La correzione dei fattori di rischio cardiovascolare come prevenzione oncologica

Prof. Marco Metra

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Risk factors in cancer and CV disease

- **Cancer and CAD**
  - Epidemiology
  - Pathophysiology
  - Diagnosis
  - Implications for treatment
- **Cancer and HF**
  - Epidemiology
  - Pathophysiology
  - Implications for treatment

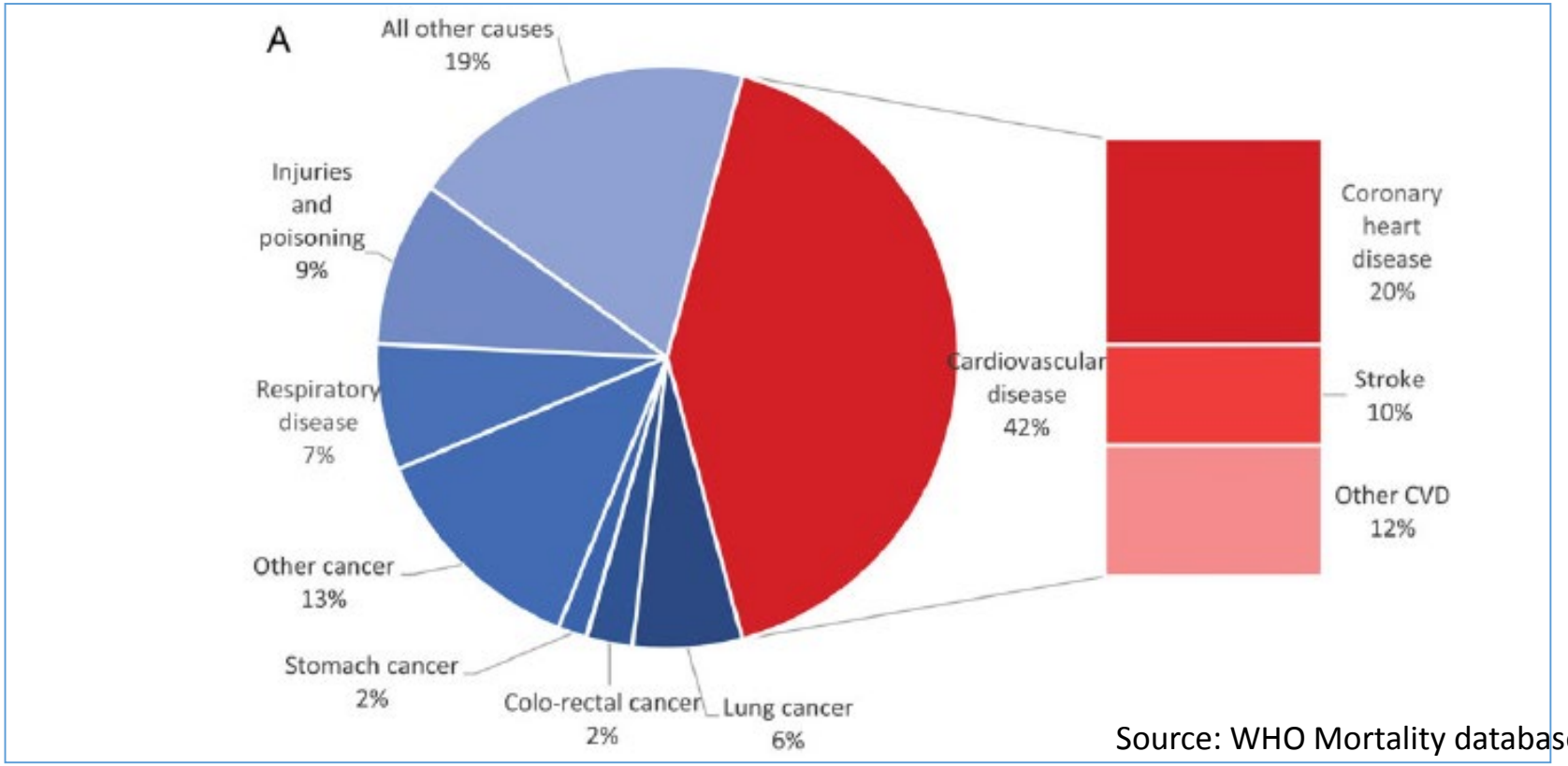
European Heart Journal (2014) **35**, 2950–2959
doi:10.1093/eurheartj/ehu299

SPECIAL ARTICLE

Cardiovascular disease in Europe 2014: epidemiological update

Melanie Nichols[1,2], Nick Townsend[1]*, Peter Scarborough[1], and Mike Rayner[1]

Proportion of all deaths due to major causes in men



Source: WHO Mortality database

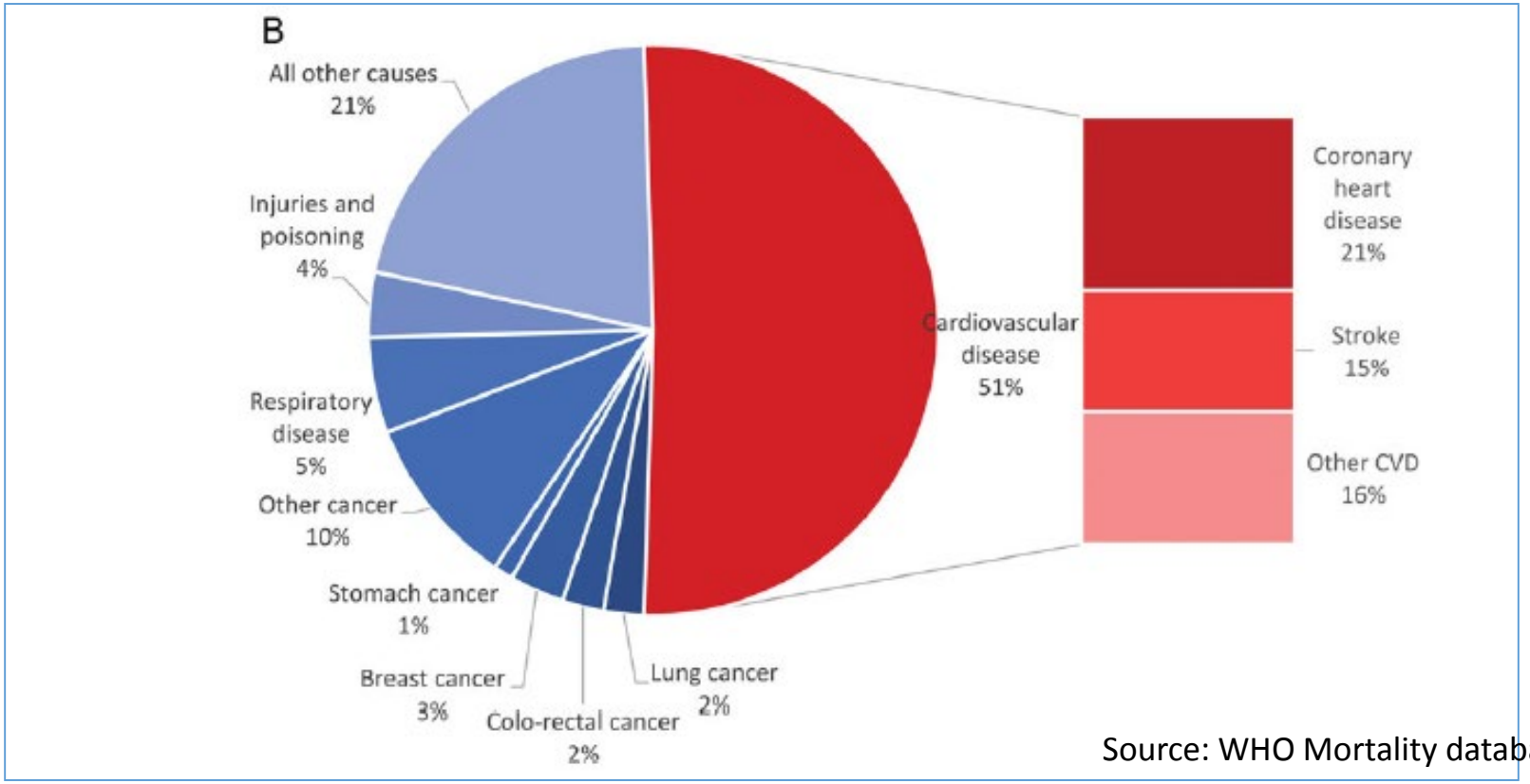
European Heart Journal (2014) **35**, 2950–2959
doi:10.1093/eurheartj/ehu299

SPECIAL ARTICLE

Cardiovascular disease in Europe 2014: epidemiological update

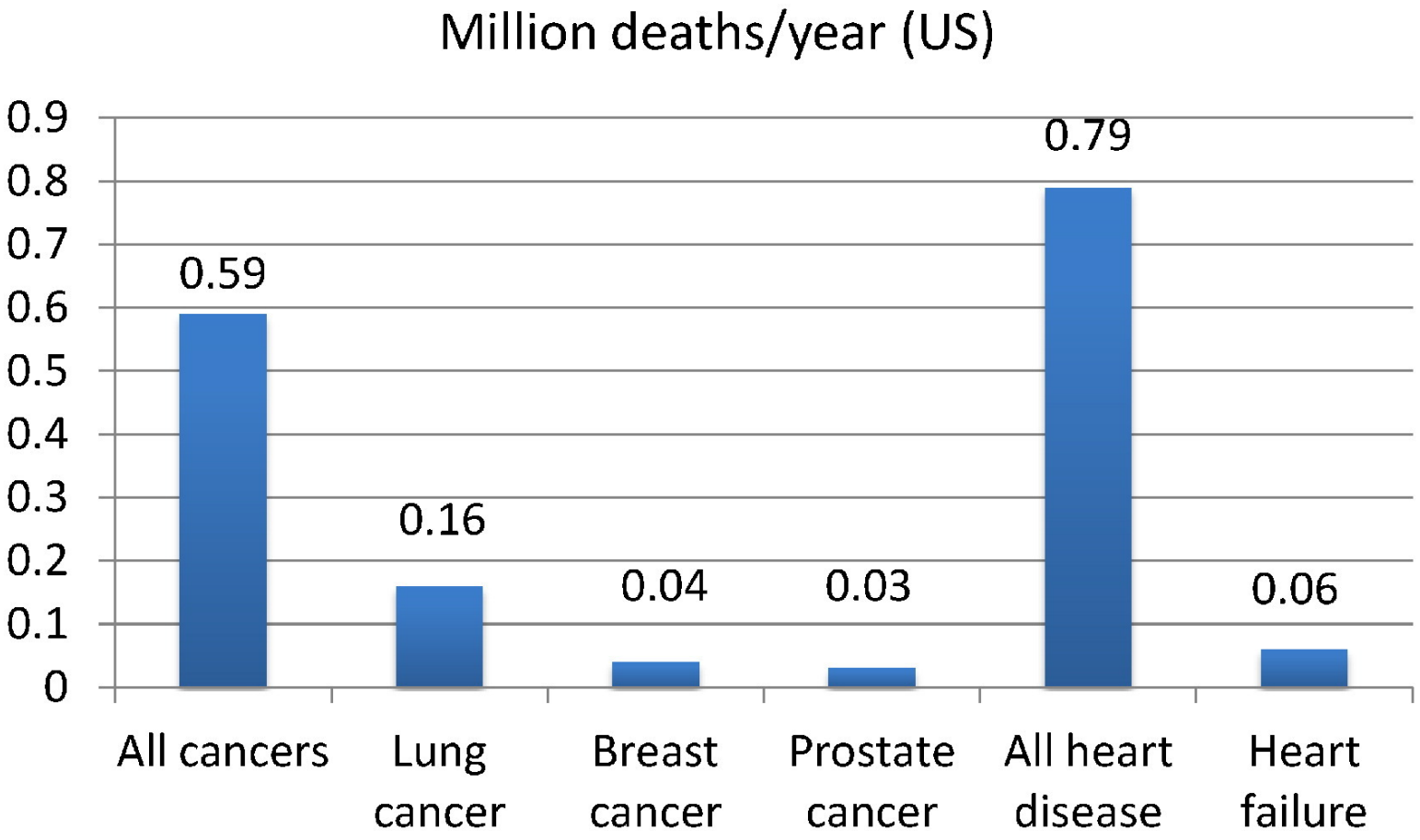
Melanie Nichols[1,2], Nick Townsend[1]*, Peter Scarborough[1], and Mike Rayner[1]

Proportion of all deaths due to major causes in women



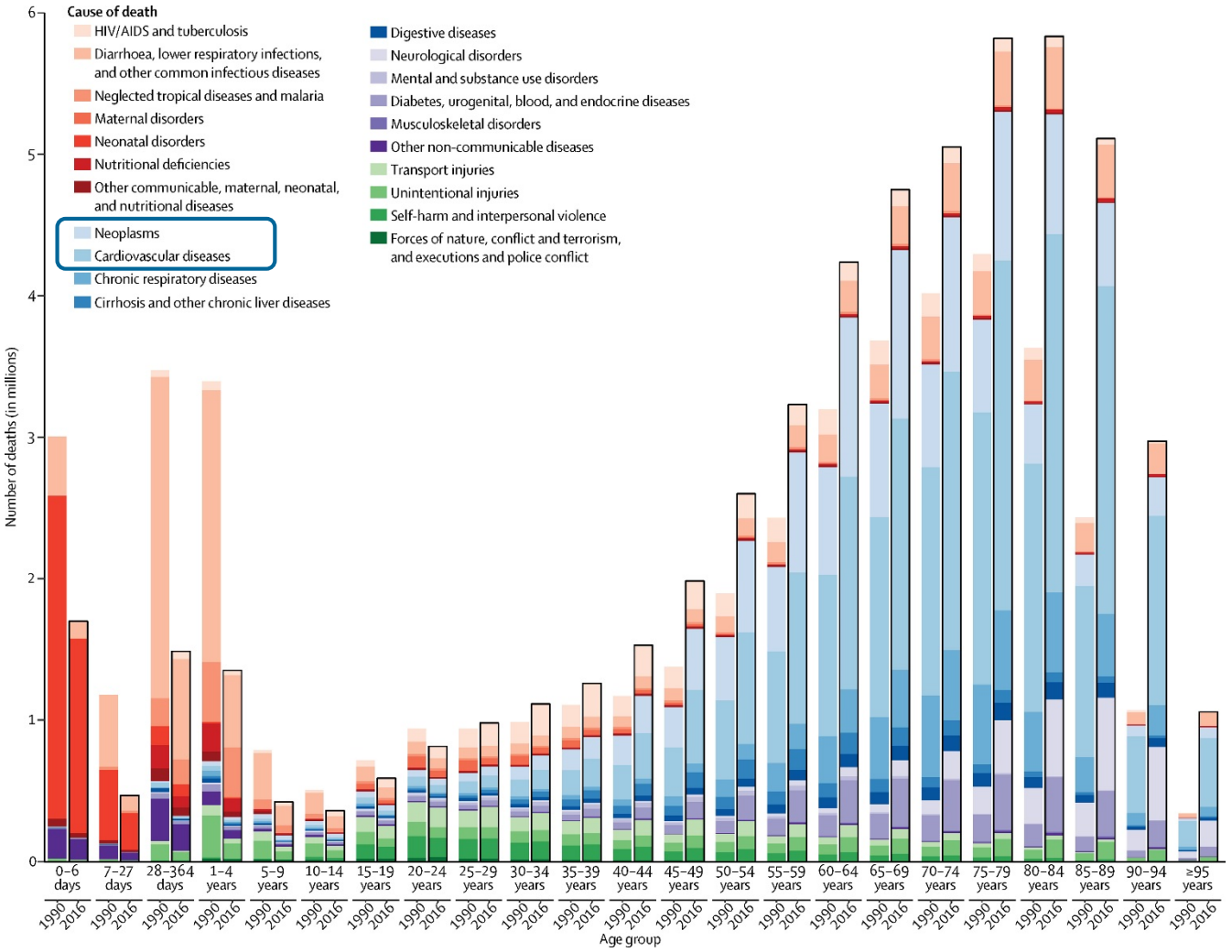
Source: WHO Mortality database

Annual number of deaths by cancer and CV disease in US



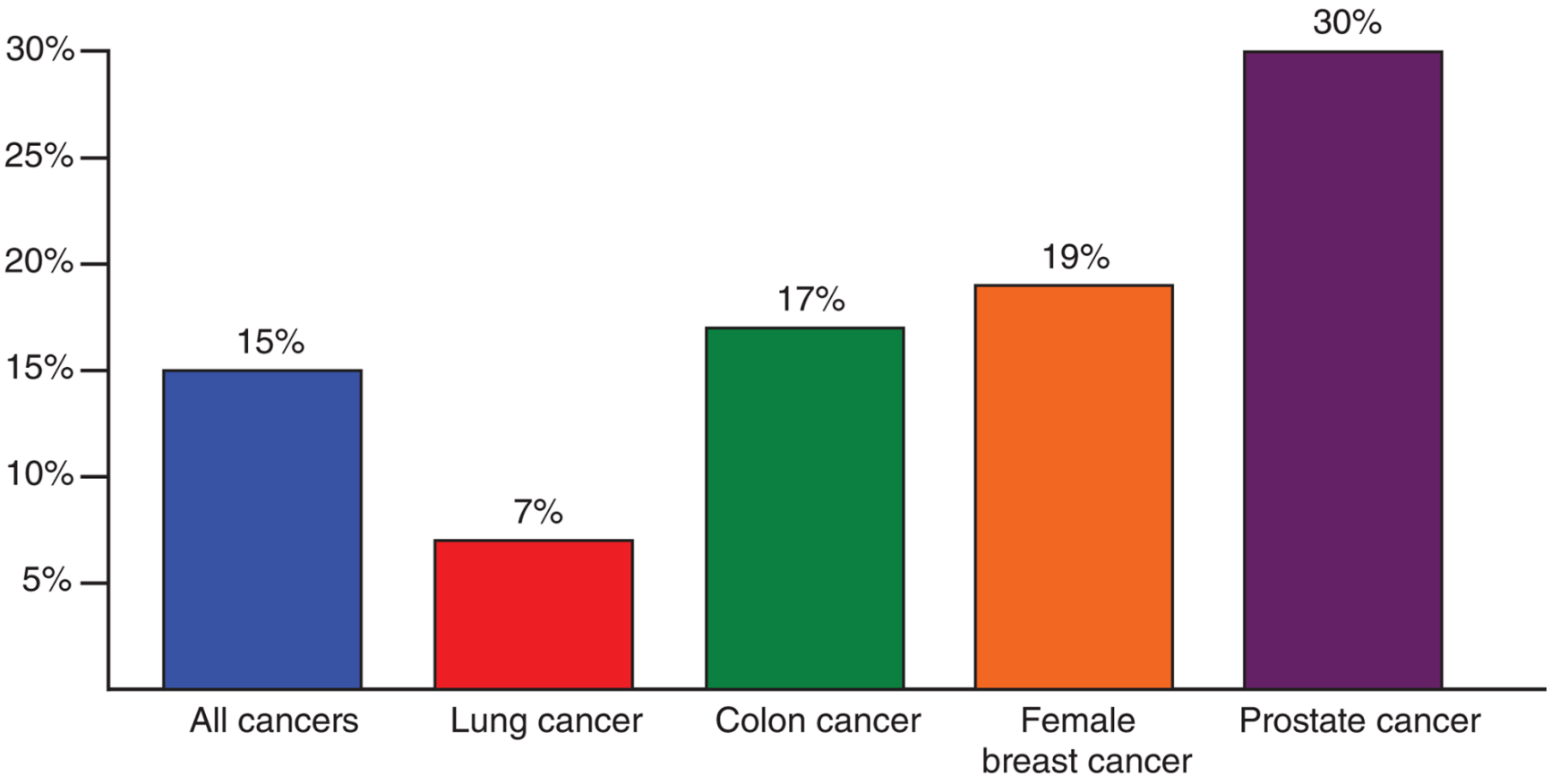
Farmakis et al. Int J Cardiol 2016 203, 279-281DOI: (10.1016/j.ijcard.2015.10.172)

Global composition of number of deaths for 23 age groups, both sexes combined, 1990 versus 2016: Global Burden of Disease Study



The Lancet 2017 390, 1151-1210DOI: (10.1016/S0140-6736(17)32152-9)

Estimates for frequency of cardiovascular deaths in 1.2 million cancer patients



Anker MS et al. *Eur J Heart Fail* 2018; 20: 1382-1384
Brown et al. *J Natl Cancer Inst* 1993;**85**:979–987.

Breast Cancer Research and Treatment (2018) 170:119–127
https://doi.org/10.1007/s10549-018-4723-0

EPIDEMIOLOGY

The risk of cardiovascular disease following breast cancer by Framingham risk score

Sofie A. M. Gernaat[1,9] · Jolanda M. A. Boer[2] · Desiree H. J. van den Bongard[3] · Angela H. E. M. Maas[4] · Carmen C. van der Pol[5] · Rhodé M. Bijlsma[6] · Diederick E. Grobbee[1] · Helena M. Verkooijen[7] · Petra H. Peeters[1,8]

Received: 15 February 2018 / Accepted: 16 February 2018 / Published online: 28 February 2018

Abstract

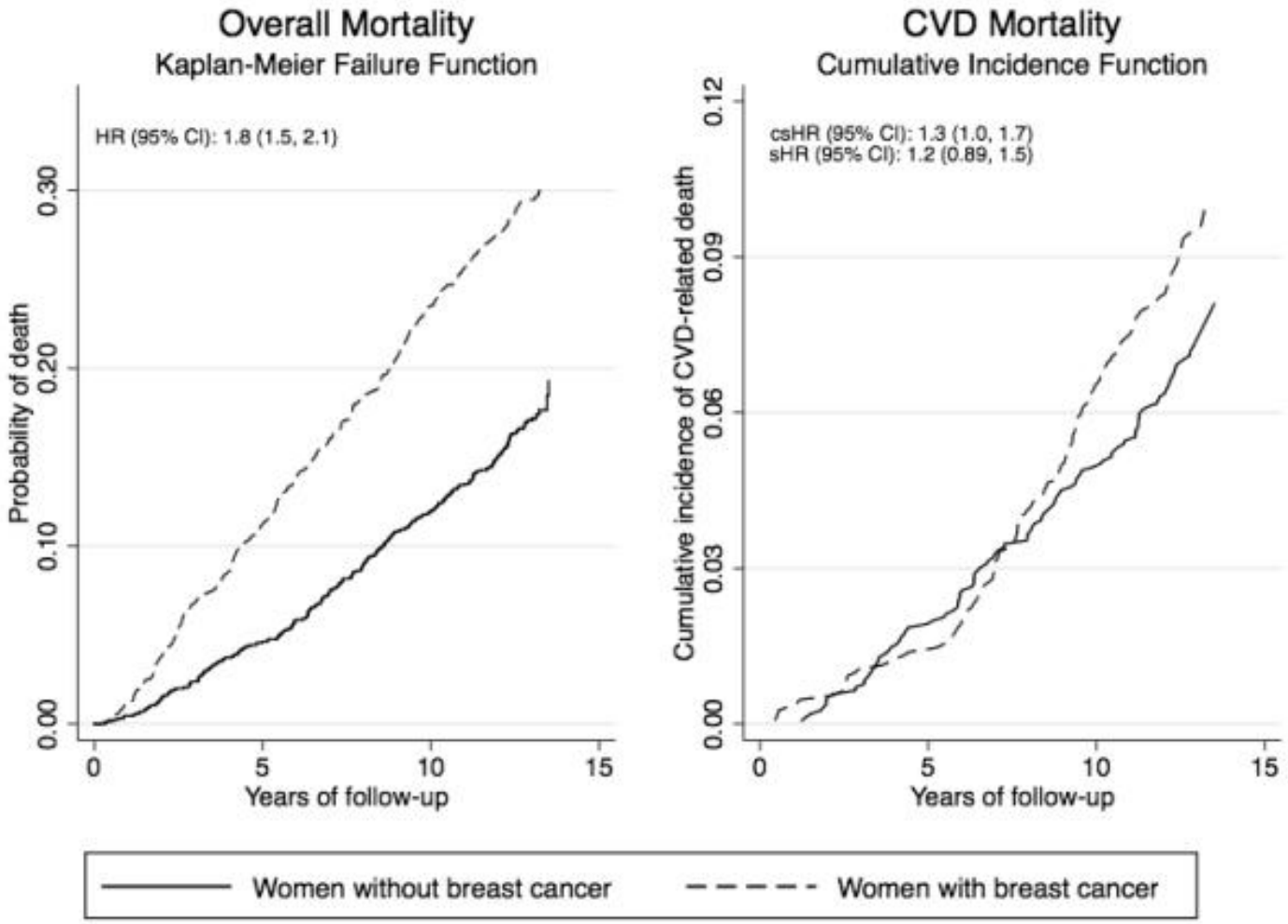
Objectives This study evaluates the risk of cardiovascular disease (CVD) following breast cancer, accounting for baseline CVD risk.

Methods Within the EPIC-NL (Dutch part of the European Prospective Investigation into Nutrition and Cancer) cohort, 1103 women were diagnosed with breast cancer. For every breast cancer patient, 3–4 women without breast cancer ($n = 4328$) were

Table 3 The risk of cardiovascular disease hospitalization and/or death following breast cancer for the total study population and by low, intermediate or high Framingham risk prior to diagnosis until at most December 31, 2010

	Number of women	Total PY	Number of CVD (%)[a]	Number of CVD per 100 PY	Unadjusted HR[b]	Adjusted HR[b,c]	Adjusted HR[b,d]
CVD event (hospitalization or death)							
Total study population ($n = 5431$)							
Women without breast cancer	4328	28,035	325 (7.5)	1.2	1	1	1
Women with breast cancer	1103	6401	92 (8.3)	1.4	1.23 (0.97–1.55)	1.17 (0.92–1.57)	1.16 (0.92–1.47)

Overall and cardiovascular mortality among 1 413 breast cancer survivors



Bradsha et al. Epidemiology. 2016;27:6–13.

Prevalence of Colorectal Neoplasm Among Patients With Newly Diagnosed Coronary Artery Disease

Annie On On Chan, MD, PhD
Man Hong Jim, MD
Kwok Fai Lam, PhD
Jeffrey S. Morris, PhD
David Chun Wah Siu, MD
Teresa Tong, BSc
Fook Hong Ng, MD
Siu Yin Wong, MD
Wai Mo Hui, MD
Chi Kuen Chan, MD
Kam Chuen Lai, MD

Context Colorectal neoplasm and coronary artery disease (CAD) share similar risk factors, and their co-occurrence may be associated.

Objectives To investigate the prevalence of colorectal neoplasm in patients with CAD in a cross-sectional study and to identify the predisposing factors for the association of the 2 diseases.

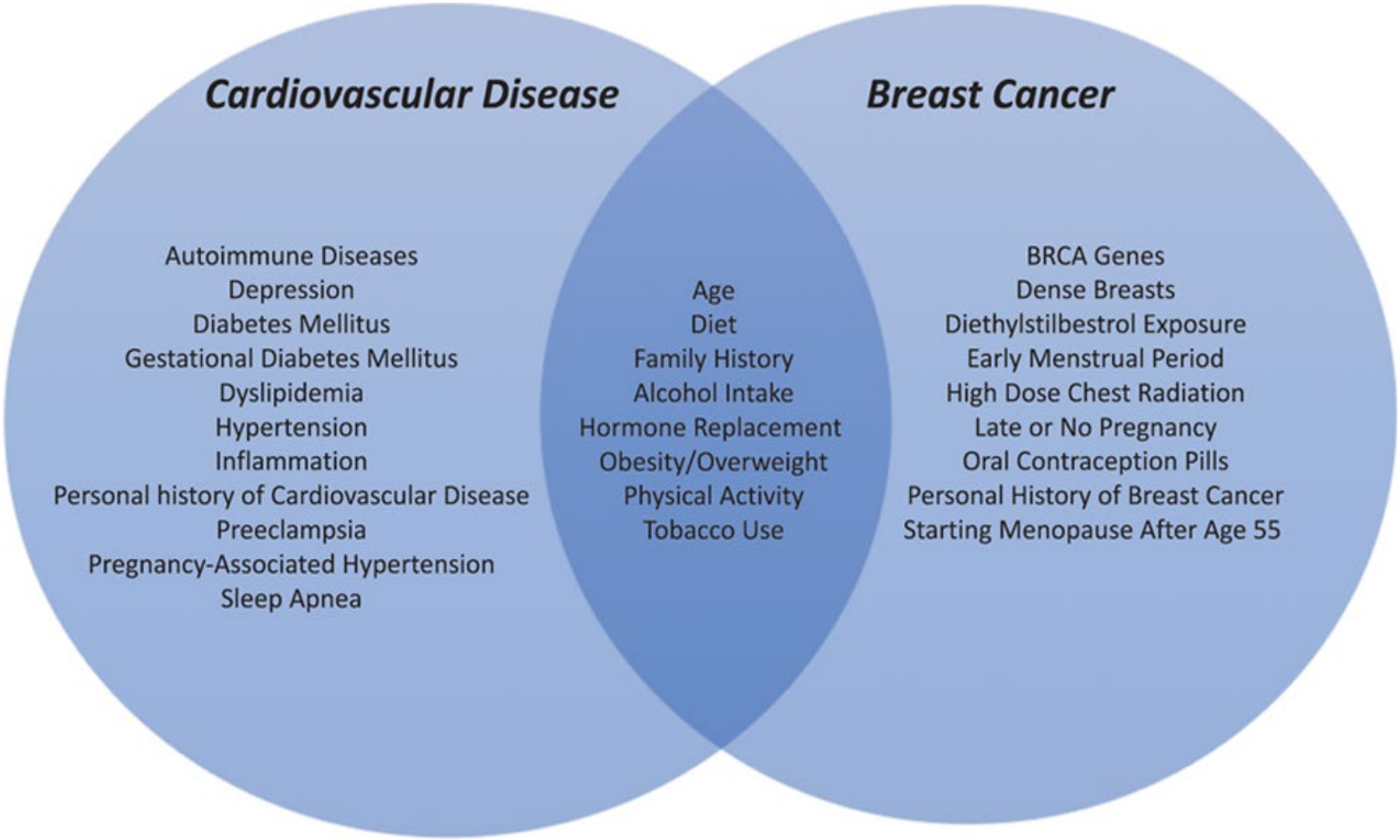
Design, Setting, and Participants Patients in Hong Kong, China, were recruited for screening colonoscopy after undergoing coronary angiography for suspected CAD during November 2004 to June 2006. Presence of CAD (n=206) was defined as at least 50% diameter stenosis in any 1 of the major coronary arteries; otherwise, patients were considered CAD-negative (n=208). An age- and sex-matched control group was recruited from the general population (n=207). Patients were excluded for use of aspirin or statins, personal history of colonic disease, or colonoscopy in the past 10 years.

Table 3. Type and Prevalence of Colonic Lesions in the CAD-Positive, CAD-Negative, and General Population Groups

Type of Colonic Lesion	No. (%)			*P* Value Comparing the Prevalence in All 3 Groups[a]	Adjusted *P* Value Comparing All 3 Groups Using Holm Method (Rank)[b]	*P* Value Comparing CAD-Positive and General Population Groups (Holm-Adjusted *P* Value)[c]
	CAD-Positive Group (n = 206)	CAD-Negative Group (n = 208)	General Population Group (n = 207)			
Endoscopic polyp	84 (40.8)	59 (28.4)	69 (33.3)	.03	.055 (4)	.12 (.24)
Colorectal neoplasm	70 (34.0)	39 (18.8)	43 (20.8)	<.001	.002 (2)[d]	<.001 (.01)
Hyperplastic polyp	17 (8.3)	10 (4.8)	15 (7.2)	.33	.33 (5)	.70 (.70)
Advanced lesion	38 (18.4)	18 (8.7)	12 (5.8)	<.001	.001 (1)[d]	<.001 (.001)
Colorectal cancer	9 (4.4)	1 (0.5)	3 (1.4)	.02	.06 (3)	.09 (.26)

Abbreviation: CAD, coronary artery disease

Shared and separate risk factors for cardiovascular disease (CVD) and breast cancer



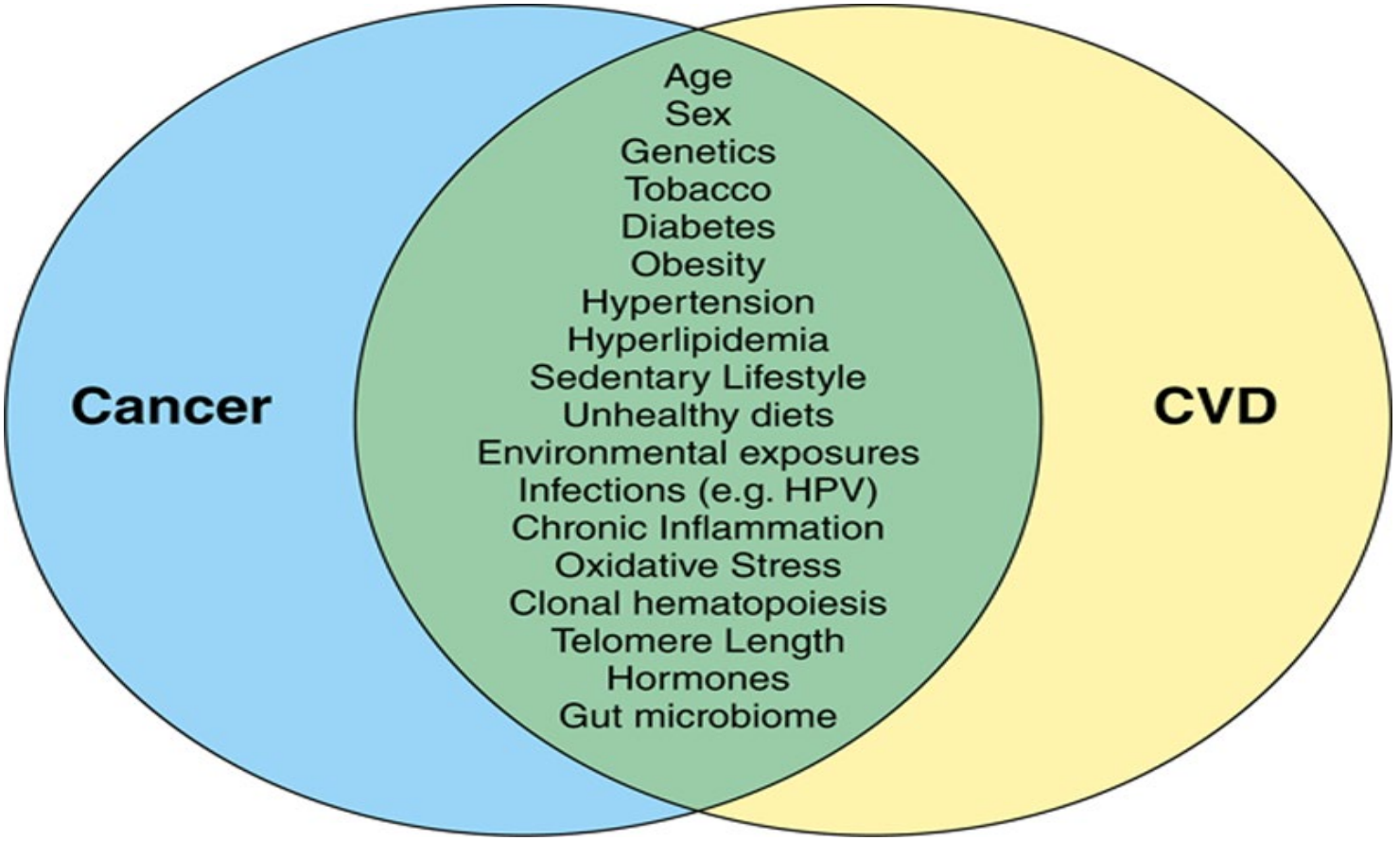
Metha LS et al. Circulation 137: e30-e66

Factors associated with development of cardiovascular disease (CVD) and breast cancer

	Risk of CVD	Risk of Breast Cancer
Healthy Diet	↓	↓
Western Diet	↑	↑
Light-Moderate Alcohol Intake	↓	↑
Red/Processed Meat	↑	↑
Physical Activity	↓	↓
Sedentary Lifestyle	↑	↑
Premenopausal Obesity	↑	↓
Smoking	↑	↑
Early Menarche	↑	↑
Early Menopause	↑	↓
Hormone Replacement Therapy	↑	↑

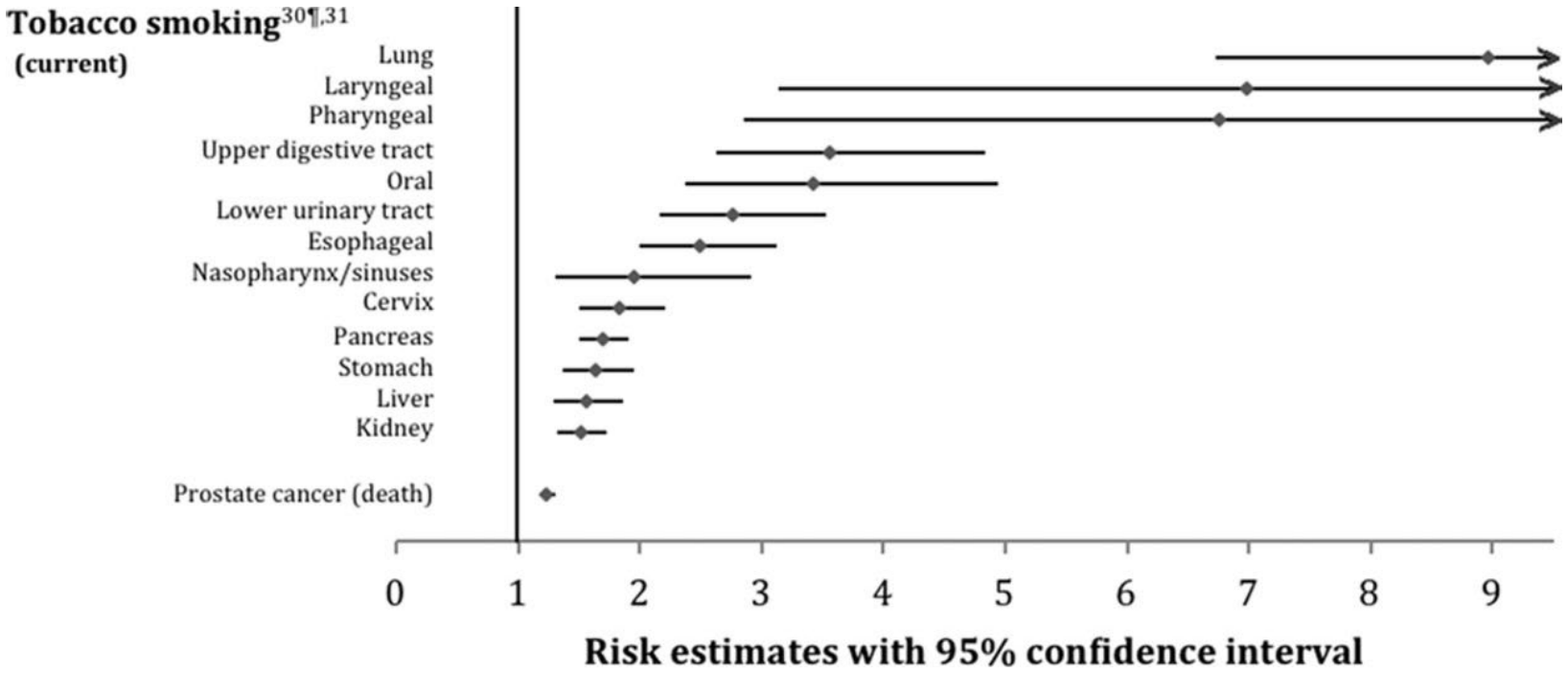
Metha LS et al. Circulation 137: e30-e66

Pathophysiological links between cancer and cardiovascular disease (CVD)



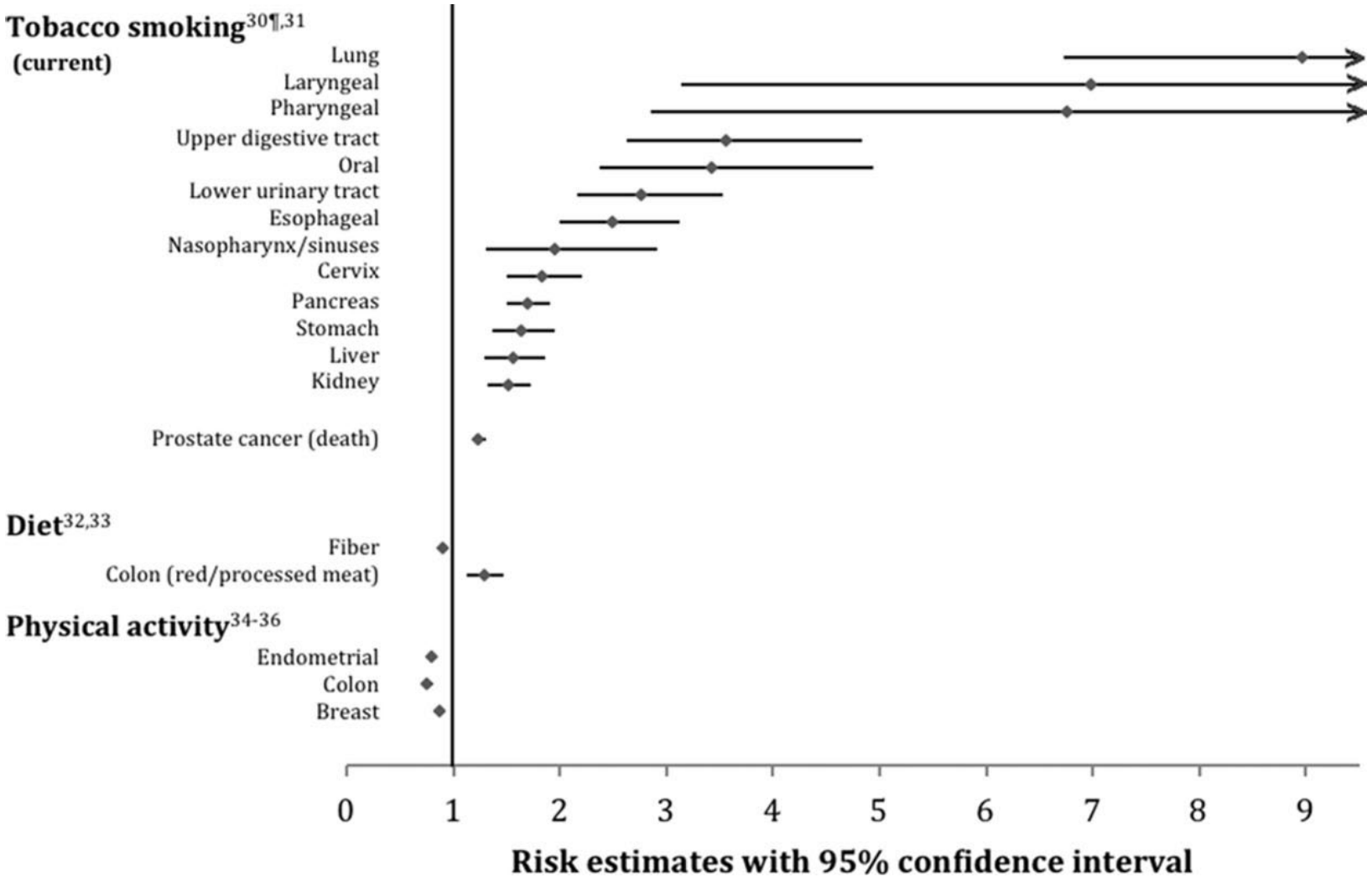
Handy et al. Circulation 138, Issue: 7, Pages: 727-734

Shared Risk Factors in CVD and Cancer



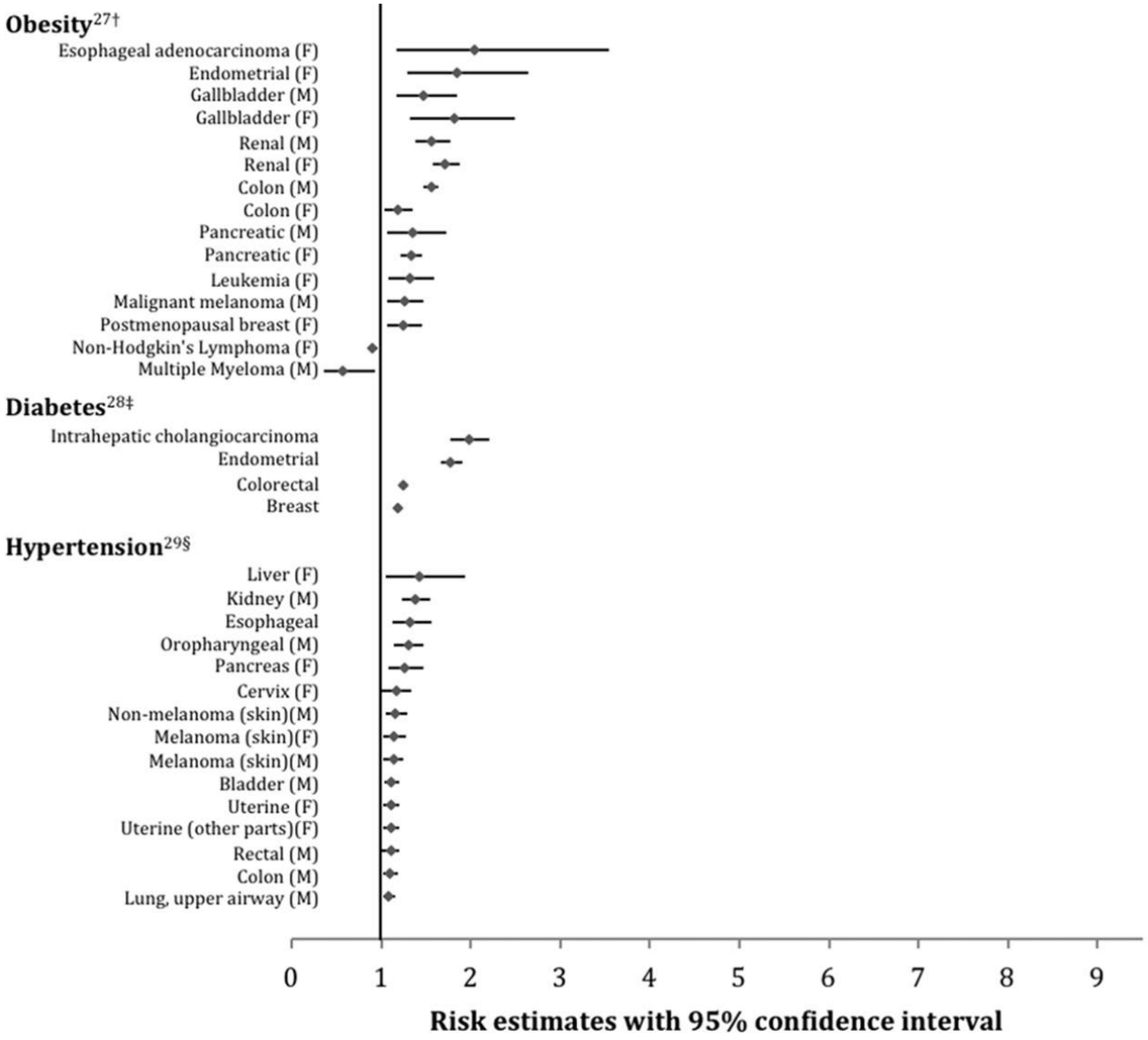
Koene et al. Circulation 133: 1104-1114

Shared Risk Factors in CVD and Cancer



Koene et al. Circulation 133: 1104-1114

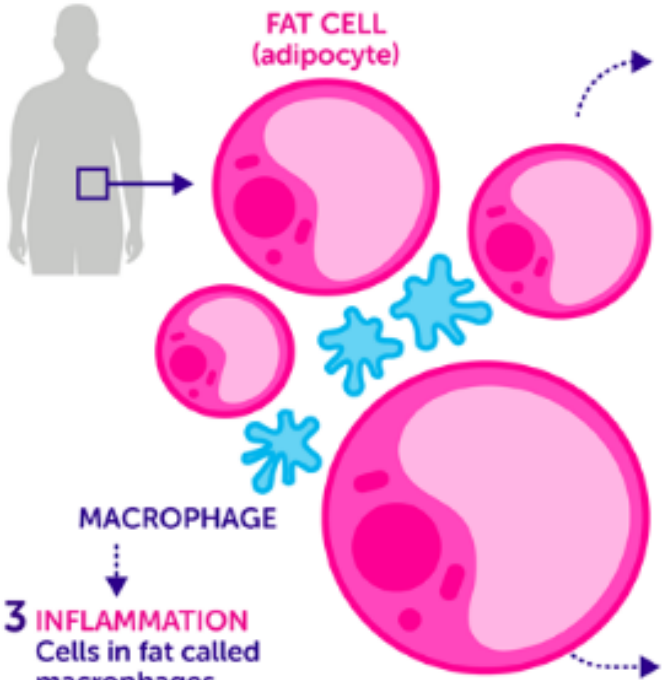
Shared Risk Factors in CVD and Cancer



Koene et al. Circulation 133: 1104-1114

HOW COULD OBESITY LEAD TO CANCER?

Research has identified three main ways



1 OESTROGEN
After the menopause, oestrogen made by fat cells can make cells multiply faster in the breasts and womb, increasing the risk of cancer.

2 INSULIN AND GROWTH FACTORS
Excess fat can cause levels of insulin and other growth factors to rise, which can also tells cells to divide more rapidly.

3 INFLAMMATION
Cells in fat called macrophages release chemicals called cytokines, encouraging cells to divide (including cancer cells).

There are other theories too, but these are the main ideas being studied. More research is needed to understand this in more detail.

Circulation

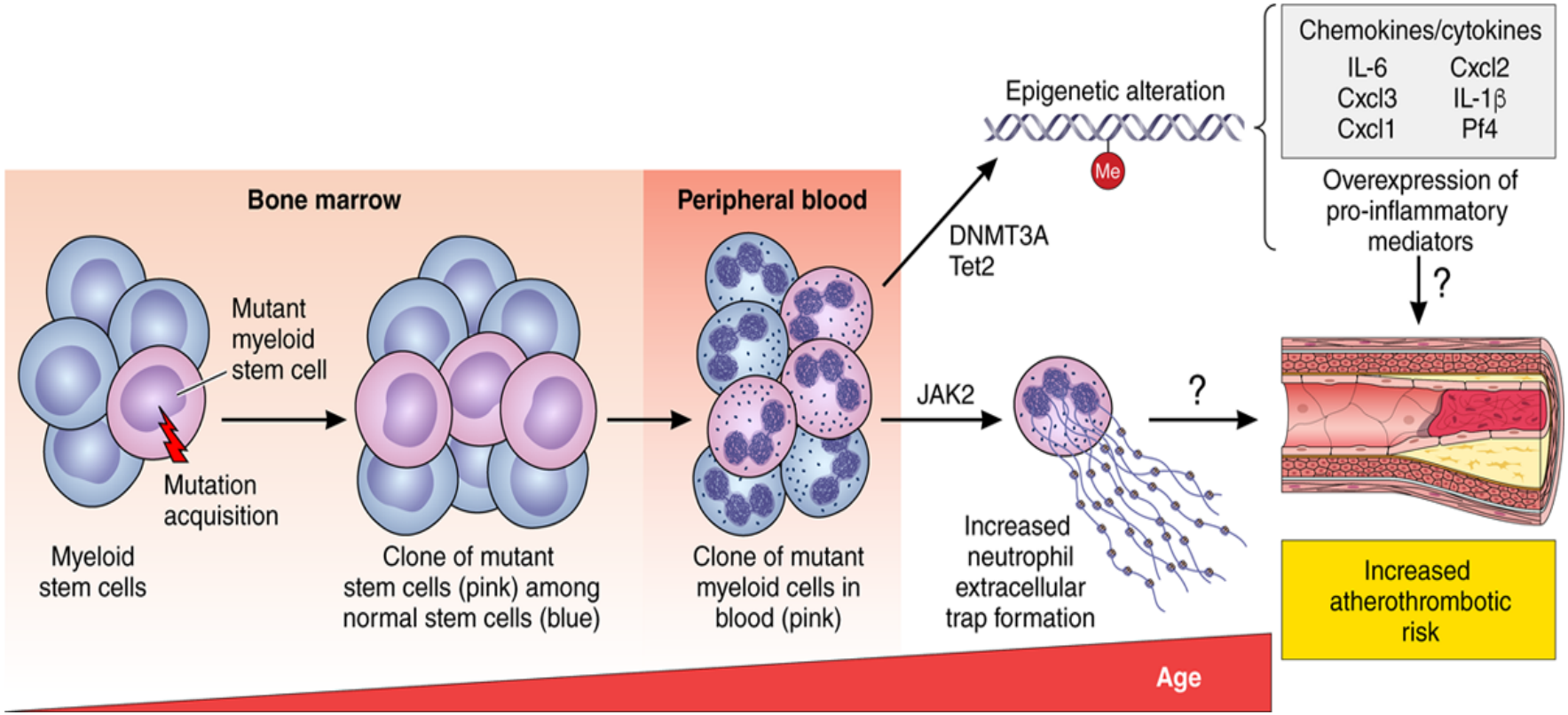
CLINICAL IMPLICATIONS OF BASIC RESEARCH

CHIP (Clonal Hematopoiesis of Indeterminate Potential)

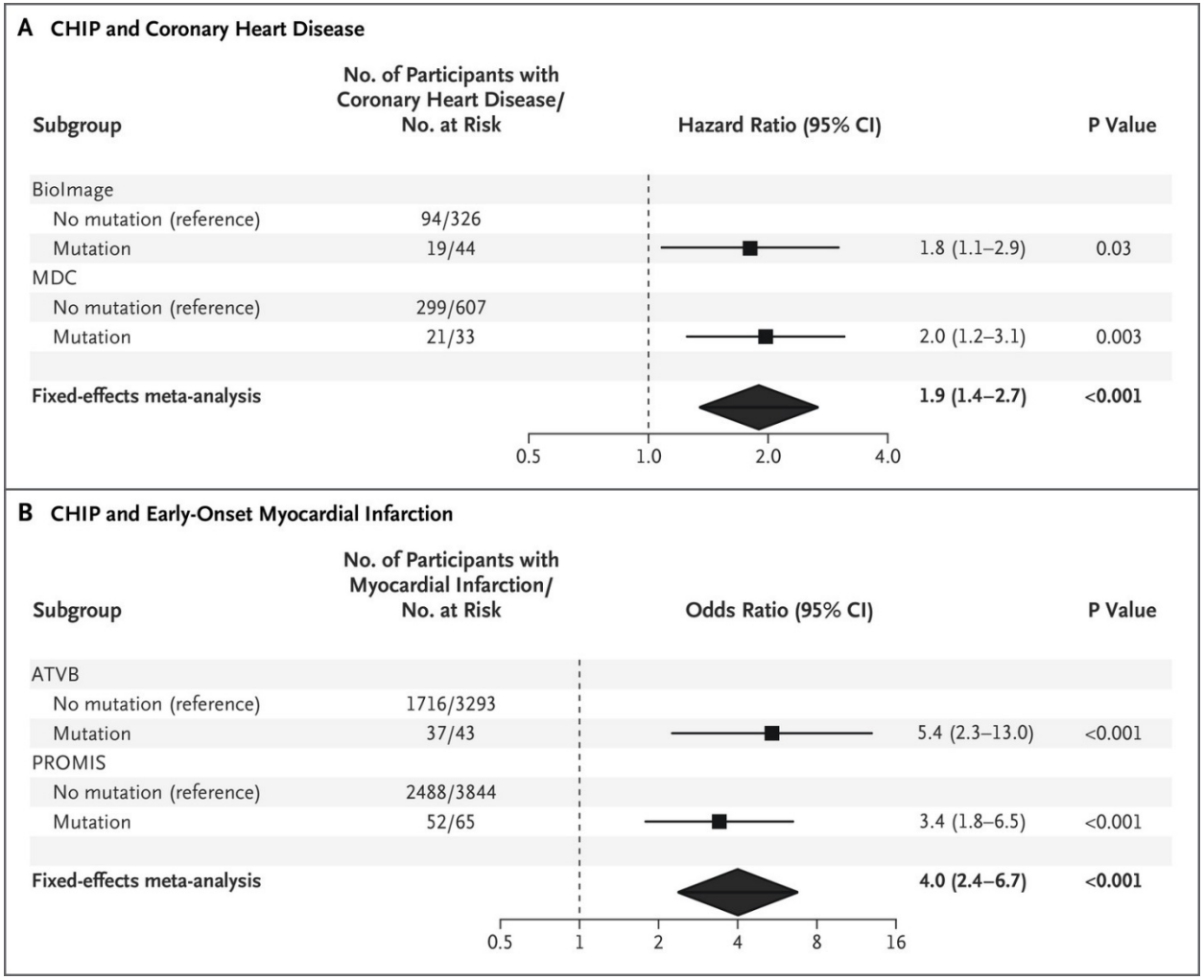
Potent and Newly Recognized Contributor to Cardiovascular Risk

Peter Libby, MD
Benjamin L. Ebert, MD, PhD

The coining of the concept of cardiovascular risk factors emerged from the Framingham Heart Study in the 1960s. Since then we have made major inroads into controlling the traditional risk for atherosclerosis including hyper-



Association between Clonal Hematopoiesis of Indeterminate Potential (CHIP) and Coronary Heart Disease and Early-Onset Myocardial Infarction.



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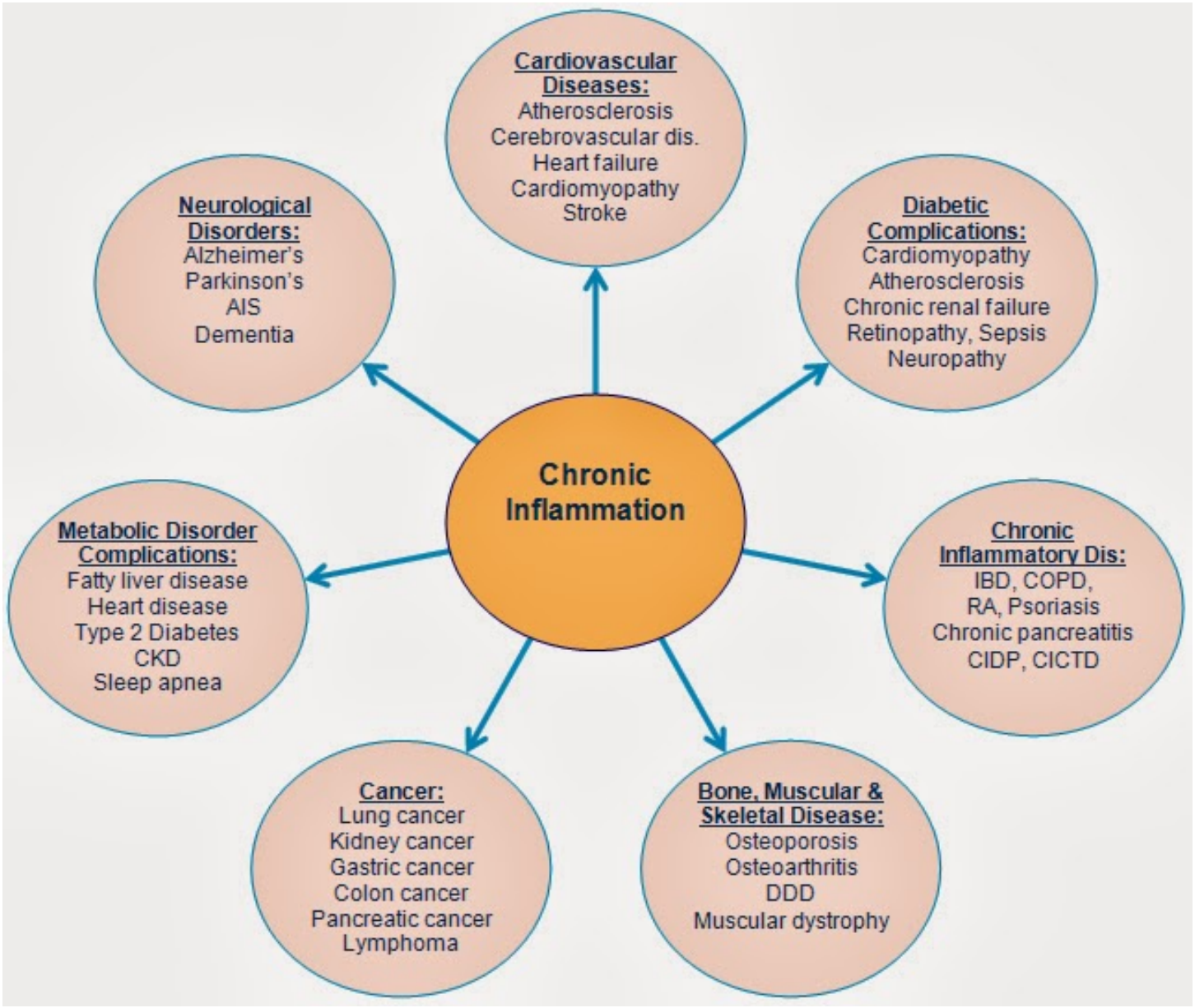


From: Are you on fire? Market America Journey
http://hc818.blogspot.com/2013/10/v-behaviorurldefaultvmlo.html

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

ABSTRACT

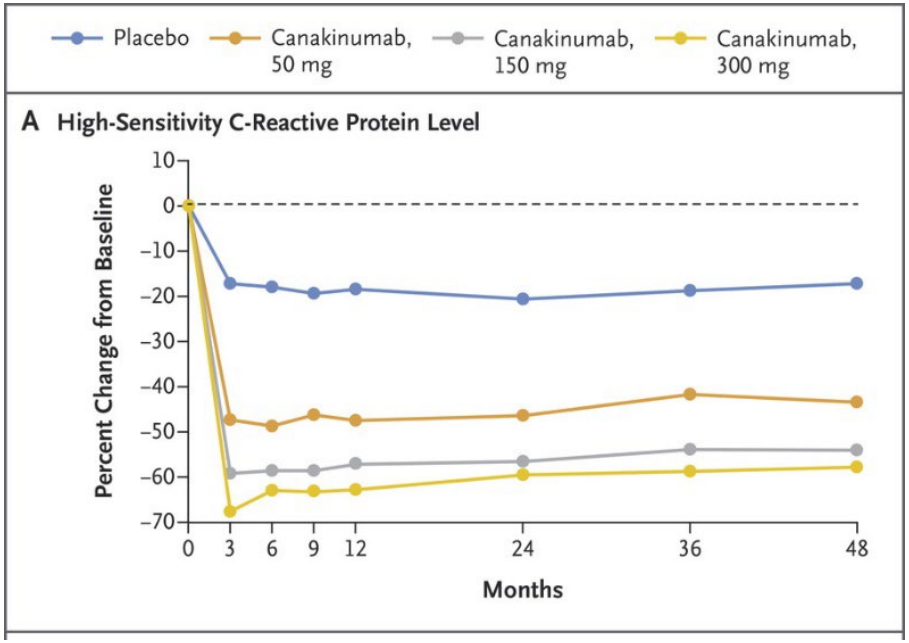
BACKGROUND

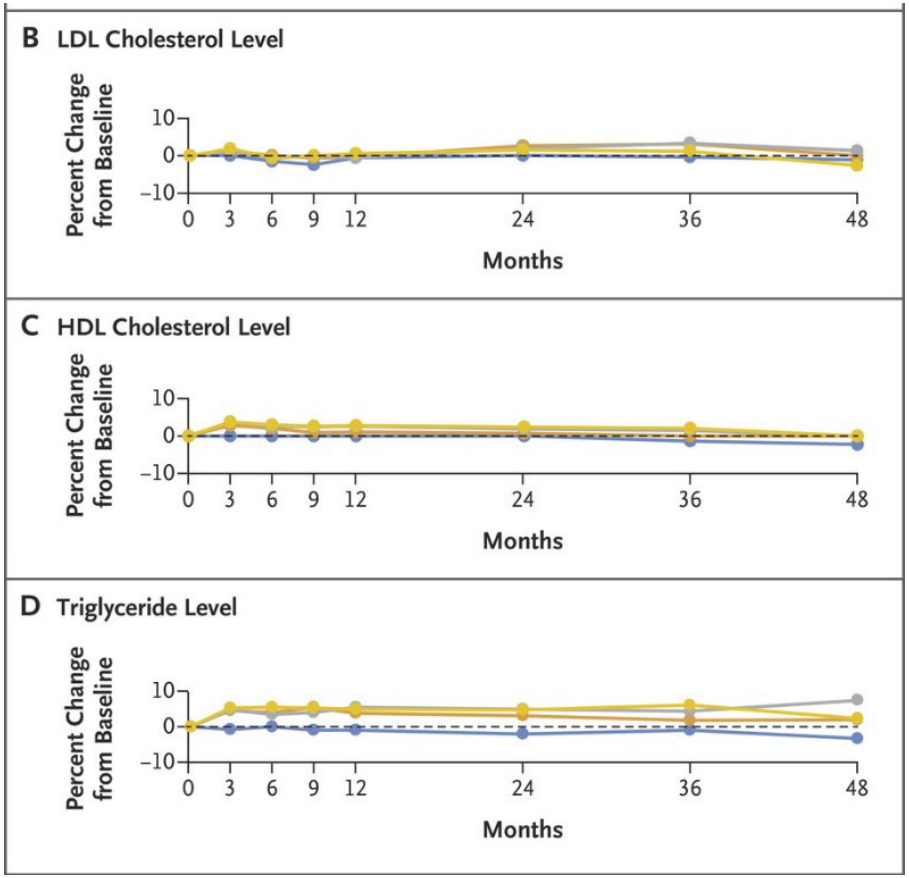
Experimental and clinical data suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease. Yet, the inflammatory hypothesis of atherothrombosis has remained unproved.

METHODS

We conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter. The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

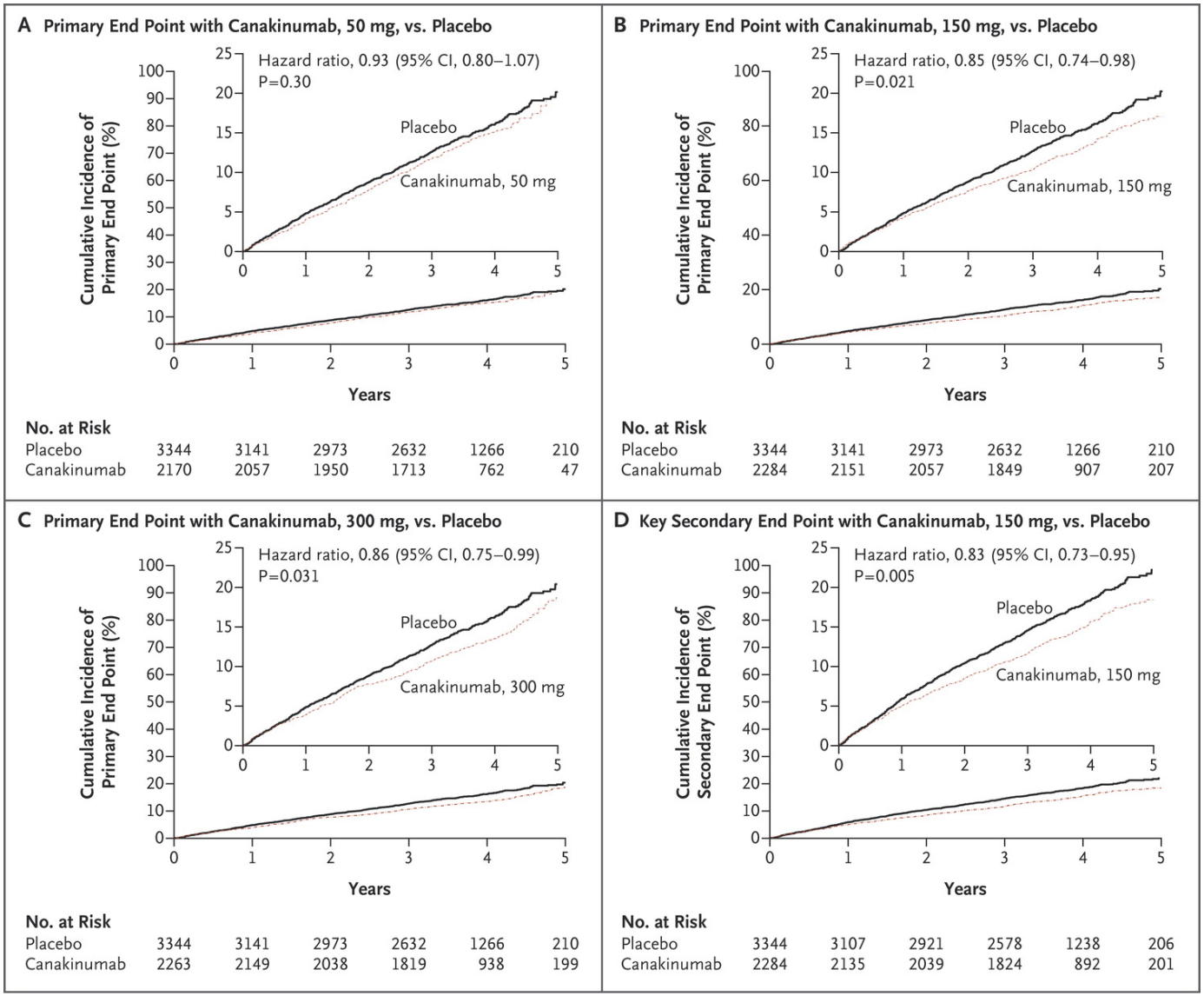
Effects of Canakinumab, as Compared with Placebo, on Plasma Levels of High-Sensitivity C-Reactive Protein and Lipoproteins





Ridker PM et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1707914

Cumulative Incidence of the Primary End Point and the Key Secondary Cardiovascular End Point.



Ridker PM et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1707914

Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

Paul M Ridker, Jean G MacFadyen, Tom Thuren, Brendan M Everett, Peter Libby, Robert J Glynn*, on behalf of the CANTOS Trial Group†*

Summary

Background Inflammation in the tumour microenvironment mediated by interleukin 1β is hypothesised to have a major role in cancer invasiveness, progression, and metastases. We did an additional analysis in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), a randomised trial of the role of interleukin-1β inhibition in atherosclerosis, with the aim of establishing whether inhibition of a major product of the Nod-like receptor protein 3 (NLRP3) inflammasome with canakinumab might alter cancer incidence.

Methods We did a randomised, double-blind, placebo-controlled trial of canakinumab in 10 061 patients with atherosclerosis who had had a myocardial infarction, were free of previously diagnosed cancer, and had concentrations of high-sensitivity C-reactive protein (hsCRP) of 2 mg/L or greater. To assess dose–response effects, patients were randomly assigned by computer-generated codes to three canakinumab doses (50 mg, 150 mg, and 300 mg, subcutaneously every 3 months) or placebo. Participants were followed up for incident cancer diagnoses, which were adjudicated by an oncology endpoint committee masked to drug or dose allocation. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, NCT01327846. The trial is closed (the last patient visit was in June, 2017).

Findings Baseline concentrations of hsCRP (median 6·0 mg/L *vs* 4·2 mg/L; p<0·0001) and interleukin 6 (3·2 *vs* 2·6 ng/L; p<0·0001) were significantly higher among participants subsequently diagnosed with lung cancer than among those not diagnosed with cancer. During median follow-up of 3·7 years, compared with placebo, canakinumab was associated with dose-dependent reductions in concentrations of hsCRP of 26–41% and of interleukin 6 of 25–43% (p<0·0001 for all comparisons). Total cancer mortality (n=196) was significantly lower in the pooled canakinumab group than in the placebo group (p=0·0007 for trend across groups), but was significantly lower than placebo only in the 300 mg group individually (hazard ratio [HR] 0·49 [95% CI 0·31–0·75]; p=0·0009). Incident lung cancer (n=129) was significantly less frequent in the 150 mg (HR 0·61 [95% CI 0·39–0·97]; p=0·034) and 300 mg groups (HR 0·33 [95% CI 0·18–0·59]; p<0·0001; p<0·0001 for trend across groups). Lung cancer mortality was significantly less common in the canakinumab 300 mg group than in the placebo group (HR 0·23 [95% CI 0·10–0·54]; p=0·0002) and in the pooled canakinumab population than in the placebo group (p=0·0002 for trend across groups). Fatal infections or sepsis were significantly more common in the canakinumab groups than in the placebo group. All-cause mortality did not differ significantly between the canakinumab and placebo groups (HR 0·94 [95% CI 0·83–1·06]; p=0·31).

Interpretation Our hypothesis-generating data suggest the possibility that anti-inflammatory therapy with canakinumab targeting the interleukin-1β innate immunity pathway could significantly reduce incident lung cancer and lung cancer mortality. Replication of these data in formal settings of cancer screening and treatment is required.

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See Online/Comment
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*These authors contributed equally

†CANTOS Trial Group listed in the appendix

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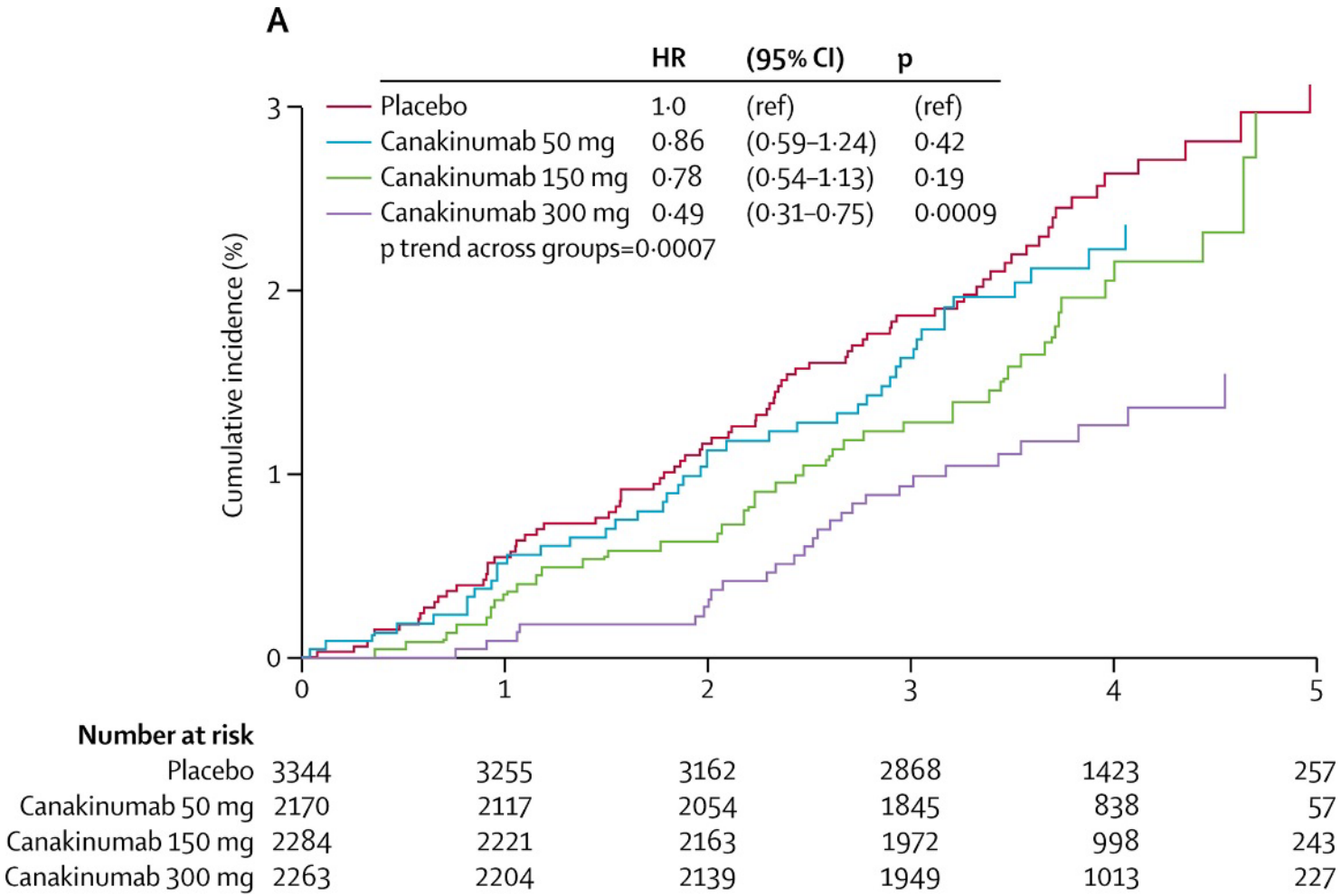
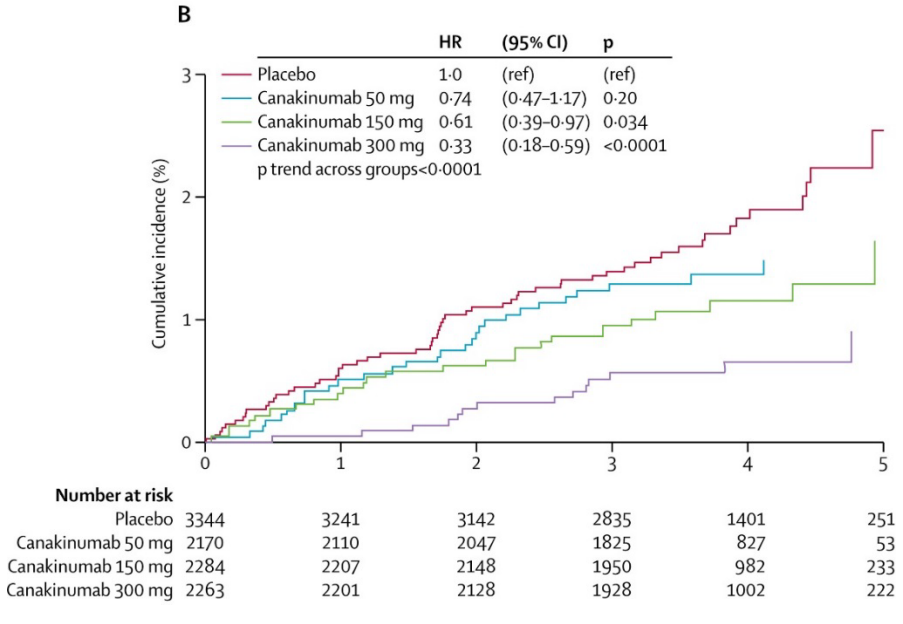
See Online for appendix

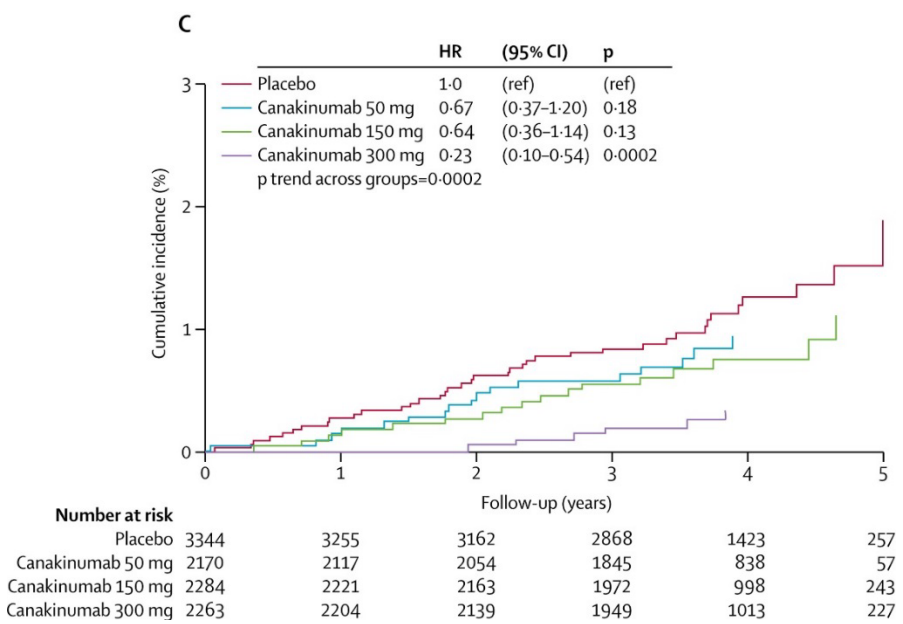
Cumulative incidence of all fatal cancer



Ridker PM et al. Lancet t. 2017 Oct 21;390(10105):1833-1842.

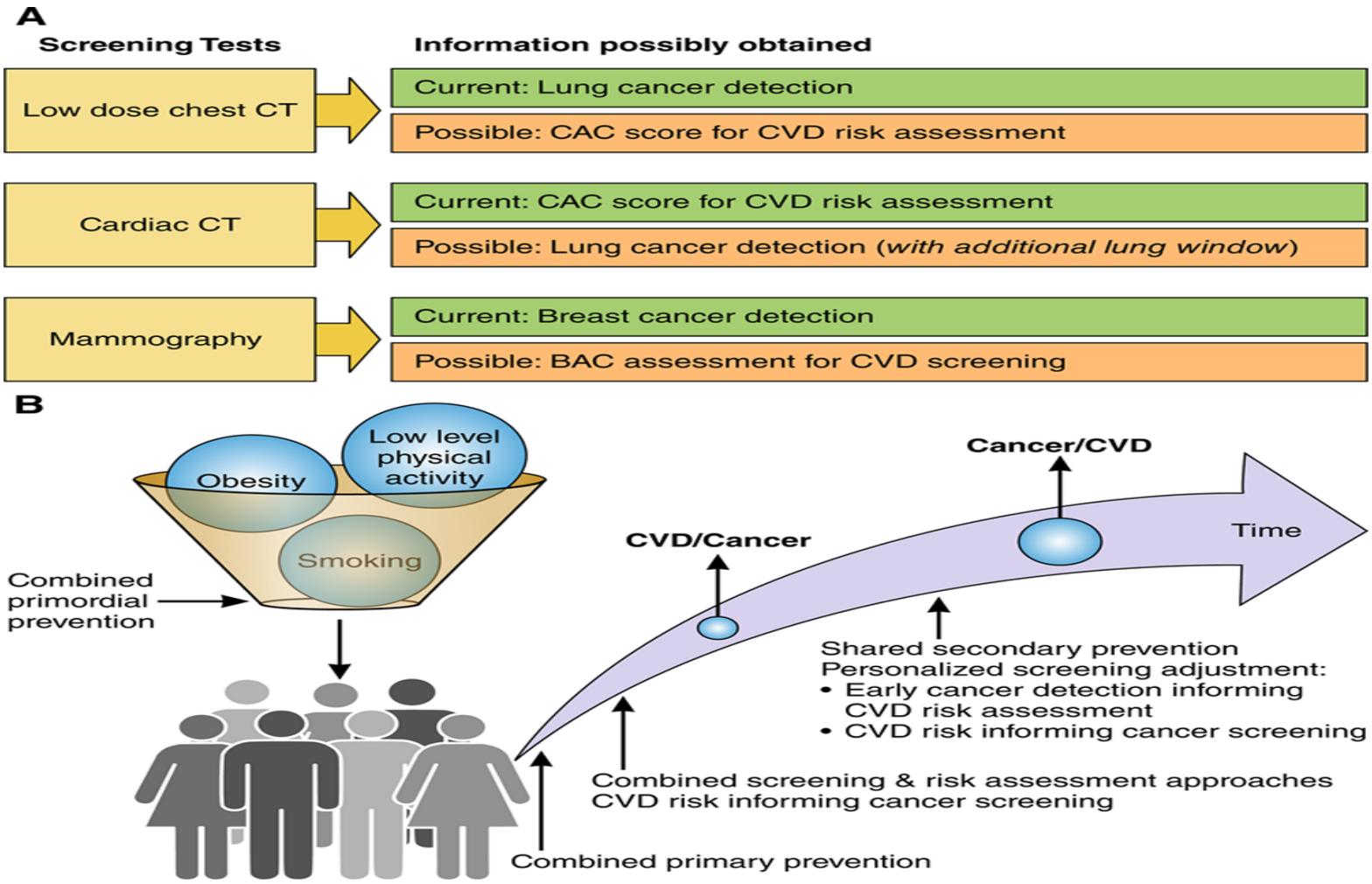
Cumulative incidence of lung cancer (B) and fatal lung cancer (C)





Ridker PM et al. Lancet t. 2017 Oct 21;390(10105):1833-1842.

Opportunities for combined screening and prevention



Handy et al. Circulation 2018; 138: 727-734

Atherosclerosis 263 (2017) 343–351

Contents lists available at ScienceDirect

Atherosclerosis

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

Review article

Cardiovascular disease and cancer: Evidence for shared disease pathways and pharmacologic prevention

Farzad Masoudkabir [a], Nizal Sarrafzadegan [b, c, *], Carolyn Gotay [c, d], Andrew Ignaszewski [e], Andrew D. Krahn [e], Margot K. Davis [e], Christopher Franco [e], Arya Mani [f]

Potential drugs for joint pharmacologic prevention of cardiovascular disease and cancer.

Drug	Direct Target	Indirect Targets	Action on CVD	Action on Cancer
Statins	HMG-CoA-reductase inhibition	• AMPK activation • Inhibition of Cyclines & cycline-dependent kinases • Up-regulation of tumor-suppressors (p53, p27, p21) • Inhibition of PI3K, serine–threonine kinases, NF–κB, and MAPKs signaling pathways	Improving endothelial function Plaque stabilization ↓ Atherosclerosis progression ↓ Myocardial infarction and stroke ↓ Cardiovascular mortality	Tumor-suppressor and anti-cancer role through: ↑Apoptosis ↓Proliferation ↓Invasion ↑Radiosensitization ↓DNA damage
ASA	Inhibition of COX1	• AMPK activation?	↓ Myocardial infarction and stroke ↓ Cardiovascular mortality	↓ Cancer incidence ↓ Cancer death
ACEIs/ ARBs	ACE inhibition/ Angiotensin II receptor antagonism	• ↓ VEGF expression • PPAR-γ activation	Improving endothelial function Plaque stabilization ↓ Atherosclerosis progression ↓ Myocardial infarction and stroke ↓ Cardiovascular mortality	↓ Cancer incidence Tumor-suppressor and anti-cancer role through: ↓ DNA damage ↑Apoptosis ↑Differentiation ↓Angiogenesis ↓ Cell growth
Metformin	Unknown	• AMPK activation		↓ Cancer incidence Tumor suppression by regulating cellular proliferation, cell cycle progression and cellular survival
TZDs	PPAR-γ agonism	• AMPK activation • Wnt/β-catenin signaling pathway inhibition • IGF-1 inhibition • Inhibition of leptin gene expression	↓ Coronary and carotid atherosclerosis ↓ Thrombus formation and acute myocardial infarction and stroke ↓ Blood pressure	Tumor suppression through: ↓Angiogenesis ↑Apoptosis ↓Self-renewal of cancer cells ↑Differentiation

HMG-CoA-reductase, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; AMPK, Adenosine 5′ monophosphate -activated protein kinase; PI3K, phosphoinositide 3- kinase; NF–κB, nuclear factor kappa-B; MAPK, mitogen-activated kinases; CVD, cardiovascular disease; COX1, cyclooxygenase 1; ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists; ACE, angiotensin-converting enzyme; VEGF, vascular endothelial growth factor; PPAR-γ, peroxisome proliferator-activated receptor-γ; TZDs, thiazolidinediones.

Thrombosis Research 170 (2018) 175–180

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

Full Length Article

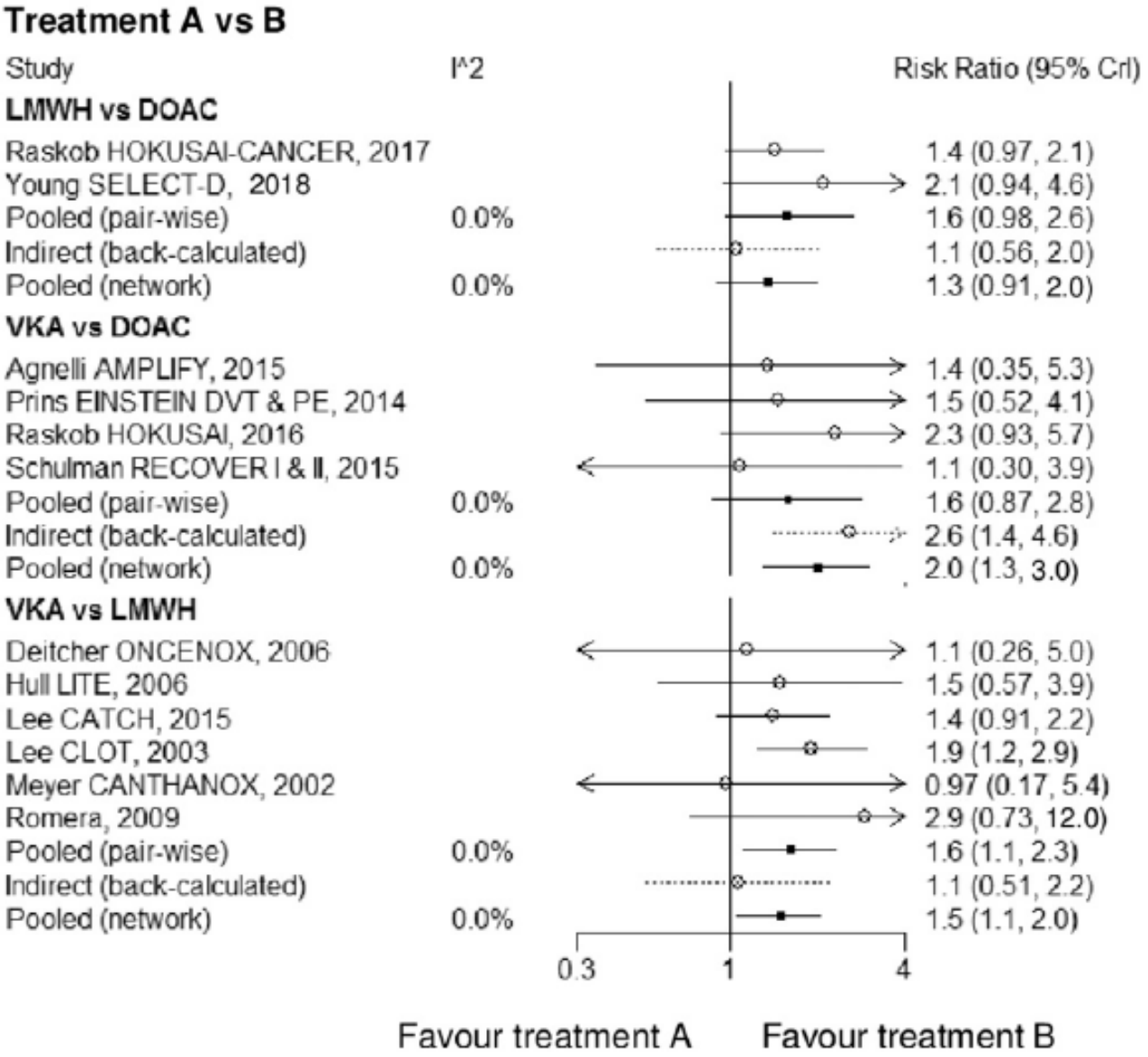
Efficacy and safety of anticoagulant agents in patients with venous thromboembolism and cancer: A network meta-analysis☆

Maria Cristina Vedovati[a,*], Michela Giustozzi[a], Gianluca Bonitta[b], Giancarlo Agnelli[a], Cecilia Becattini[a]

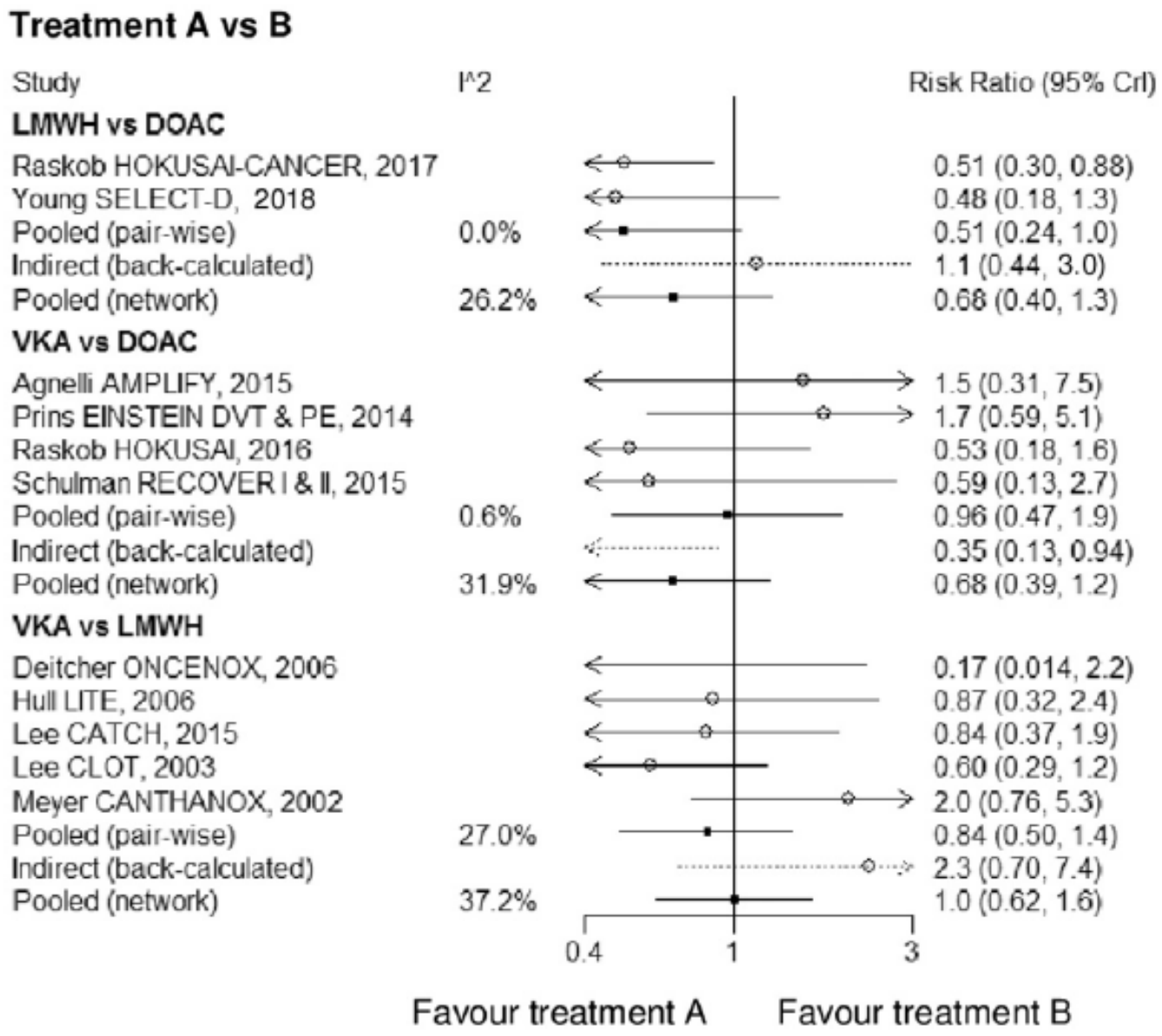
[a] Internal and Cardiovascular Medicine – Stroke Unit, University of Perugia, Italy
[b] Arrhythmia and Electrophysiology Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

Author	Study name	Study design	Pub. year	Study drug	Comparator	TTR (%)	Study period	Active cancer at baseline (n)	Anti-cancer treatment (%)	Mean or median age	Incidental cancer[b] (n)	Metastatic disease (%)	Definition of active cancer
Meyer [9]	CANTHANOX	Open	2002	Enoxaparin	Enoxaparin/ VKA	41	3 months	146	73	66	–	53%	Solid or hematologic cancers, either active or in remission with ongoing antitumor treatment (no definition of active cancer reported)
Lee [8]	CLOT	Open	2003	Dalteparin	Dalteparin/ VKA	46	6 months	676	78	63	–	67%	Recurrent or metastatic cancers, or cancer diagnosis or treatment within 6 months
Deitcher [11]	ONCENOX	Open	2006	Enoxaparin	Enoxaparin/ VKA	n.a.	6 months	101	49[d]	n.a	–	58%	Measurable disease or histo-cytological diagnosis ± elevated tumor markers
Hull [10]	LITE	Open	2006	Tinzaparin	UFH/VKA	n.a.	3 months	200	n.a.	n.a.	–	n.a	Specific definition for active cancer not reported
Romera [33]	–	Open	2009	Tinzaparin	Tinzaparin/ VKA	n.a.	6 months	69	n.a.	62	–	n.a	Specific definition for active cancer not reported
Prins [14]	EINSTEIN DVT & PE sub-analysis	Open	2014	Rivaroxaban	Heparin/VKA	57	12 months	462	29	n.a	193	22%	Specific definition for active cancer not reported
Agnelli [15]	AMPLIFY sub-analysis	Double-blind	2015	Apixaban	Heparin/VKA	61[c]	6 months	159	n.a.	65	25	33%	Diagnosed or treated within 6 months
Lee [34]	CATCH	Open	2015	Tinzaparin	Tinzaparin/ VKA	47	6 months	900	53	59	–	55%	Histologic diagnosis or anticancer therapy within 6 months or recurrent,/metastatic disease
Schulman [13]	RECOVER I & II sub-analysis	Double-blind	2015	Heparin/ Dabigatran	Heparin/VKA	53	6 months	221	n.a.	64	114	13%	Diagnosis of cancer, recurrent or metastatic disease, or cancer treatment within 5 years
Raskob [16]	HOKUSAI-VTE sub-analysis	Double-blind	2017	Heparin/ Edoxaban	Heparin/VKA	64	12 months	370[a]	34	66	175	24%	Specific definition for active cancer not reported
Raskob [17]	HOKUSAI-cancer	Open	2017	Heparin/ Edoxaban	Dalteparin	–	12 months	1024	72	65	–	53%	Diagnosis of cancer, recurrent or metastatic disease, or cancer treatment within 6 months
Young [35]	SELECT-D	Open	2018	Rivaroxaban	Dalteparin	–	6 months	406	70	67	–	59%	Diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) recurrent or metastatic disease, or cancer treatment within 6 months.

Anticoagulants and DVT recurrence in active cancer.

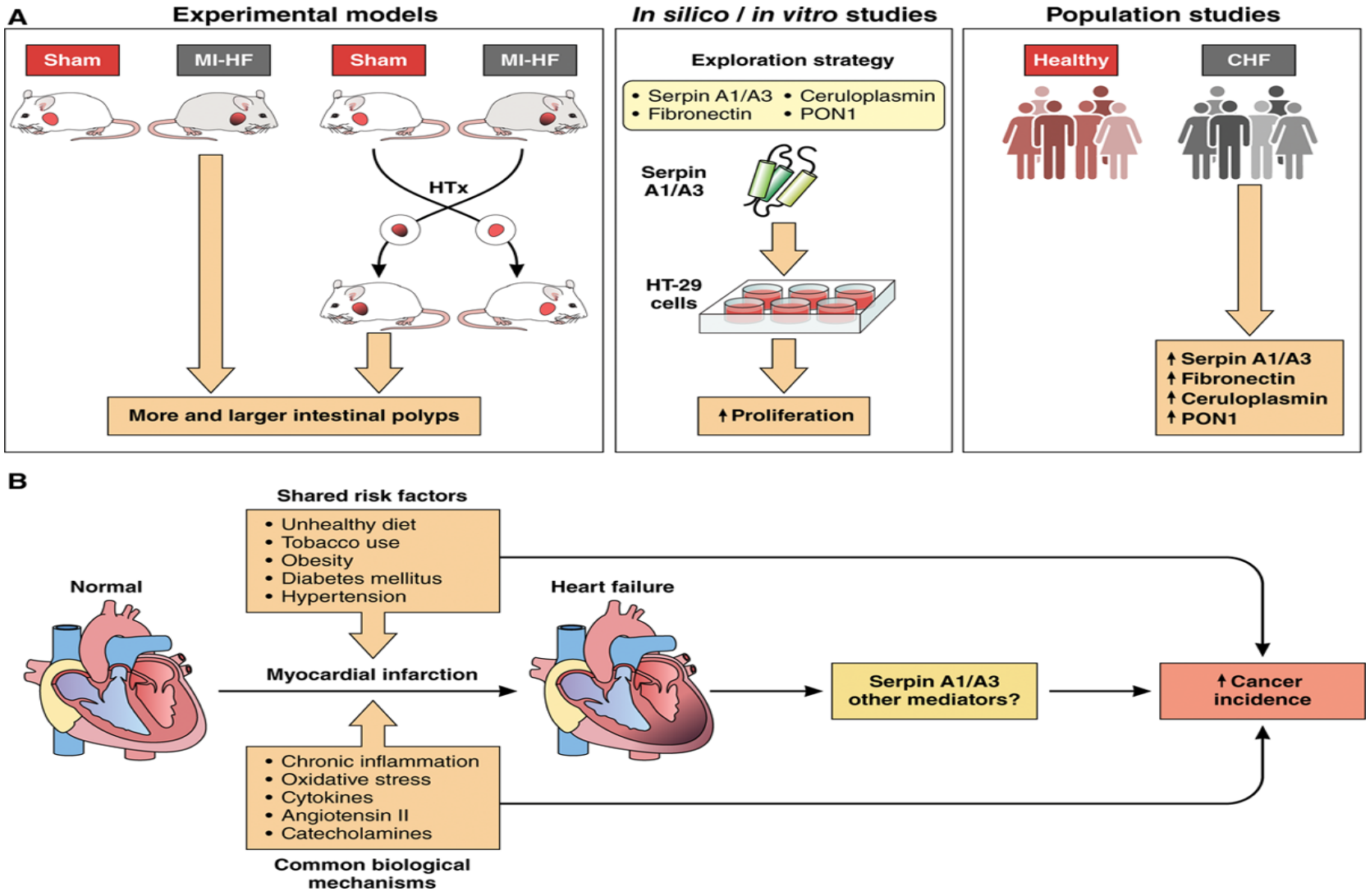


Anticoagulants and major bleeding in active cancer.



Heart Disease and Cancer

Are the Two Killers Colluding?



Kitsis et al. Circulation, 2018; 138: 692-695

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Patients With Heart Failure Have an Increased Risk of Incident Cancer

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Rochester Minnesota; and Petah Tikva and Tel Aviv, Israel

Objectives This study sought to evaluate the risk of cancer in patients with heart failure (HF) compared with community controls and to determine the impact of cancer post-HF on outcomes.

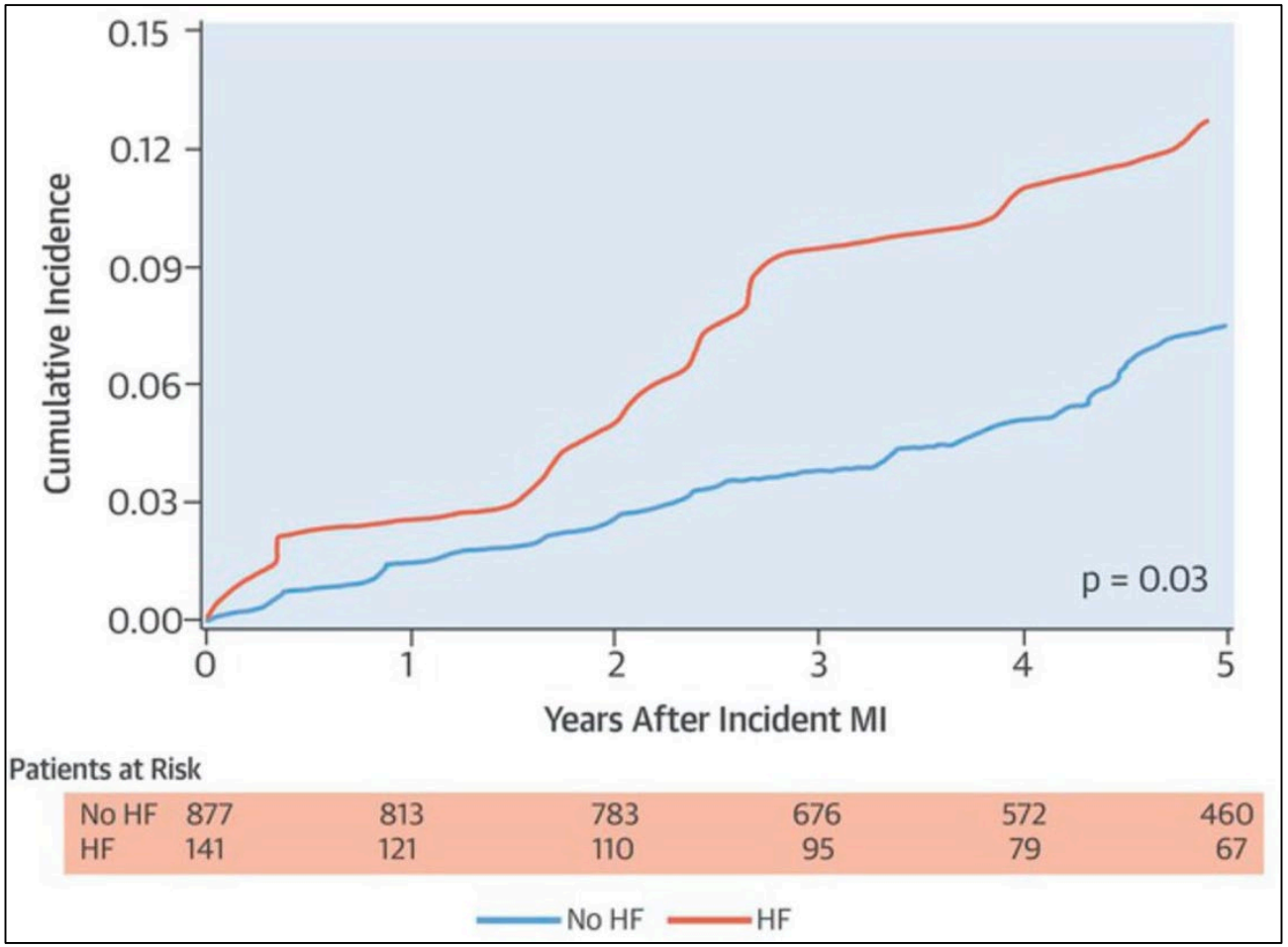
Background HF is associated with excess morbidity and mortality. Noncardiac causes of adverse outcomes in HF are increasingly recognized, but not fully characterized.

Methods In a case-control study, we compared the history of cancer among community subjects newly diagnosed with HF from 1979 to 2002 to age-, sex-, and date-matched community controls without HF (961 pairs). Individuals without cancer at the index date (596 pairs) were followed for cancer in a cohort design, and the survival of HF patients who developed cancer was assessed.

Results Before the index date, 22% of HF cases and 23% of controls had a history of cancer (odds ratio [OR]: 0.94; 95% confidence interval [CI]: 0.75 to 1.17). During 9,203 person-years of follow-up (7.7 ± 6.4 years), 244 new cancer cases were identified; HF patients had a 68% higher risk of developing cancer (hazard ratio [HR]: 1.68; 95% CI: 1.13 to 2.50) adjusted for body mass index, smoking, and comorbidities. The HRs were similar for men and women, with a trend toward a stronger association among subjects ≤75 years of age ($p = 0.22$) and during the most recent time period ($p = 0.075$). Among HF cases, incident cancer increased the risk of death (HR: 1.56; 95% CI: 1.22 to 1.99) adjusted for age, sex, index year, and comorbidities.

Conclusions HF patients are at increased risk of cancer, which appears to have increased over time. Cancer increases mortality in HF, underscoring the importance of noncardiac morbidity and of cancer surveillance in the management of HF patients. (J Am Coll Cardiol 2013;62:881–6) © 2013 by the American College of Cardiology Foundation

Incidence of cancer in patients with and without heart failure 30 days after acute myocardial infarction



Tal Hasin et al. JACC 2016;68:265-271

European Journal of Heart Failure (2016) 18, 260–266
doi:10.1002/ejhf.472

RESEARCH ARTICLE

Incidence of cancer in patients with chronic heart failure: a long-term follow-up study

Ann Banke[1]*, Morten Schou[2], Lars Videbæk[1], Jacob E. Møller[1], Christian Torp-Pedersen[3], Finn Gustafsson[4], Jordi S. Dahl[1], Lars Køber[4], Per R. Hildebrandt[5], and Gunnar H. Gislason[6]

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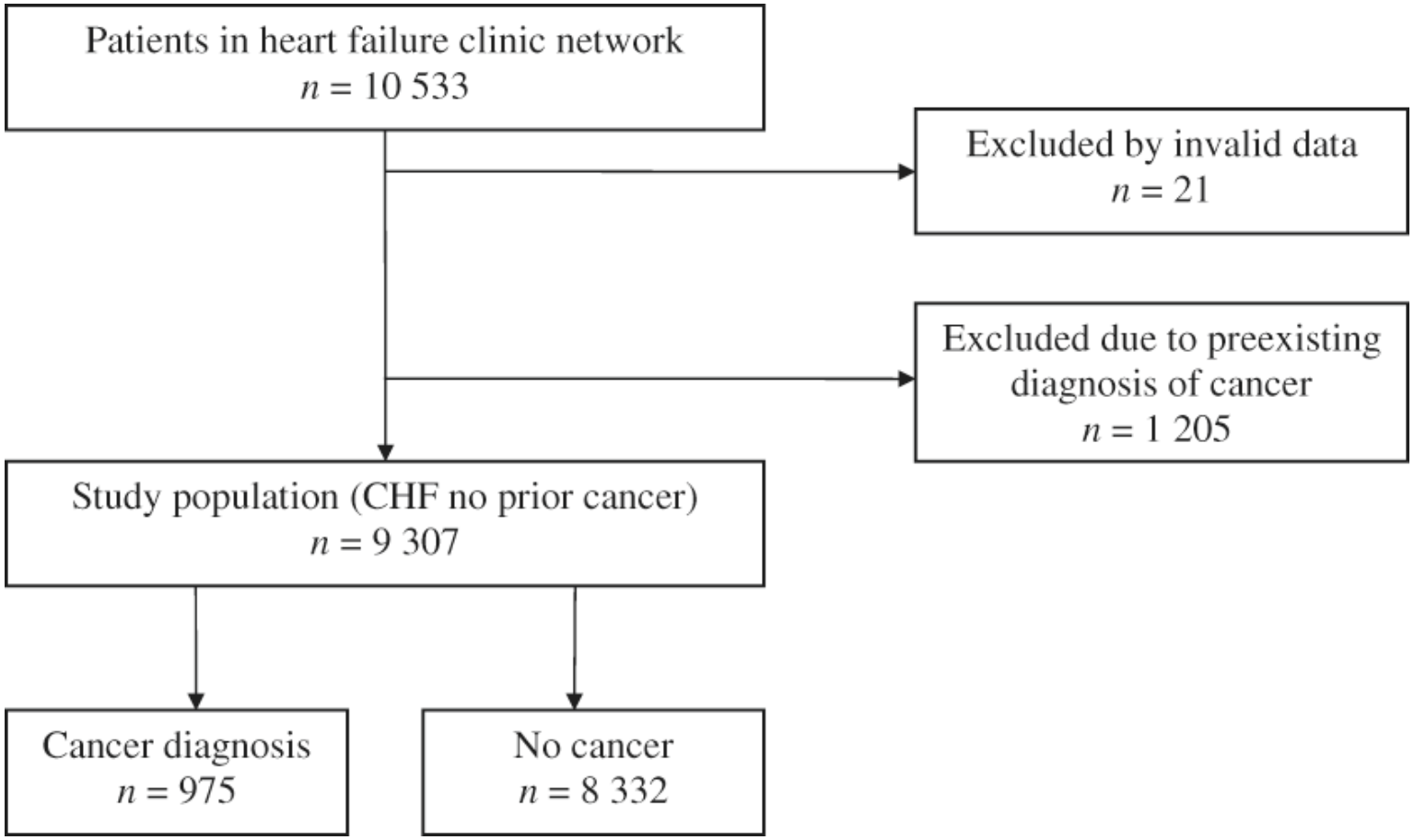
Received 7 August 2015; revised 19 November 2015; accepted 27 November 2015; online publish-ahead-of-print 10 January 2016

Aims With improvement in survival of chronic heart failure (HF), the clinical importance of co-morbidity is increasing. The aim of this study was to assess the incidence and risk of cancer and all-cause mortality in a large Danish HF cohort.

Methods and results A total of 9307 outpatients with verified HF without a prior diagnosis of cancer (27% female, mean age 68 years, 89% with LVEF <45%) were included in the study. A diagnosis of any cancer and all-cause mortality was obtained from Danish national registries. Outcome was compared with the general Danish population. Overall and type-specific risk of cancer was analysed in an adjusted Poisson and Cox regression analysis. The 975 diagnoses of cancer in the HF cohort and 330 843 in the background population corresponded to incidence rates per 10 000 patient-years of 188.9 [95% confidence interval (CI) 177.2–200.6] and 63.0 (95% CI 63.0–63.4), respectively. When stratified by age, incidence rates were increased in all age groups in the HF cohort. Risk of any type of cancer was increased, with an incidence rate ratio of 1.24 (95% CI 1.15–1.33, $c < 0.0001$). Type-specific analysis demonstrated an increased hazard ratio for all major types of cancer except for prostate cancer. All-cause mortality was higher in HF patients with cancer compared with cancer patients from the background population.

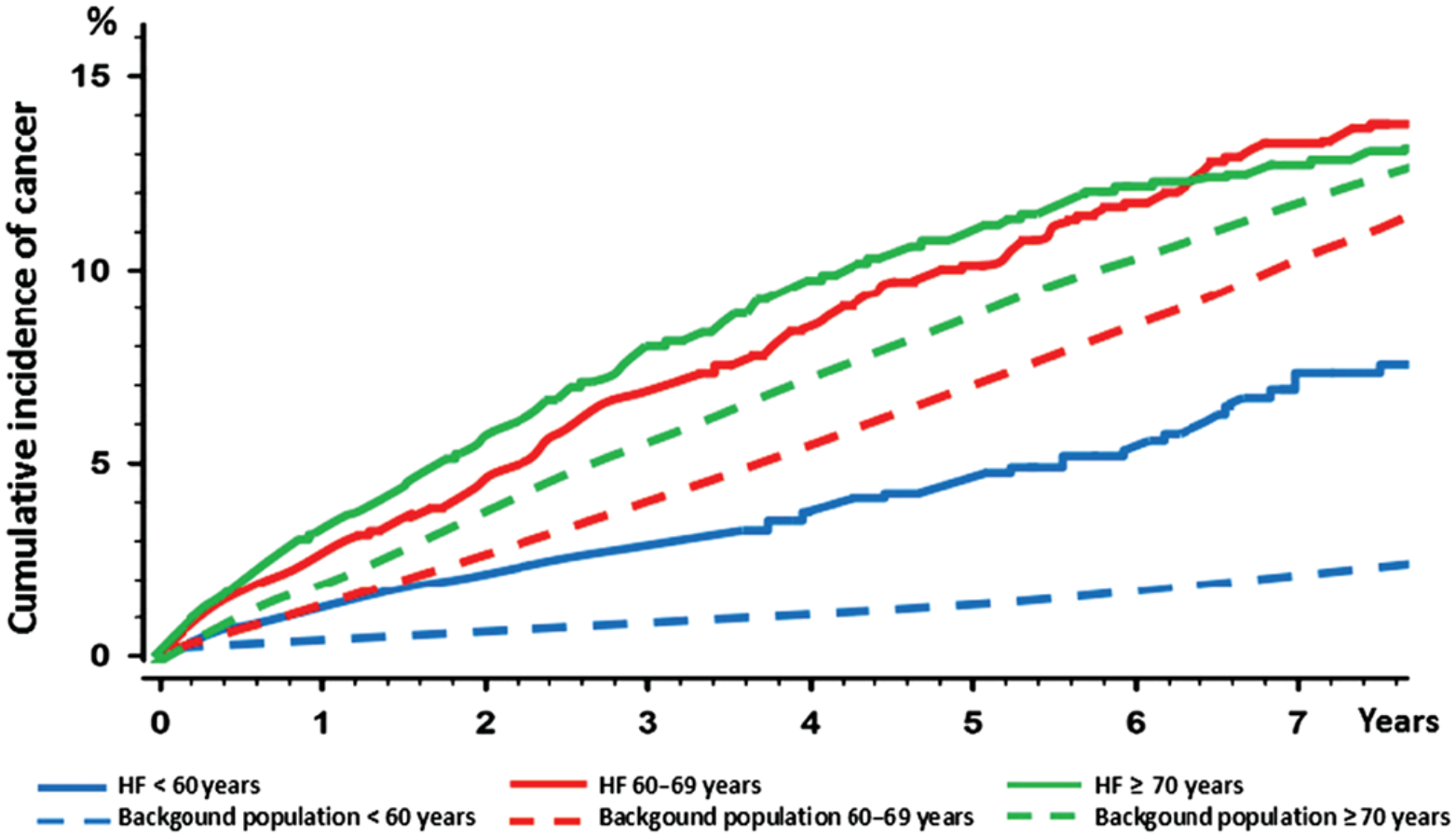
Conclusions Patients with HF have an increased risk of cancer, which persists after the first year after the diagnosis of HF, and their prognosis is worse compared with that of cancer patients without HF.

Incidence of cancer in patients with chronic heart failure: a long-term follow-up study



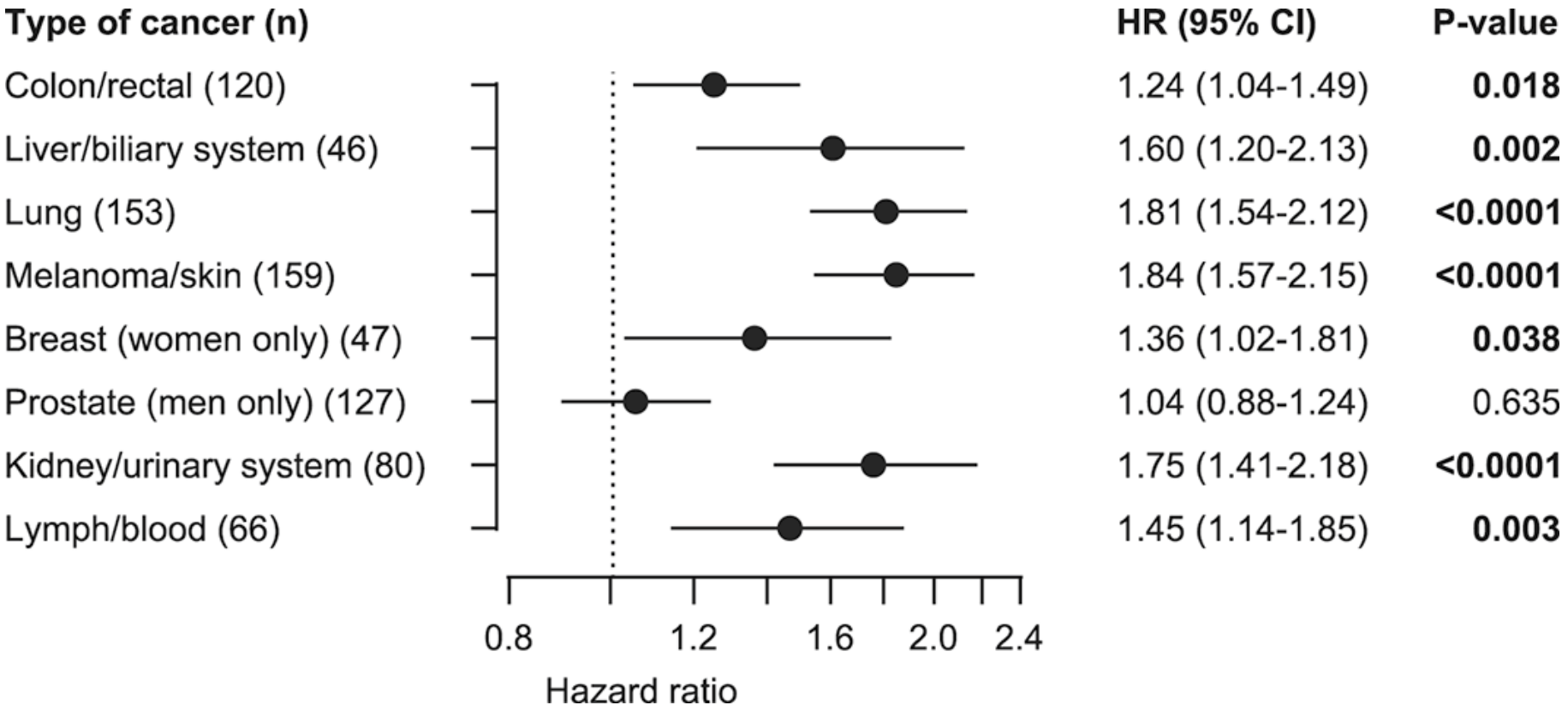
Banke et al. Eur J Heart Fail 2016; 18: 260-266

Incidence of cancer in patients with chronic heart failure: a long-term follow-up study



Banke et al. Eur J Heart Fail 2016; 18: 260-266

Incidence of cancer in patients with chronic heart failure: a long-term follow-up study



Banke et al. Eur J Heart Fail 2016; 18: 260-266

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VOL. 71, NO. 14, 2018

ORIGINAL INVESTIGATIONS

Lack of Association Between Heart Failure and Incident Cancer

Senthil Selvaraj, MD, MA,[a,b,c] Deepak L. Bhatt, MD, MPH,[d] Brian Claggett, PhD,[e] Luc Djoussé, MD, DSc,[b,f] Sanjiv J. Shah, MD,[g] Jiaying Chen, MS,[c] Tasnim F. Imran, MD,[b,c] Saadia Qazi, DO, MPH,[b,c] Howard D. Sesso, ScD, MPH,[c] J. Michael Gaziano, MD, MPH,[b,f] Deborah Schrag, MD, MPH[h]

ABSTRACT

BACKGROUND Several recent studies have suggested an increased cancer risk among patients with heart failure (HF). However, these studies are constrained by limited size and follow-up, lack of comprehensive data on other health attributes, and adjudicated cancer outcomes.

OBJECTIVES This study sought to determine whether HF is associated with cancer incidence and cancer-specific mortality.

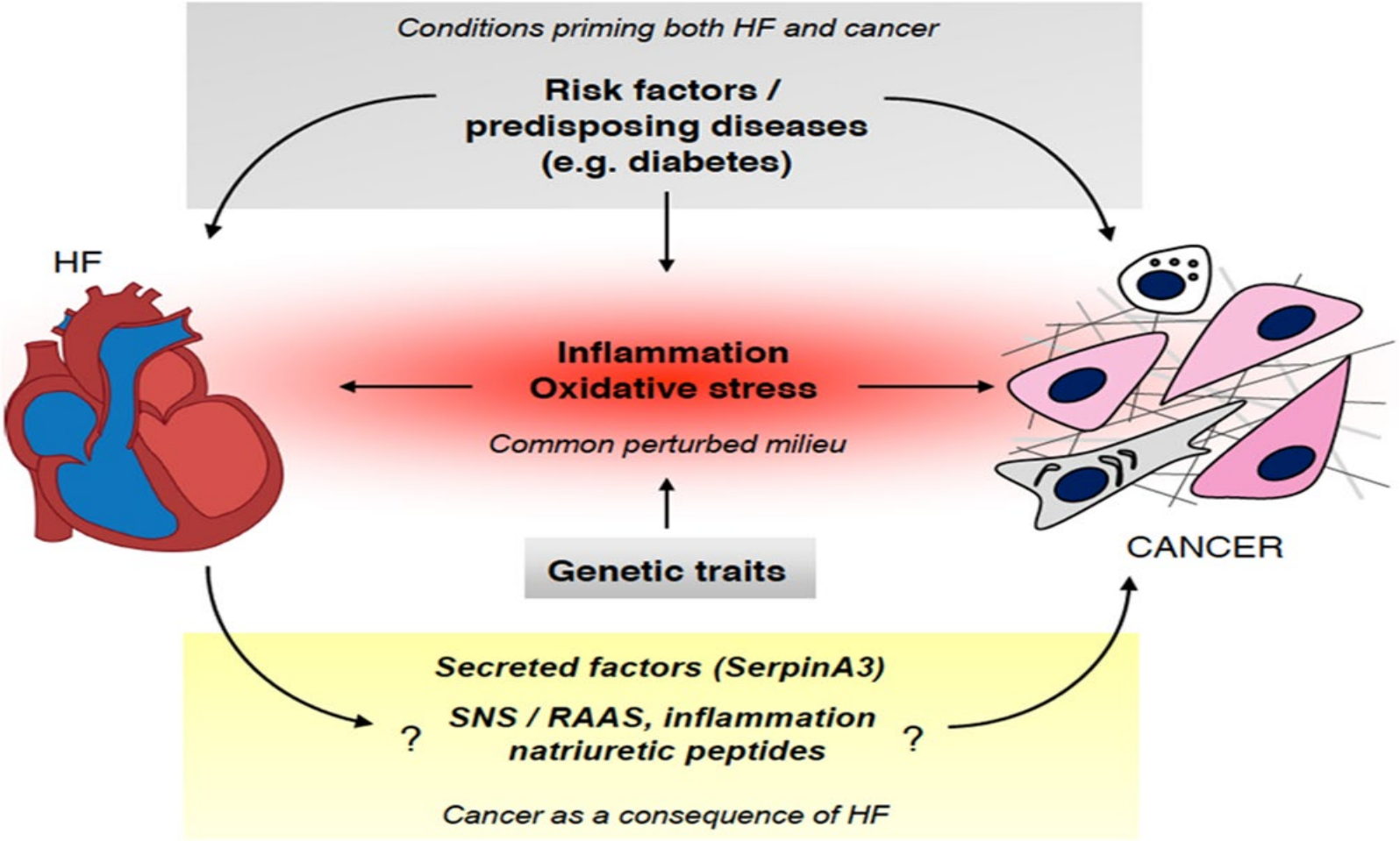
METHODS The study assembled a cohort from the Physicians' Health Studies I and II, 2 randomized controlled trials of aspirin and vitamin supplements conducted from 1982 to 1995 and from 1997 to 2011, respectively, that included annual health evaluations and determination of cancer and HF diagnoses. In the primary analysis, the study excluded participants with cancer or HF at baseline and performed multivariable-adjusted Cox models to determine the relationship between HF and cancer, modeling HF as a time-varying exposure. In a complementary analysis, the study used the landmark method and identified cancer-free participants at 70 years of age, distinguishing between those with and without HF, and likewise performed Cox regression. Sensitivity analyses were performed at 65, 75, and 80 years of age.

Restricted to male patients
Diagnosis of HF based on self-reporting

CONCLUSIONS HF is not associated with an increased risk of cancer among male physicians. (J Am Coll Cardiol 2018;71:1501-10) Published by Elsevier on behalf of the American College of Cardiology Foundation.

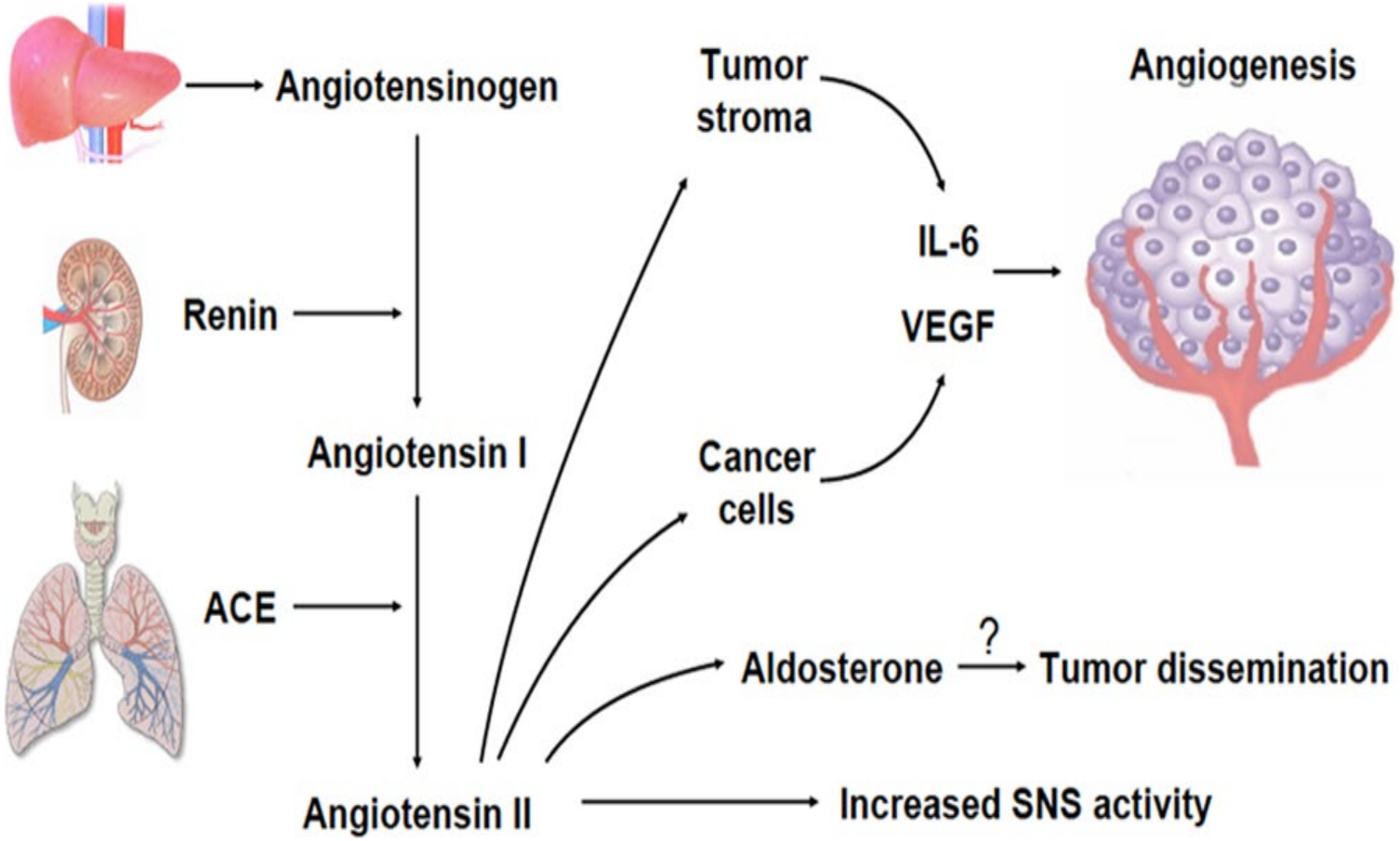
Selvaraj et al, J Am Coll cardiol 2018; 71: 1501-10

Possible pathways linking heart failure to cancer



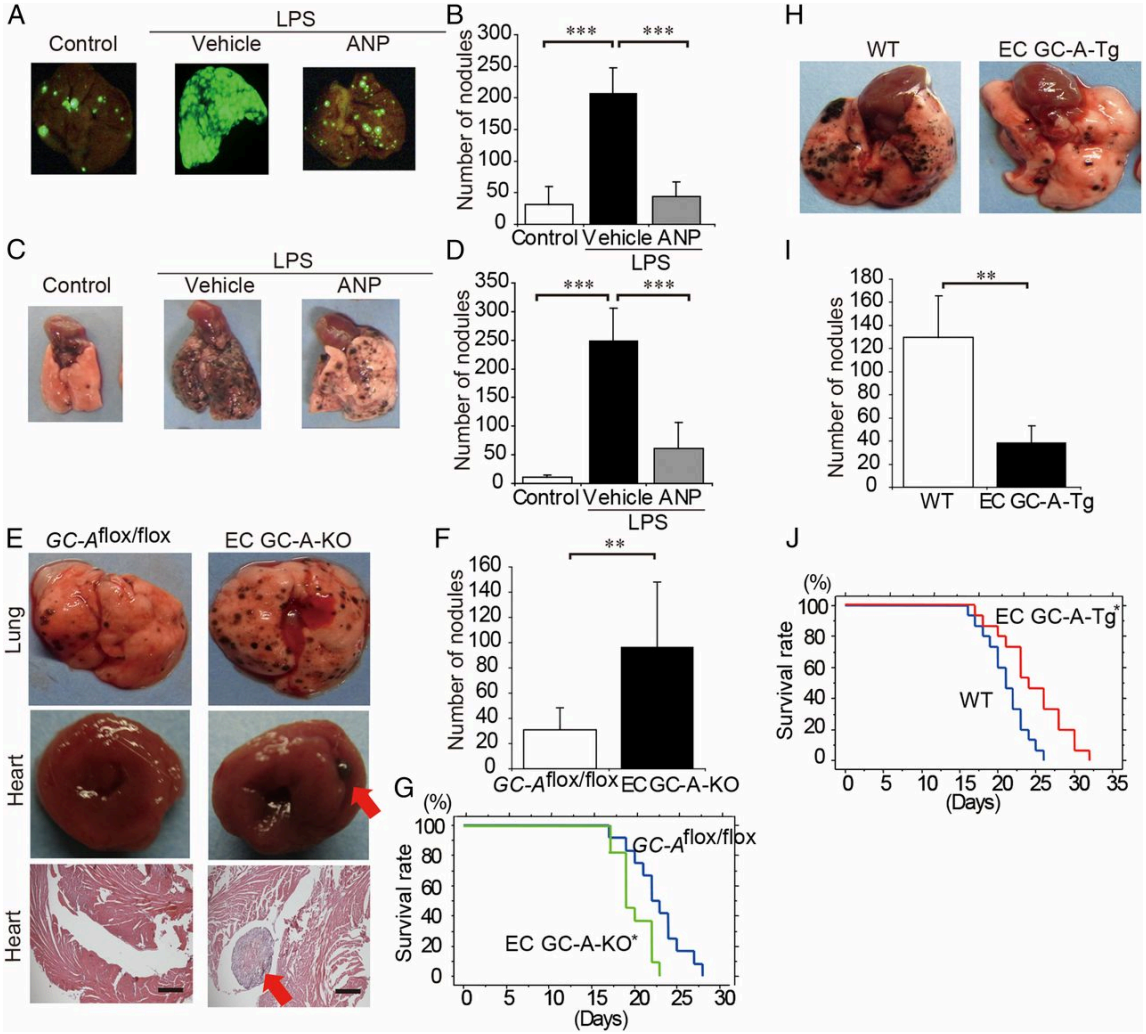
Bertero et al. Circulation Circulation. 2018;138:735–742

Effects of renin angiotensin system on cancer



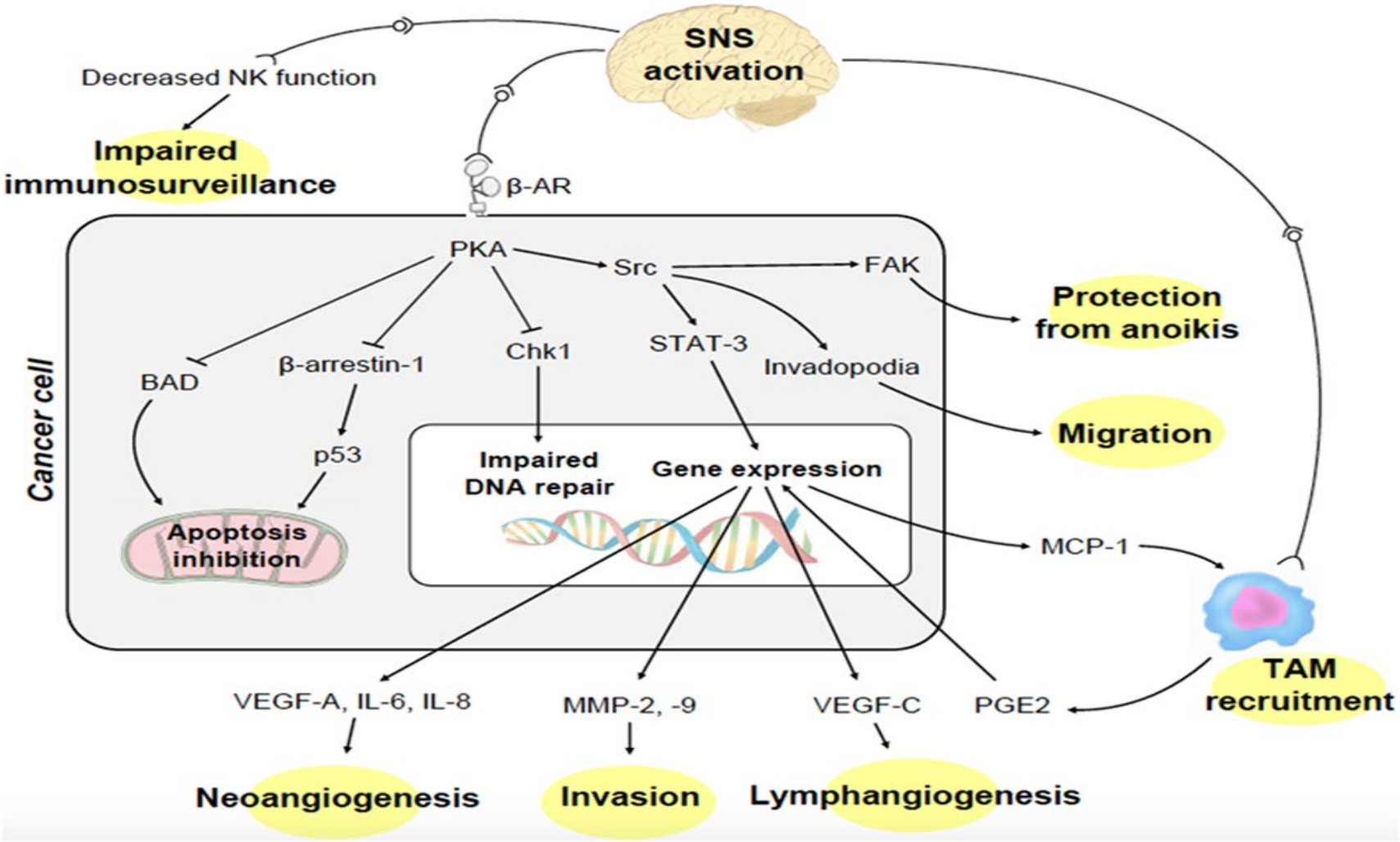
Bertero et al. Circulation Circulation. 2018;138:735–742

ANP inhibits the LPS-augmented metastasis of A549-EGFP lung cancer cells and B16/F10 mice melanoma cells to the lung.



Takashi Nojiri et al. PNAS 2015;112:13:4086-4091

Effects of sympathetic nervous system on cancer



Bertero et al. Circulation Circulation. 2018;138:735–742

Published OnlineFirst September 7, 2010; DOI: 10.1158/0008-5472.CAN-10-0522

Microenvironment and Immunology

Cancer Research

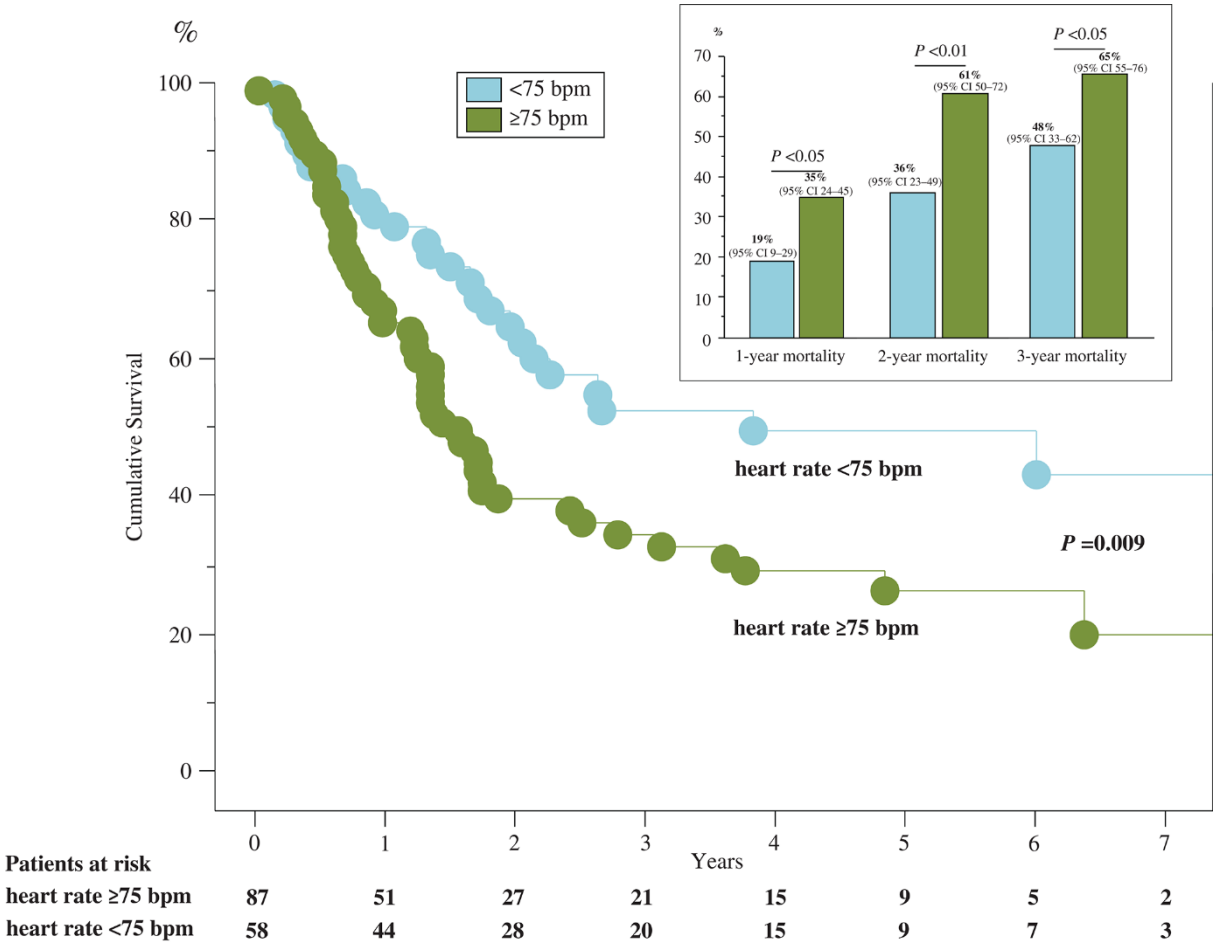
The Sympathetic Nervous System Induces a Metastatic Switch in Primary Breast Cancer

Erica K. Sloan[1,2,3], Saul J. Priceman[4], Benjamin F. Cox[1], Stephanie Yu[1], Matthew A. Pimentel[1], Veera Tangkanangnukul[1], Jesusa M.G. Arevalo[1,2], Kouki Morizono[2], Breanne D.W. Karanikolas[4], Lily Wu[4], Anil K. Sood[6], and Steven W. Cole[1,2,3,5]

Abstract

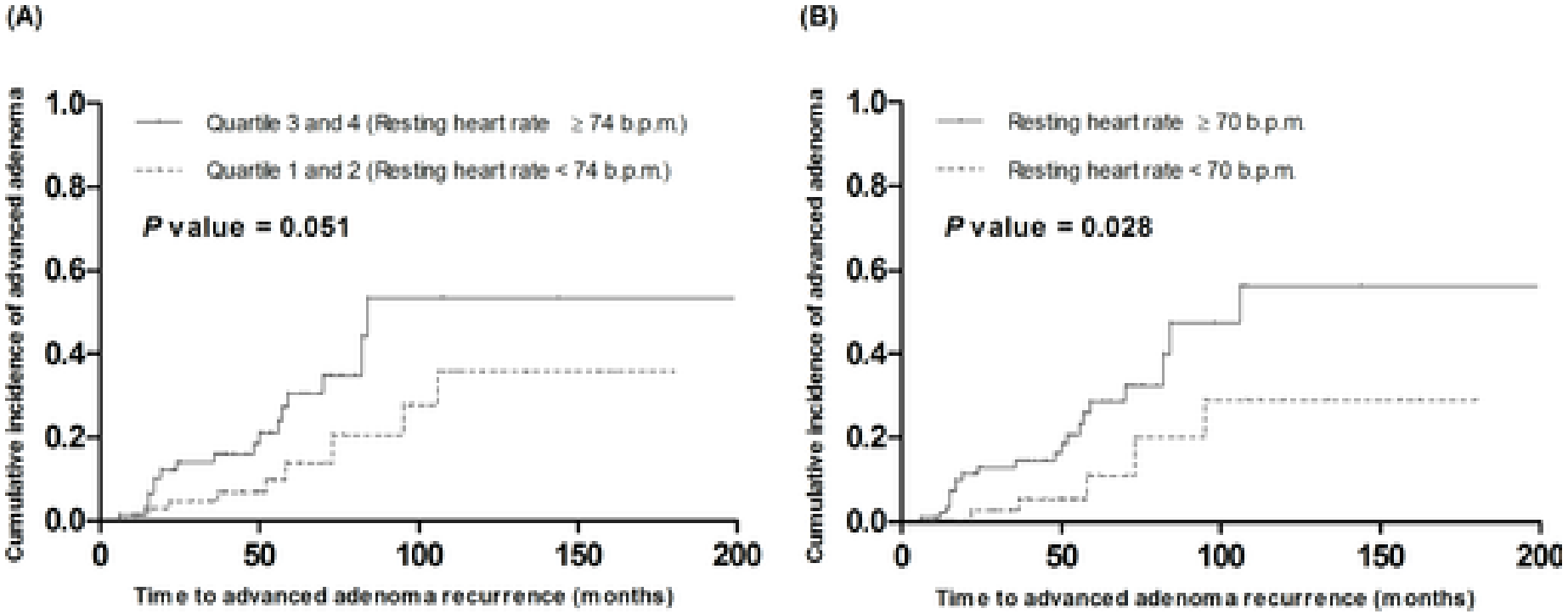
Metastasis to distant tissues is the chief driver of breast cancer–related mortality, but little is known about the systemic physiologic dynamics that regulate this process. To investigate the role of neuroendocrine activation in cancer progression, we used *in vivo* bioluminescence imaging to track the development of metastasis in an orthotopic mouse model of breast cancer. Stress-induced neuroendocrine activation had a negligible effect on growth of the primary tumor but induced a 30-fold increase in metastasis to distant tissues including the lymph nodes and lung. These effects were mediated by β-adrenergic signaling, which increased the infiltration of $CD11b^{+}F4/80^{+}$ macrophages into primary tumor parenchyma and thereby induced a prometastatic gene expression signature accompanied by indications of M2 macrophage differentiation. Pharmacologic activation of β-adrenergic signaling induced similar effects, and treatment of stressed animals with the β-antagonist propranolol reversed the stress-induced macrophage infiltration and inhibited tumor spread to distant tissues. The effects of stress on distant metastasis were also inhibited by *in vivo* macrophage suppression using the CSF-1 receptor kinase inhibitor GW2580. These findings identify activation of the sympathetic nervous system as a novel neural regulator of breast cancer metastasis and suggest new strategies for antimetastatic therapies that target the β-adrenergic induction of prometastatic gene expression in primary breast cancers. *Cancer Res; 70(18); 7042–52.* ©2010 AACR.

Survival curves of patients with colorectal, pancreatic, and non-small cell lung cancer subdivided by their resting heart rate



Anker MS et al. Eur J Heart Fail 2016; 18: 1524-1534

Cumulative rate of advance adenoma in patients subdivided by baseline resting heart rate



Park J et al. PLOS ONE 2018; 13(3): e0193753. https://doi.org/10.1371/journal.pone.0193753

Circulation

ORIGINAL RESEARCH ARTICLE

Heart Failure Stimulates Tumor Growth by Circulating Factors

Editorial, see p 692

BACKGROUND: Heart failure (HF) survival has improved, and nowadays, many patients with HF die of noncardiac causes, including cancer. Our aim was to investigate whether a causal relationship exists between HF and the development of cancer.

METHODS: HF was induced by inflicting large anterior myocardial infarction in APC^{min} mice, which are prone to developing precancerous intestinal tumors, and tumor growth was measured. In addition, to rule out hemodynamic impairment, a heterotopic heart transplantation model was used in which an infarcted or sham-operated heart was transplanted into a recipient mouse while the native heart was left in situ. After 6 weeks, tumor number, volume, and proliferation were quantified. Candidate secreted proteins were selected because they were previously associated both with (colon) tumor growth and with myocardial production in post–myocardial infarction proteomic studies. Myocardial gene expression levels of these selected candidates were analyzed, as well as their proliferative effects on HT-29 (colon cancer) cells. We validated these candidates by measuring them in plasma of healthy subjects and patients with HF. Finally, we associated the relation between cardiac specific and inflammatory biomarkers and new-onset cancer in a large, prospective general population cohort.

RESULTS: The presence of failing hearts, both native and heterotopically transplanted, resulted in significantly increased intestinal tumor load of 2.4-fold in APC^{min} mice (all $P<0.0001$). The severity of left ventricular dysfunction and fibrotic scar strongly correlated with tumor growth ($P=0.002$ and $P=0.016$, respectively). We identified several proteins (including serpinA3 and A1, fibronectin, ceruloplasmin, and paraoxonase 1) that were elevated in human patients with chronic HF (n=101) compared with healthy subjects (n=180; $P<0.001$). Functionally, serpinA3 resulted in marked proliferation effects in human colon cancer (HT-29) cells, associated with Akt-S6 phosphorylation. Finally, elevated cardiac and inflammation biomarkers in apparently healthy humans (n=8319) were predictive of new-onset cancer (n=1124) independently of risk factors for cancer (age, smoking status, and body mass index).

CONCLUSIONS: We demonstrate that the presence of HF is associated with enhanced tumor growth and that this is independent of hemodynamic impairment and could be caused by cardiac excreted factors. A diagnosis of HF may therefore be considered a risk factor for incident cancer.

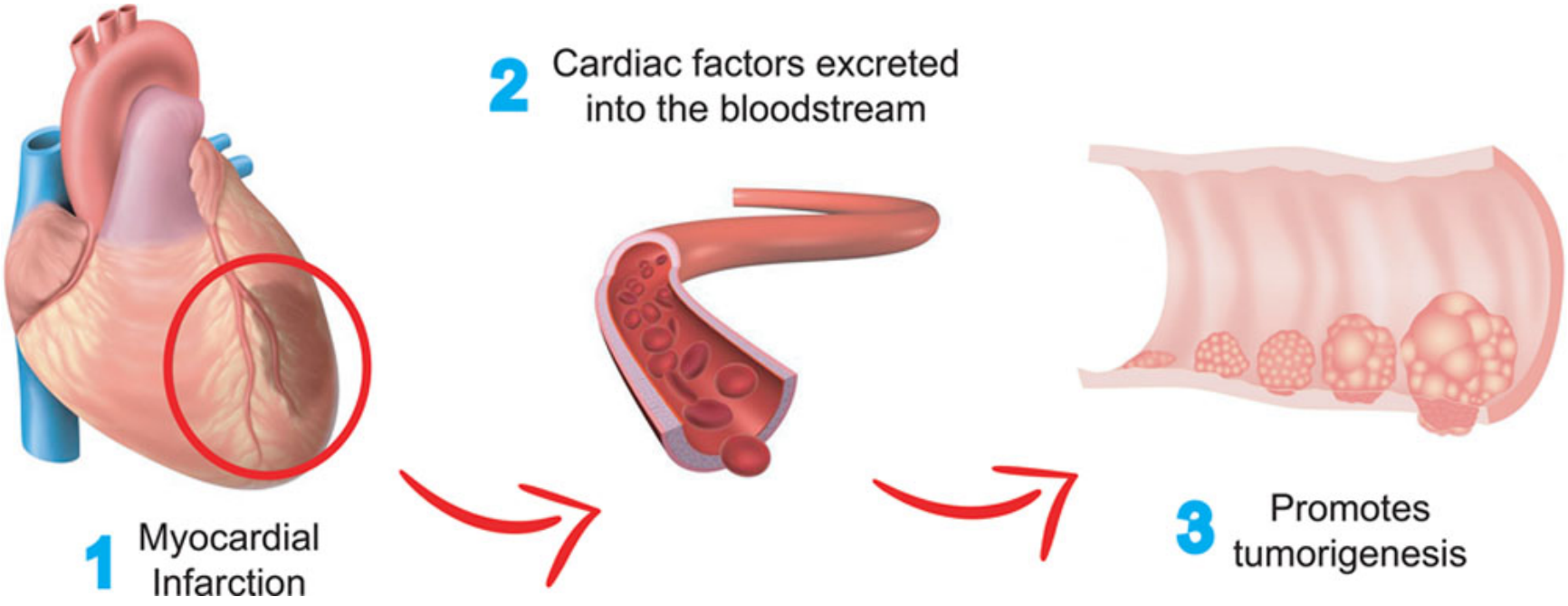
Wouter C. Meijers, MD
Manuel Maglione, MD, PhD
Stephan J.L. Bakker, MD, PhD
Rupert Oberhuber, MD, PhD
Lyanne M. Kieneker, MSc
Steven de Jong, PhD
Bernhard J. Haubner, MD, PhD
Wouter B. Nagengast, MD, PhD
Alexander R. Lyon, MD, PhD
Bert van der Vegt, MD, PhD
Dirk J. van Veldhuisen, MD, PhD
B. Daan Westenbrink, MD, PhD
Peter van der Meer, MD, PhD
Herman H.W. Silljé, PhD
Rudolf A. de Boer, MD, PhD

Key Words: biomarkers ■ heart failure ■ myocardial infarction ■ neoplasms ■ proteomics

Sources of Funding, see page 689

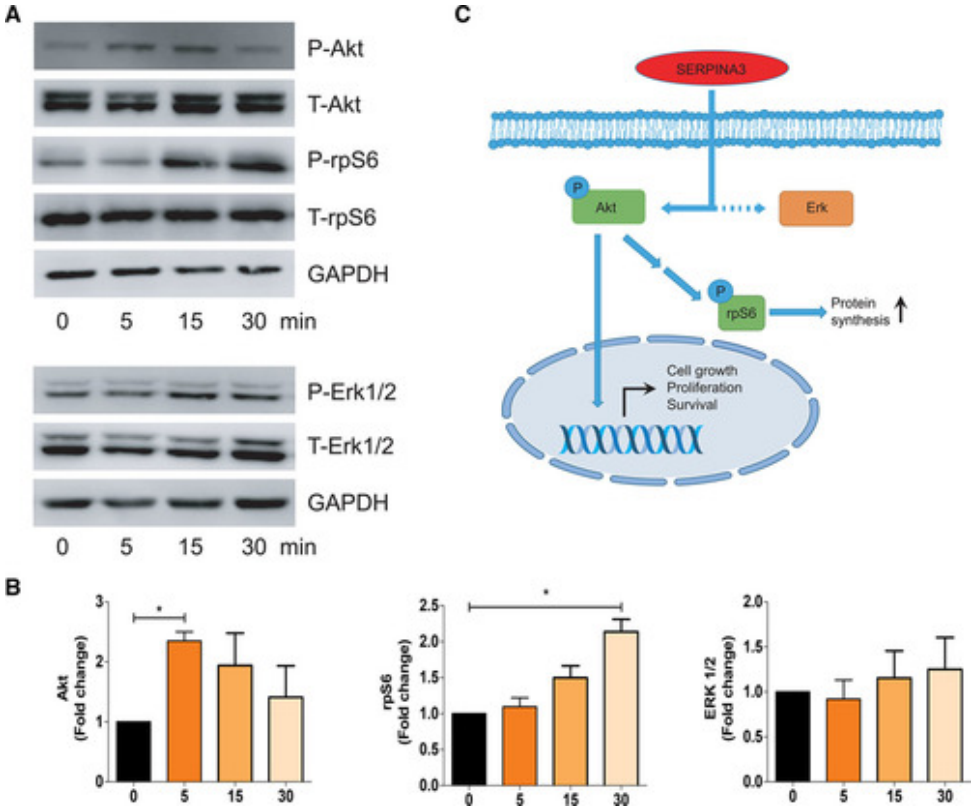
https://www.ahajournals.org/journal/circ

Heart Failure Stimulates Tumor Growth by Circulating Factors



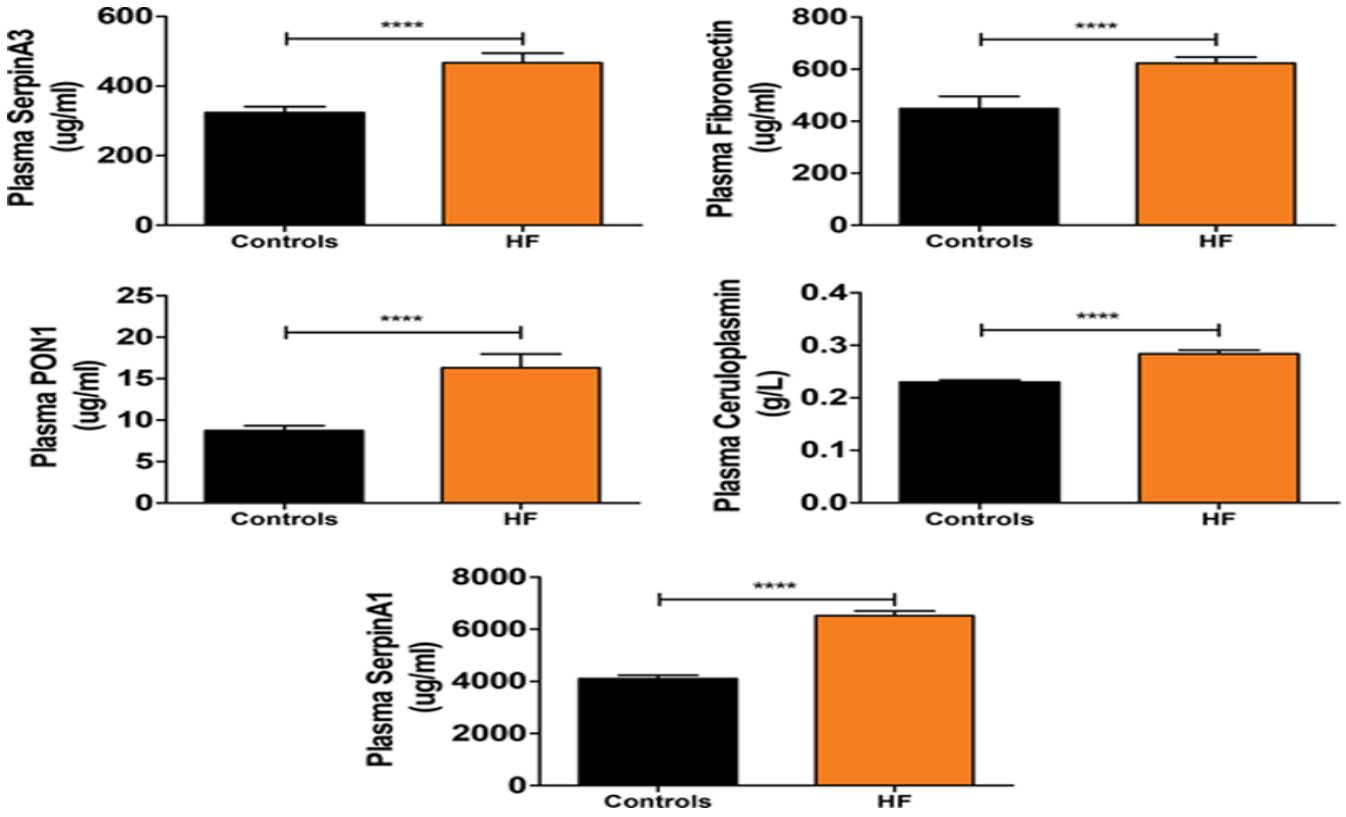
Mejiers et al. Volume: 138, Issue: 7, Pages: 678-691

Growth pathways in colon cells in response to SerpinA3



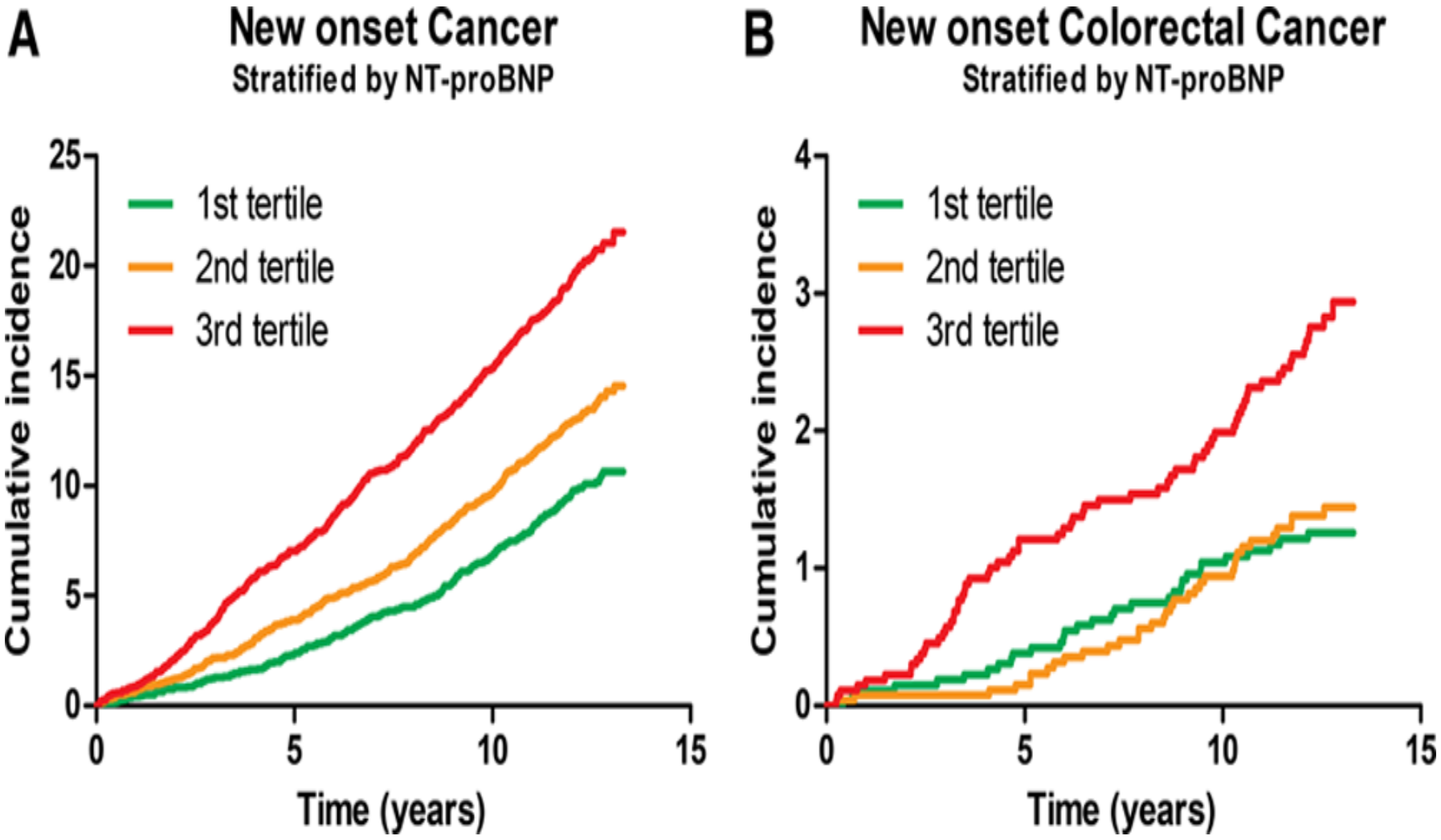
Mejiers et al. Volume: 138, Issue: 7, Pages: 678-691

Plasma levels of candidate tumorogenetic factors in controls and HF patients



Mejiers et al. Volume: 138, Issue: 7, Pages: 678-691

Cumulative incidence of cancer per NT-proBNP level in PREVENT



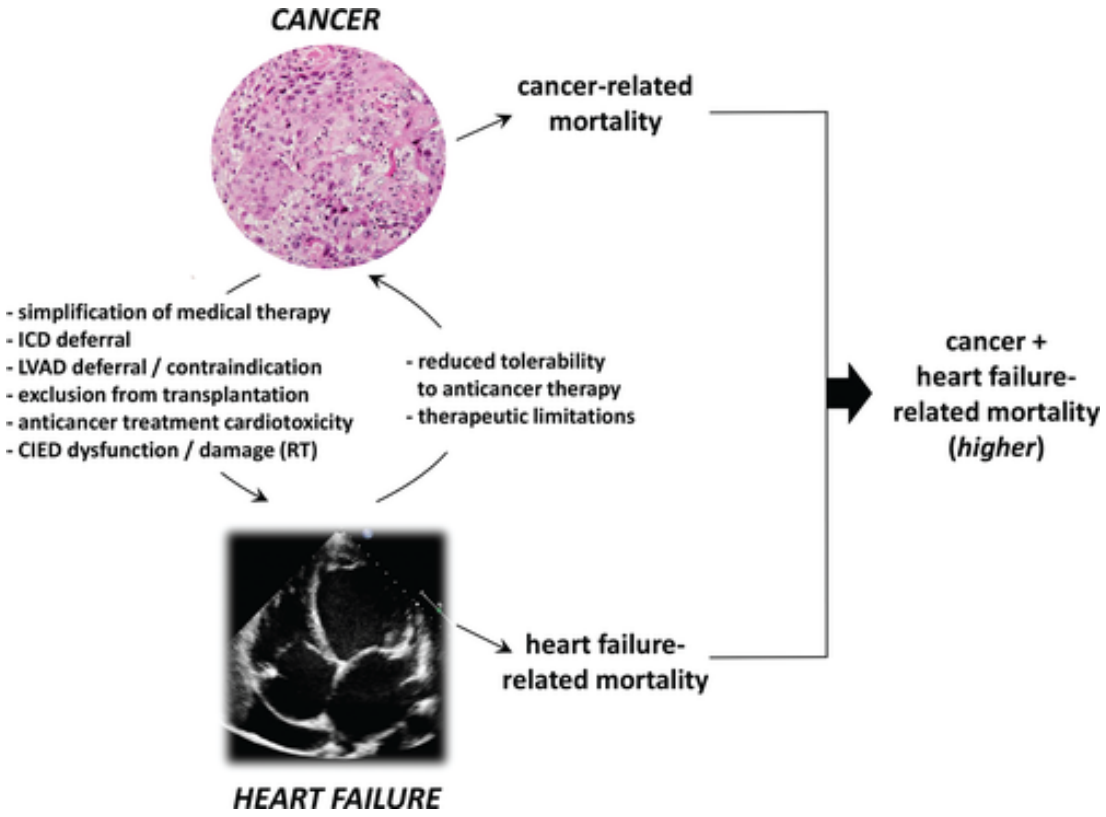
Mejiers et al. Volume: 138, Issue: 7, Pages: 678-691

European Journal of Heart Failure (2018) 20, 879–887
doi:10.1002/ejhf.1165

REVIEW

Cancer diagnosis in patients with heart failure: epidemiology, clinical implications and gaps in knowledge

Pietro Ameri[1†], Marco Canepa[1†], Markus S. Anker[2], Yury Belenkov[3], Jutta Bergler-Klein[4], Alain Cohen-Solal[5], Dimitrios Farmakis[6], Teresa López-Fernández[7], Mitja Lainscak[8], Radek Pudil[9], Frank Ruschitska[10], Petar Seferovic[11], Gerasimos Filippatos[6], Andrew Coats[12], Thomas Suter[13], Stephan Von Haehling[14], Fortunato Ciardiello[15], Rudolf A. de Boer[16], Alexander R. Lyon[17]*, and Carlo G. Tocchetti[18]*, for the Heart Failure Association Cardio-Oncology Study Group of the European Society of Cardiology



European Journal of Heart Failure (2018) 20, 879–887
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REVIEW

Cancer diagnosis in patients with heart failure: epidemiology, clinical implications and gaps in knowledge

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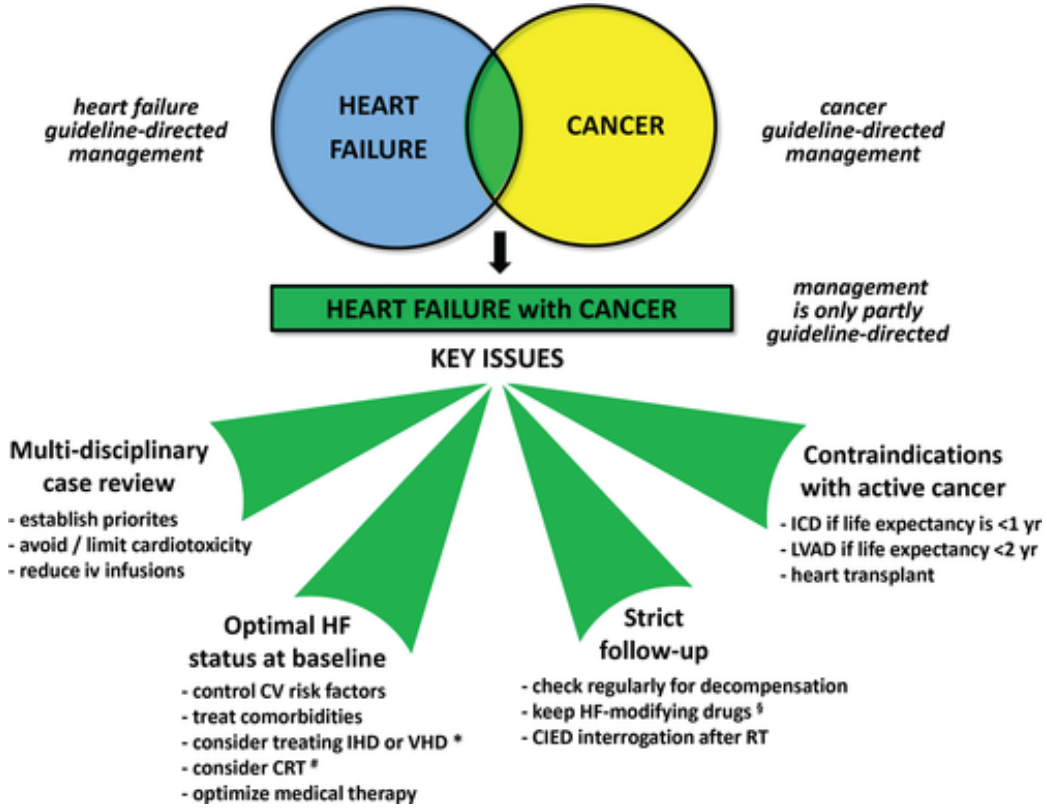

Grazie!