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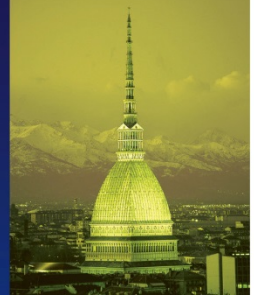


UNIVERSITÀ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

# Cancer survivors: let's not forget them!

Enrico Brignardello

SSD Unità di Transizione per Neoplasie Curate in Età Pediatrica

AOU Città della Salute e della Scienza di Torino

# *Cancer Survivors*

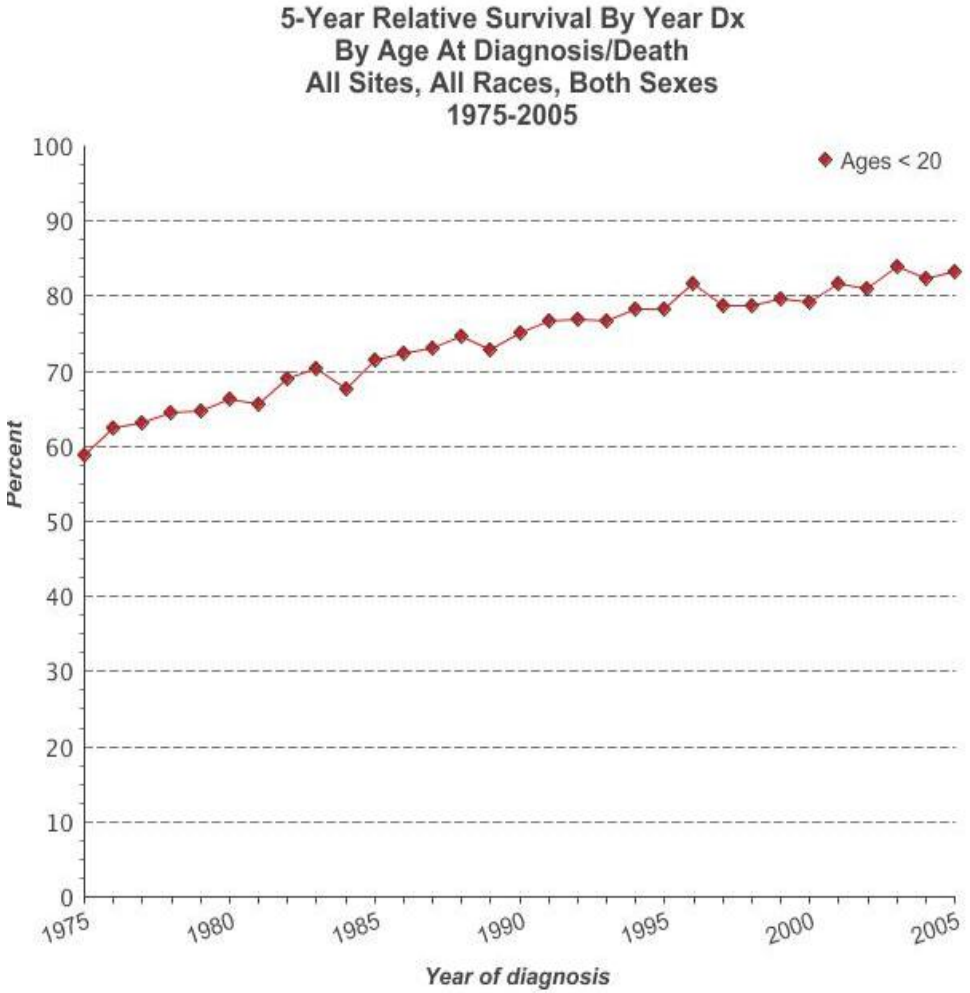
- Someone with cancer **from the moment of diagnosis through the end of the life** (Mullan, NCCS, 1986)

- Someone who have **survived cancer for 5 years or longer** (Beimling, 2007)

# Background

As a result of advances in treatment, about 80% of children and adolescents who receive a diagnosis of cancer become **childhood cancer survivors**.

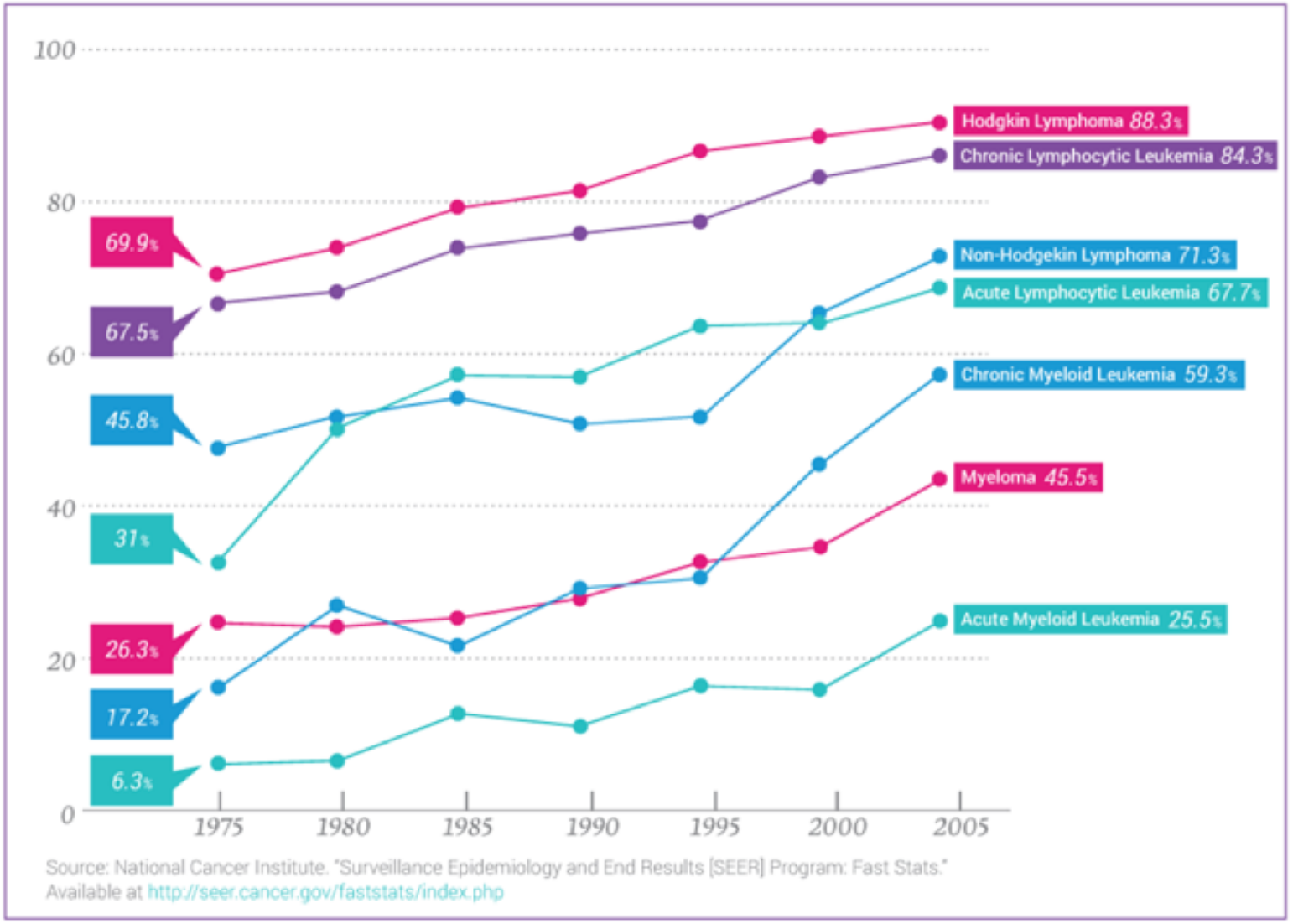
The prevalence of childhood cancer survivors, in Italy, is about 0.10 %, meaning a total number of about 60.000 CCS




**SEER Cancer Statistics, NCI**

# ADULT CANCER SURVIVORS

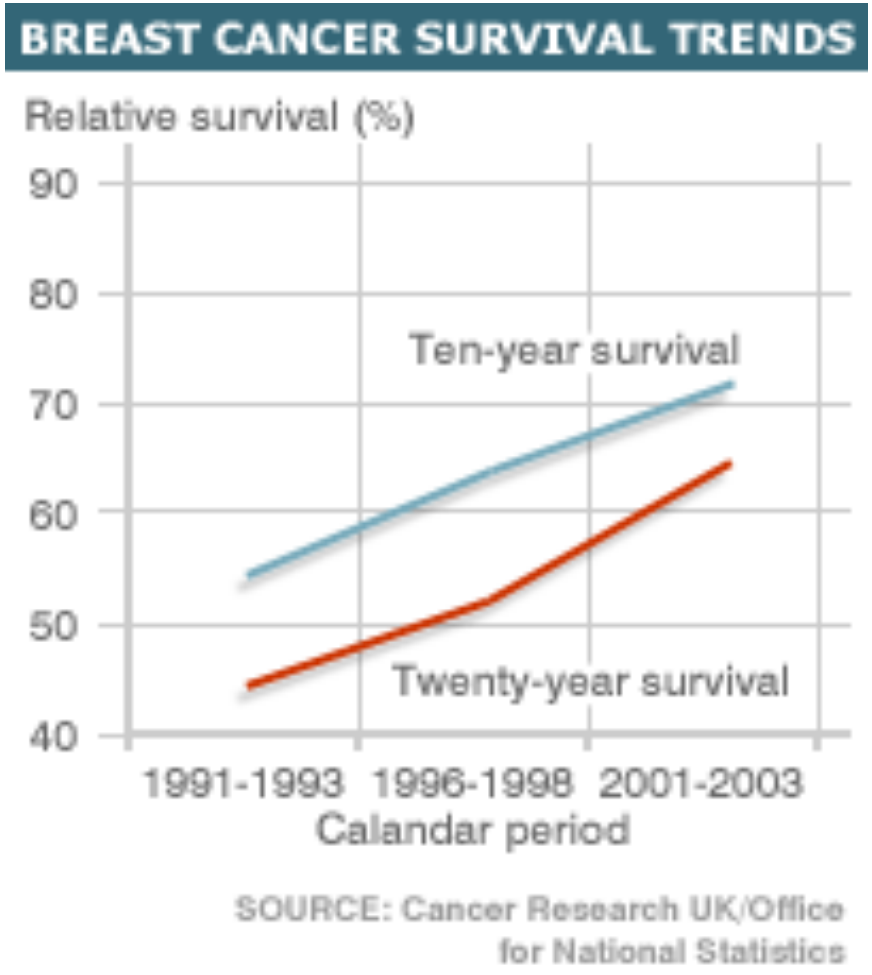
## Hematological malignancies



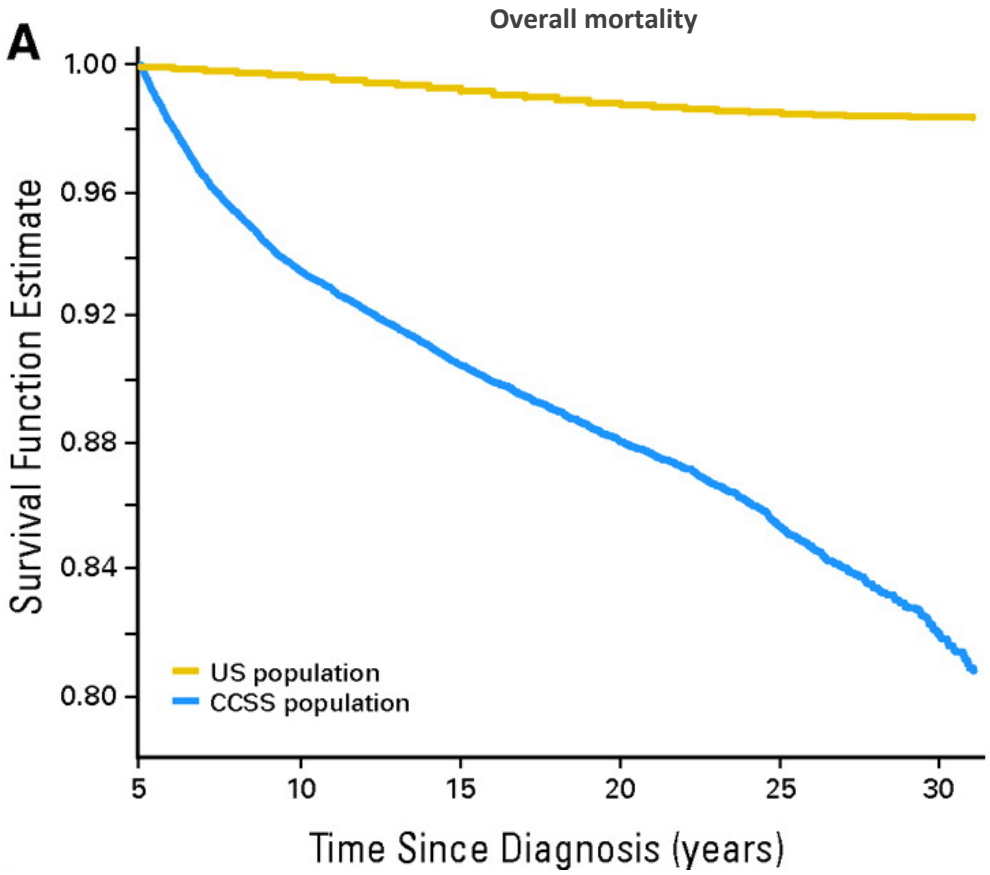

**SEER Cancer Statistics, NCI**

# ADULT CANCER SURVIVORS

## Breast cancer



# Background




Unfortunately, **this increased rate of survival does not come without a cost to the survivor**.

There is **significant long-term morbidity and mortality associated with treatment** of childhood cancer, the incidence of which continues to increase long after completion of therapy.

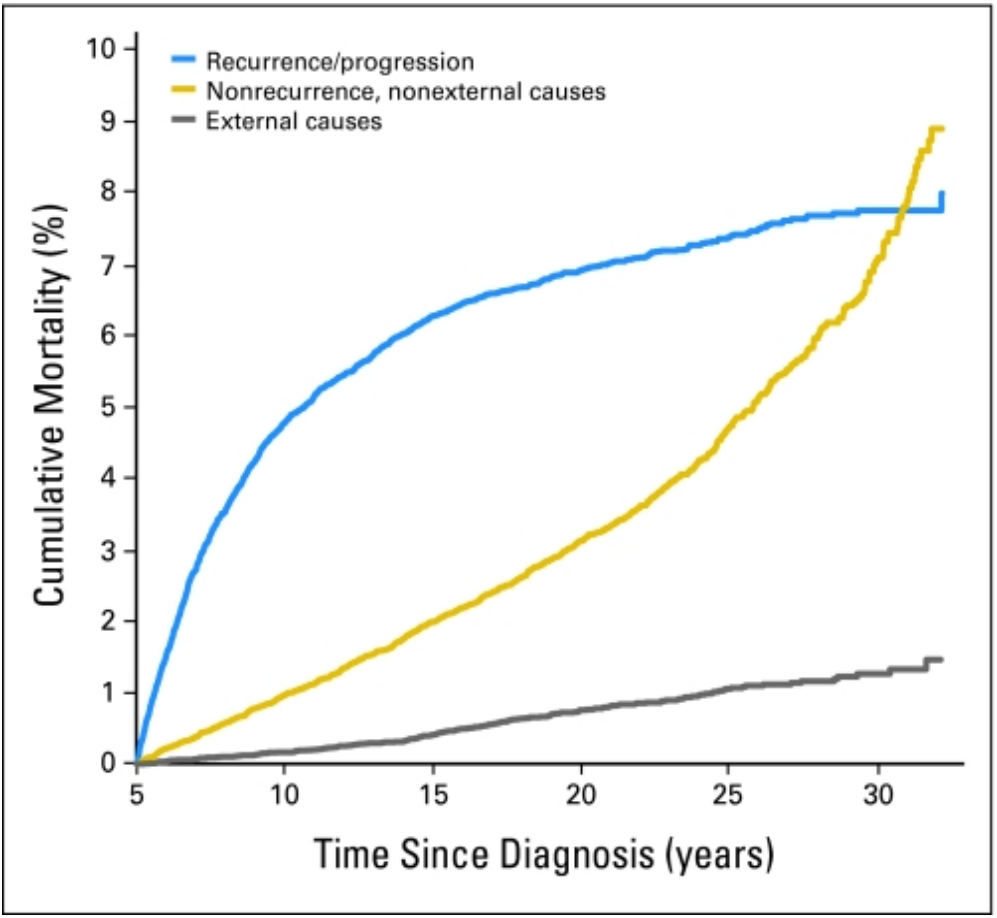
**Armstrong et al., JCO, 2009**

VOLUME 27 · NUMBER 14 · MAY 10 2009

JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

# Late Mortality Among 5-Year Survivors of Childhood Cancer: A Summary From the Childhood Cancer Survivor Study

*Gregory T. Armstrong, Qi Liu, Yutaka Yasui, Joseph P. Neglia, Wendy Leisenring, Leslie L. Robison, and Ann C. Mertens*

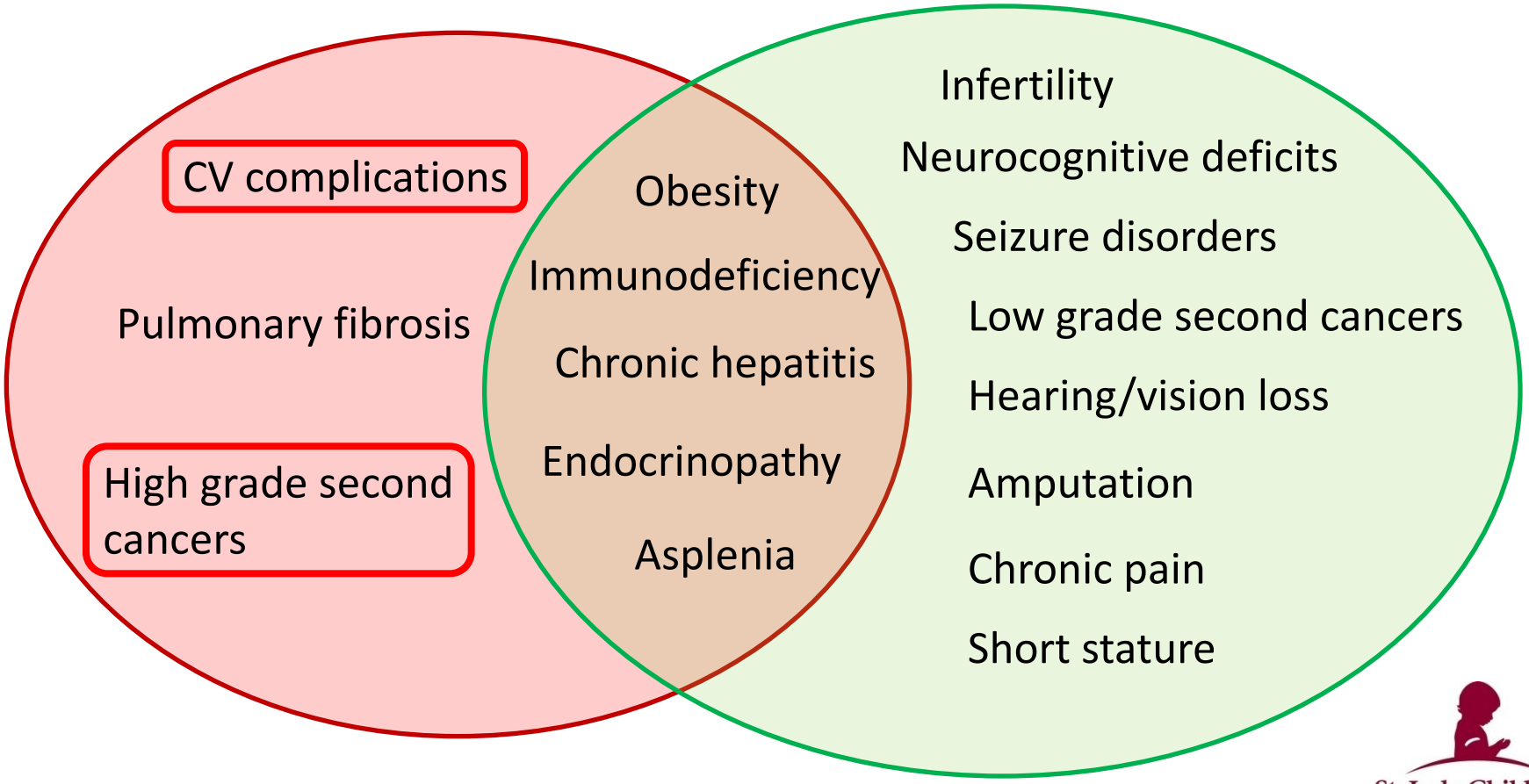



With time mortality attributable to recurrence or progression of primary disease is decreasing, with **increases in rates of mortality attributable to late effects** of anticancer treatments.

**Subsequent noplasms** (SMR, 15.2; 95% CI, 13.9 to 16.6) and **cardiac death** (SMR, 7.0; 95% CI, 5.9 to 8.2) are the most common cause of death.

# Spectrum of Physical Late Effects

Life Threatening → Life Altering



# Acute and late cardiotoxicity

**Table 1 – Most common cardiotoxic anticancer treatments.**

| Treatment | Main mechanism | Clinical manifestations | Time of manifestation |
|---|---|---|---|
| Anthracyclines | Non-ischemic degeneration of the myocytes | Progressive heart failure | Acute and chronic |
| Chest Radiotherapy | Microcirculatory damage with subsequent progressive interstitial fibrosis | Heart failure, Coronary artery stenosis, Valvular diseases, Arrhythmias, Constrictive pericarditis | Usually chronic |
| Trastuzumab and other HER2 blockers | Inhibition of HER2 receptors on myocytes membrane | Heart failure | Acute |
| 5-flourouracil and other antimetabolites | Coronary vasospasm | Myocardial ischemia and infarction | Acute |
| Taxanes | Impairment of microtubule systems in cardiomyocytes | Myocardial ischemia, arrhythmias and heart failure | Acute |
| Tyrosine-kinase inhibitors | Inhibition of targeted pathways in heart and endothelial cells | Left ventricular dysfunction and heart failure, myocardial ischemia | Acute |

**Felicetti […] Brignardello, Diab Res Clin Pract 2018**

DIABETES RESEARCH AND CLINICAL PRACTICE 143 (2018) 432–442

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Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Invited review

# Cancer survivors: An expanding population with an increased cardiometabolic risk

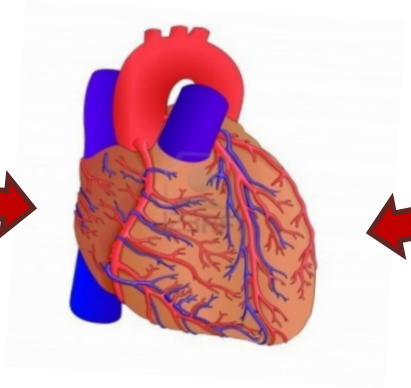
*Francesco Felicetti, Nicoletta Fortunati, Enrico Brignardello* *

*Transition Unit for Childhood Cancer Survivors, Città della Salute e della Scienza Hospital, Turin, Italy*

**Late cardiotoxicity** is related both to the **direct effects of cancer treatments** on heart function and structure **and to the worsening of CV risk factors**, which can also be induced by anticancer therapies

# Direct effect of cancer treatments

**Radiotherapy**

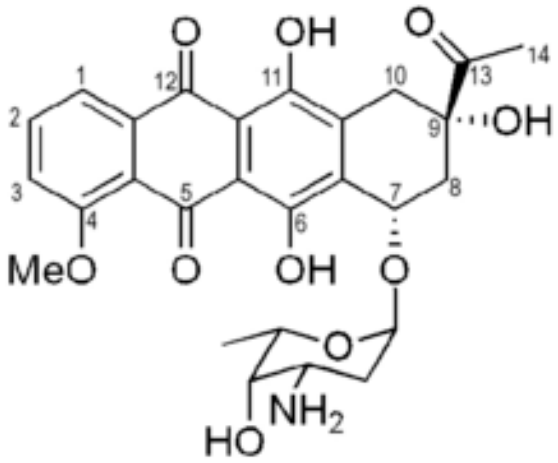


**Anthracyclines**

# Anthracycline Cardiotoxicity

## - Anthracycline

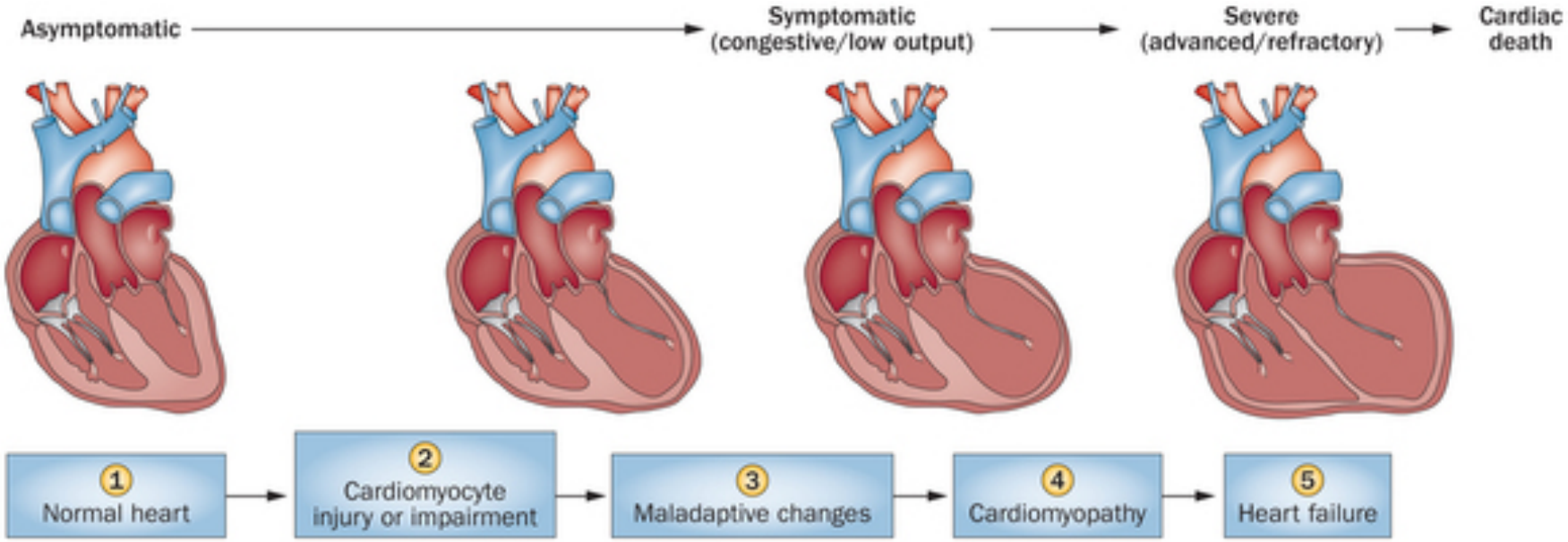
- 5-FU, capecitabine
- Taxanes
- Alkylating agents
- TK-inhibitors
- Monoclonal Ab (trastuzumab)




*"Doxorubicin administration was associated with a doserelated **increase in the degree of myocyte damage**, and 27 of 29 patients biopsied at doses ≥ 240 mg/m$^2$ had doxorubicin-associated degenerative changes identified on biopsy. "*

*Ann Intern Med* **1978**;88(2):168-175.

# Anthracycline: pathophysiology




***Non-ischemic cellular degeneration*** → ***Diastolic dysfunction and later systolic dysfunction*** → ***Symptomatic cardiac dysfuncion***

Lipshulz SE et al, Nature Reviews Clinical Oncology 2013

# Anthracycline Cardiotoxicity

- Anthracycline **late-onset cardiotoxicity is dose-dependent**
- Clinical manifestations **may occur several years after administration**, **often triggered by other factors** (e.g., infection, pregnancy, etc.)
- The mechanism by which anthracyclines induces cardiotoxicity is not fully understood, but the generation of **reactive oxygen species** (which contribute to the anthracyclines antitumor activity) seem to play a crucial role

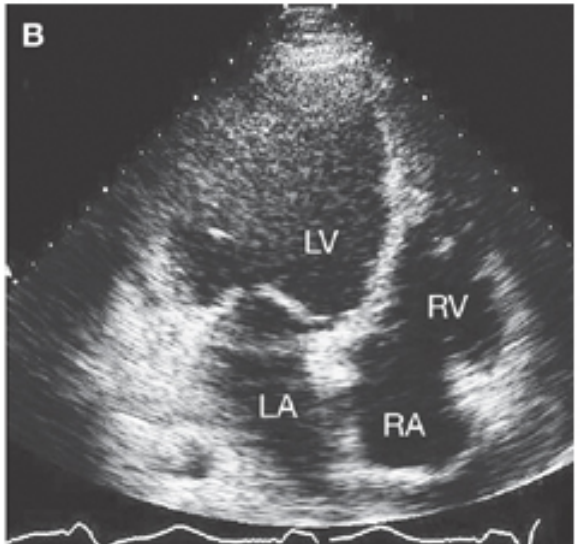
# Anthracycline Cardiotoxicity

**Major risk factors:**

- Cumulative dose

- Age at first administration (< 5 or > 65 yrs)

- Concomitant RT involving the heart




Lipshulz et al, Circulation 2013

# Anthracycline Cardiotoxicity: prevalence

**Review and Meta-Analysis of Incidence and Clinical Predictors of Anthracycline Cardiotoxicity**

- **18 studies** published from 1979 to 2011 were included
- **49,017 patients** with cancer were included, with **22,815 treated with anthracyclines**.
- After a **median follow-up of 9 years**, clinically **overt cardiotoxicity occurred in 6.3%**, whereas **subclinical cardiotoxicity developed in 17.9%.**

**Lotrionte et al, Am J Cardiol 2013**

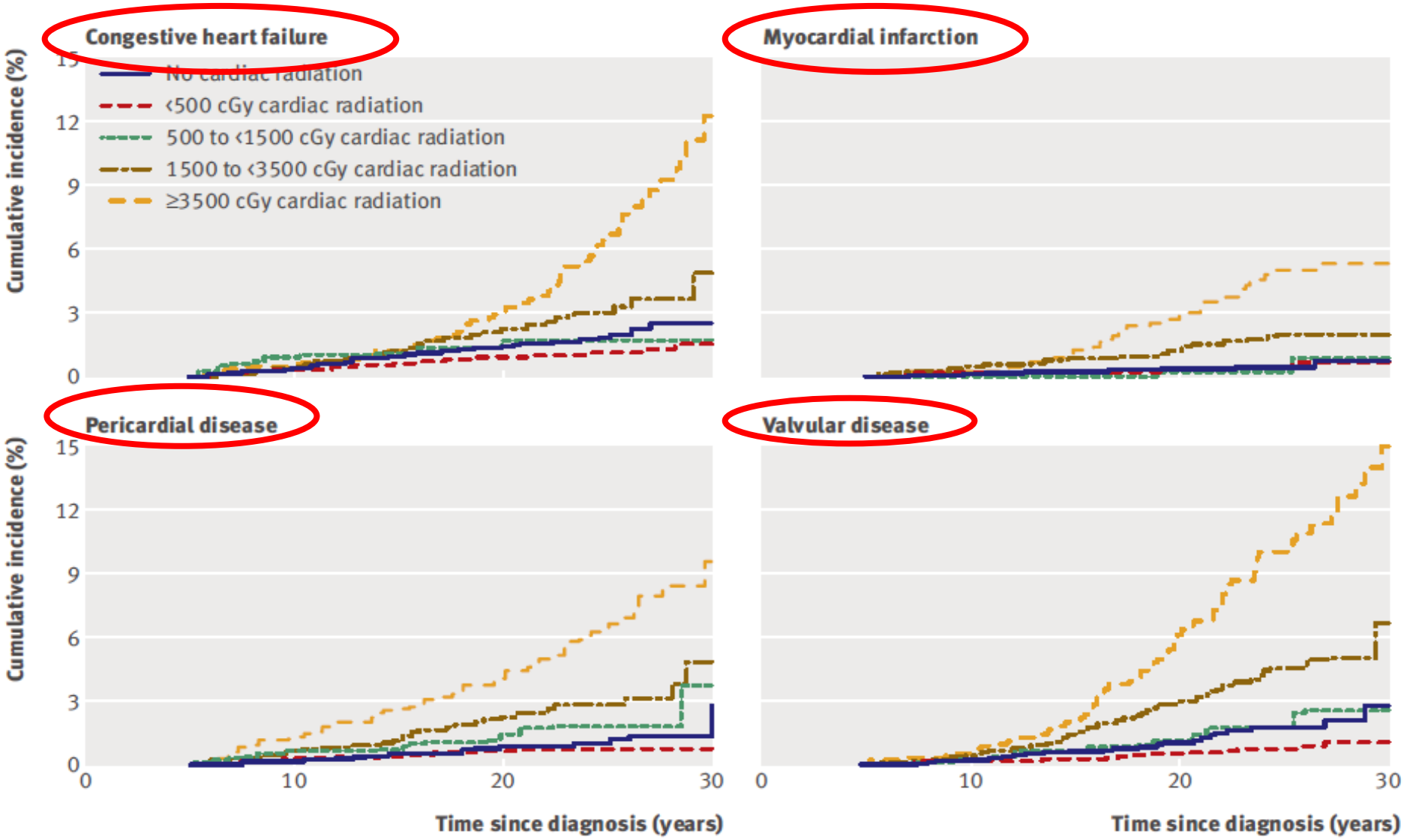



Fig 4 | Cumulative incidence of cardiac disorders among childhood cancer survivors by average cardiac radiation dose

Mulrooney et al, BMJ 2009

# RT and classical CV risk factors

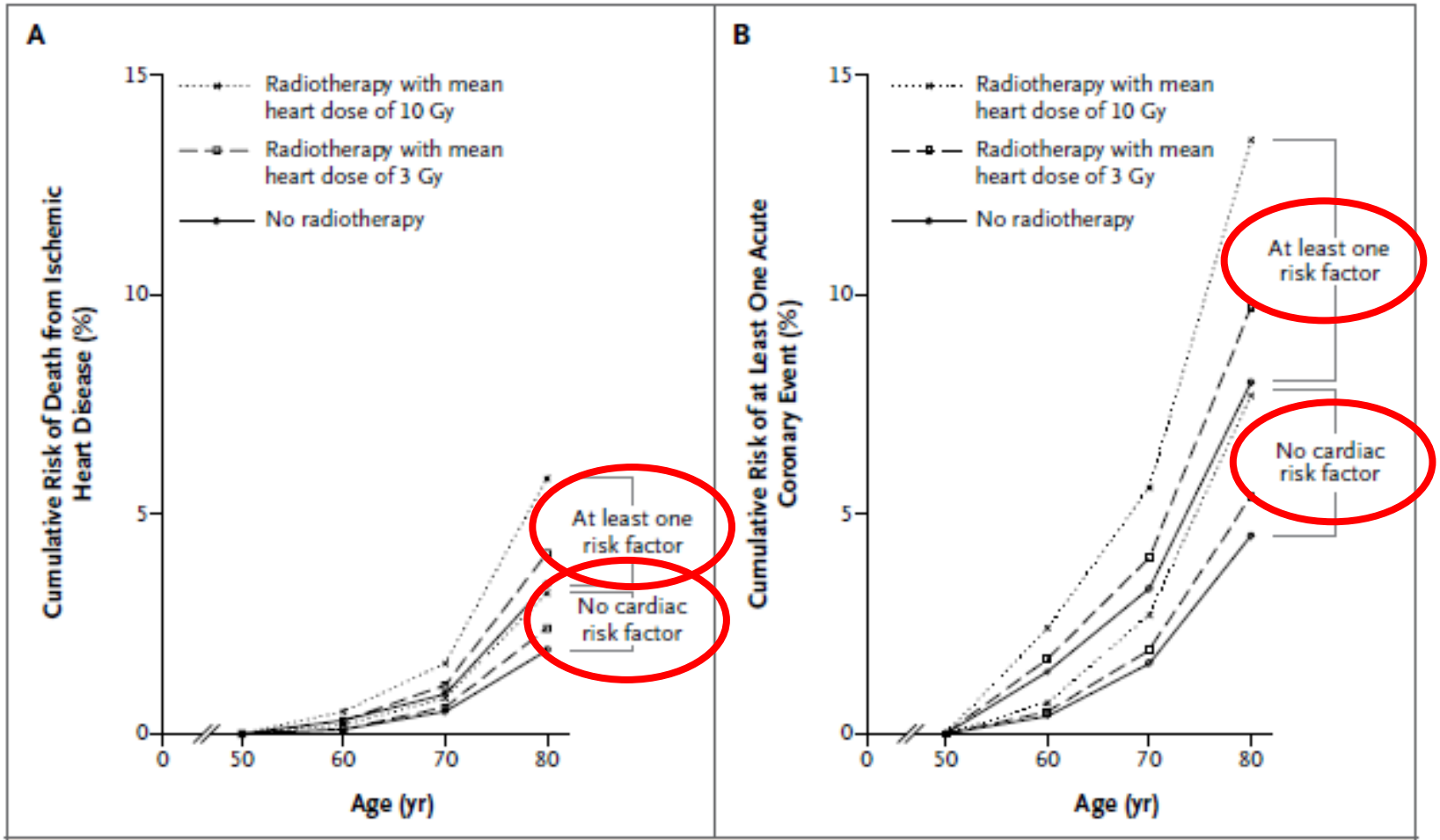



**Figure 2. Cumulative Risks of Death from Ischemic Heart Disease and of at Least One Acute Coronary Event.**

Darby et al, NEJM 2013

DIABETES RESEARCH AND CLINICAL PRACTICE 143 (2018) 432–442

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Late cardiotoxicity is related both to the direct effect of cancer treatments on heart function and structure and to the **worsening of CV risk factors**, which can also be induced by anticancer therapies.

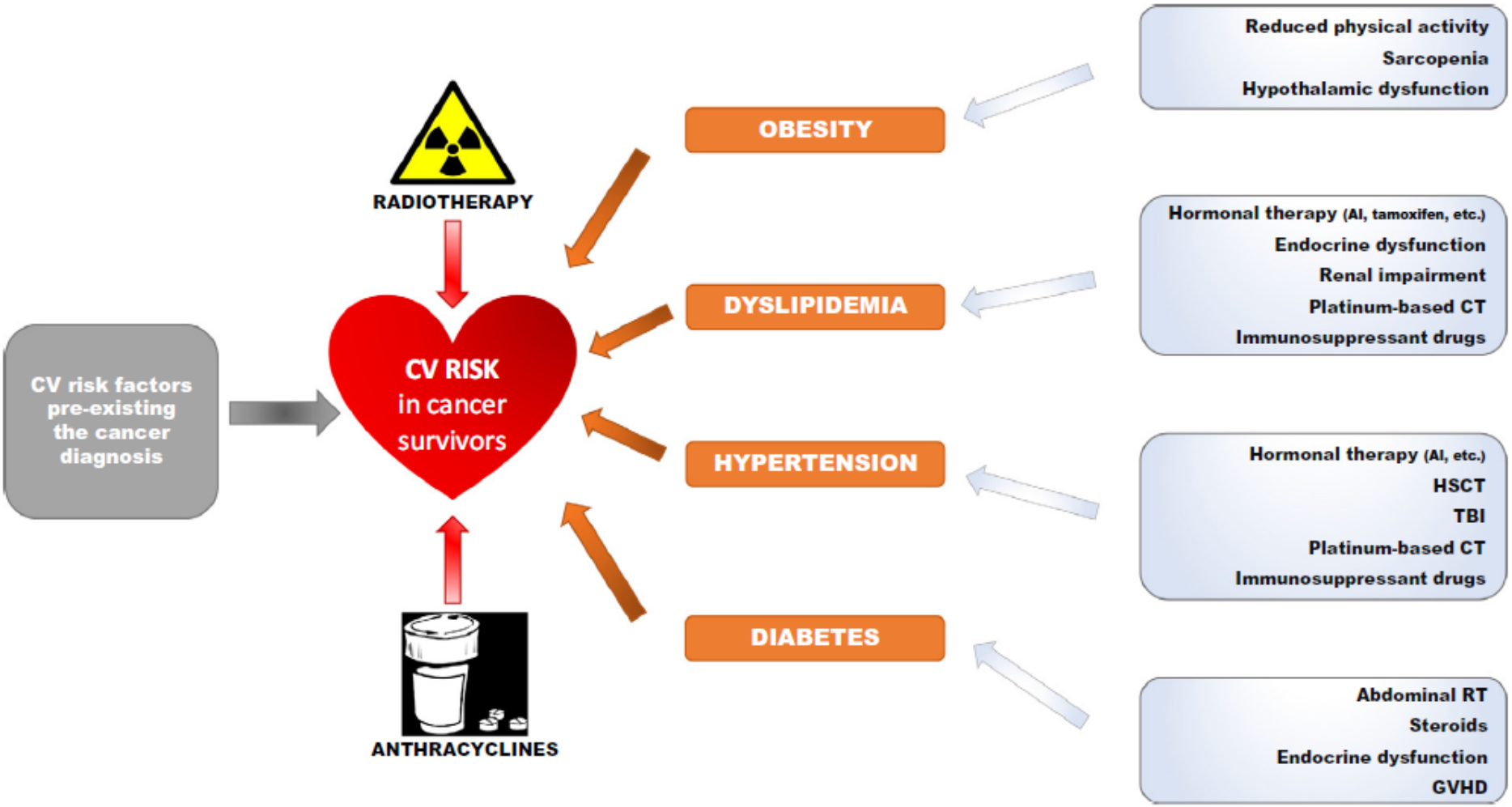


Fig. 1 – Cardiovascular risk factors in cancer survivors.

**Felicetti […] Brignardello, Diab Res Clin Pract 2018**

# Clinical management of cardiometabolic risk in cancer survivors

**AWARENESS**
(of the physician and survivor)

**YEARLY MEDICAL EXAMINATION**
(including blood pressure, BMI and waist circumference)

**INSTRUMENTAL AND LABORATORY TESTS**

## Cancer prevention 1

# Cardiotoxic effects of anthracycline-based therapy: what is the evidence and what are the potential harms?

*Bennett E Levis, Phillip F Binkley, Charles L Shapiro*

Although the cardiotoxic effects of anthracyclines have been known for at least 40 years, **no evidence-based guidelines exist for post-treatment monitoring and prevention of treatment-related cardiotoxicity** in clinically asymptomatic adult survivors of breast cancer. Hence, the recommendations of various national and international policy-making institutions vary greatly and are inconsistent, leaving clinicians and breast cancer survivors in a quandary about what approach is best […]

*Lancet Oncol* 2017; 18: e445–56

Canadian Journal of Cardiology 32 (2016) 831–841

Society Guidelines

# Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy

## Detection and Prevention of Cardiotoxicity

There are currently no consistent recommendations on the frequency and modality with which cardiac imaging should be performed in patients at risk of LV dysfunction related to cancer therapy. **Existing surveillance protocols are on the basis of methodology from clinical trials and expert opinion**.

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Saro H Arn
Sadhna Sh
Leontien C

| | North American Children's Oncology Group | Dutch Childhood Oncology Group | UK Children's Cancer and Leukaemia Group | Scottish Intercollegiate Guidelines Network | Concordance/ discordance |
|---|---|---|---|---|---|
| **Who needs cardiomyopathy surveillance?** | | | | | |
| Treatments that increase risk | | | | | |
| Anthracyclines | Yes | Yes | Yes | Yes | Concordance |
| Mitoxantrone | Yes | Yes | Yes | Yes | Concordance |
| Differing risk by anthracycline analogues | Yes | Not stated | Not stated | Not stated | Discordance |
| Chest radiation | Yes | Yes | Yes | Yes | Concordance |
| Cardiovascular risk factors | Yes | Yes | Yes | Yes | Concordance |
| Highest risk factors | ≥300 mg/m² anthracyclines ≥30 Gy RT involving heart* Anthracyclines + chest RT Younger age at treatment Pregnancy | ≥300 mg/m² anthracyclines ≥30 Gy RT involving heart* Anthracyclines + chest RT Pregnancy | >250 mg/m² anthracyclines Anthracyclines + chest RT History of transient cardiomyopathy during treatment Pregnancy | >250 mg/m² anthracyclines ≥30 Gy RT involving heart* Anthracyclines + chest RT | Discordance |
| **What surveillance modality should be used?** | | | | | |
| Screening for cardiomyopathy | | | | | |
| Echocardiography | Yes | Yes | Yes | Yes | Concordance |
| Radionuclide angiography | Yes | Yes | No | No | Discordance |
| **At what frequency and for how long should cardiomyopathy surveillance be performed?** | | | | | |
| Screening begins | ≥2 years after treatment or ≥5 years after diagnosis (whichever is first) | ≥5 years after diagnosis | 1–3 months after treatment | ≥5 years after completion of treatment | Discordance |
| Screening frequency | Every 1–5 years | Every 2–5 years | Every 3–5 years | Every 2–5 years | Discordance |
| Duration of screening | Lifelong | Lifelong | Not stated | Not stated | Discordance |
| Closer monitoring during pregnancy | Yes | Yes | Yes | Yes | Concordance |
| **What should be done when abnormalities are identified?** | | | | | |
| Refer to cardiologist | Yes | Yes | Yes | Yes | Concordance |
| Consider ACE inhibitors | Not stated | Yes | Not stated | Yes | Discordance |

RT=radiotherapy. ACE=angiotensin converting enzyme. *RT involving the heart: mediastinal, thoracic, spinal, left or whole upper abdominal or total body irradiation.

*Table 1:* **Concordances and discordances in cardiomyopathy surveillance recommendations**

# Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

*Saro H Armenian, Melissa M Hudson, Renee L Mulder, Ming Hui Chen, Louis S Constine, Mary Dwyer, Paul C Nathan, Wim J E Tissing, Sadhna Shankar, Elske Sieswerda, Rod Skinner, Julia Steinberger, Elvira C van Dalen, Helena van der Pal, W Hamish Wallace, Gill Levitt, Leontien C M Kremer*

Owing to the absence of data, **recommendations** for initiation and frequency of surveillance **are largely consensus based.**

There was a consensus **that surveillance should begin no later than 2 years after completion of cardiotoxic therapy and continue for a minimum of every 5 years thereafter**, as pharmacological interventions in individuals with asymptomatic cardiomyopathy can delay the onset of congestive heart failure and decrease mortality.

*Lancet Oncol* 2015; 16: e123–36

# Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

*Saro H Armenian, Melissa M Hudson, Renee L Mulder, Ming Hui Chen, Louis S Constine, Mary Dwyer, Paul C Nathan, Wim J E Tissing, Sadhna Shankar, Elske Sieswerda, Rod Skinner, Julia Steinberger, Elvira C van Dalen, Helena van der Pal, W Hamish Wallace, Gill Levitt, Leontien C M Kremer*

| | Anthracycline dose | Chest radiation dose | Anthracycline + chest radiation |
|---|---|---|---|
| High | ≥250 mg/m² | ≥35 Gy | ≥100 mg/m² (anthracycline) + ≥15 Gy (radiation) |
| Moderate | 100 to <250 mg/m² | ≥15 to <35 Gy | .. |
| Low | <100 mg/m² | .. | .. |

*Table 3:* Definitions of cardiomyopathy risk groups

**More frequent cardiomiopathy surveillance is reasonable for high risk survivors.**

*Lancet Oncol* 2015; 16: e123–36

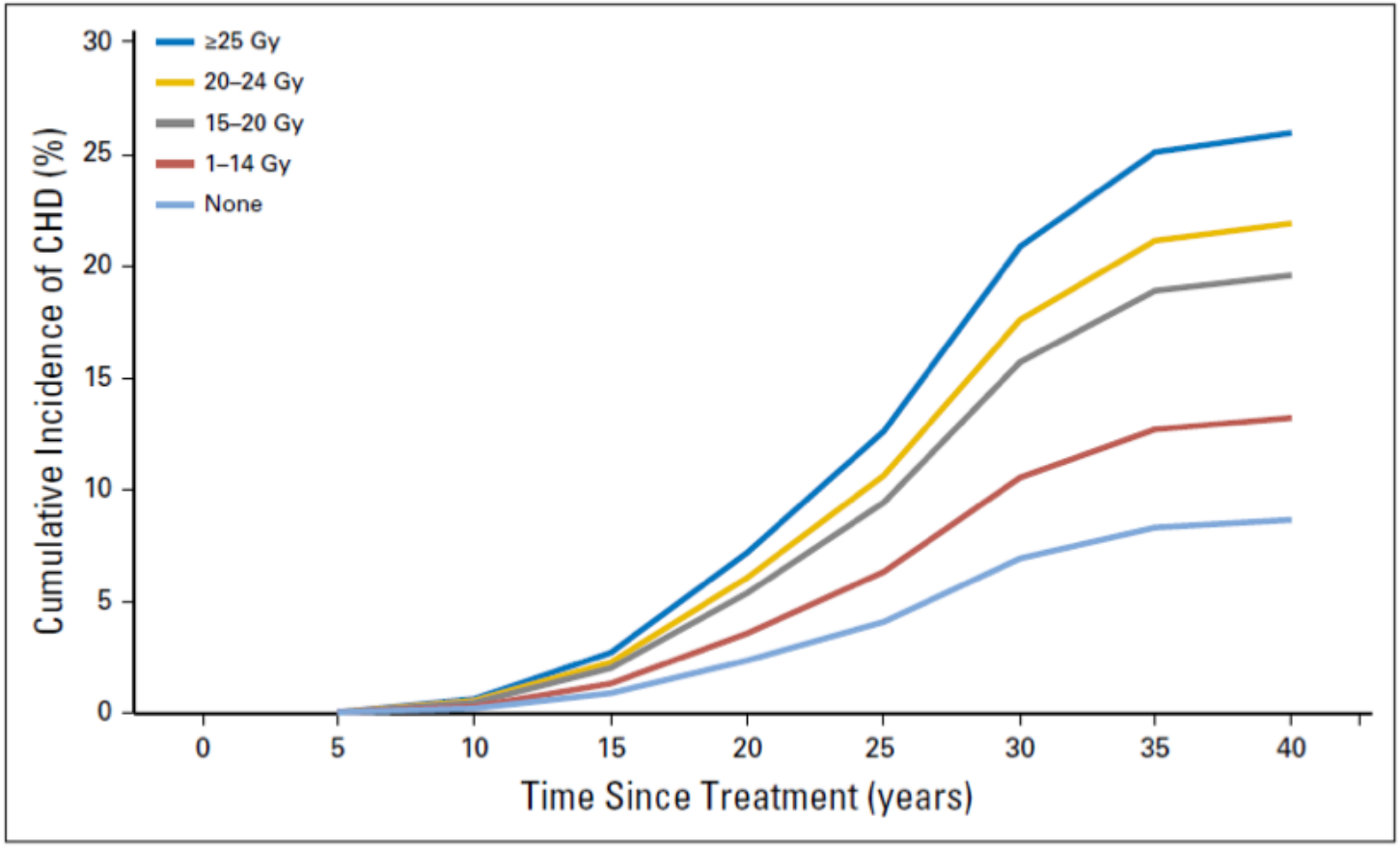
VOLUME 34 · NUMBER 3 · JANUARY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Radiation Dose-Response Relationship for Risk of Coronary Heart Disease in Survivors of Hodgkin Lymphoma

*Frederika A. van Nimwegen, Michael Schaapveld, David J. Cutter, Cècile P.M. Janus, Augustinus D.G. Krol, Michael Hauptmann, Karen Kooijman, Judith Roesink, Richard van der Maazen, Sarah C. Darby, Berthe M.P. Aleman, and Flora E. van Leeuwen*



# Prospective Coronary Heart Disease Screening in Asymptomatic Hodgkin Lymphoma Patients Using Coronary Computed Tomography Angiography: Results and Risk Factor Analysis

- **179 consecutive asymptomatic patients with Hodgkin lymphoma**
- **Median follow-up: 11.6 years**
- **Median age at CCTA: 42.0 years**
- **Coronary artery abnormalities were demonstrated in 46 patients (26%)**
- **Severe stenoses** were observed **in 12 (6.7%)** of the patients, **entailing surgery** with either angioplasty with stent placement or bypass grafting

**Girinsky et al., Int J Radiat Oncol Biol Phys 2014**

VOLUME 25 · NUMBER 1 · JANUARY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Screening for Coronary Artery Disease After Mediastinal Irradiation for Hodgkin's Disease

*Paul A. Heidenreich, Ingela Schnittger, H. William Strauss, Randall H. Vagelos, Byron K. Lee, Carol S. Mariscal, David J. Tate, Sandra J. Horning, Richard T. Hoppe, and Steven L. Hancock*

**Results**

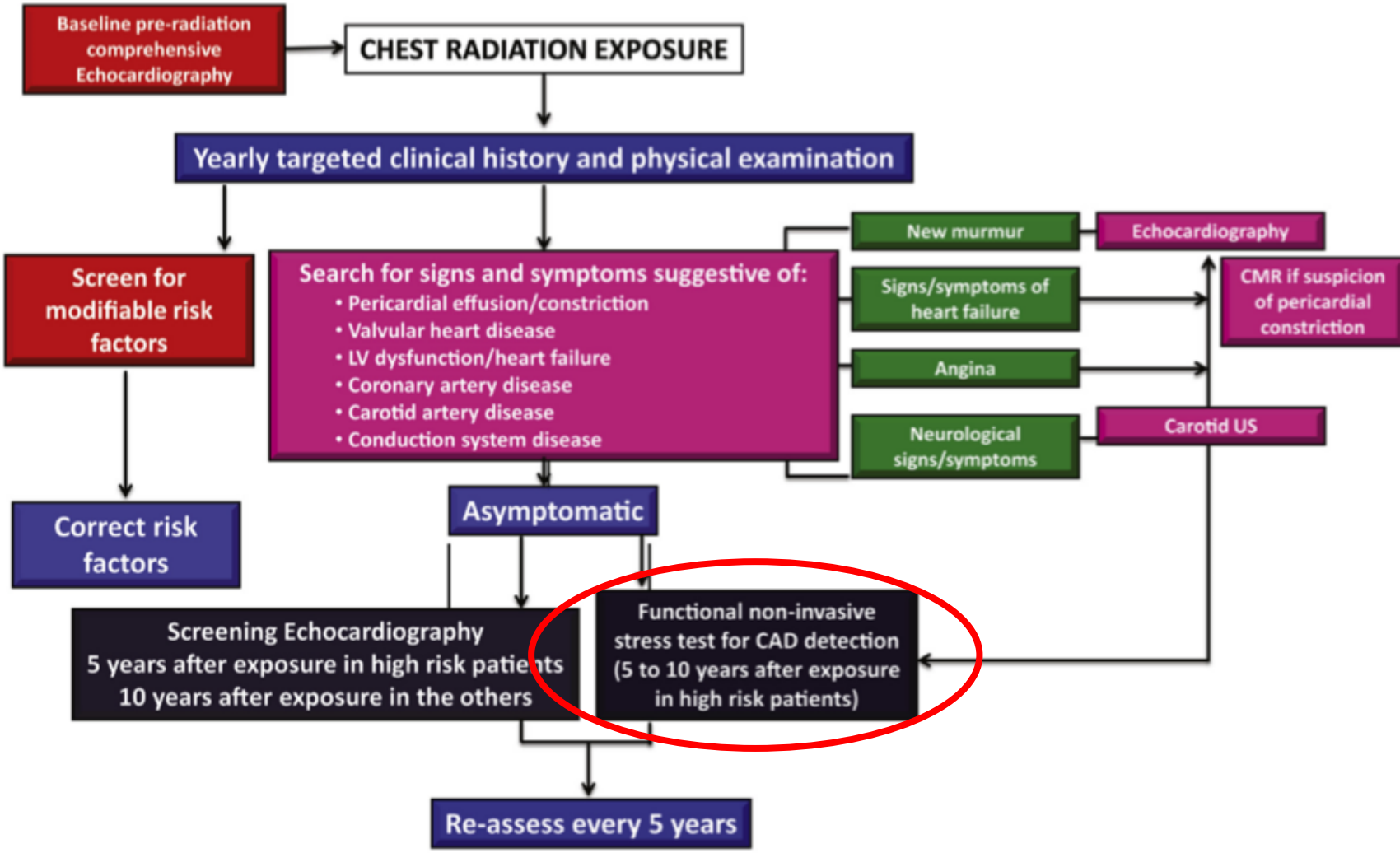
Among the 294 participants, 63 (21.4%) had abnormal ventricular images at rest, suggesting prior myocardial injury. During stress testing, 42 patients (14%) developed perfusion defects (n = 26), impaired wall motion (n = 8), or both abnormalities (n = 8). Coronary angiography showed stenosis ≥ 50% in 22 patients (55%), less than 50% in nine patients (22.5%), and no stenosis in nine patients (22.5%). Screening led to bypass graft surgery in seven patients. Twenty-three patients developed coronary events during a median of 6.5 years of follow-up, with 10 acute myocardial infarctions (two fatal).

**Conclusion**

Stress-induced signs of ischemia and significant coronary artery disease are highly prevalent after mediastinal irradiation in young patients. Stress testing identifies asymptomatic individuals at high risk for acute myocardial infarction or sudden cardiac death.

- Current expert opinion by the European Association of Cardiovascular Imaging and the American Society of Echocardiography recommend screening with a functional noninvasive stress test in asymptomatic individuals for CAD detection 5–10 years after exposure in high-risk patients, with reassessment every 5 years

# Algorithm for patient management after chest radiotherapy




LV, Left ventricle; US, ultrasound. Modifiable risk factors refer to: hypertension, tobacco use, hypercholesterolaemia, obesity, and diabetes.

Lancellotti et al., J Am Soc Echocardiogr. 2013

- Current expert opinion by the European Association of Cardiovascular Imaging and the American Society of Echocardiography recommend screening with a functional noninvasive stress test in asymptomatic individuals for CAD detection 5–10 years after exposure in high-risk patients, with reassessment every 5 years

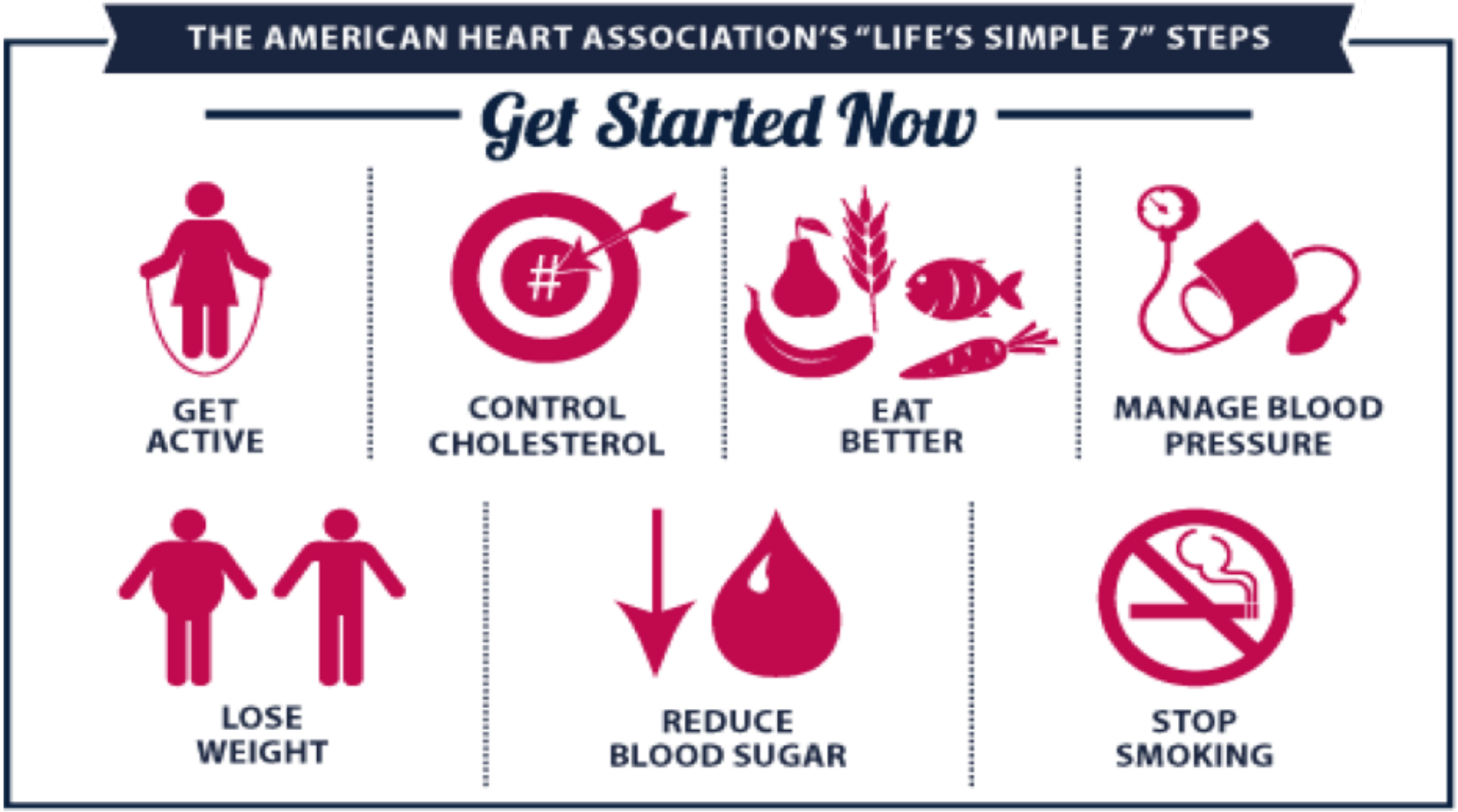
- **While these are opinions, and not guidelines, the true impact of screening asymptomatic patients is unclear and consideration should be given to whether this is the best practice**.

# Cardiac follow-up of cancer survivors

Eiman Jahangir, MD MPH, Nichole Polin, MD

*European Heart Journal*, Volume 37, Issue 36, 21 September 2016, Pages 2745–2747,
https://doi.org/10.1093/eurheartj/ehw362

**Issues with stress testing in asymptomatic individuals**, that may derive no symptomatic improvement or mortality benefit, **range from false positive tests to increased radiation exposure in an already exposed group**. False-positive test results **may lead to unnecessary anxiety and may have adverse consequences related to work**, **insurance, etc**. while typically leading to further testing

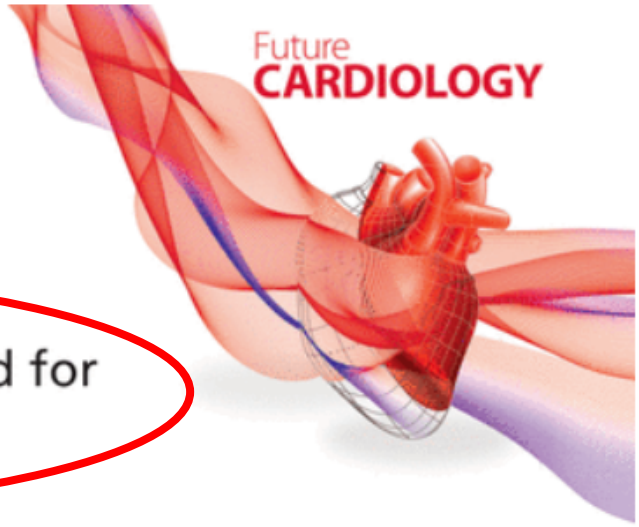



International Guideline Harmonization Group
for Late Effects of Childhood Cancer

Generally, health-care providers **are asked to educate and counsel all survivors** of childhood cancer about the importance of maintaining **a heart-healthy lifestyle** […]. Extensive studies done in non-oncology populations support the benefits of interventions to reduce modifiable risk factors […].

Armenian S et al, Lancet Oncol 2015

Future CARDIOLOGY



Editorial

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# Statins and cancer survivors: the need for structured guidelines

Zakaria Almuwaqqat[1,2], Olivia Hung[3] & Susmita Parashar*[,3]

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[2]Rollins School of Public Health, Emory University, Atlanta, GA 30322, USA

[3]Division of Cardiology, Department of Medicine, Emory School of Medicine, Atlanta, GA 30322, USA

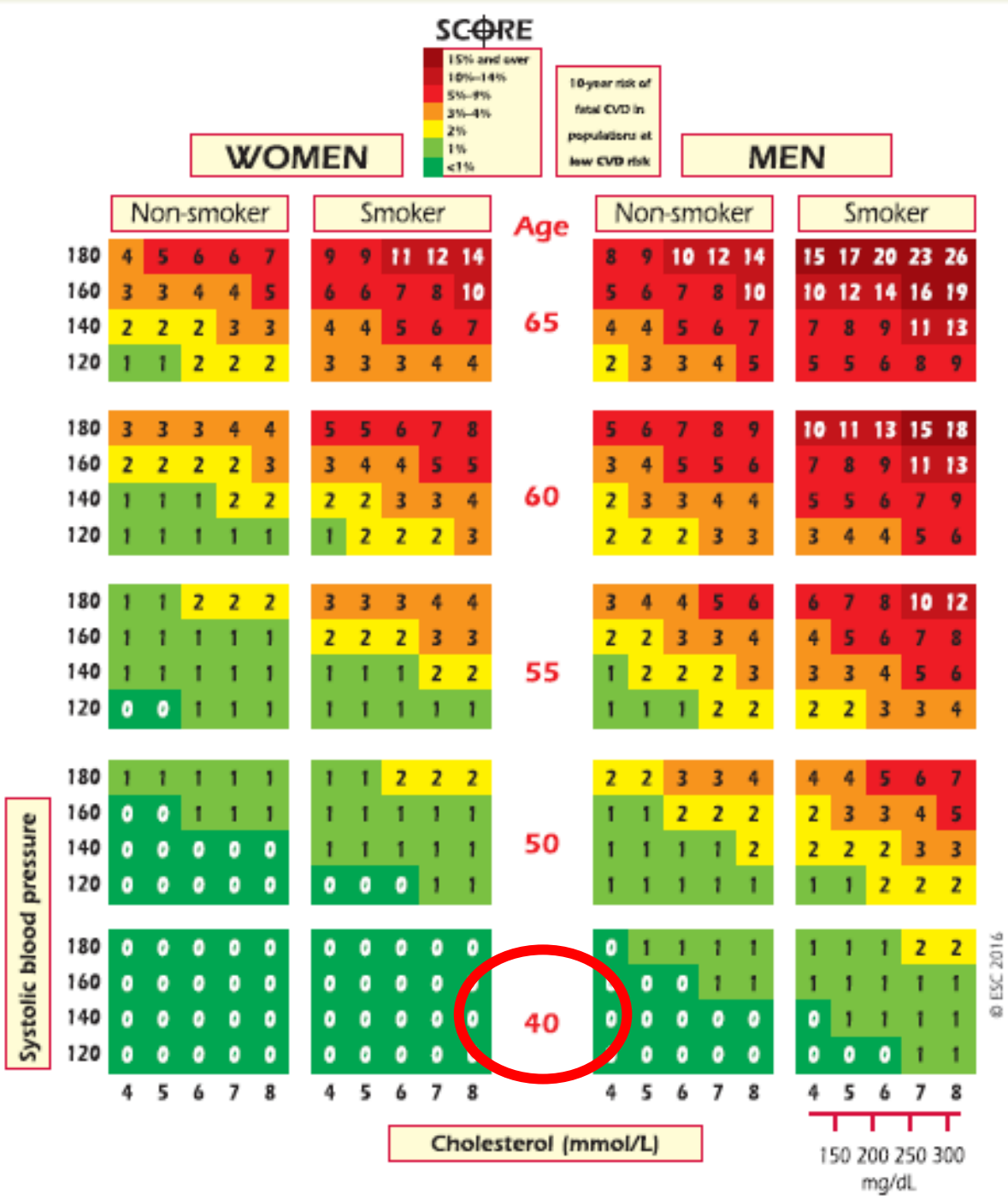
* Author for correspondence: smalik@emory.edu

"The discussion of CVD risk prevention should be integrated into the discussion of curative treatments among cancer survivors and oncology populations in general."

First draft submitted: 5 September 2017; Accepted for publication: 17 October 2017; Published online: 23 November 2017

**Keywords:** atherosclerosis • atherosclerotic cardiovascular disease • cancer survivors • guidelines • statins

The population of children and adult cancer survivors in the USA is estimated to grow to more than 19 million in 2024 according to the American Cancer Society [1,2]. This rapidly growing population has been exposed to various diagnostic and therapeutic modalities that may impact cardiovascular health [3]. In addition, cancer survivors have a higher prevalence of traditional cardiovascular disease (CVD) risk factors compared with age-matched populations [4]. Moreover, there is evidence that the 10-year predicted risk of developing a myocardial infarction or stroke is at least comparable to breast cancer recurrence risk among breast cancer survivors [5]. Thus, pursuing CVD risk prevention in survivorship care through appropriate and structured guidelines is of utmost importance. However, despite having a higher prevalence of CVD risk factors, a significant proportion of cancer survivors do


SCORE
≥5% and over
4%–4%
2%
1%
<1%
10-year risk of fatal CVD in populations at low CVD risk
WOMEN
MEN
Non-smoker
Smoker
Non-smoker
Smoker
Age
65
60
55
50
40
Systolic blood pressure
180 160 140 120
4 5 6 7 8
Cholesterol (mmol/L)
150 200 250 300
mg/dL
© ESC 2016

# RACCOMANDAZIONI PER IL MONITORAGGIO A LUNGO TERMINE DEI PAZIENTI PRECEDENTEMENTE CURATI PER LINFOMA DI HODGKIN, LINFOMA PRIMITIVO DEL MEDIASTINO E LINFOMI NON- HODGKIN AGGRESSIVI TRATTATI CON INTENTO CURATIVO

**A cura del Gruppo di Studio del Monitoraggio clinico a lungo termine del paziente: tossicità delle terapie antitumorali**

**Coordinatore:** Enrico Brignardello

**Partecipanti:**

Elisa Bellini, Eleonora Biasin, Carola Boccomini, Elena Buzzi, Margherita Caramuta, Simona Chiadò Cutin, Maria Teresa Corsetti, Nerina Denaro, Diego Dongiovanni, Francesco Felicetti, Nicoletta Fortunati, Luisa Giaccone, Francesco Moretto, Cristina Piva, Patrizia Piano, Andrea Pizzini, Maria Antonia Polimeni, Agostino Ponzetti, Patrizia Pregno, Roberto Sorasio.

## 3.2 CARDIOTOSSICITA' INDIRETTA

Nei *lymphoma survivors* la dislipidemia, che contribuisce ad aumentare il rischio cardiovascolare, può essere sostenuta ed aggravata da alterazioni ormonali (ipogonadismo, ipotiroidismo, diabete) anch'esse - almeno in parte - causate dalle terapie antitumorali. Vi sono evidenze che indicano, in questi soggetti, l'efficacia delle indagini di screening e degli interventi terapeutici per la riduzione del rischio cardiovascolare correlato a dislipidemia.

**Nei pazienti sottoposti a irradiazione mediastinica** è stato proposto come ragionevole lo **screening lipidologico (determinazione di colesterolo totale + HDL e trigliceridi) a cadenza triennale, iniziando nel 5° anno** dopo il completamento delle terapie e con durata indefinita.

**La terapia farmacologica di elezione per il trattamento delle dislipidemie è rappresentata dalle statine.** In assenza di indicazioni specifiche, per i pazienti sottoposti a terapie potenzialmente cardiotossiche, è ragionevole l'utilizzo dei target proposti per pazienti a medio e alto rischio CV. La

| | Senza FRCV | Con uno o più FRCV |
|---|---|---|
| Colesterolo LDL | < 115 mg/d | < 100 mg/dl |

# 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

**Table 5** Intervention strategies as a function of total cardiovascular risk and low-density lipoprotein cholesterol level

| Total CV risk (SCORE) % | LDL-C levels | | | | |
|---|---|---|---|---|---|
| | <70 mg/dL <1.8 mmol/L | 70 to <100 mg/dL 1.8 to <2.6 mmol/L | 100 to <155 mg/dL 2.6 to <4.0 mmol/L | 155 to <190 mg/dL 4.0 to <4.9 mmol/L | ≥190 mg/dL ≥4.9 mmol/L |
| <1 | No lipid intervention | No lipid intervention | No lipid intervention | No lipid intervention | Lifestyle intervention, consider drug if uncontrolled |
| Class[a]/Level[b] | I/C | I/C | I/C | I/C | IIa/A |
| ≥1 to <5 | No lipid intervention | No lipid intervention | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention, consider drug if uncontrolled |
| Class[a]/Level[b] | I/C | I/C | IIa/A | IIa/A | I/A |
| ≥5 to <10, or high-risk | No lipid intervention | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention |
| Class[a]/Level[b] | IIa/A | IIa/A | IIa/A | I/A | I/A |
| ≥10 or very high-risk | Lifestyle intervention, consider drug | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention |
| Class[a]/Level[b] | IIa/A | IIa/A | I/A | I/A | I/A |

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| | |
|---|---|
| **Lipids LDL-C is the primary target** | **Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline[a] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL). |
| | **High-risk: LDL-C <2.6 mmol/L (100 mg/dL)** or a reduction of at least 50% if the baseline[a] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL). |
| | **Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).** |
| | Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively. |
| | HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk. |
| | TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors. |


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