Heart diseases in breast cancer survivors

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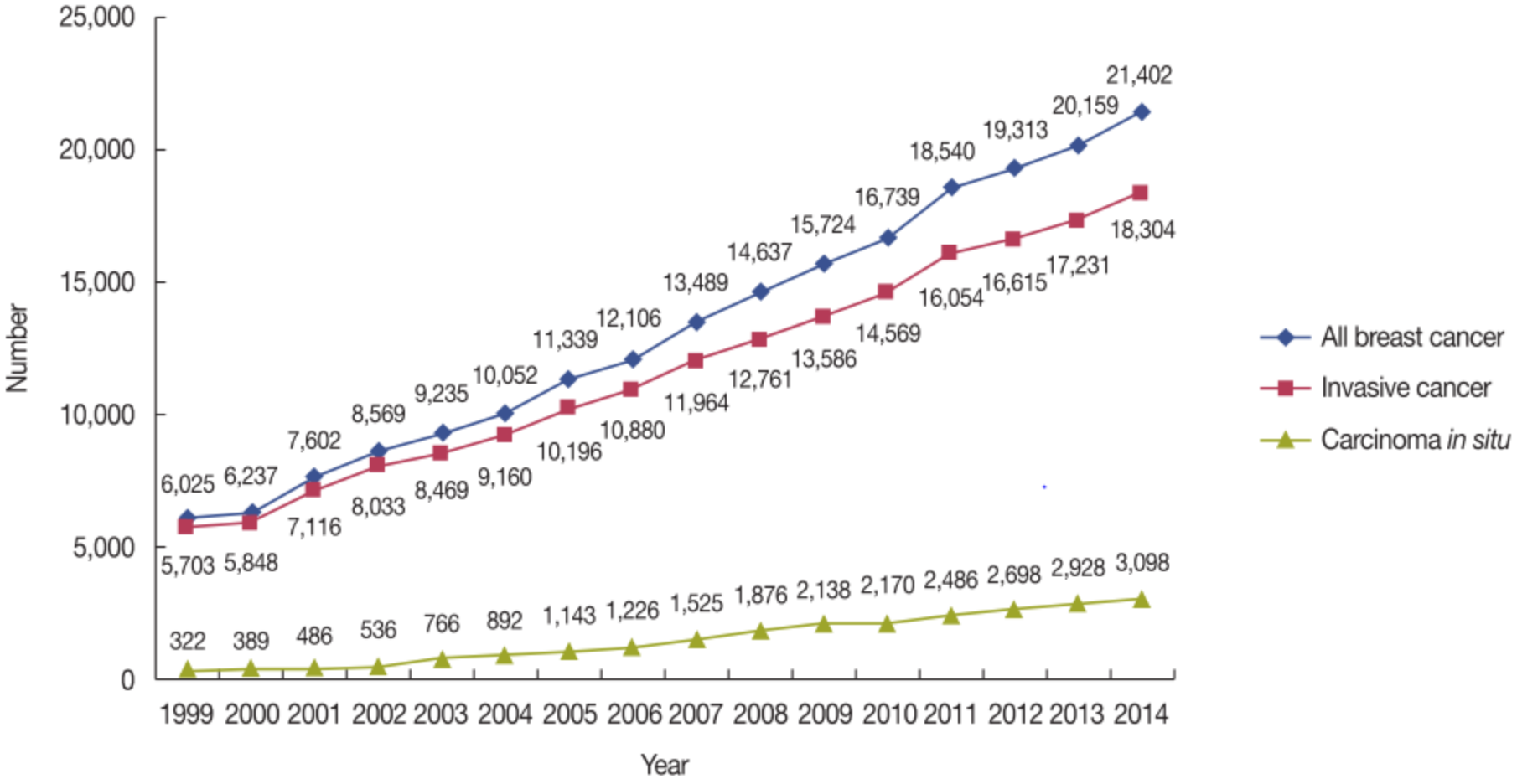
the Study of Multi-disciplinARy Teamwork for breast cancer survivorSHIP (SMARTSHIP)

Korean Breast Cancer Survivorship Research Group

The SMARTSHIP group

- Risk of cardiac disease in breast cancer survivors
- Risk related to breast cancer treatment
- Prevention, management, and optimal surveillance strategy
- Nationwide cohort in Korean population

Annual incidence of breast cancer diagnosis



Park et al. J Breast Cancer (2017)

Surveillance for breast cancer survivors

Breast cancer surveillance	History and physical examination every 4 to 6 months for 5 years, then annually **Mammography** annually
Second primary cancer risk	Increased risk of **second primary breast cancer** in ipsilateral and contralateral breasts Increased risk of **ovarian and colorectal cancers** Increased risk of **endometrial cancer** if tamoxifen is used (recommended gynecologic examination annually if uterus present)
Complications from disease and treatment	**Lymphedema; ovarian failure; endometrial cancer; sexual dysfunction; cardiac toxicities; pulmonary toxicities; osteopenia** **Bone mineral density testing** at initiation of aromatase inhibitor therapy and periodically throughout therapy

Willbur et al. Am Fam Physician (2015)

Research

JAMA Cardiology | Brief Report

A Population-Based Study of Cardiovascular Mortality Following Early-Stage Breast Cancer

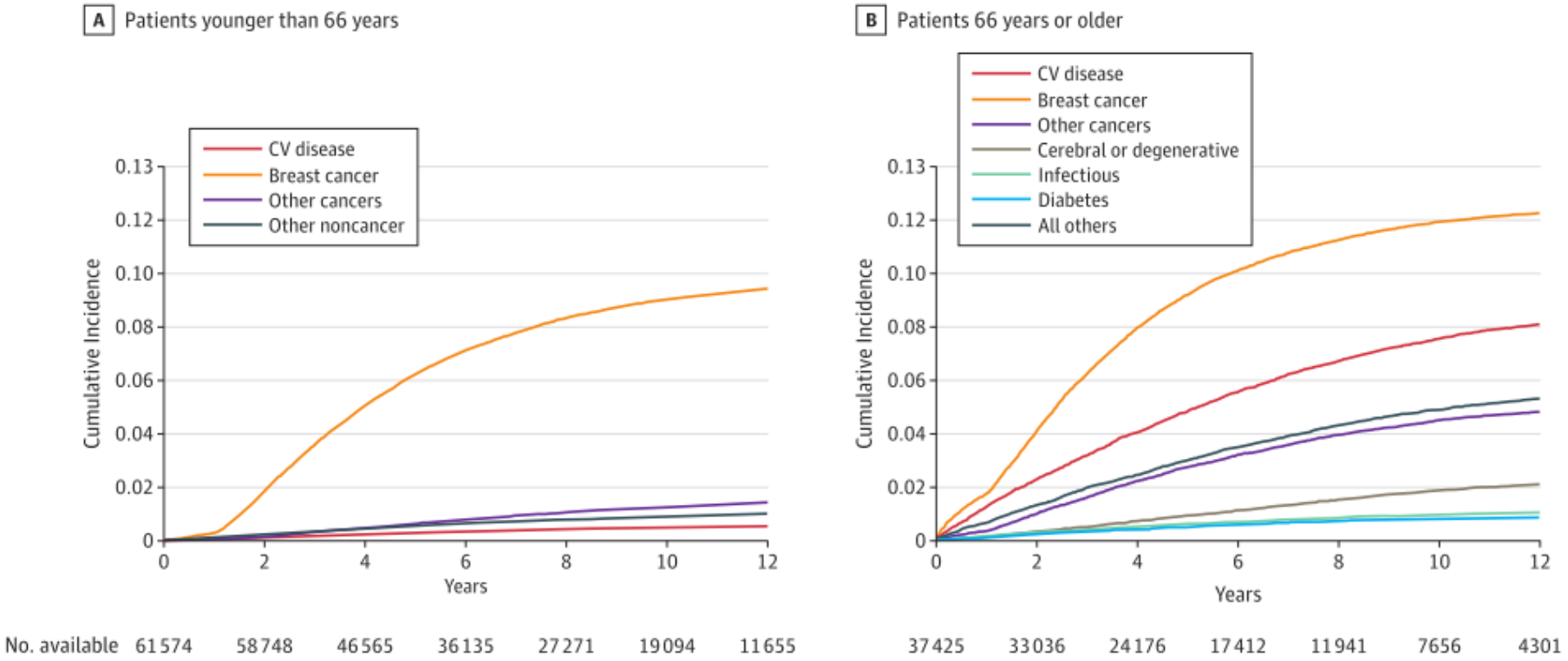
Husam Abdel-Qadir, MD; Peter C. Austin, PhD; Douglas S. Lee, MD, PhD; Eitan Amir, MB, ChB, PhD; Jack V. Tu, MD, PhD; Paaladinesh Thavendiranathan, MD, MSc; Kinwah Fung, MSc; Geoffrey M. Anderson, MD, PhD

- A population-based cohort study was conducted among 98,999 women diagnosed with early-stage breast cancer (1998 – 2012) (The Ontario Health Insurance Plan)
  Median follow-up was 6.6years (IQR, 3.6-10.4 yrs)

- Cause of death during follow up
  : 49.9% from breast cancer
  16.3% from cardiovascular disease

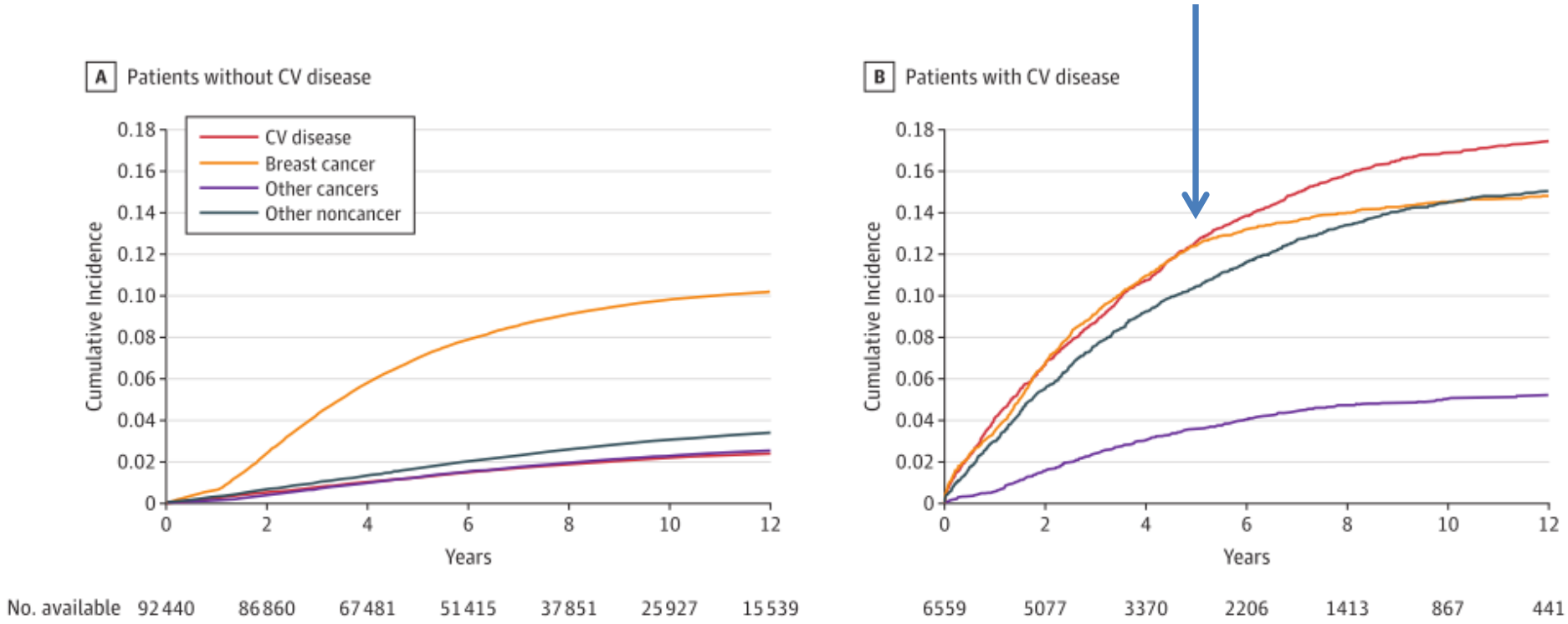
Abdel-Qadir et al. JAMA Cardiol 2016

- Cumulative Incidence of Cause-Specific Death Based on Patient Age at Time of Breast Cancer Diagnosis



Abdel-Qadir et al. JAMA Cardiol 2016

- Cumulative Incidence of Cause-Specific Death Based on History of Cardiovascular (CV) Disease Before Breast Cancer Diagnosis



Abdel-Qadir et al. JAMA Cardiol 2016

PLOS ONE

RESEARCH ARTICLE

Cardiovascular disease and mortality after breast cancer in postmenopausal women: Results from the Women's Health Initiative

Na-Jin Park[1☯*], Yuefang Chang[2☯], Catherine Bender[1‡], Yvette Conley[1‡], Rowan T. Chlebowski[3‡], G. J. van Londen[4‡], Randi Foraker[5‡], Sylvia Wassertheil-Smoller[6‡], Marcia L. Stefanick[7‡], Lewis H. Kuller[8☯]

- incident CVD events and total and cause-specific death rates were compared between postmenopausal women with (n = 4,340) and without (n = 97,576) incident invasive breast cancer over 10 years
- CVD affected mostly women age 70–79 with localized breast cancer (**79%** of breast cancer cases in 70–79 age group) only 17% died from breast cancer and **CVD was the leading cause of death (22%)**
- Compared to age-matched women without breast cancer, women age 70–79
  - similar HR of 1.01 (95% [CI]: 0.76–1.33) for coronary heart disease
  - a lower risk of composite CVD (HR = 0.84, 95% CI: 0.70–1.00)
  - Higher risk of total mortality (HR = 1.20, 95% CI: 1.04–1.39).

Park et al. Plos one. Sep 2017

Health Profiles of 814 Very Long-Term Breast Cancer Survivors

Charles Stava,[1] L. Todd Weiss,[2] Rena Vassilopoulou-Sellin[1]

- health information provided by **814 breast cancer survivors** whose cancer was diagnosed **≥15 years** earlier
- compared the information with that of **female survivors of other cancers**

Health Effect	Overall Breast Cancer Survivors (n = 814)	Survivors of Other Cancer Types (n = 1894)	*P* Value (Breast vs. Other Cancers)
Abdominal Pain	47 (5.7)	161 (8.5)	0.0146
Arthritis/Osteoporosis	349 (42.8)	626 (33.1)	< 0.0001
Bleeding	24 (2.9)	78 (4.1)	0.1426
Cataracts	201 (24.7)	343 (18.1)	< 0.0001
Circulation Problems	78 (9.6)	233 (12.3)	0.0418
Diabetes/Sugar in Urine	64 (7.8)	176 (9.3)	0.2299
Dizziness	64 (7.8)	170 (8.9)	0.3444
Frequent Infections	52 (6.4)	137 (7.2)	0.4287
Hearing Problems	94 (11.5)	201 (10.6)	0.4737
Heart Problems	165 (20.3)	286 (15.1)	0.0009
Kidney Problems	58 (7.1)	239 (12.6)	< 0.0001
Liver Problems	8 (0.9)	36 (1.9)	0.0832
Loss of Memory	75 (9.2)	126 (6.6)	0.0197
Lung Problems	70 (8.6)	102 (5.6)	0.0017
Migraines	33 (4.1)	103 (5.4)	0.1305
Psychologic Problems	33 (4.1)	57 (3)	0.1644
Seizures	3 (0.4)	20 (1.1)	0.0739
Skin Problems	37 (4.5)	113 (5.9)	0.1383
Strokes	25 (3.1)	78 (4.1)	0.1915
Thyroid Problems	98 (12.1)	263 (13.8)	0.1949
Other/Secondary Cancers	94 (11.5)	255 (13.5)	0.1725

Stava et al. Clin Breast Cancer (2014)

Cardiovascular late effects

- **Chemotherapeutic agents**
  →congestive heart failure
  ischemia
  hypertension
  myocardial depression
  arrhythmia

- **Early menopause**
  →increases cholesterol level

Trastuzumab

Radiotherapy

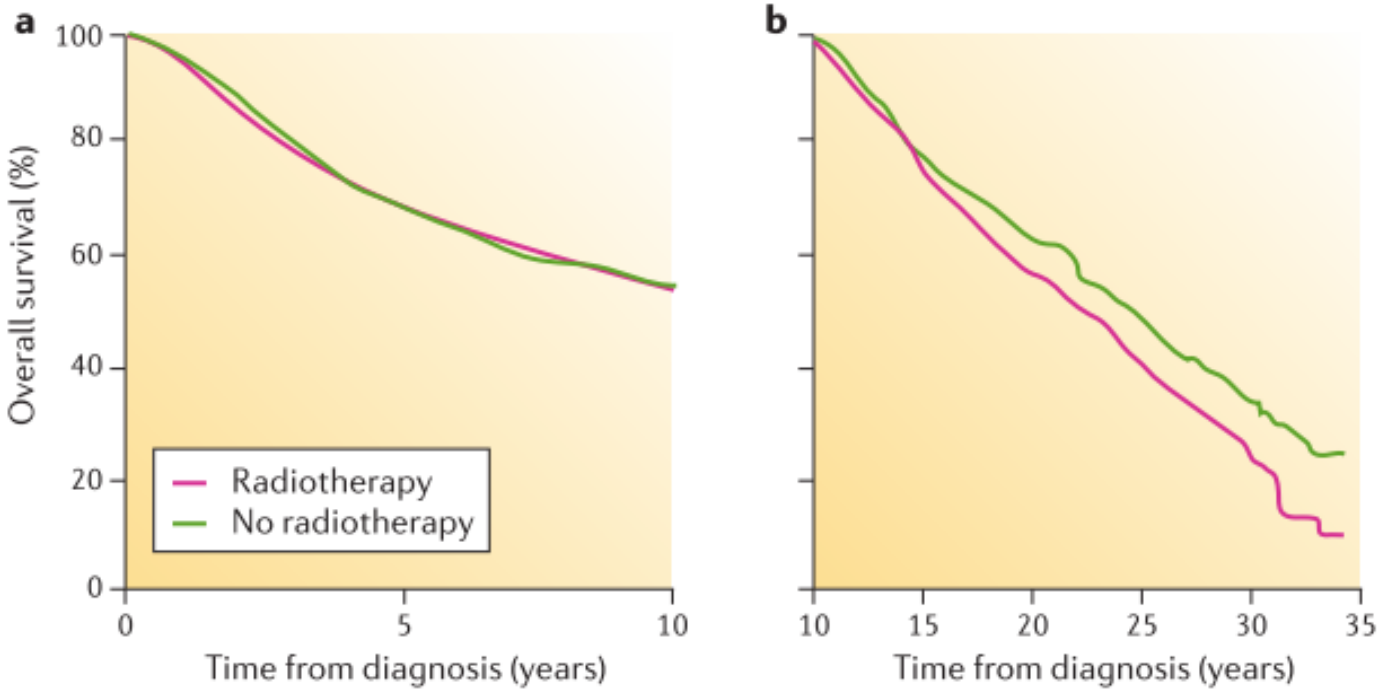
Endocrine treatment

Anthracycline

Radiotherapy

- **Older methods** of delivering adjuvant RT resulted in much more extensive incidental cardiac irradiation than is seen with current techniques

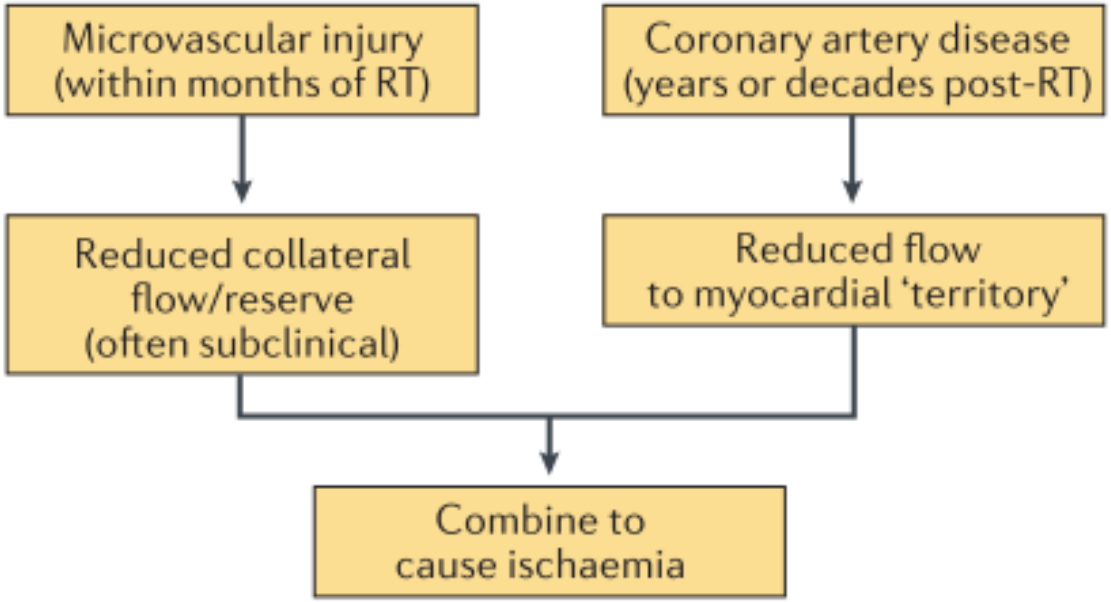
- 25-year overall survival who underwent mastectomy with radiation reflects cardiac injury compared to first 10 years (Cuzick J. et al. 1987)

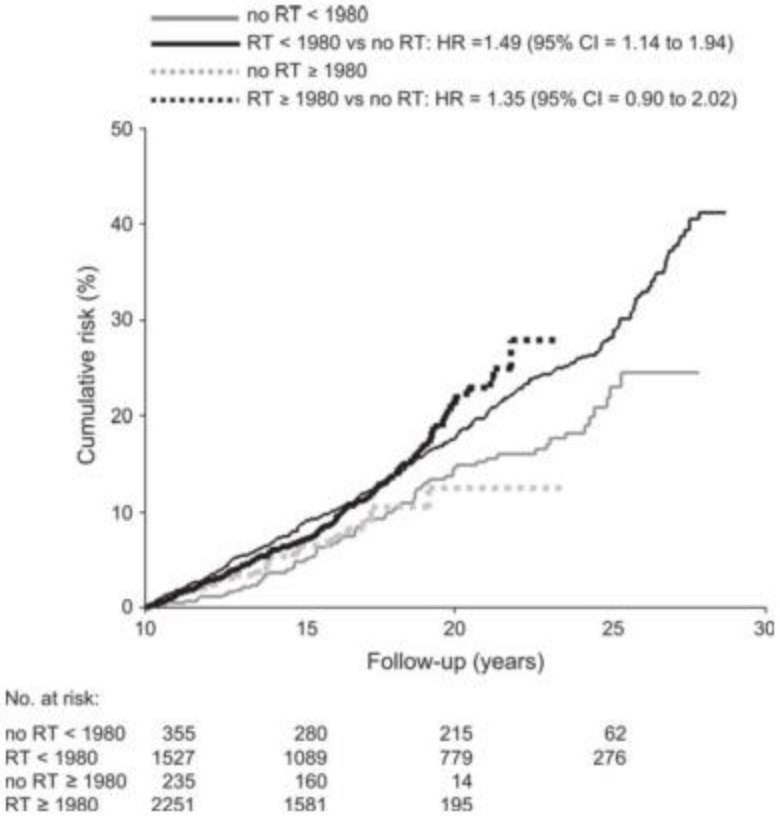


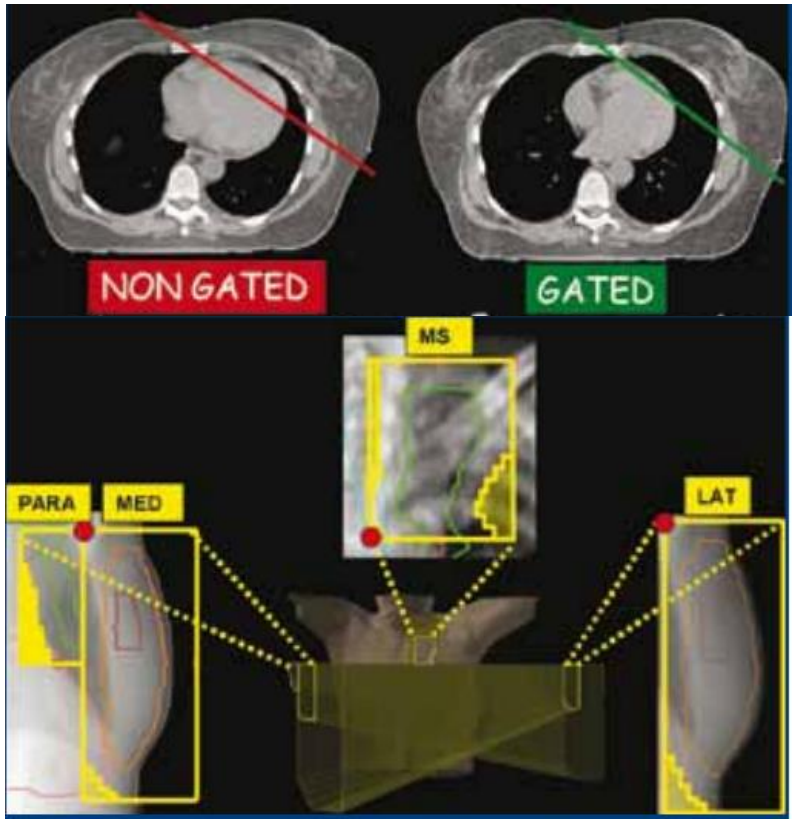
Radiotherapy

- **Microvascular injury**
  Decrease in capillary density that might reduce the degree of potential collateral flow

- **Macrovascular injury**
  radiation therapy accelerates atherosclerosis of larger blood vessels







- **Modern radiotherapy** has a low risk of cardiac toxicity
  (Hooning et al. 2007)

- Deep breast inspiration hold, proton radiotherapy,
  3D planning, prone position
  Accelerated partial breast irradiation(ABPI)
  Image-guided RT (IGRT)

Erven K et al. BJMO (2008)

TABLE 1 Anticancer Agents Associated With HF/Left Ventricular Dysfunction

Chemotherapy Agents	Frequency of Use	Incidence (%)	Prevention/Treatment
Anthracyclines			
Doxorubicin	++++	3-26	Monitor EF, GLS, troponin dexrazoxane, continuous infusion, liposomal preparation, BB/ACEI
Epirubicin	+		
Idarubicin	++		
Alkylating agents			
Cyclophosphamide	++++		
Ifosfamide	+++		
Antimetabolites			
Decitabine	++		
Clofarabine	+		
Antimicrotubule agents			
Docetaxel	++		
Monoclonal antibody-based tyrosine kinase inhibitors			
Trastuzumab	+++		
Bevacizumab	++		
Adotrastuzumab emtansine	+		
Pertuzumab	+		

TABLE 3 Anticancer Agents Associated With Myocardial Infarction/Ischemia

Chemotherapy Agents	Frequency of Use	Incidence (%)	Prevention/ Treatment
Antimetabolites			
Capecitabine	++++	3-9	Ischemia workup and treatment
Flourouracil	++++	1-68	
Monoclonal antibody-based tyrosine kinase inhibitors			
Bevacizumab	+++	0.6-8.5	
Small molecule tyrosine kinase inhibitors			
Nilotinib	++++	5.0-9.4	
Ponatinib	+	12	
Angiogenesis inhibitors			
Lenalidomide	+++	0-1.9	
Antimicrotubule agents			
Paclitaxel	++++	<1.5	

Chang H et al. J Am Coll Cardiol (2017)

Chemotherapeutic agents with a prominent vascular side effect profile

	HTN	Angina	AMI	Takotsubo	Raynaud's	Raynaud's Stroke	PAD	Pulm HTN	DVT/PE
Antimetabolites									
5-Fluorouracil		X	X	X	X				
Capecitabine		X	X	X	X				
Gemcitabine		X	X		X				
Antimicrotubule agents									
Paclitaxel	X	X	X						X
Alkylating agents									
Cisplatin	X	X	X		X	X	X		
Cyclophosphamide		X						X	
Antitumor antibiotics									
Bleomycin		X	X		X	X		X	
Vinca alkaloids									
Vincristine	X	X	X		X				
mTOR inhibitors									
Everolimus	X	X							X
Temsirolimus	X	X							X

Herrmann et al. Circulation (2016)

Anthracyclines

- **Daunorubicin, doxorubicin, idarubicin, and epirubicin**

→dose-related cardiotoxicity
peak incidence above a cumulative dose of 450 mg/m^2

→ Type I cardiac toxicity is dose-dependent and irreversible
→ generation of reactive oxygen species(ROS) : myocyte damage
→ binding to Top2a (tumor cell, normal cardiac myocyte)

- **10-year prevalence of heart failure of breast cancer survivors**

→50% anthracycline-based chemotherapy
35% if chemotherapy without anthracycline
27% if they had had no chemotherapy
VS
10% prevalence among similarly aged women

Anthracyclines

Table 1 | Incidence of doxorubicin-induced CHF in the metastatic setting.

Study	Number of patients in analysis	Malignancy	Overall incidence of CHF (%)	Incidence of CHF based on cumulative dose of doxorubicin
Von Hoff et al. (4)	4018	Variety of tumors	2.2[a]	3% at 400 mg/m^2 7% at 550 mg/m^2 18% at 700 mg/m^2
Swain et al. (10)	630	Metastatic breast cancer and small cell lung cancer	5.1[b]	5% at 400 mg/m^2 16% at 500 mg/m^2 26% at 550 mg/m^2 48% at 700 mg/m^2

Guo et al. Front Oncol. 2014

- Heart failure can occur even at low cumulative dose

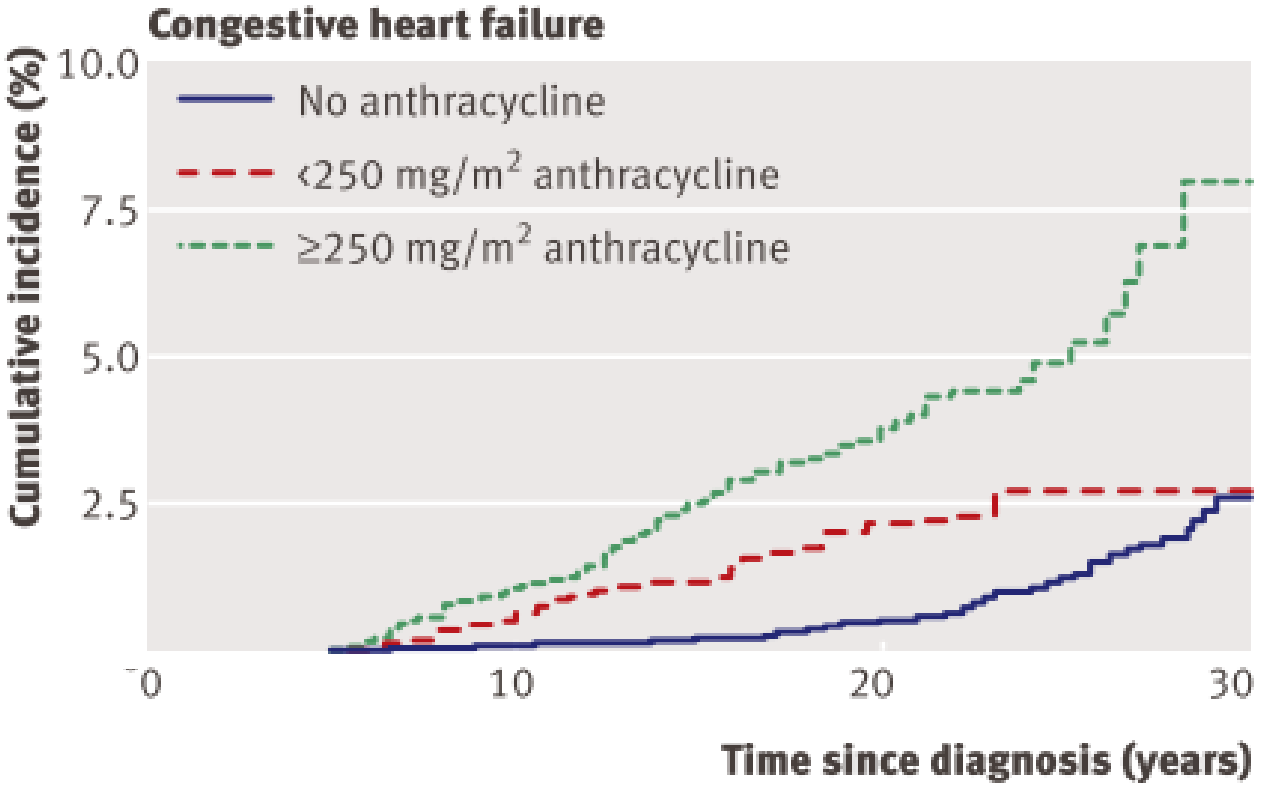


Fig 3 | Cumulative incidence of cardiac disorders among childhood cancer survivors by anthracycline dose

Mulrooney et al. BMJ (2009)

Table 1. Risk of Cardiotoxicity Associated With Chemotherapy

Risk Factor	Anthracycline	Trastuzumab
Cumulative dose >550 mg/m^2	Yes	
Age	Yes (≥64 years)	Yes (≥50 years)
Hypertension	Yes	Yes
Previous heart disease	Yes	
Previous radiation therapy	Yes	
Concurrent chemotherapy	Yes	Yes[a]
Hematopoietic cell transplantation	Yes	
Host susceptibility[5]	Yes	
Obesity (BMI ≥30)		Yes
Diabetes	Yes	No[b]

Blank cells in the table denote characteristics that are not risk factors or are inconclusive.
BMI, body mass index.
[a]Especially with concurrent anthracycline use.
[b]Small study suggests association in elderly women with diabetes.[6]

Domecant et al. 2016

J Cancer Surviv (2015) 9:252–259
DOI 10.1007/s11764-014-0408-9

Predictors of late-onset heart failure in breast cancer patients treated with doxorubicin

Angel Qin · Cheryl L. Thompson · Paula Silverman

Anthracycline cardiotoxicity can occur at three different time periods: during administration of the drug (acute),
within 1 year after therapy **(early-onset),**
or more than **1 year after exposure (late-onset)**

1153 patients received doxorubicin-based chemotherapy for invasive cancer
Average follow-up of 7.6 years

Qin et al. J Cancer Surviv. 2015

Table 2 Potential heart failure risk factors. The two heart failure groups were compared to the control group and then to one another for each of the risk factors

	Early HF (N=34)	Late HF (N=86)	Control (N=1,033)	p value (early versus control)	p value (late versus control)	p value (early versus late)
Age at diagnosis, mean (SD)	57.3 (10.7)	53.7 (11.2)	52.4 (11.1)	0.012	0.31	0.11
ER-positive, N (%)	22 (64.7 %)	55 (64.0 %)	680 (65.8 %)	0.89	0.73	0.94
PR-positive, N (%)	20 (58.8 %)	44 (51.2 %)	601 (58.2 %)	0.94	0.21	0.45
HER2-positive, N (%)	15 (44.1 %)	26 (30.2 %)	205 (19.9 %)	0.001	0.02	0.14
Left-sided radiation, N (%)	15 (44.1 %)	36 (41.9 %)	423 (41.0 %)	0.71	0.87	0.82
Doxorubicin						
≤240 mg/m^2, N (%)	31 (91.2 %)	78 (90.7 %)	951 (92.1 %)	0.75	0.65	0.99
>240 mg/m^2, N (%)	3 (8.8 %)	8 (9.3 %)	82 (7.9 %)			
Trastuzumab received, N (%)	13 (38.2 %)	17 (19.8 %)	92 (8.9 %)	<0.0001	0.001	0.035
DMII, N (%)	4 (11.8 %)	20 (23.3 %)	84 (8.1 %)	0.45	<0.001	0.16
CAD, N (%)	4 (11.8 %)	15 (17.4 %)	32 (3.1 %)	0.006	<0.001	0.59
HTN, N (%)	21 (61.8 %)	54 (62.8 %)	367 (35.5 %)	0.002	<0.001	0.55
DLD, N (%)	14 (41.2 %)	29 (33.7 %)	221 (21.4 %)	0.006	0.008	0.44
Smoking, former/current, N (%)	12 (35.3 %)	25 (29.1 %)	355 (34.4 %)	0.91	0.32	0.51

DMII type II diabetes mellitus, *CAD* coronary artery disease, *DLD* dyslipidemia, *HTN* hypertension, *HF* heart failure

Qin et al. J Cancer Surviv. 2015

Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

We assessed **LVEF**, at baseline, every 3 months during chemotherapy and for the following year, every 6 months over the following **4 years**, and yearly afterward in a heterogeneous cohort of 2625 patients receiving **anthracycline-containing therapy**

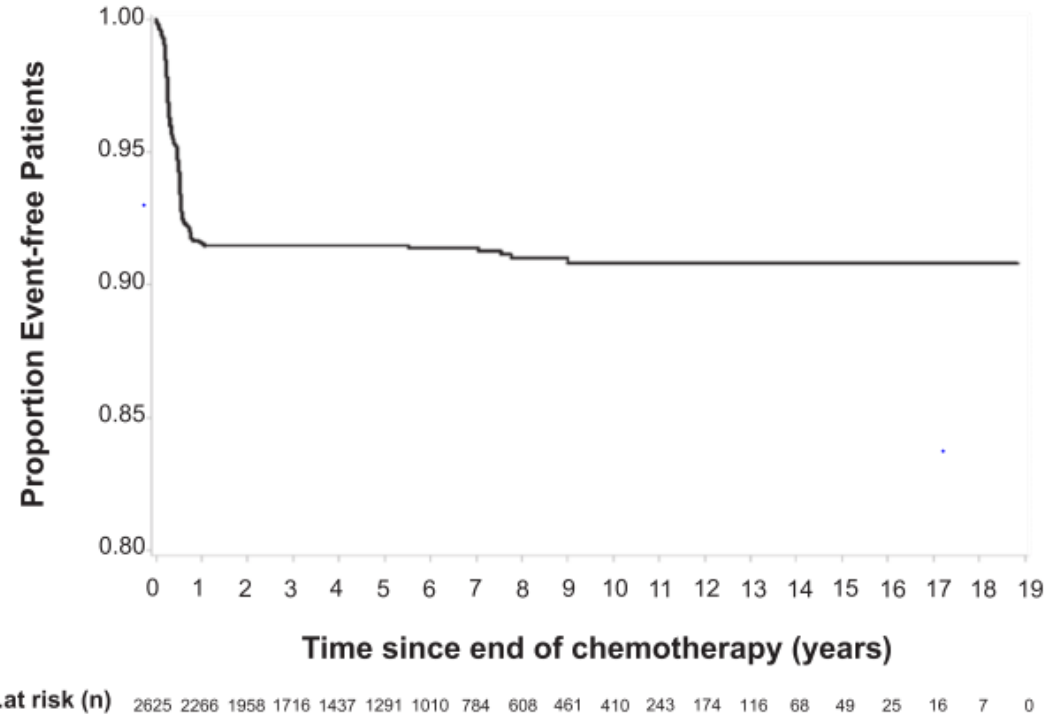


Figure 1. Kaplan–Meier curve showing the cumulative incidence of cardiotoxicity in the study population. Pts. indicates patients.

Cardinale et al. circulation. 2015

Trastuzumab

- **non–dose-related cardiac dysfunction**

→ that ranges from **asymptomatic decreases** in left ventricular ejection fraction (LVEF; in up to **17%** of patients) to **symptomatic heart failure** (**<4%** incidence)

- **altered signaling pathways**

→ reversible, nonstructural myocardial dysfunction almost always reversible and generally responds to standard heart failure treatment

→ Binding of trastuzumab to HER2 is thought to disrupt HER2-HER4 heterodimerization, thus disabling the protective mechanisms in the cardiac myocyte that are essential during exposure to adverse conditions or cardiac toxins

- A population-based retrospective cohort study was conducted among 18,540 women diagnosed with stage I-III breast cancer (2007 – 2012)

- Patient receiving trastuzumab had higher risk of cardiotoxicity HR 1.76 (95% C.I 1.19 – 2.60)

Table 4. Cox Proportional Hazards Model for the Primary Outcome, Sensitivity Analysis, and Secondary Outcomes Based on Treatment Groups

Event	Hazard Ratio (95% CI)			*P*
	Anthracyclines Without Trastuzumab*	Trastuzumab Without Anthracyclines†	Sequential Therapy	
Major cardiac events	0.97 (0.73 to 1.27)	1.76 (1.19 to 2.60)	3.96 (3.01 to 5.22)	< .001
Hospital-based CHF events (sensitivity outcome)	1.08 (0.67 to 1.74)	0.95 (0.45 to 2.02)	1.86 (1.07 to 3.22)	.031
Cardiovascular death	0.94 (0.41 to 2.20)	0.87 (0.19 to 4.04)	0.81 (0.25 to 2.66)	.988
All-cause death	1.03 (0.87 to 1.23)	1.14 (0.85 to 1.52)	0.82 (0.66 to 1.02)	.024

NOTE. Adjusted for age, age^2, prior ischemic heart disease, acute myocardial infarction, rheumatic heart disease, valvular heart disease, hypertension, diabetes, baseline radiation, follow-up radiation (as a time-varying covariate), cancer stage, and income quantile. The reference group was patients receiving other chemotherapy, defined as nonanthracyclines and non–trastuzumab-based therapy. The reported *P* value is a global test for differences between the four treatment groups.
Abbreviation: CHF, congestive heart failure.
*With or without other chemotherapy.
†With or without other non–anthracycline-based chemotherapy.

Thaveendiranathan et al. J Clin Oncol. 2014

Other HER-2 therapy

Table 3 | Incidence of cardiac events with other HER2-directed therapies.

Trial	Number of patients in analysis	HER2-directed therapy	Incidence of cardiac events (%)	Definition of cardiac event
Geyer et al. (72)	161	Capecitabine	0.7	Symptomatic decline in LVEF or decrease ≥20% from baseline to below institution's lower limit of normal
	163	Lapatinib plus Capecitabine	2.4	
ALTTO (74)	2097	Trastuzumab alone	0.86	NYHA Class III/IV CHF or cardiac death
	2091	Trastuzumab followed by Lapatinib	0.25	
	2093	Trastuzumab concurrent with Lapatinib	0.97	
CLEOPATRA (76)	397	Trastuzumab + docetaxel plus placebo	6.6	LVEF decline to <50% with decrease ≥10% from baseline
	407	Trastuzumab + docetaxel plus Pertuzumab	3.8	
EMILIA (77)	445	Lapatinib + capecitabine	1.6	LVEF decline to <50% with decrease ≥15% from baseline
	481	T-DM1	1.7	

ALTTO: The incidence of NYHA Class III/IV heart failure was <1% in all arms

Guo et al. Front Oncol. 2014

Endocrine treatment

- **Tamoxifen** consistently **decreases low-density lipoprotein and total cholesterol levels** among postmenopausal women
- **Less consistent in AI** : There have been large trials that have shown aromatase inhibitors to either increase, decrease, or cause no changes in blood lipid

- Tamoxifen is associated with an increased risk of **arterial** and **venous thromboembolic disease** but no statistically significant effect on myocardial infarction or overall cardiac death

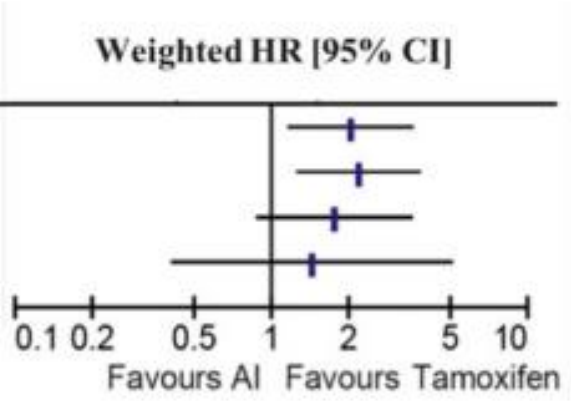
- negative cardiovascular outcomes in the adjuvant setting is generally low. (<5% in BIC1-98 trial)

The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer

Observational population-based cohort study
women aged >55 years diagnosed with stage I-III breast cancer between 2005 and 2010
Women treated with AIs or tamoxifen were followed to March 2012
7409 aromatase inhibitor-treated and **1941 tamoxifen-treated** women

primary outcome was hospitalisation for **myocardial infarction (MI)**
Inverse probability of treatment weighing (IPTW) using the propensity score (PS)

	Aromatase inhibitors		Tamoxifen	
Study or Subgroup	Events	Total	Events	Total
Full cohort	106	7409	17	1941
Aged 66 years and above	98	5869	16	1640
Prior IHD	46	1256	11	328
Lower-risk cohort	21	3426	<6	798



Abdel et al. Eur J Cancer. 2016

The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer

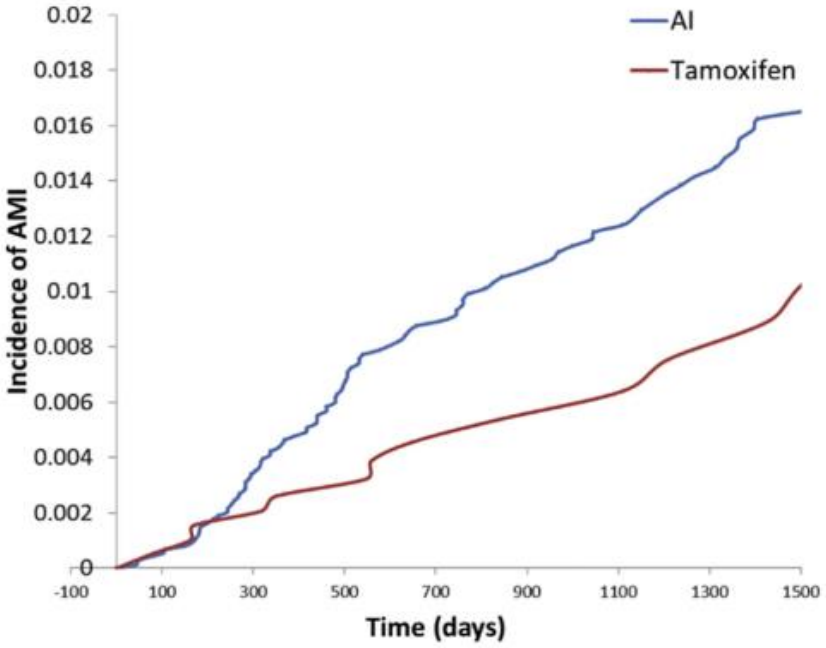


Fig. 2. **Cumulative incidence of myocardial infarction**. This figure illustrates the proportion of women with breast cancer exposed to aromatase inhibitors (AI) or tamoxifen who develop myocardial infarction during follow-up.

- **Potential limitations**

-without data on cumulative anthracycline exposures in individual patients
-musculoskeletal side effects; this may lead to increased non-steroidal anti-inflammatory use

VS

the PS-based methods achieved good balance
the prevalence of prior IHD was similar between the two groups

Abdel et al. Eur J Cancer. 2016

Research

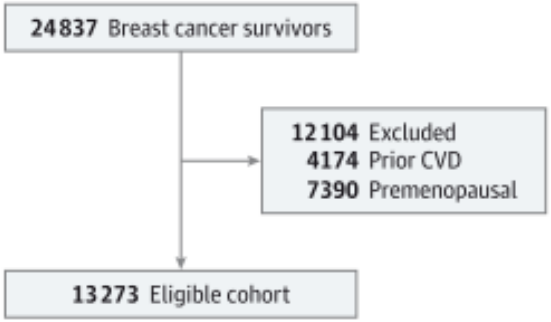
Original Investigation

Cardiovascular Disease After Aromatase Inhibitor Use

Reina Haque, PhD; Jiaxiao Shi, PhD; Joanne E. Schottinger, MD; Joanie Chung, MPH; Chantal Avila, MA; Britta Amundsen, MA; Xiaoqing Xu, PharmD; Ana Barac, MD; Rowan T. Chlebowski, MD

- 13,273 postmenopausal women with HR+ve breast cancer (**78,886 person-years of follow up)**
- without prior CVD

Figure. Breast Cancer Survivors Diagnosed Between 1991 and 2010 and Followed up Through 2011



CVD indicates cardiovascular disease.

Haque et al. JAMA Oncol. 2016

Table 3. Adjusted HRs for CVD Events by Endocrine Treatment Use in 13 273 Women[a]

Type of CVD	Breast Cancer Treatment, HR (95% CI)			
	Tamoxifen Only	AI Only	Tamoxifen and AI	No Hormones
Cardiac ischemia (myocardial infarction and angina)				
Overall	1 [Reference]	0.80 (0.63-0.98)	0.87 (0.70-1.07)	0.98 (0.81-1.19)
Adjusted	1 [Reference]	0.97 (0.78-1.22)	1.03 (0.83-1.29)	1.09 (0.89-1.33)
Adjusted, stages I-III (n = 12 924)	1 [Reference]	0.98 (0.78-1.23)		
Propensity score + IPTW model	1 [Reference]	0.81 (0.66-0.99)		
Stroke				
Overall	1 [Reference]	0.77 (0.57-1.05)		
Adjusted	1 [Reference]	0.97 (0.70-1.33)		
Adjusted, stages I-III (n = 12 924)	1 [Reference]	0.94 (0.68-1.30)		
Propensity score + IPTW model	1 [Reference]	0.82 (0.63-1.06)		
Heart failure and cardiomyopathy				
Overall	1 [Reference]	0.97 (0.77-1.23)	1.21 (0.96-1.52)	1.22 (0.98-1.53)
Adjusted	1 [Reference]	1.10 (0.86-1.40)	1.27 (0.99-1.60)	1.38 (1.10-1.74)
Adjusted, stages I-III (n = 12 924)	1 [Reference]	1.09 (0.84-1.40)	1.19 (0.93-1.52)	1.34 (1.06-1.69)
Propensity score + IPTW model	1 [Reference]	0.96 (0.77-1.18)	1.30 (1.08-1.56)	1.30 (0.97-1.74)
Other CVD (dysrhythmia, valvular dysfunction, and pericarditis)				
Overall	1 [Reference]	1.09 (0.93-1.25)	1.13 (0.98-1.29)	1.17 (1.02-1.34)
Adjusted	1 [Reference]	1.29 (1.11-1.50)	1.26 (1.09-1.45)	1.18 (1.02-1.35)

Adjusted for
CVD medications,
race/ethnicity, stage and age at breast cancer,
geocoded income,
DM, HTN
first-course chemotherapy use

Haque et al. JAMA Oncol. 2016

"Cardio-Oncology"

- integrative medical approach that involves close interaction between cardiologists and oncologists with the goal of mitigating cardiac risk and providing optimal care to patients who will be receiving cardiotoxic agents or radiotherapy

Role of cardio-oncologist

Pre-cancer treatment
Assess baseline risk
Address modifiable risk factors
Develop monitoring strategy

During cancer treatment
Monitor for cardiotoxicity
Facilitate patient treatment

Continue to address modifiable risk factors and/or side effects such as HTN

If CV toxicity, start appropriate Rx and discuss risk/benefits of cancer treatment strategies with oncology

Post-cancer treatment
Continue to modify risk factors to decrease late cardiac toxicity and CV morbidity

Educate on long term side effects
Manage CV toxicities

Table 2. Prevention of Anthracycline-Induced Cardiomyopathy

Treatment Modification	Comments
Anthracycline dose limitation	Dose limited to <550 mg/m^2
Infusion timing	Slow infusion during a 6-hour or more period preferred over boluses
Encapsulation	
Dexrazoxane	
Structural modification	Less cardiotoxic alternatives: epirubicin, mitoxantrone
Risk Factors Reduction	**Comments**
Screening for cardiomyopathy	Echocardiography most common modality
Hypertension	ACEI/ARB and/or β-blockers
Diabetes	ACEI, glucose control
Advanced age	ACEI/ARB and/or β-blockers

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; β, beta.

Domercant et al. Ochsner J. 2016

VOLUME 35 · NUMBER 8 · MARCH 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Increased risk for developing cardiac dysfunction:

- **High-dose anthracycline** (eg, doxorubicin ≥ 250 mg/m^2, epirubicin ≥ 600 mg/m^2)
- **High-dose radiotherapy** (RT;≥ 30 Gy) where the heart is in the treatment field
- Lower-dose anthracycline (eg, doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) in combination with lower-dose RT (>30 Gy) where the heart is in the treatment field

- Treatment with lower-dose anthracycline or trastuzumab alone, and presence of any of the following risk factors:

  Multiple cardiovascular risk factors (≥ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy

  Older age (≥ 60 years) at cancer treatment

  Compromised cardiac function (eg, borderline low LVEF [50% to 55%], history of myocardial infarction, moderate valvular heart disease)

- Treatment with low dose anthracycline followed by trastuzumab (sequential therapy)

Armenian S et al. J Clin Oncol (2016)

- Echocardiography
  - No radiation
  - Information of hemodynamics, valvular disease, diastolic function
  - interobserver variability of LVEF assessment (5-10%)
  - abnormal EF is often a late finding

- American Society Clinical Oncology
- American Heart Association
- Heart Failure Society of America

- Recommends serial assessment of LVEF
- Within 6 to 12 months after chemotherapy
- **“How often”?**
- **“until when”?**

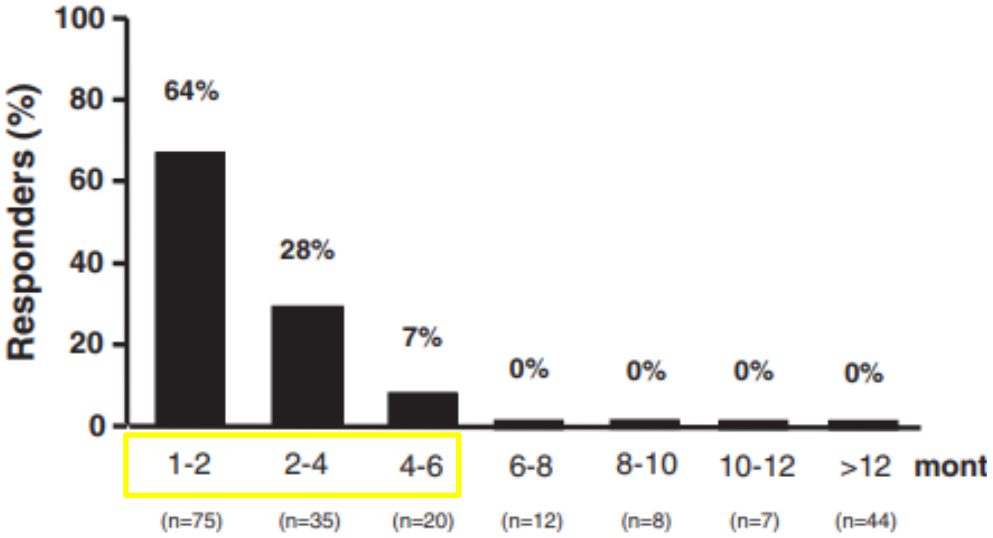
Journal of the American College of Cardiology

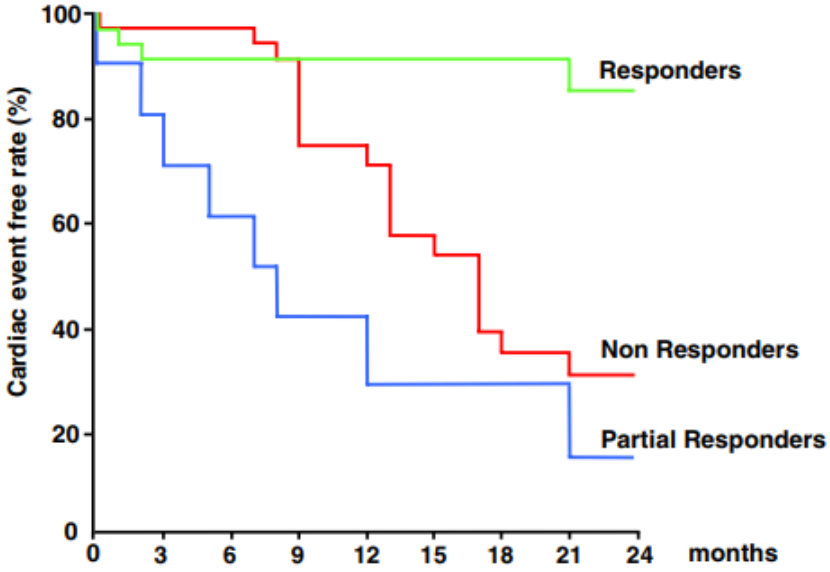
Published by Elsevier Inc.

Anthracycline-Induced Cardiomyopathy

Clinical Relevance and Response to Pharmacologic Therapy

- 201 patients with a LVEF≤45% due to AC-cardiomyopathy
  Median time to treatment 4 months (2 to 14 mon)





Cardinale et al. J Am Coll Cardiol (2010)

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Survivorship

VOLUME 35 · NUMBER 8 · MARCH 10, 2017

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ASCO SPECIAL ARTICLE

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

- **Cardiac Biomarkers**

Early elevation in biomarkers precede changes in LVEF by echocardiography

- Troponin I
  - the optimal timing of troponin assessment is unclear (72 hours to one month)
  - the sensitivity and specificity is low (48% and 73%)
  - predictive markers of LV dysfunction is unclear

- BNP and NT-proBNP
  - its use in asymptomatic patient with cancer is investigational

Breast Cancer Res Treat
DOI 10.1007/s10549-017-4133-8

EPIDEMIOLOGY

Adiposity, post-diagnosis weight change, and risk of cardiovascular events among early-stage breast cancer survivors

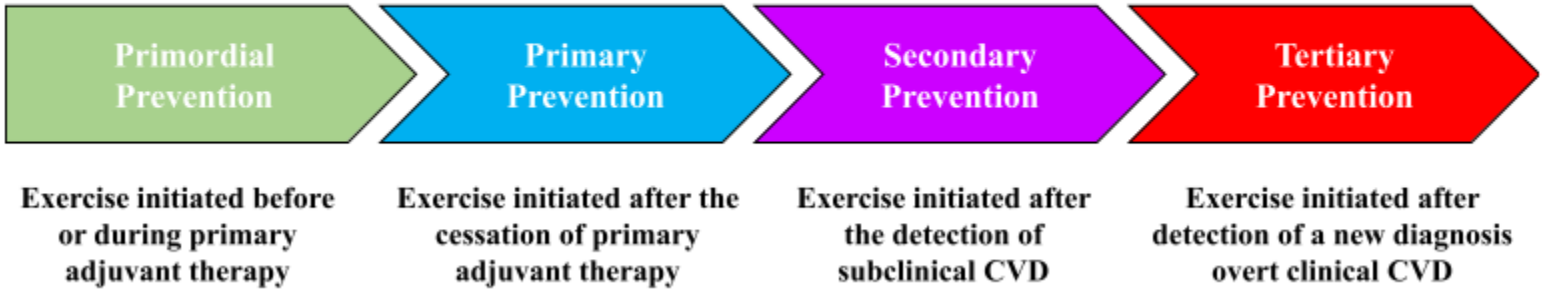
Stage I–III breast cancer survivors 18 to < 80 years,
without pre-existing CVD,
diagnosed from 1997 to 2013 at Kaiser Permanente.

Table 3 Post-diagnosis waist circumference and incident CVD event or death $n = 1898$; events = 596

	80 to <90 cm $N = 480$	90 to <100 cm $N = 463$	≥100 cm $N = 417$	<80 cm $N = 535$	Per 5 cm $N = 1898$
Mean (SD) waist circumference	84.64 (2.71)	94.61 (2.86)	110.66 (10.60)	73.38 (4.67)	89.61 (14.78)
	Hazard ratio for CVD (95% CI)				
CVD event or death[a]	154	162	156	124	596
Age and race-adjusted[b]	1.31 (1.02, 1.68)	1.34 (1.04, 1.73)	1.63 (1.26, 2.11)	Ref.	1.06 (1.03, 1.09)
+Lifestyle and BMI[c]	1.52 (1.15, 2.00)	1.67 (1.20, 2.32)	2.01 (1.37, 2.94)	Ref.	1.09 (1.05, 1.14)
+Tumor and treatment[d]	1.50 (1.14, 1.97)	1.63 (1.17, 2.26)	2.02 (1.37, 2.97)	Ref.	1.09 (1.04, 1.14)
+Pre-existing CVD risk factors[e]	1.48 (1.12, 1.95)	1.60 (1.15, 2.22)	1.93 (1.31, 2.84)	Ref.	1.08 (1.03, 1.13)

Cespedes et al. Breast Cancer Res Treat. 2017

CVD-Cancer Continuum



- **Adherence to national exercise guidelines** for adult patients with cancer (i.e,9 metabolic equivalent [MET] hours per week) was associated with an adjusted **23% reduction in the risk of CVD** events in comparison with not meeting the guidelines (< 9 MET hours per week; P< 0.0002).
- The association with exercise did not differ according to age, CVD risk factors, menopausal status, or anticancer treatment.

Scott et al. Can J Cardiol. 2016

Cancer patients often have **co-existing** heart diseases;
Cancer therapies can **cause** cardiovascular (CV) complications

Cardiologists and cancer specialists should work together
to identify high-risk patients & modify CV risk factors

Cardiomyopathy

Strategies for reducing cardiotoxicity:

Anthracycline: Dose reduction, continuous infusion, liposomal doxorubicin, dexrazoxane

Trastuzumab: Avoid concomitant anthracycline

VSP inhibitors: Treat hypertension

Consider cardio-protection (Beta Blocker/ACE Inhibitors), if:

Ejection fraction (EF) <50% or EF drop>10%

Global Longitudinal Strain >15% drop

Myocardial damage (assessed via troponin)

Withhold certain cancer therapies as a last resort:

Anthracycline (withhold if EF<45%)

Trastuzumab (withhold if EF<40%)

Ischemia

Ischemia workup:
Stress test,
cardiac catheterization

Treatment:
As per ACC/AHA guidelines

If platelet count lower than 100,000/microliter of blood:

Aspirin if platelet >10K

Dual anti-platelet therapy with aspirin and clopidogrel for drug eluting stents if platelet >30K

Cardiac catheterization via radial approach

Chang et al. J Am Coll Cardiol (2017)

Nationwide cohort in Korean population

- **A retrospective cohort using National Health insurance claim database**

- **Breast cancer survivors** older than age 20 (2007-2013)
  Age-sex matched 1:5 for **cancer-free cohort**
  (excluded: Previous history of MI, CHF)
  The incidence of MI, CHF, and all-cause death

- **Operational definitions of outcomes and subgroup**
  MI: ICD-10 I21, I22 with PCI, CABG, hospitalization
  CHF: I50 with hospitalization
  adjuvant treatment within 12 months from first claim

Subjects at risk (MI)	1y	3y	5y	7y
Breast cancer survivors				
< 50 y at breast cancer diagnosis	65959	53491	33005	15338
51-65 at breast cancer diagnosis	35208	27345	15625	6768
≥66 at breast cancer diagnosis	8486	6282	3462	1401
total	109653	87118	52092	23507
Cancer free cohort				
< 50 y	333756	279714	177641	84345
51-65	179598	144771	85715	38242
≥66	44953	35529	20674	8568
total	558307	460014	284030	131155

Subjects at risk (CHF)	1y	3y	5y	7y
Breast cancer survivors				
< 50 y at breast cancer diagnosis	65957	53492	33009	15332
51-65 at breast cancer diagnosis	35175	27285	15611	6790
≥66 at breast cancer diagnosis	8444	6240	3434	1389
total	109576	87017	52054	23511
Cancer free cohort				
< 50 y	333822	279871	177789	84458
51-65	179686	144902	85877	38337
≥66	44902	35413	20532	8463
total	558410	460186	284198	131258

	Breast cancer survivors N(%)	Non-cancer controls N(%)	*p* value
Total	112058 (100)	560290 (100)	
AGE	48.26±9.54	48.26±9.54	1
<=50	66849 (59.7)	334245 (59.7)	
51-65	36050(32.2)	180250 (32.2)	
>=66	9159 (8.2)	45795 (8.2)	
Charlson comorbidity index(CCI)	3.1 ± 1.5	0.8 ± 1.3	<.0001
hypertension	22120 (19.8)	93738 (16.8)	<.0001
Diabetes	7892 (7.0)	30481(5.4)	<.0001
dyslipidemia	13751 (12.3)	59835 (10.7)	<.0001
income quartile			<.0001
Q1	31701 (28.2)	169702 (30.3)	
Q2	23551 (21.0)	124515 (22.2)	
Q3	25277 (22.6)	126061 (22.5)	
Q4	31529 (28.1)	140012 (25.0)	

Development of MI, CHF, mortality(all cause) in breast cancer survivor and cancer-free cohort

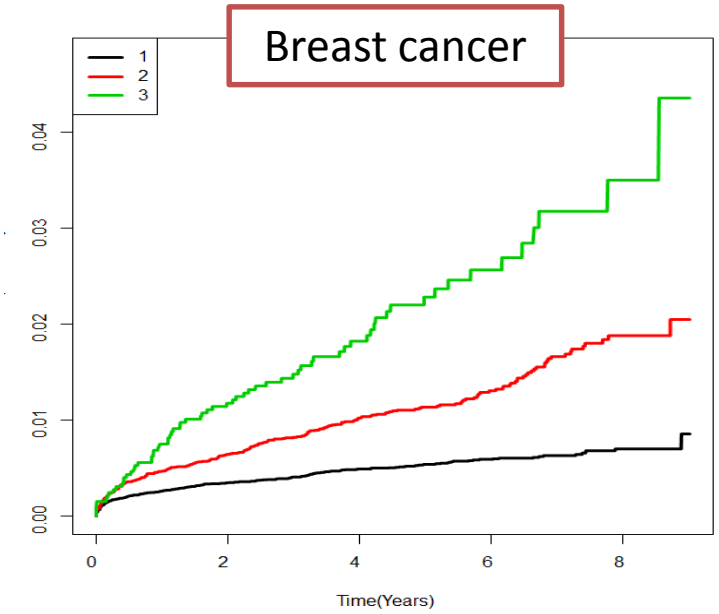
					HR(95% CI)	
		N	EVENT	IR(per 1000)	MODEL1*	MODEL2**
MI	control	560290	3526	1.21297	1(REF.)	1(REF.)
	Case	112058	**867**	1.57007	**1.326(1.231,1.428)**	**1.258(1.168,1.355)**
CHF	Control	560290	4197	1.44329	1(REF.)	1(REF.)
	Case	112058	**1509**	2.73489	**1.973(1.86,2.092)**	**1.86(1.753,1.973)**
DEATH	Control	560290	9129	3.1302	1(REF.)	1(REF.)
	Case	112058	10135	18.2678	5.976(5.809,6.147)	6.019(5.851,6.193)

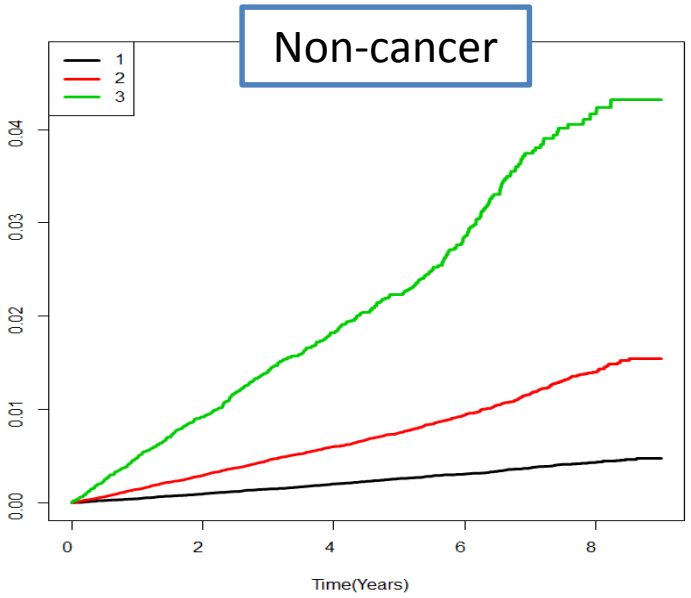
*model1: adjusted by age

**model2: adjusted by age, income, diabetes, hypertension, dyslipidemia

Age is the important risk factor both in controls and cases

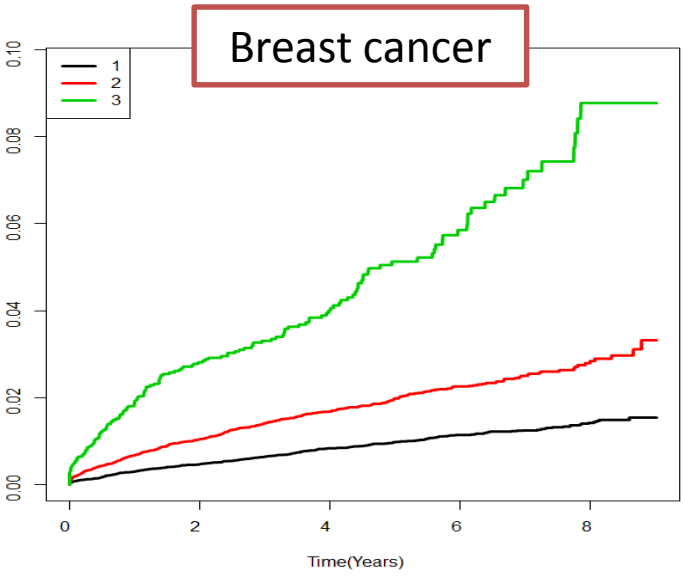
MI

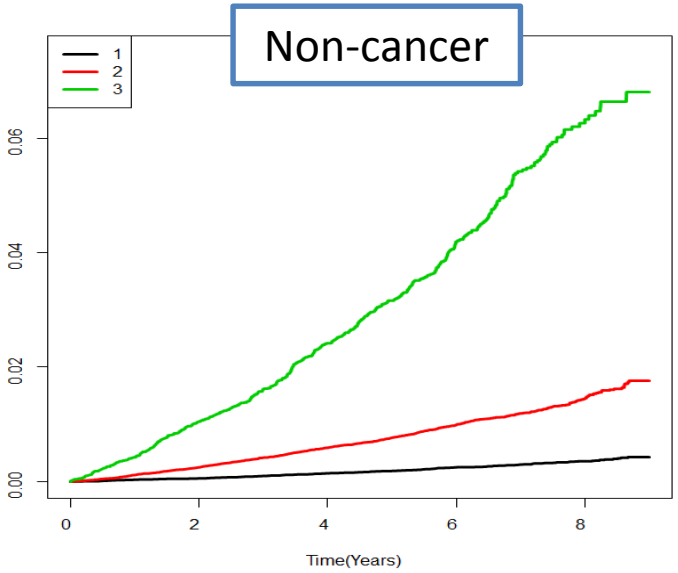




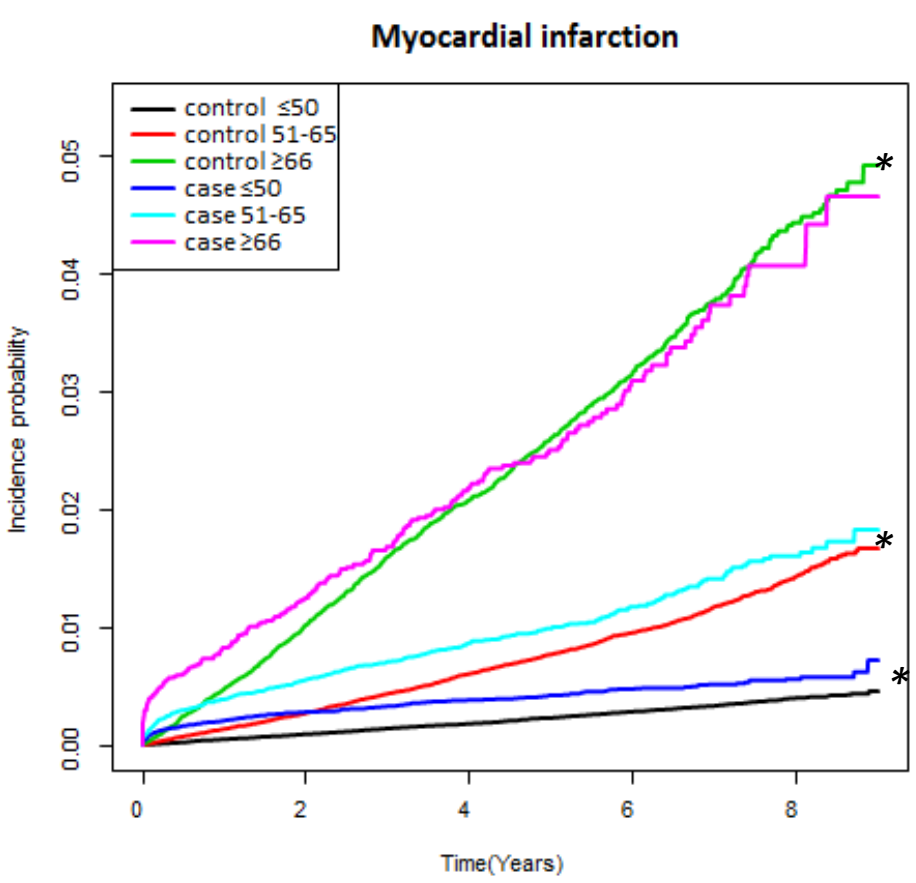
Black:<=50
Red: 51-65
Green:>=66

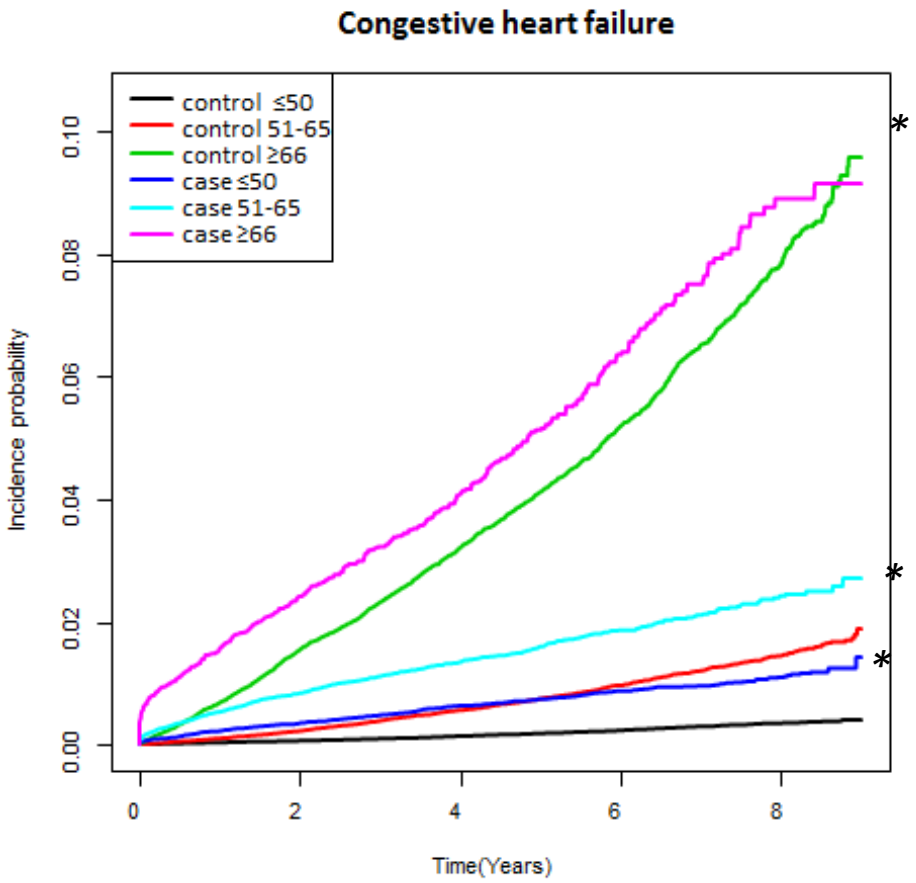
CHF





Development of MI and CHF following age subgroups





*p<0.001

Following breast cancer treatment: CHF

	No MI	MI	*p* value	HR (95% CI)
Number	110549	1509		
Chemotherapy (any)			<.001	
No	43817(39.6)	520(34.5)		1 (ref.)
Yes	66732(60.4)	989(65.5)		1.4(1.2 - 1.7)
Anthracycline use			0.083	
No	53764(48.6)	700(46.4)		1 (ref.)
Yes	56785(51.4)	809(53.6)		1.1(0.9 - 1.3)
Taxane use			<.001	
No	80307(72.6)	965(64.0)		1 (ref.)
Yes	30242(27.4)	544(36.0)		1.7(1.4 - 1.9)
Radiotherapy			<.001	
No	39636(35.9)	799(53.0)		1 (ref.)
Yes	70913(64.1)	710(47.0)		0.7(0.7 - 0.8)
Trastuzumab			<.001	
No	99920(90.4)	1324(87.7)		1 (ref.)
Yes	10629(9.6)	185(12.3)		1.2(1.04-1.5)
Endocrine treatment			<.001	
No	37122(33.6)	702(46.5)		1 (ref.)
Tamoxifen	50409(45.6)	372(24.7)		0.7(0.6 - 0.8)
AI	23018(20.8)	435(28.8)		0.8(0.7– 0.96)

*adjusted by age, income, history of diabetes, history of hypertension, history of dyslipidemia, anthracycline use, taxane use, radiotherapy, trastuzumab use, endocrine treatment

Following breast cancer treatment: Myocardial infarction

	No MI	MI	*p* value	HR (95% CI)
Number	111191	867		
Chemotherapy (any)			0.093	
No	44108(39.6)	319(36.7)		1 (ref.)
Yes	67173(60.4)	548(63.2)		1.2(1.0 - 1.6)
Anthracycline use			0.614	
No	54050(48.6)	414(47.7)		1 (ref.)
Yes	57141(51.4)	453(52.2)		1.2(1.0 - 1.5)
Taxane use			0.025	
No	80671(72.6)	601(69.3)		1 (ref.)
Yes	30520(27.5)	266(30.7)		1.3(1.1 - 1.5)
Radiotherapy			<.001	
No	33972(36.0)	463(53.4)		1 (ref.)
Yes	71219(64.1)	404(46.6)		0.7(0.6 - 0.8)
Trastuzumab			0.701	
No	100464(90.4)	780(90.0)		1 (ref.)
Yes	10727(9.65)	87(10.0)		1.0(0.8 - 1.3)
Endocrine treatment			<.001	
No	37429(33.7)	395(45.6)		1 (ref.)
Tamoxifen	50550(45.5)	231(26.6)		0.7(0.6 - 0.9)
AI	23212(21.0)	241(27.8)		0.8(0.7 - 0.9)

*adjusted by age, income, history of diabetes, history of hypertension, history of dyslipidemia, anthracycline use, taxane use, radiotherapy, trastuzumab use, endocrine treatment

Nationwide cohort in Korean population

- **Limitations**

  Not available information of breast cancer subtypes
  Not available information of adjuvant treatment regimen
  Advanced cancer not excluded
  Cause of mortality not evaluated

- Incidence of MI and CHF were higher in the breast cancer survivor than the non-cancer controls.

- **Summary**

- Breast cancer survivors are increasing and there will be increase in number of patients with cardiac late effects from cancer-related therapies.

- Anthracyclines, HER-2 targeted agents, endocrine therapy can be related to development cardiac diseases.

- Collaboration with cardiology might be important to improve outcomes and survivorship for breast cancer patients.

Thank you for your attention