared: 0%)	244	3531	242	3531	100	1.01 [0.85, 1.20]
Extended Adjuvant (T vs NT)						
ATLAS	127	6454	163	6440	34.22	0.78 [0.62, 0.98]
SITAM-01	24	943	21	958	7.67	1.16 [0.65, 2.07]
NSABP-B14	6	583	3	569	1.44	1.95 [0.49, 7.77]
UK Over 50s	302	1725	319	1724	56.67	0.95 [0.82, 1.09]
Subtotal (I-squared: 24.05%)	459	9705	506	9691	100	0.91 [0.77, 1.07]
Adjuvant - Upfront (T vs P or NT)						
Scottish	32	661	47	651	78.58	0.67 [0.43, 1.04]
NSABP-B14 phase 1	8	1435	12	1450	18.79	0.67 [0.28, 1.64]
Cummings FJ et al.	1	85	2	83	2.63	0.49 [0.05, 5.28]
Subtotal (I-squared: 0%)	41	2181	61	2184	100	0.67 [0.45, 0.98]

Ann Oncol. 2016;28(3):487-496. doi:10.1093/annonc/mdw673

Potential risk factors:

- Patient related risk factors:
  - preexisting cardiac risk factors such as obesity, hypertension, diabetes mellitus, increasing age, and postmenopausal status.

Foglietta J, Clinical Breast Cancer 2017



Buhlmann et al, Läkartidningen 26-27/2016

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