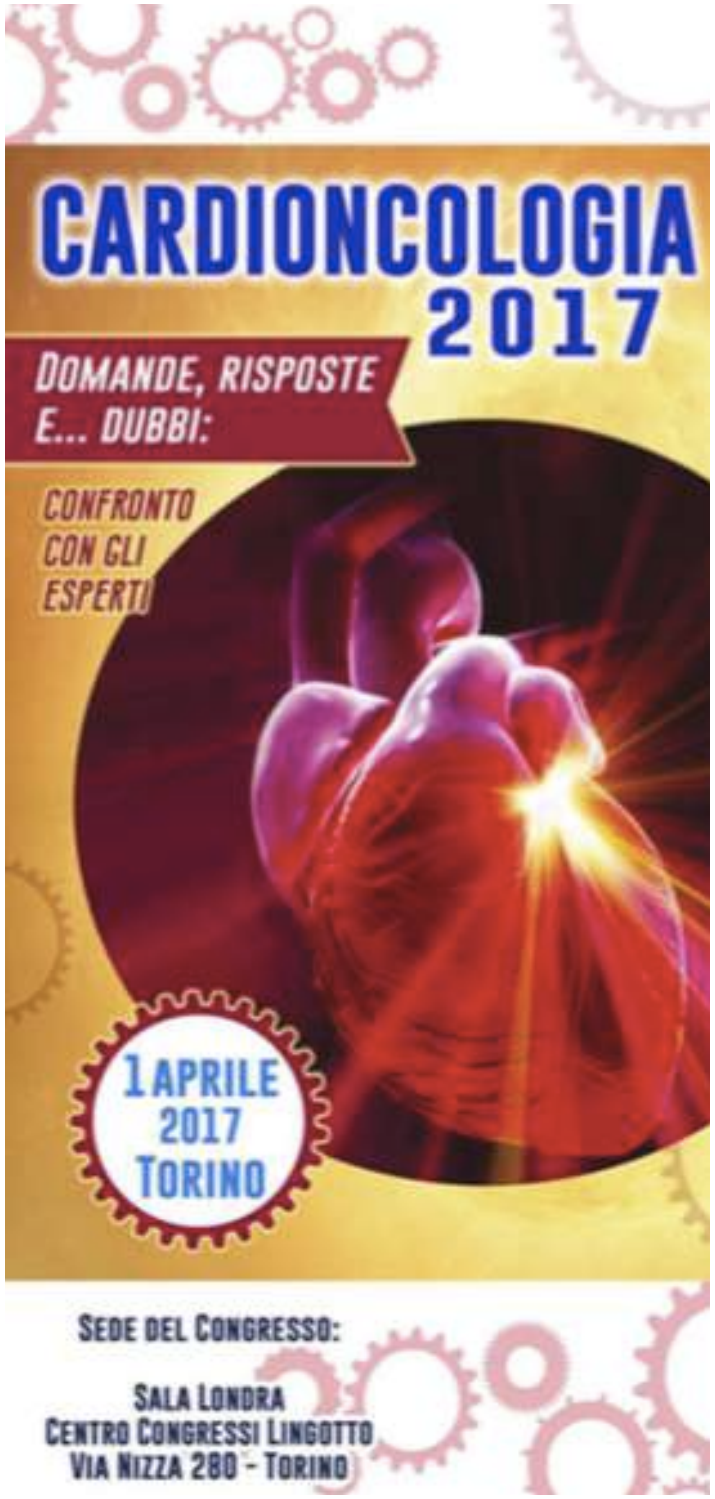


SINDROME METABOLICA, TERAPIE ONCOLOGICHE E MECCANISMI INDIRETTI DI RISCHIO CV NEI CANCER SURVIVORS

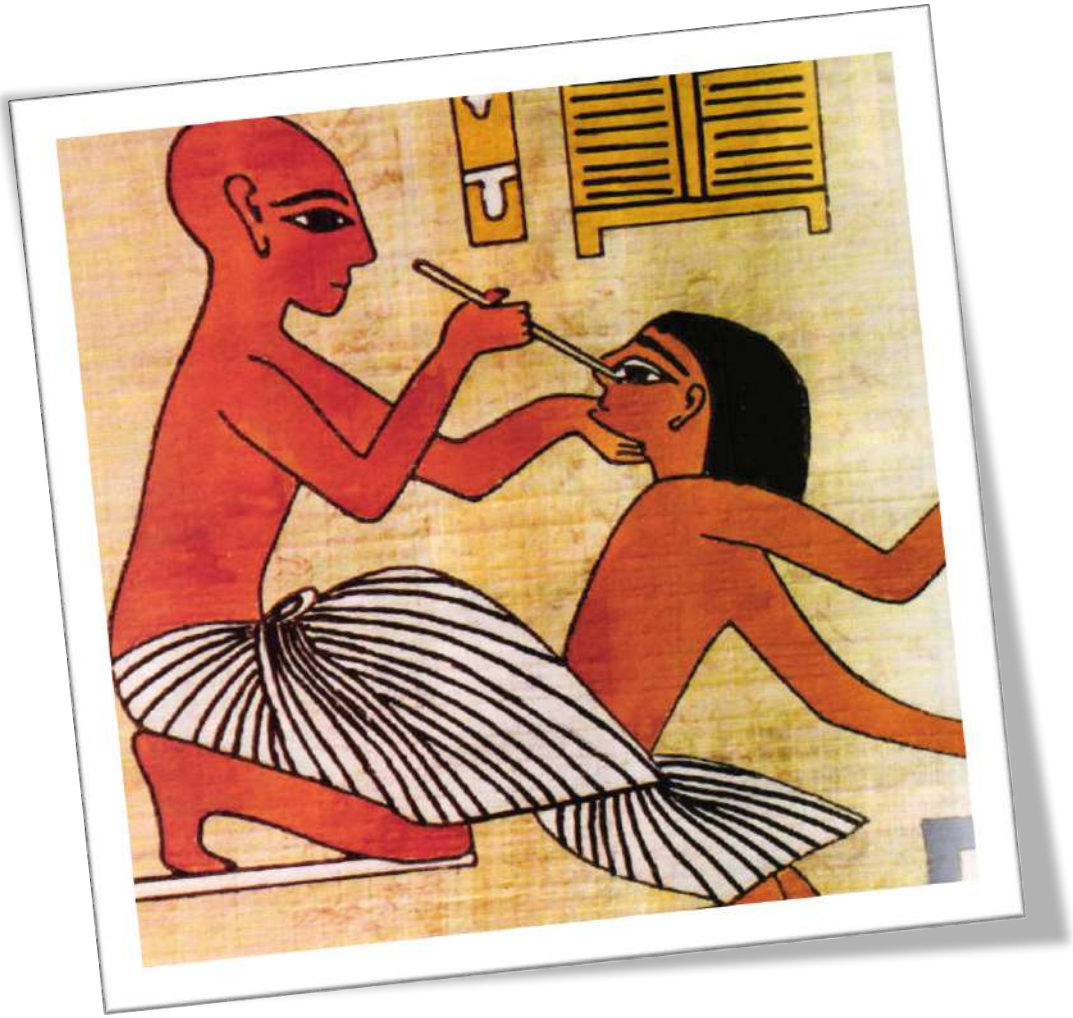
Francesco Felicetti, MD

SSD Unità di Transizione per Neoplasie Curate in Età Pediatrica

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

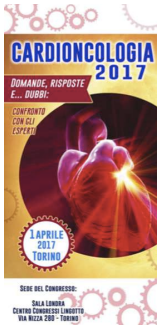

CARDIONCOLOGIA
2017
DOMANDE, RISPOSTE E... DUBBI:
1 APRILE
2017
TORINO


1990?



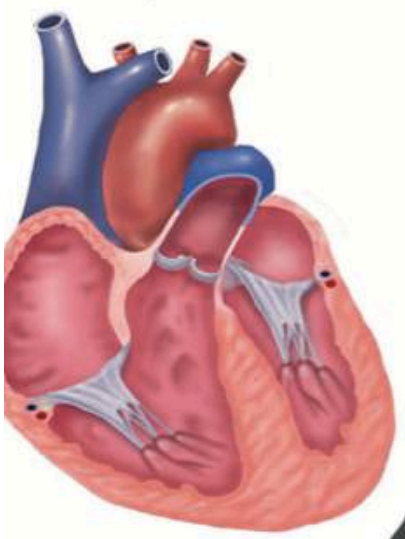

CARDIONCOLOGIA
2017
DOMANDE, RISPOSTE E... DUBBI:
1 APRILE 2017 TORINO


1990?

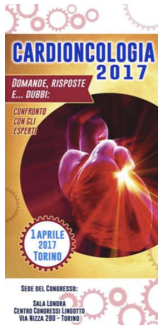


Cardiovascular Health of Patients With Cancer and Cancer Survivors

A Roadmap to the Next Level

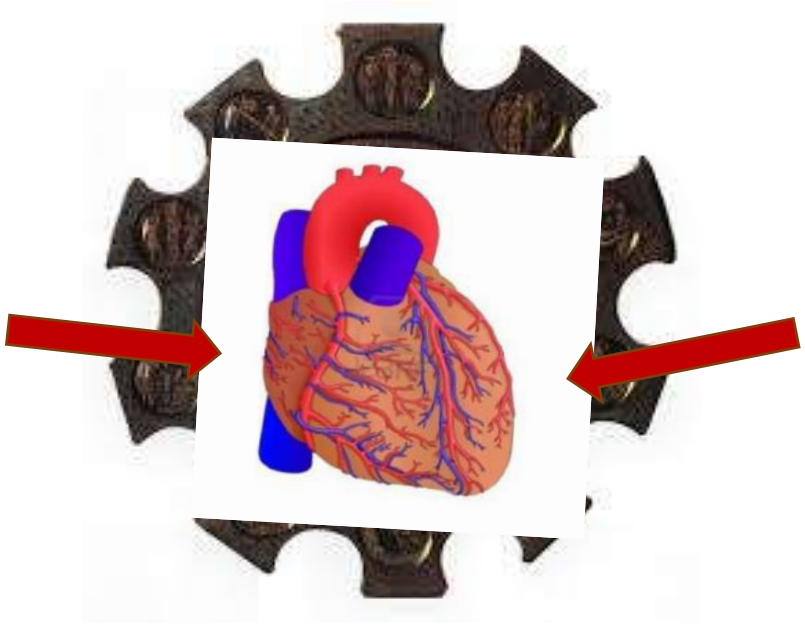


Cancer Prevention	Cancer Diagnosis and Treatment Planning	Cancer Treatment	Cancer Survivorship
CV Risk Factor Management (Primary CV Prevention)	Pre-cancer treatment CV risk stratification Decision about CV risk and management with respect to chosen cancer therapy	On-treatment CV monitoring Preventive CV interventions for high-risk patients	Long-term CV monitoring Preventive CV interventions for high-risk patients



RISCHIO CARDIO

Radioterapia



Antracicline

RISCHIO CARDIOMETABOLICO

Scarsa attività fisica (pat. ortopediche, fatigue...)

Ipertensione

CT , RT

Obesità

Fumo

Radioterapia

Antracicline

GHD
Ipogonadismo
(Ipotiroidismo)

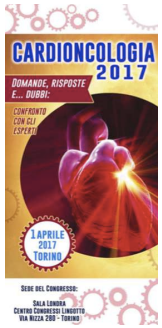
HSCT

CT (steroidi)

Diabete

Dislipidemia

CT (platino der.)



The NEW ENGLAND JOURNAL of MEDICINE

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

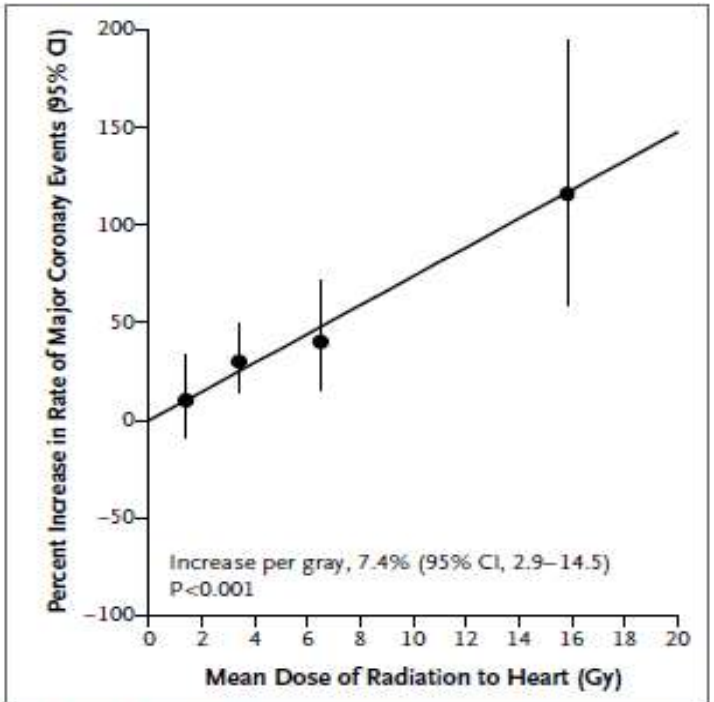


Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

- Studio caso-controllo sul rischio di eventi cardiovascolari maggiori (MACE).

- 2168 donne sottoposte **ad RT per tumore della mammella** fra in 1958 e il 2001 in Svezia e Danimarca (963 casi; 1205 controlli). Dose media di RT erogata al cuore 4.9 Gy (range 0.03 - 27.72).

- L'**incidenza** di MACE **aumenta linearmente con l'aumentare della dose**, con un incremento del 7.4% per gray (95% CI, 2.9 -14.5; P<0.001).

- L'aumento del rischio inizia **a 5 anni dalla RT e si mantiene fino alla terza decade.**

Darby et al, NEJM 2013

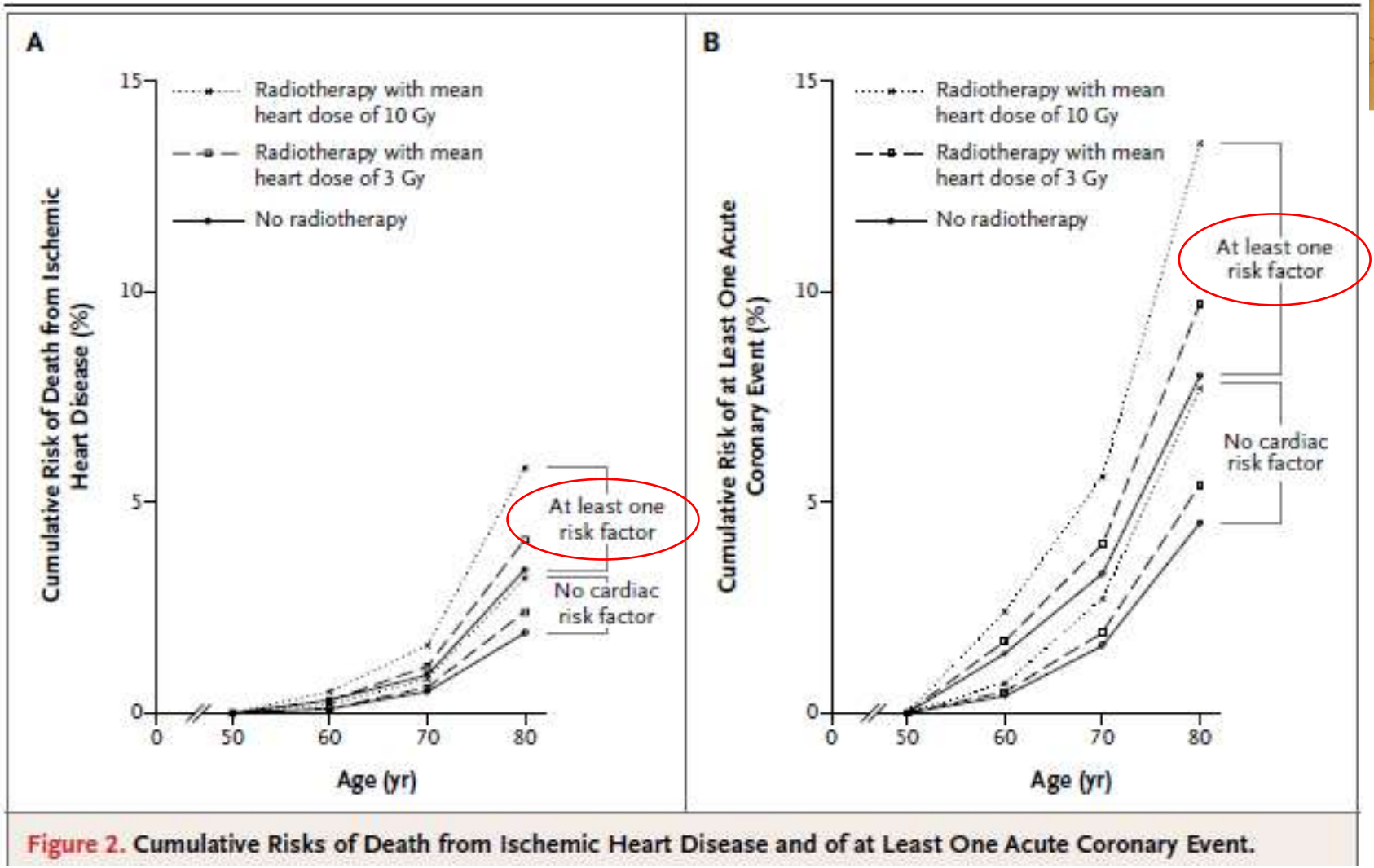


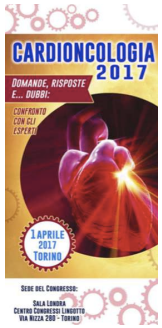
Figure 2. Cumulative Risks of Death from Ischemic Heart Disease and of at Least One Acute Coronary Event.

Darby et al, NEJM 2013

VOLUME 34 · NUMBER 10 · APRIL 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study

Saro H. Armenian, Lanfang Xu, Bonnie Ky, Canlan Sun, Leonardo T. Farol, Sumanta Kumar Pal, Pamela S. Douglas, Smita Bhatia, and Chun Chao

A retrospective cohort study design was used to describe the magnitude of CVD risk in **36,232 2-year survivors of adult-onset cancer** compared with matched (age, sex, and residential ZIP code) noncancer controls (n = 73,545).

Survivors of multiple myeloma (incidence rate ratio [IRR], 1.70; P < .01), carcinoma of the lung/bronchus (IRR, 1.58; P < .01), non-Hodgkin lymphoma (IRR, 1.41; P < .01), and breast cancer (IRR, 1.13; P < .01) had significantly higher CVD risk when compared with noncancer controls. Conversely, prostate cancer survivors had a lower CVD risk (IRR, 0.89; P < .01) compared with controls. **Cancer survivors with two or more CVRFs had the highest risk of CVD** when compared with noncancer controls with less than two CVRFs **(IRR, 1.83 to 2.59; P < .01). Eight-year overall survival was significantly worse among cancer survivors who developed CVD (60%) when compared with cancer survivors without CVD (81%; P < .01).**

SINDROME METABOLICA

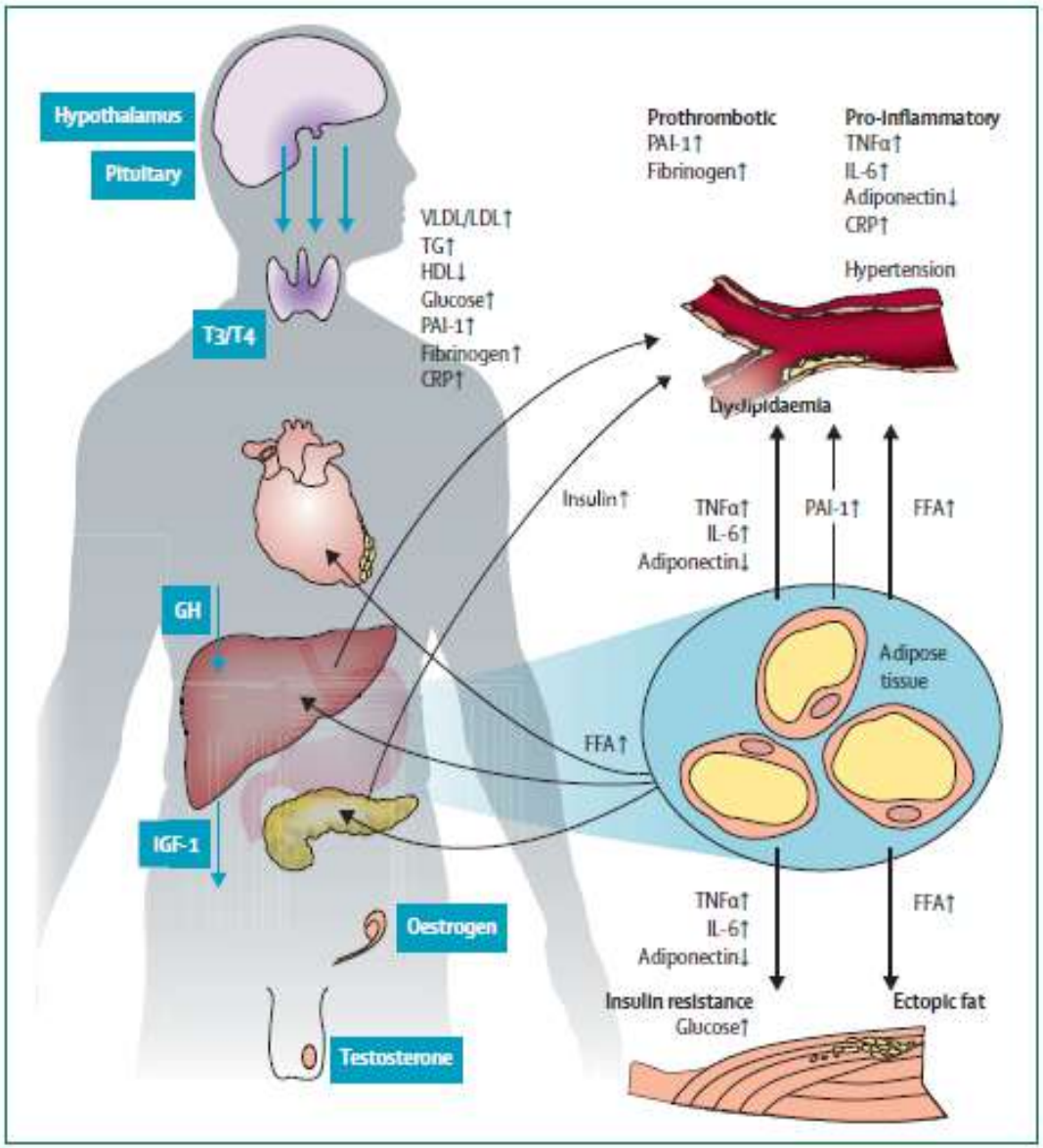
Table 1. Definitions of metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), the International Diabetes Federation (IDF), the American Heart Association (AHA) and the World Health Organization (WHO)

	WHO 1998	*NCEP ATPIII 2005*	*IDF/AHA 2009*
Definition	DM/IFG or IGT or IR plus ⩾2 risk factors	⩾3 risk factors	⩾3 risk factors
Risk factor			
Abdominal obesity	Waist circumference: dependent on ethnicity	Waist circumference: >102 cm (>40 in) in men; >88 cm (>35 in) in women	Waist circumference: population- and country-specific definitions
Triglycerides	⩾150 mg/dL (⩾1.7 mmol/L)	⩾150 mg/dL (⩾1.7 mmol/L) or drug treatment for elevated levels	⩾150 mg/dL (⩾1.7 mmol/L) or drug treatment for elevated levels
HDL cholesterol			
Men	<35 mg/dL (0.9 mmol/L)	<40 mg/dL (<1.0 mmol/L) or drug treatment for reduced levels	<40 mg/dL(<1.0 mmol/L) or drug treatment for reduced levels
Women	<39 mg/dL (1.0 mmol/L)	<50 mg/dL (<1.3 mmol/L) or drug treatment for reduced levels	<50 mg/dL (<1.3 mmol/L) or drug treatment for reduced levels
Blood pressure	⩾140/⩾90 mm Hg	⩾130/⩾85 mm Hg or drug treatment for HTN	⩾130/⩾85 mm Hg or drug treatment for HTN
Fasting glucose	IGT, IFG, or type 2 DM	⩾100 mg/dL (⩾6.11 mmol/L) or drug treatment for DM	⩾100 mg/dL (⩾5.6 mmol/L) or drug treatment for DM
Microalbuminuria	>30 mg albumin per g creatinine		

Abbreviations: DM = diabetes mellitus; HDL = high-density lipoprotein cholesterol; HTN = hypertension; IGT = impaired glucose tolerance (2-h postprandial glucose 140–199 mg/dL (7.8–11.1 mmol/L)); IFG = impaired fasting glucose (fasting glucose 100–126 mg/dL (5.6–7 mmol/L)); IR = insulin resistance.

MetS and cardiovascular disease following HCT
Z DeFilipp *et al*

SINDROME METABOLICA IN *CS: prevalenza*

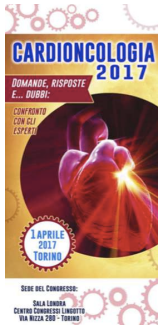


La prevalenza di **sindrome metabolica** è compresa fra il **30 e il 55 %** in alcune categorie di *cancer survivors* (post-trapianto di midollo, neoplasie testicolari).

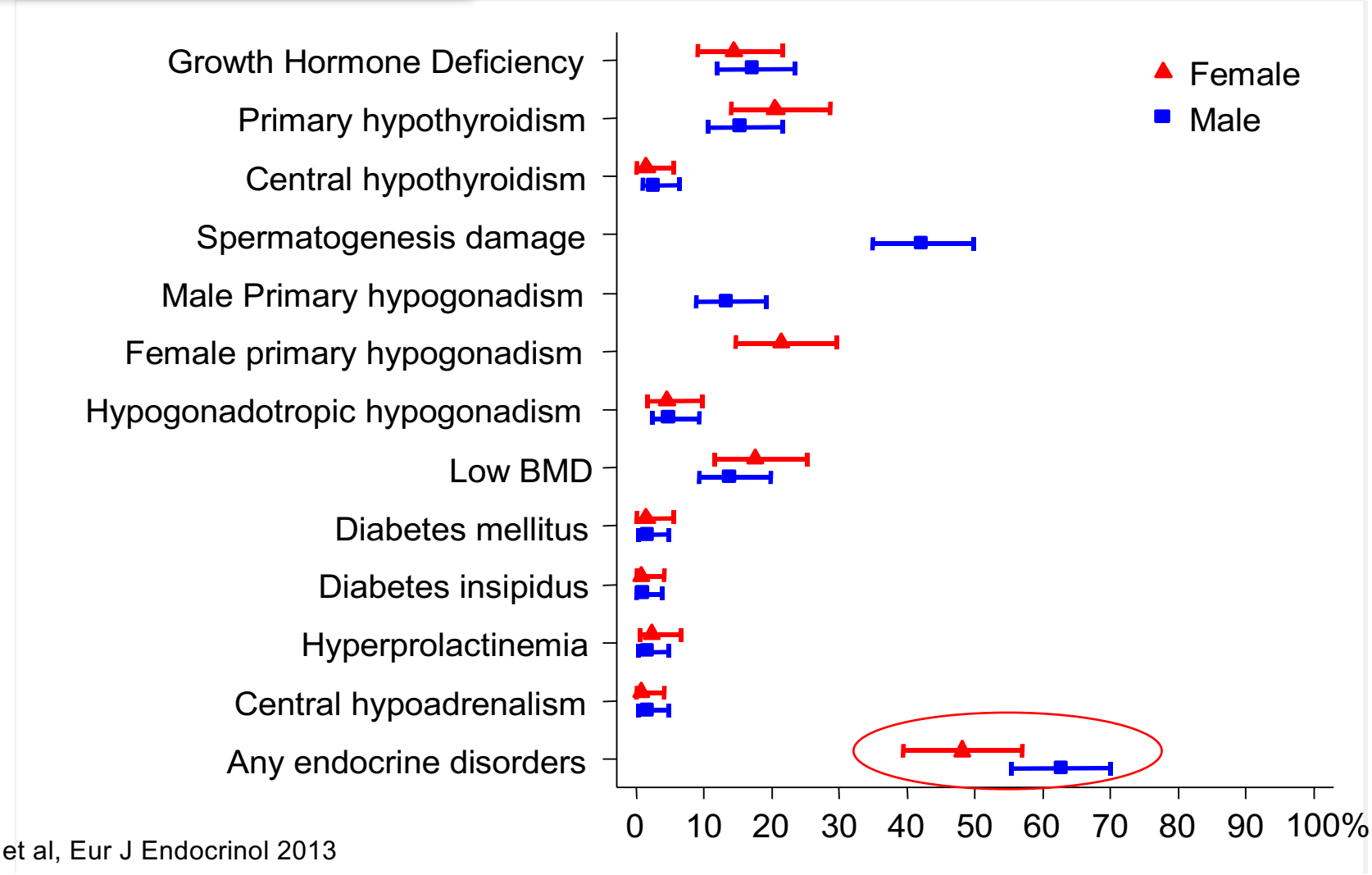
Deficit endocrini (spesso multipli) contribuisco in modo determinante allo sviluppo della sindome metabolica.

De Haas et al, Lancet Oncol 2010

ENDOCRINOPATIE IN CANCER SURVIVORS



330 *childhood cancer survivors*
Follow-up mediano 16 anni



Brignardello et al, Eur J Endocrinol 2013

SINDROME METABOLICA IN *CS: prevalenza*

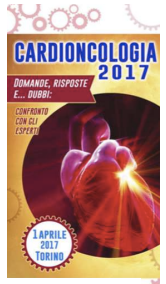
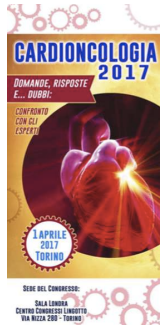


Table 3
Increased risk of cancer treatment-induced metabolic syndrome described in several studies in different patient groups with odds ratios or relative risk compared to controls.

Patient group	Author, journal and year of publication	Number of patients	Control group	Metabolic syndrome OR or RR	95% CI	Follow-up time in years	Treatment type with most impact
Breast cancer survivors (postmenopausal)	Buttros Dde et al. (2013) *Menopause*	104	208 postmenopausal women	OR 1.66	1.04–2.68	Mean 9.4 (SD 4.4) years after diagnosis	NS
Prostate cancer patients treated with ADT	Braga-Basaria et al. (2006) *J Clin Oncol*	20	18 non-ADT and 20 healthy, all age-matched	OR 4.58	1.41–14.86	Still under treatment	Androgen deprivation (hormonal) therapy
Survivors of childhood cancer	Meacham et al. (2010) *Cancer Epidemiol Biomarkers Prev*	8599	2936 siblings	OR 1.3[a]	0.9–1.9	5 years or more after diagnosis, not further specified	Radiotherapy, especially total body irradiation and to the chest
Survivors of childhood acute myeloid leukaemia	Blijdorp et al. (2013) *Leukemia research*	12 CT and 9 SCT[b]	60 siblings, friends or neighbours with same sex and age range of 5 yr related to survivor	OR 1.31 and OR 24.1	NS	Median 21.6 (Range 9.1–30.7) and 19.0 (Range 11.6-30.0)	Stem cell transplantation
Survivors of haematologic malignancies	Li et al. (2015) *Med Oncol*[c]	191	2406 healthy controls	OR 2.37	1.70–3.31	NS	Hematologic stem cell transplantation
Survivors of acute lymphoblastic leukaemia	Nottage et al. (2014) *Br J Haematol*	784	777 age, sex and race-matched controls	RR 1.43	1.22–1.69	26.1 (11–45.3)	Cranial radiotherapy
Hereditary breast and/or ovarian cancer patient	Michelsen et al. (2009) *Eur J Cancer*	326	679 age adjusted, general population with no removal of uterus/ovaries	OR 2.46	1.63–3.73	Mean 6.5 (SD 4.4) after surgery	Surgery
Testicular cancer survivors	Willemse et al. (2013) Br J Cancer	251	360 healthy, age-adjusted	OR 1.9	1.1–3.2	Mean 7.8 (SD 7.4) after treatment	Combination chemotherapy
	Haugnes et al. (2007) *Ann Oncol*	1135	1150 healthy controls < 60 year, without testosterone suppletion	OR 2.1[d]	1.3–3.4	Median 9.4 (Range 5–20)[e]	Combination chemotherapy with cumulative cisplatin dose > 850 mg

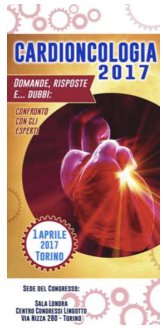
SINDROME METABOLICA IN *CS: fisiopatologia*



N.L. Westerink et al. / Critical Reviews in Oncology/Hematology 108 (2016) 128–136

Specified treatment	Mechanism	Associated with
Brain surgery with damage to pituitary and hypothalamus.	Hormonal disturbance: deficiency of growth hormone, thyroidtropin, gonadotropin, adenocorticotropin.	Obesity
Orchiectomy	Hypogonadism	CTIMetS
Risk-reducing salpingo-oophorectomy	Hypogonadism	CTIMetS
Cranial radiotherapy	Hormonal disturbance: deficiency of growth hormone by damage to the hypothalamus-pituitary axis	Obesity, dyslipidaemia, insulin resistance
Radiation thyroid gland region	Hypothyroidism: lower basal metabolism	Obesity
Total body, chest or abdomen	Multiple mechanisms with damage to one or more organs	Hypertension, dyslipidaemia, insulin resistance
Cisplatin	Possibly damage to vascular endothelium, possibly through damage to mitochondria and production of ROS	CTIMetS, in particular obesity and dyslipidaemia
Alkylators, anthracyclines, camptothecins, epipodophyllotoxins	Possibly through damage to mitochondria and production of ROS	Insulin resistance
Antimetabolites	Impaired lipid transport	Insulin resistance
In breast cancer patients	Sarcopenic obesity	CTIMetS, in particular weight gain
Androgen-deprivation therapy	Hypogonadism	CTIMetS, in particular dyslipidaemia and insulin resistance
Anti-estrogenic therapy	Hormonal disturbance, possibly by inhibition of aromatase and less production of NO with less protective effect on ischemia	Cardiovascular risk increase, dyslipidaemia
Muscle atrophy and inactivity	Decreased insulin-stimulated glucose uptake	Insulin resistance, obesity
Dietary restriction and antibiotics	Disruption and damage to the intestinal flora with reduced dietary uptake and insulin secretion	Insulin resistance

DISLIPIDEMIA IN CS



- **Profilo lipidico "aterogeno"** è stato evidenziato in molti studi sui childood CS (tumori cerebrali, LLA), anche **in assenza di obesità** (*Steimberger J et al 2012*).
- Alterazioni del metabolismo lipidico sono state dimostrate nei *survivors* di **tumori testicolari** sottoposti a CT con derivati del platino (*Willemse PM et al 2014*).
- Pazienti affette da carcinoma mammario e trattate con **inibitori dell'aromatasi** presentano modifiche del profilo lipidico in senso aterogeno (*Redig AJ et al 2010*)
- Patogenesi complessa e non del tutto chiara.

Fattori di rischio:

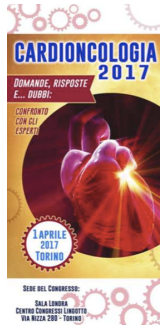
irradiazione encefalica (danno ipotalamico?)

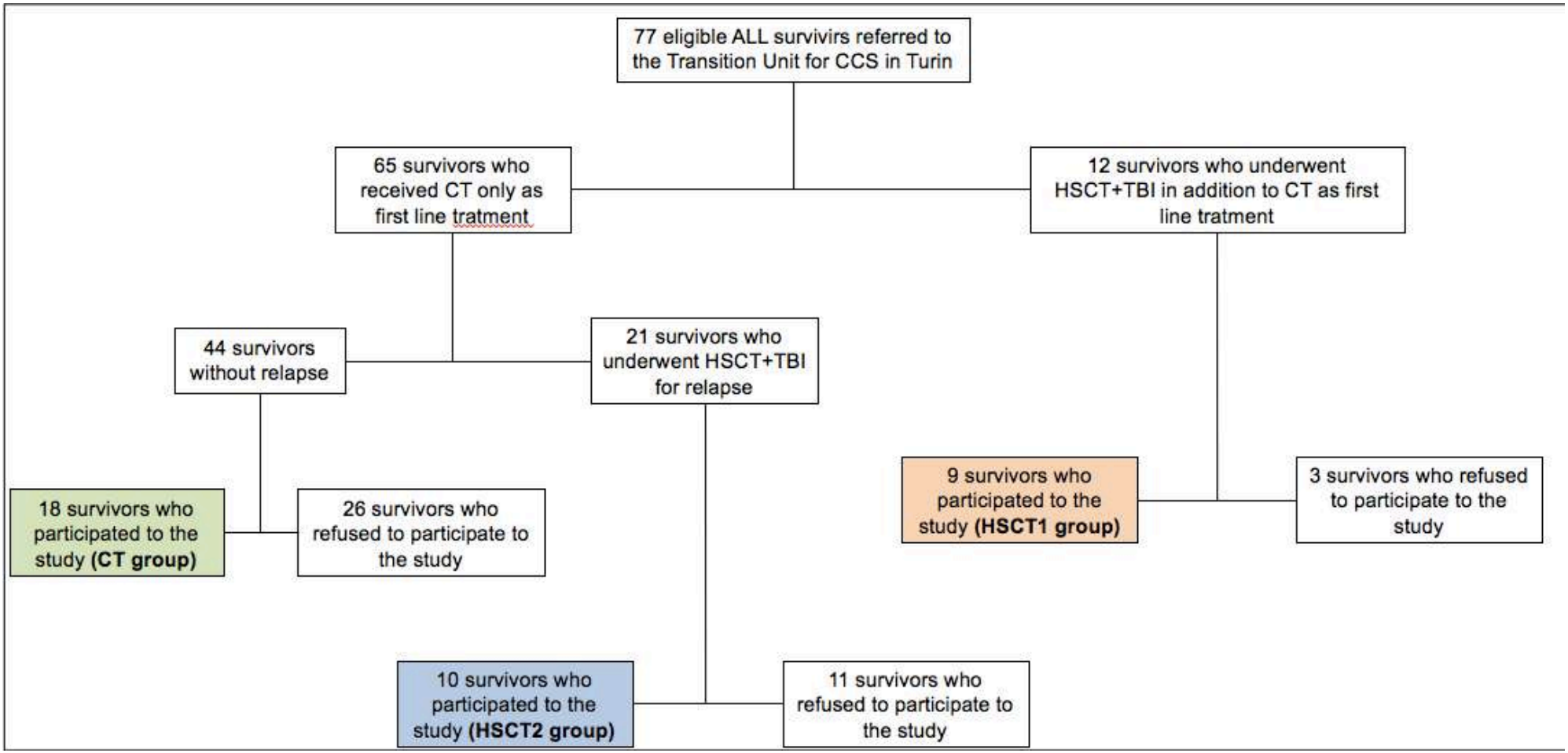
CT con derivati del platino (*survivors* ca testicolari)

scarsa attività fisica (*CNS cancer survivors*)

alterazioni endocrine (GHD, **ipogonadismo**, ipotiroidismo)

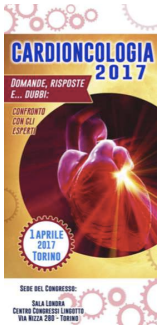
LIPID PROFILE AND CHRONIC INFLAMMATION IN ADULT SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA





Felicetti F, Brignardello E, *submitted*

LIPID PROFILE AND CHRONIC INFLAMMATION IN ADULT SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA



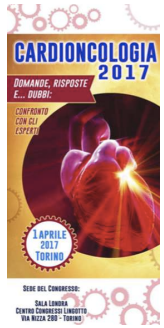
		Crude effect			Adjusted effect		
		Effect	95% CI	p-value	Effect	95% CI	p-value
Total cholesterol (mg/dL)	HSCT1	42.61	[17.07,68.16]	0.002	38.75	[7.99,69.51]	0.015
	HSCT2	38.23	[13.55,62.91]	0.003	31.76	[5.95,57.57]	0.018
HDL (mg/dL)	HSCT1	-5.11	[-14.81,4.59]	0.292	2.10	[-9.05,13.25]	0.703
	HSCT2	-7.99	[-17.36,1.38]	0.092	-5.55	[-14.91,3.80]	0.235
HDL 2(mg/dL)	HSCT1	-8.33	[-15.90,-0.77]	0.032	-5.08	[-14.28,4.13]	0.269
	HSCT2	-5.38	[-12.69,1.93]	0.144	-3.60	[-11.32,4.12]	0.349
HDL 3 (mg/dL)	HSCT1	3.11	[-2.46,8.68]	0.264	7.18	[0.76,13.60]	0.030
Apolipoprotein A1 (mg/dL)	HSCT2	-3.56	[-18.59,11.48]	0.634	-0.22	[-15.50,15.06]	0.977
Apolipoprotein B (mg/dL)	HSCT1	30.06	[11.20,48.91]	0.003	21.81	[-0.70,44.32]	0.057
	HSCT2	29.80	[11.59,48.01]	0.002	24.33	[5.44,43.22]	0.013
Apolipoprotein B / Apolipoprotein A1 [2]	HSCT1	1.30	[1.04,1.62]	0.023	1.15	[0.89,1.48]	0.274
	HSCT2	1.40	[1.13,1.73]	0.003	1.29	[1.04,1.60]	0.021
sd-LDL (mg/dL) [2] *	HSCT1	1.75	[1.18,2.58]	0.007	1.49	[0.97,2.30]	0.066
	HSCT2	2.08	[1.41,3.08]	0.001	1.77	[1.21,2.59]	0.004
CRP (mg/L) [2] **	HSCT1	1.32	[0.53,3.30]	0.539	2.00	[0.65,6.18]	0.220
	HSCT2	3.18	[1.27,7.92]	0.015	3.57	[1.36,9.38]	0.012
IL-6 (pg/ml) [2] ***	HSCT1	2.09	[0.73,5.98]	0.161	1.42	[0.33,6.04]	0.622
	HSCT2	5.17	[1.81,14.79]	0.003	5.41	[1.69,17.28]	0.006

Our data suggest a relationship among the burden of previous anticancer treatments, chronic inflammation and serum atherogenicity. Should this hypothesis be confirmed, serum inflammatory markers might become a useful tool to identify ALL survivors at higher risk of CVD.

[1] adjusted by sex, age at study time, hypertension and smoking
[2] Log-transformed variable (the effect was expressed on natural scale as ratio) .

Felicetti F, Brignardello E, *submitted*

IPERTENSIONE ARTERIOSA IN CS



• Incidenza di ipertensione arteriosa del **9% circa nei *CCS*** (età media 32 anni), **doppia** rispetto a quella dei fratelli sani (*Meacham et al, 2010*).

• Nei soggetti sottoposti a **trapianto allogenico di cellule staminali** in età evolutiva, circa **il 36 %** è affetto da ipertensione arteriosa **a 30 anni** dalle terapie (*Hoffmeister et al, 2010*).

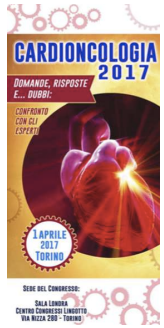
Fattori di rischio:

Cisplatino (neoplasie testicolari)

Metotrexate, Ifosfamide (danno renale)

RT addominale, TBI (stenosi arterie renali)

HSCT (danno renale da GVHD, alchilanti)



OBESITÀ IN CS

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Risk Factors for Obesity in Adult Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

- **9.284 5-years *CCS*** contattati attraverso questionari postali.
- Fattori di rischio per sviluppo di obesità: **irradiazione in regione ipotalamo-ipofisaria**, **giovane età alla diagnosi, alterazioni dell'SF 36.**

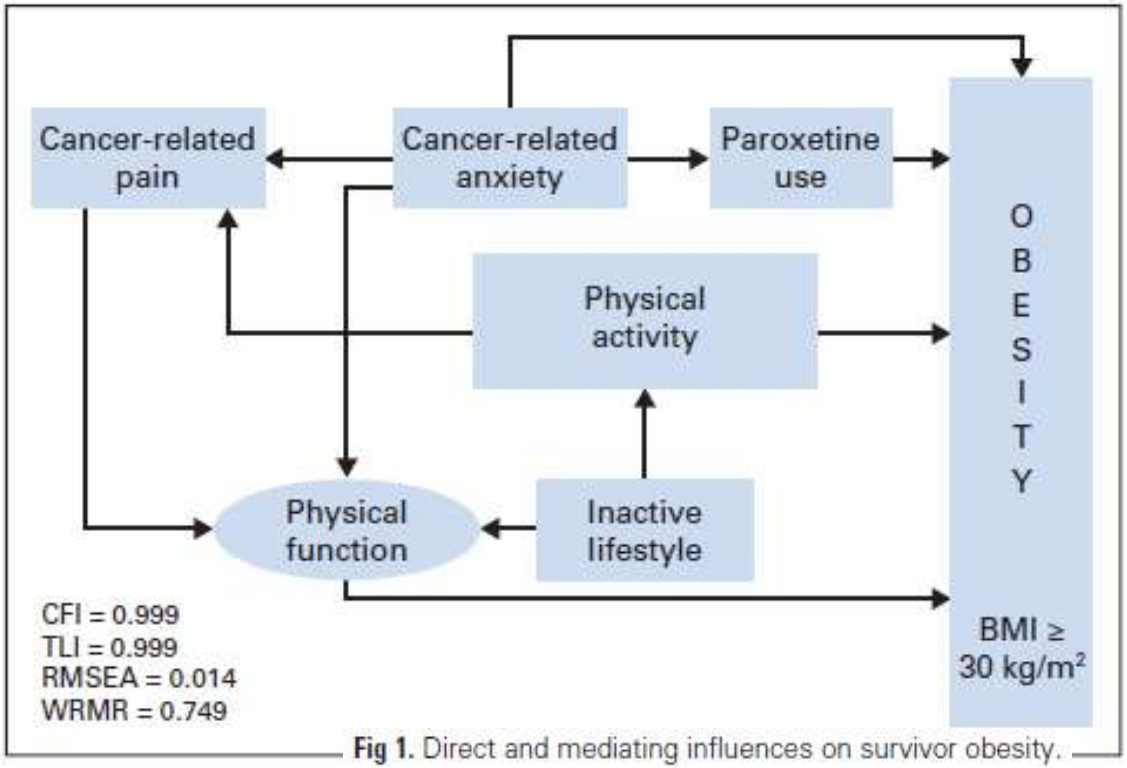
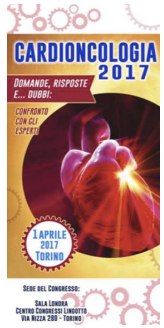


Fig 1. Direct and mediating influences on survivor obesity.

Green DM et al, J Clin Oncol 2012

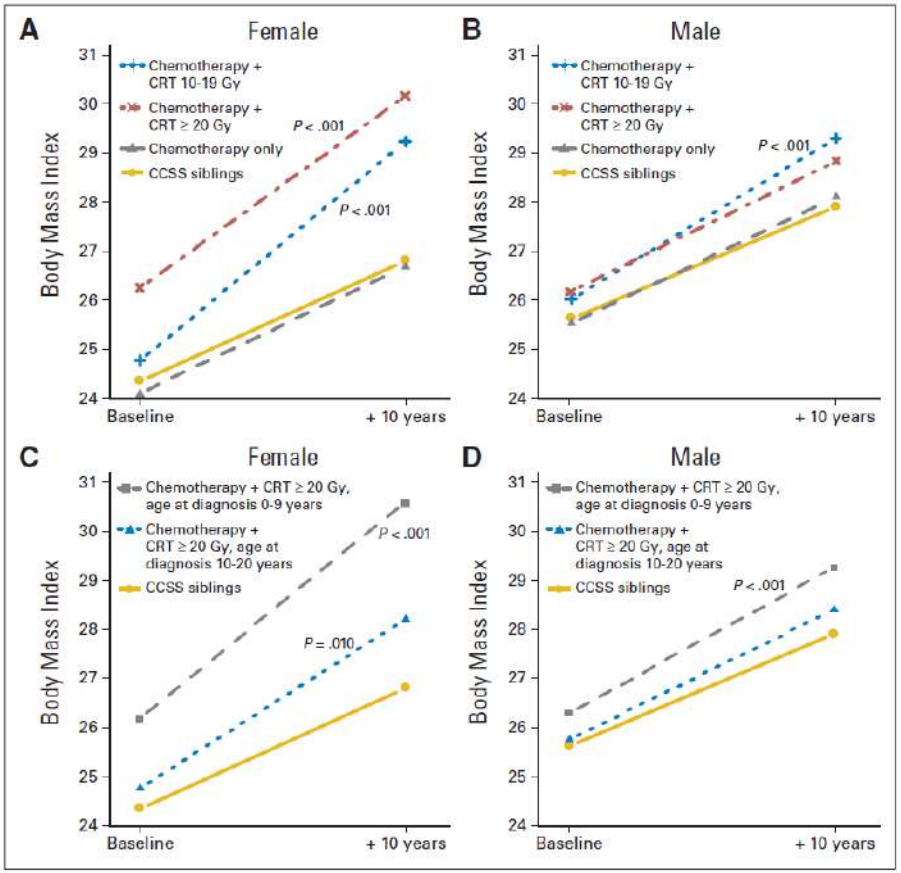
OBESITÀ IN CS



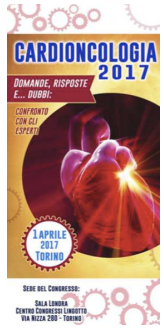
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Longitudinal Changes in Obesity and Body Mass Index Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report From the Childhood Cancer Survivor Study

- **1451 *ALL 5-years survivors*** con diagnosi fra il 1970 e il 1986 (età media 32 anni).
- 2167 controlli sani (fratelli).
- Fattori di rischio per obesità: **RT encefalica ed età più giovane alla diagnosi.**



Garmey EG et al J Clin Oncol 2008



OBESITÀ IN CS

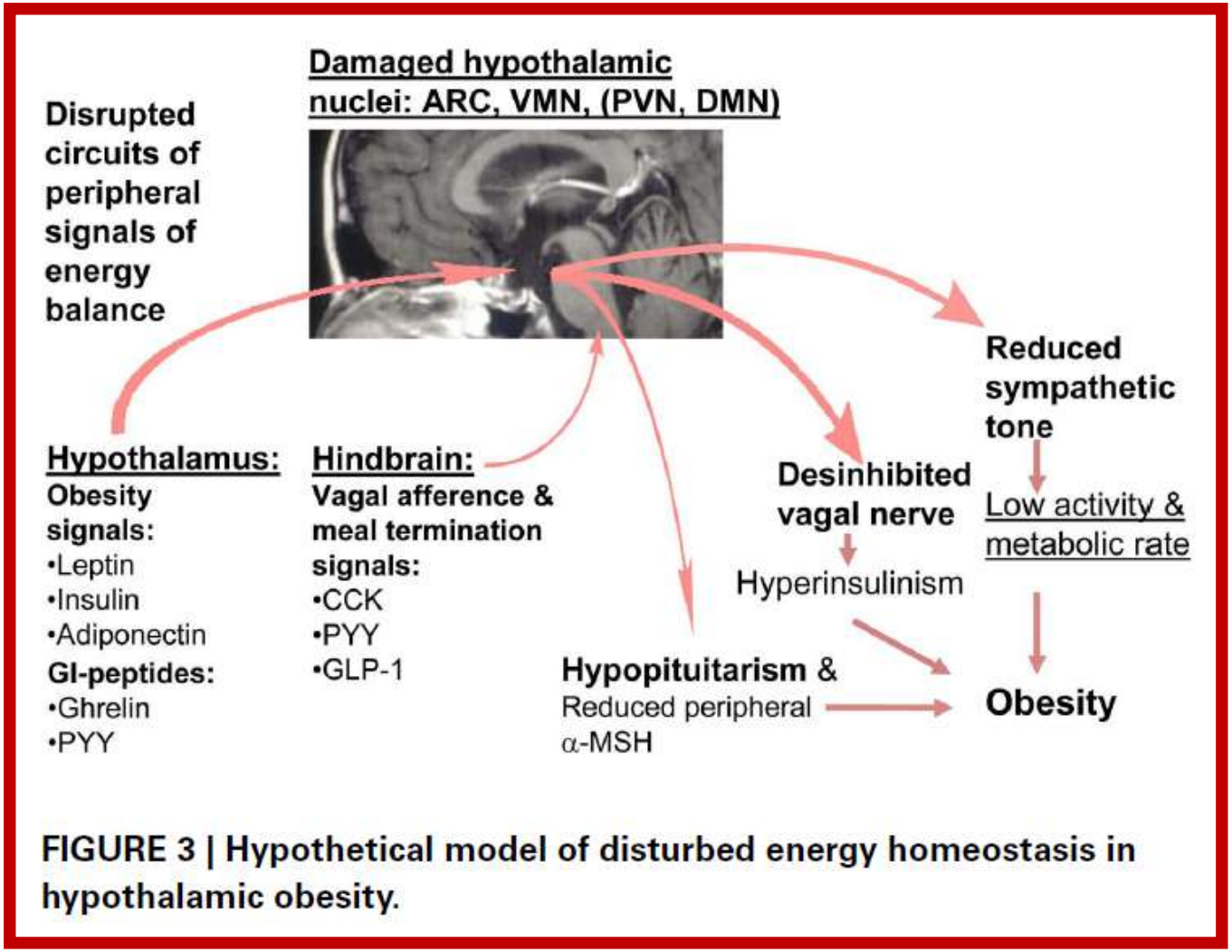
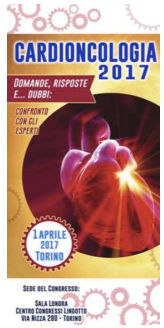


FIGURE 3 | Hypothetical model of disturbed energy homeostasis in hypothalamic obesity.

Garmey EG et al J Clin Oncol 2008



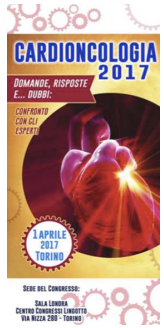
A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor–positive breast cancer prognosis

We utilized **a large prospective pooling study** to evaluate the associations of lifestyle factors with late recurrence and all-cause mortality among **6,295 5- year ER1 Stage I–III breast cancer survivors**. Pooled and harmonized data were available on clinical factors and lifestyle factors (pre- to post-diagnosis weight change, body mass index (BMI) (kg/m$_2$), recreational physical activity, alcohol intake and smoking history), **measured on average 2.1 years after diagnosis**.

Pre- to post-diagnosis weight change, *n* (%)				
Stable (±5%)	910 (43.5)	730 (47.9)	1,760 (60.8)	3,400 (52.2)
Weight loss of 5–10%	172 (8.2)	153 (10.0)	317 (10.9)	642 (9.9)
Weight loss of ≥10%	94 (4.5)	106 (7.0)	174 (6.0)	374 (5.7)
Weight gain of 5–10%	370 (17.7)	254 (16.7)	435 (15.0)	1,059 (16.3)
Weight gain of ≥10%	546 (26.1)	282 (18.5)	211 (7.3)	1,039 (16.0)

A U-shaped association was observed for late all-cause mortality and BMI using updated weight (1.42 (1.15–1.74) and 1.40 (1.09–1.81), <21.5 and 35, respectively). Smoking was associated with increased risk of late outcomes.

Int. J. Cancer: **138**, 2088–2097 (2016)



DIABETE MELLITO IN CS

- Il **rischio** di sviluppare **diabete mellito** nei *childhood cancer survivors* è circa il **doppio** rispetto ai fratelli sani (*Meacham et al, 2009*)

- In una coorte di 85 pazienti (età media alla diagnosi oncologica: 37 anni) sottoposti a HSCT/TBI per leucemia/linfoma**, il 35% aveva sviluppato insulino-resistenza dopo 9 anni di follow-up** (*Annaloro et al, 2009*).

Fattori di rischio:

RT addominale, TBI (danno pancreatico)

Deficit di GH (post-RT encefalica)

Ipogonadismo (alchilanti, derivati del platino)

Terapia steroidea ad alte dosi

CONTROLLI CLINICI: LE 5 W

Who?

Tutti i *cancer survivors*, in modo particolare quelli sottoposti a trattamenti ad alto rischio di late-effects.

When?

Almeno una volta all'anno, più frequentemente se problemi clinici attivi.

Where?

- **Medico di medicina generale**
- **Centro oncologico curante**
- ***Survivor clinics***
- Altri specialisti

What?

- **Anamnesi patologica prossima**
- **Esame obiettivo** (generale e cardiologico)

CONTROLLI CLINICI: LE 5 W

Who?

Tutti i *cancer survivors*, in modo particolare quelli so
ad alto rischio di lat

When?

Almeno una volta all'anno, più
roblemi clinici attivi.

Why?

-Promuovere **misure di prevenzione (stop fumo, attività fisica, …).**

- **Identificare** segni e sintomi in fase **precoce.**

- Pianificare gli **esami di screening** appropriati.

W

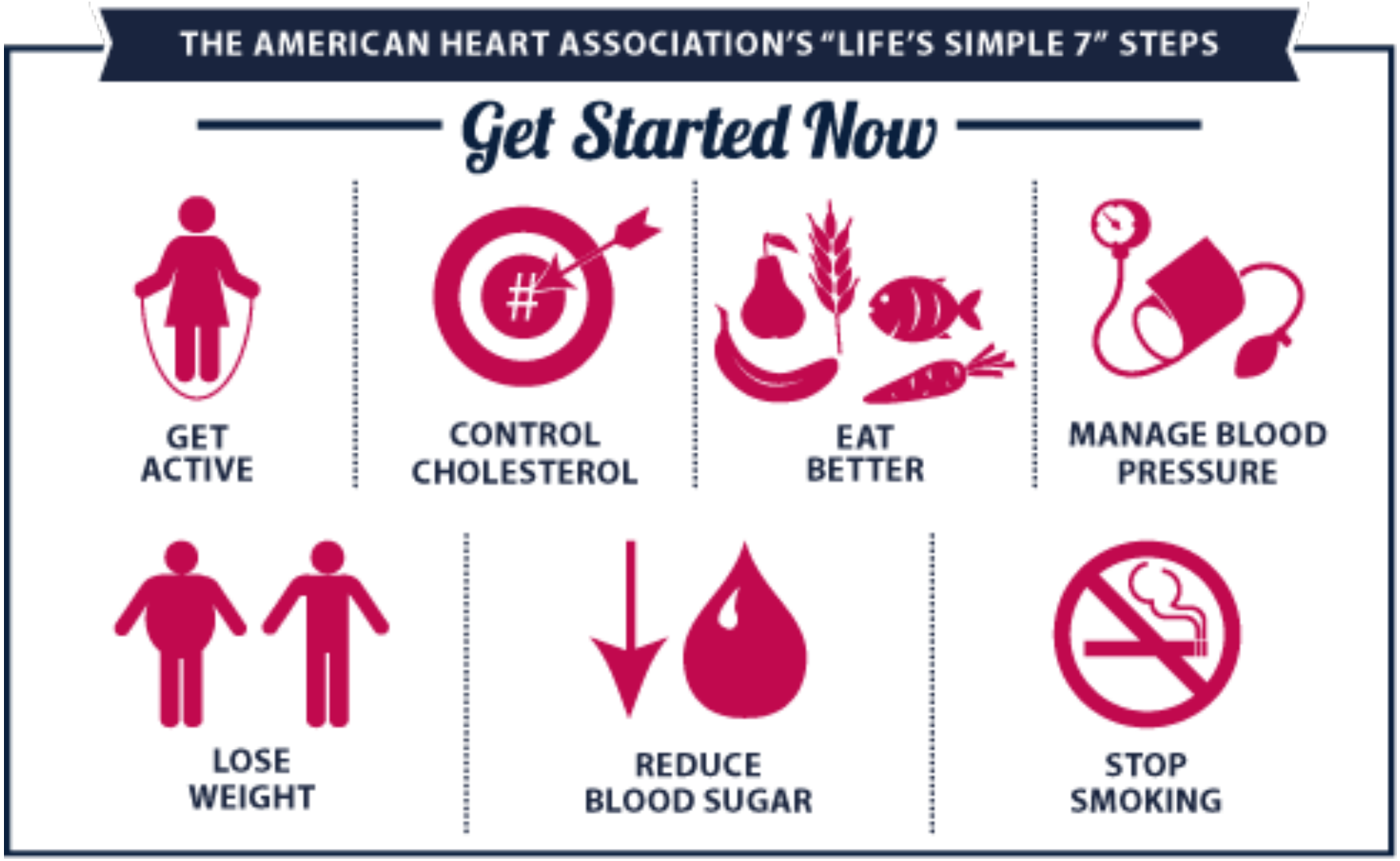
- **Medico di medi**
- **Centro oncologico curante**
- ***Survivor clinics***
- Altri specialisti

hat?

ogica prossima

- **Esame obiettivo** (generale e cardiologico)

THE AHA "LIFE'S SIMPLE 7"



Original Article

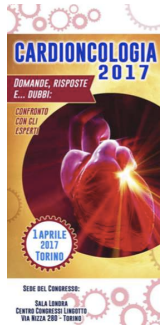
Lifestyle and Metabolic Syndrome in Adult Survivors of Childhood Cancer

A Report From the St. Jude Lifetime Cohort Study

Webb A. Smith, MS[1]; Chenghong Li, MS[2]; Kerri A. Nottage, MD[3]; Daniel A. Mulrooney, MD[1,4]; Gregory T. Armstrong, MD[1]; Jennifer Q. Lanctot, PhD[1]; Wassim Chemaitilly, MD[5]; Joseph H. Laver, MD[4]; Deo Kumar Srivastava, PhD[2]; Leslie L. Robison, PhD[1]; Melissa M. Hudson, MD[1,4]; and Kirsten K. Ness, PhD[1]

BACKGROUND: Childhood cancer survivors (CCS) are at an increased risk of developing metabolic syndrome (MetSyn), which may be reduced with lifestyle modifications. The purpose of this investigation was to characterize lifestyle habits and associations with MetSyn among CCS. **METHODS:** CCS who were ≥10 years from diagnosis, aged >18 years, and participating in the St. Jude Lifetime Cohort Study completed medical and laboratory tests and a food frequency questionnaire. The Third Report of the National Cholesterol Education Program Adult Treatment Panel criteria were used to classify participants with MetSyn. Anthropometric, food frequency questionnaire, and self-reported physical activity data were used to characterize lifestyle habits according to World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations. Those who met ≥4 of 7 recommendations were classified as having followed guidelines. Sex-stratified log-binomial regression models were used to evaluate associations between dietary/lifestyle habits and MetSyn, adjusted for age, age at cancer diagnosis, receipt of cranial radiotherapy, education, and household income. **RESULTS:** Among 1598 CCS (49.2% of whom were male, with a median age of 32.7 years [range, 18.9 years-60.0 years]), 31.8% met criteria for MetSyn and 27.0% followed WCRF/AICR guidelines. Females who did not follow WCRF/AICR guidelines were 2.4 times (95% confidence interval, 1.7-3.3) and males were 2.2 times (95% confidence interval, 1.6-3.0) more likely to have MetSyn than those who followed WCRF/AICR guidelines. **CONCLUSIONS:** Adherence to a heart-healthy lifestyle is associated with a lower risk of MetSyn among CCS. There is a need to determine whether lifestyle interventions prevent or remediate MetSyn in CCS. *Cancer* 2014;120:2742-50. © *2014 American Cancer Society.*

IJC
International Journal of Cancer

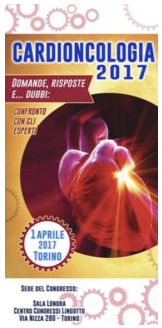


Adherence to WCRF/AICR cancer prevention recommendations and metabolic syndrome in breast cancer patients

WCRF/AICR recommendations
Physical activity
A brisk walking and/or moderate or strenuous activity
Sugary beverages
No sugary drinks
Plant foods
≥5 servings of fruits and vegetables and ≥1 serving of whole grains and/or legumes
Animal foods
≤1 portions of red meat and no portion of processed meat
Alcohol consumption
≤1 serving/die

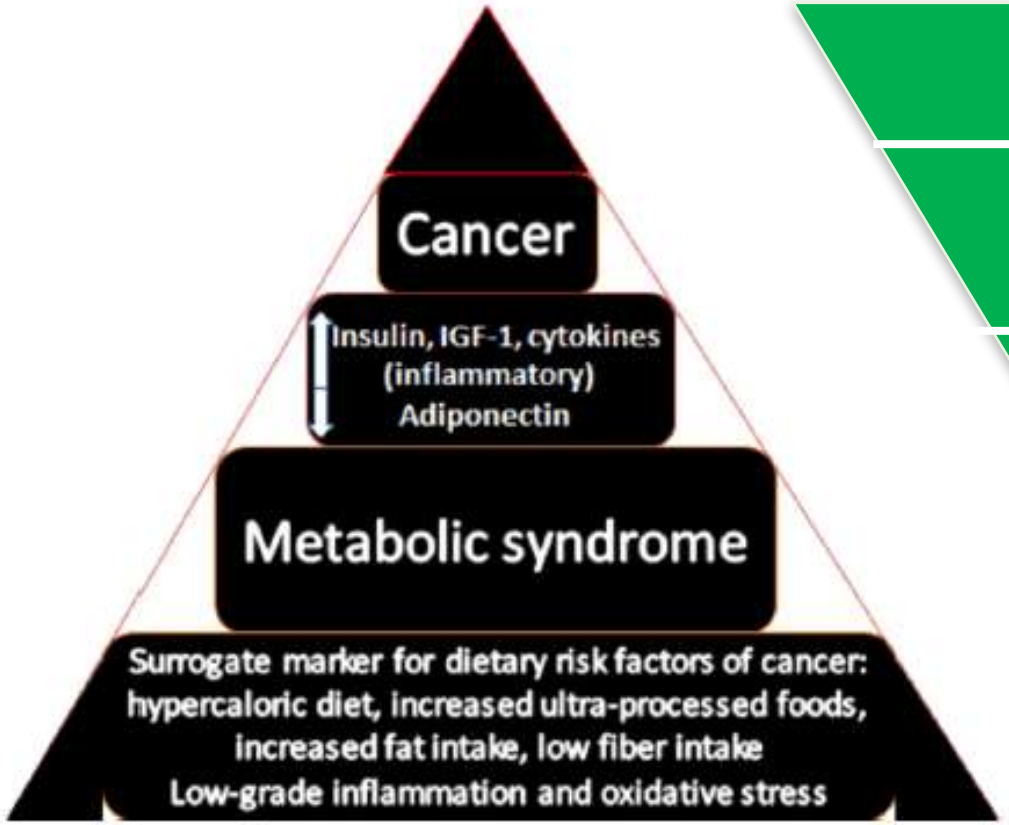
We investigated **the association between the prevalence of MetS and a score of adherence to the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) recommendations for the prevention of cancer** in a cross-sectional study of BC patients. The DIet and ANdrogen-5study (DIANA-5) for the prevention of BC recurrences recruited **2092 early stage BC survivors aged 35–70**. **The adjusted PRs of MetS decreased with increasing number of recommendations met ($p < 0.001$). Meeting all the five recommendations versus meeting none or only one was significantly associated with a 57% lower MetS prevalence (95% CI 0.35–0.73).** Our results sug- gest that adherence to WCRF/AICR recommendations is a major determinant of MetS and may have a clinical impact.

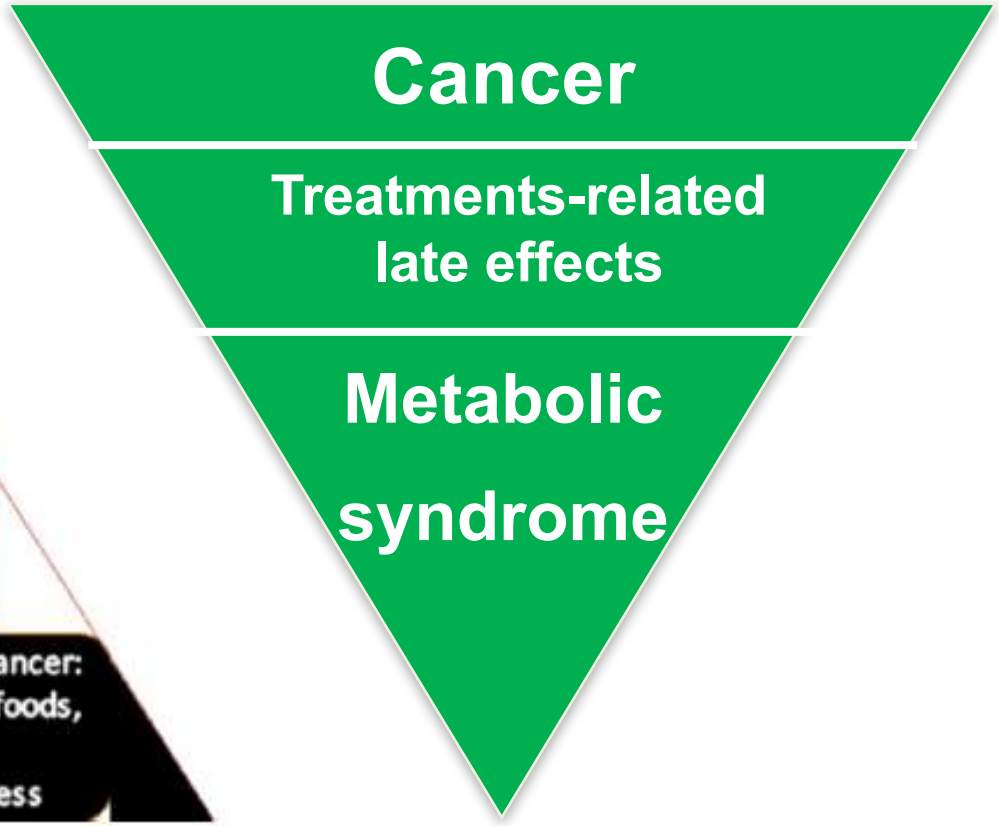
Int. J. Cancer: **138**, 237–244 (2016) © 2015 UICC



"COMMON SOIL HYPOTHESIS"

Metabolic syndrome and cancer: which direction?





Esposito K et al, Endocrine 2013

REVIEW

Metabolic syndrome and cardiovascular disease following hematopoietic cell transplantation: screening and preventive practice recommendations from CIBMTR and EBMT

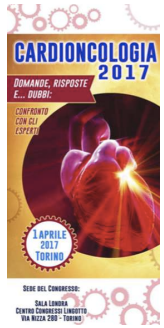


Table 4. CIBMTR/EBMT screening guidelines and preventive practice recommendations for metabolic syndrome and cardiovascular risk factors for adult and pediatric patients among the general population and HCT survivors

	Screening guidelines	*Preventive practice*
Weight, height and BMI	Weight, height and BMI assessment at every clinic visit (at least yearly)	Provide advice regarding intensive, multicomponent behavioral interventions focused on achieving and maintaining healthy weight by reducing caloric intake and increasing physical activity
	Waist circumference measurement yearly	
	Consider DXA to assess sarcopenia	
Dyslipidemia	For all allo-HCT recipients, initial lipid profile 3 months after HCT.	Lifestyle modifications and lipid-lowering therapies to achieve relative reductions in LDL is the primary goal
	For high-risk patients with ongoing risk factors (including those on sirolimus, calcineurin inhibitors and corticosteroids), repeat evaluation every 3–6 months.	In adults, the decision to initiate lipid-lowering therapy should include assessment of overall risk of heart disease (http://cvdrisk.nhlbi.nih.gov).
	For standard risk patients, lipid profile assessment every 5 years in males aged ⩾35 years and females aged ⩾45 years. The interval for screening should be shorter for people who have lipid levels close to those warranting therapy.	If TG > 500 mg/dL (5.65 mmol/L), initiate fibrate or nicotinic acid

REVIEW

Metabolic syndrome and cardiovascular disease following hematopoietic cell transplantation: screening and preventive practice recommendations from CIBMTR and EBMT

Blood pressure	Blood pressure assessment at every clinic visit (at least yearly)	Non-pharmacologic treatments may also be tried for mild hypertension and include moderate dietary sodium restriction, weight reduction in the obese, avoidance of excess alcohol intake and regular aerobic exercise. Treatment is indicated for readings >140/90 in adults on two separate visits at least 1 week apart, unless hypertension is mild or can be attributed to a temporary condition or medication (for example, cyclosporine)
Hyperglycemia	For high-risk patients with ongoing risk factors (including those on systemic corticosteroids), screen for abnormal blood glucose (HbA1C or fasting plasma glucose) 3 months after HCT with repeat evaluation every 3–6 months For standard risk adult patients, screening for abnormal blood glucose every 3 years in adults aged ⩾45 years or in those with sustained higher blood pressure (>135/80 mm Hg) For standard risk pediatric patients, fasting glucose at least every 5 years; if abnormal, screen annually	For IFG, encourage weight reduction and increased physical activity For type 2 DM, lifestyle therapy and pharmacotherapy, if necessary, should be used to achieve near-normal HbA1C (<7%)

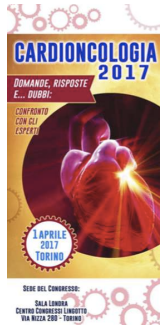
American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

TABLE 6. Guideline for Assessment and Management of Physical and Psychosocial Long-Term/Late Effects

RECOMMENDATION	LEVEL OF EVIDENCE[a]
Recommendation 3.3: Cardiotoxicity	
(a) Should monitor lipid levels and provide cardiovascular monitoring, as indicated	0 (Monitoring)
(b) Should educate breast cancer survivors on healthy lifestyle modifications, potential cardiac risk factors, and when to report relevant symptoms (shortness of breath or fatigue) to their health care provider	I (Lifestyle modifications)

It is important to educate breast cancer survivors about lifestyle modifications, including smoking cessation, diet, and exercise (see Recommendations 4.3-4.5), that may reduce the risk or severity of cardiotoxicity or cardiovascular diseases in general. Patients should be advised to be aware

. CA Cancer J Clin 2016;66:43-73.



QUANTIFICARE IL RISCHIO CV NEI *CS*

Heart Failure Risk Prediction in Childhood Cancer Survivors: Where Is Our Crystal Ball?

Elizabeth C. Bluhm, *MedStar Washington Hospital Center, Washington, DC*
Ana Barac, *MedStar Washington Hospital Center; and MedStar Heart Institute, Washington, DC*

- 40 anni, non fumatrice
- Linfoma di Hodgkin all'età di 15 anni (antracicline 180 mg/m^2, RT "mantellina" con dose non specificata)
- BMI 22
- Colesterolo Tot: 200 mg/dl; HDL: 45 mg/dl; LDL 135 mg/dl; Tg 100 mg/dl.
- Non ipertensione, non diabete.

Framingham Heart Study
A Project of the National Heart, Lung, and Blood Institute and Boston University

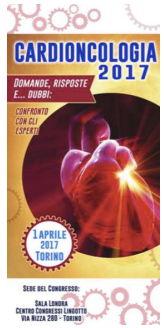
Rischio di CVD (a 10 anni): 2,3-4,1 %

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Individual Prediction of Heart Failure Among Childhood Cancer Survivors

Rischio di CHF: 9,1-16 %

Bluhm et al, J Clin Oncol 2014



TERAPIA IPOLIPEMIZZANTE IN CS

• Le Linee Guida disponibili consigliano di **trattare in maniera aggressiva** i *cancer survivors* con livelli **elevati di colesterolo LDL**. Le **statine** rappresentano il farmaco di elezione.

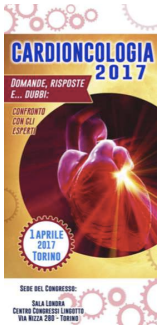
• L'*American Heart Association* consiglia nei ***CCS* di età superiore a 8 anni** un **trattamento farmacologico** (dopo fallimento di un intervento di 6-12 mesi sullo stile di vita) in caso di valori di LDL >190 mg/dl senza fattori di rischio CV aggiuntivi, e **con LDL >160 mg/dl in presenza di altri fattori.**

• Negli ***adult cancer survivors*** non vi sono chiare indicazioni (**stessi target dei soggetti diabetici?**)

NOTA 13 Allegato 1

Classificazione in base al livello di rischio

… *"Sono da considerare pazienti a rischio alto, oltre a coloro che presentano un risk score ≥5% e < 10% per CVD fatale a 10 anni, i pazienti con dislipidemie familiari o con ipertensione severa, i pazienti diabetici senza fattori di rischio CV e senza danno d'organo"*, ***i pazienti con pregressa esposizione a trattamenti oncologici potenzialmente cardiotossici*** *"e i pazienti con IRC moderata (FG 30-59 ml/min/1.73m^2.)"…*



CARDIOTOSSICITÀ INDIRETTA

Nei pazienti sottoposti a irradiazione mediastinica è opportuno avviare **lo screening lipidologico (determinazione di colesterolo totale e HDL, trigliceridi) 5 anni dopo il completamento delle terapie**. Se il profilo lipidico risulta normale, dal punto di vista del rapporto costo-efficacia è stato proposto come ragionevole ripetere tali esami a cadenza triennale.

TERAPIA

Per quanto riguarda il trattamento delle alterazioni del metabolismo lipidico, deve essere sottolineato il **ruolo chiave dello stile di vita, in particolar modo per gli adolescenti ed i giovani adulti per i quali, rispetto alle fasce d'età più avanzate, sono disponibili minori evidenze relative all'efficacia e alla sicurezza dei farmaci ipolipemizzanti.**

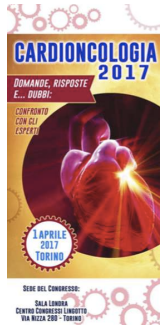
Per quanto riguarda la terapia farmacologica, le linee guida disponibili suggeriscono di trattare in maniera aggressiva i cancer survivors con livelli elevati di colesterolo LDL. **La terapia farmacologica di elezione per il trattamento delle dislipidemie è rappresentata dalle statine.** Considerando che - sulla base delle considerazioni precedenti - gli HL survivors hanno un rischio cardiovascolare aumentato, può essere **ipotizzabile l'utilizzo degli stessi target individuati per altre categorie di pazienti ad elevato rischio CV**, come ad esempio i pazienti diabetici:

	senza precedenti CV	con precedenti CV
Colesterolo LDL	<100 mg/dl	<70 mg/dl
Colesterolo HDL	>40-50 mg/dl (M-F)	
trigliceridi	<150 mg/dl	

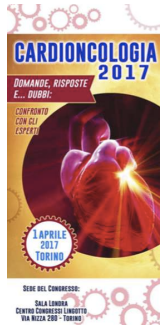
In tutti gli HL survivors devono comunque essere considerati e - per quanto possibile - **corretti sia gli stili di vita inadeguati (fumo, dieta, sedentarietà), sia i fattori di rischio cardiovascolare modificabili (ipertensione arteriosa, obesità, diabete)** e le cardiopatie pre-esistenti.

Inoltre, quando non controindicato, **in presenza di deficit ormonali specifici** (ipotiroidismo, ipogonadismo, deficit di GH) **è opportuno il trattamento ormonale sostitutivo.**

TAKE HOME MESSAGES



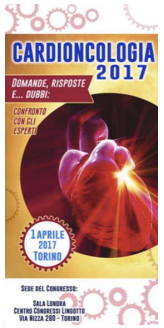
- Lo sviluppo di **sindrome metabolica o di alcune fra le sue componenti** è un evento tutt'altro che infrequente nei *cancer survivors* e può contribuire in modo determinante **all'insorgenza e alla progressione delle malattie CV** in questi pazienti.
- La patogenesi della sindrome metabolica nei *CS* multifattoriale, e giocano un ruolo importante le alterazioni del sistema endocrino.
- Il rischio cardiovascolare nei CV va quindi inteso in modo globale e l'approccio a queste problematiche deve essere multidisciplinare.
- **La promozione di un corretto stile di vita** per ridurre l'impatto negativo dei **fattori di rischio CV modificabili** (fumo, obesità, ecc) ha un ruolo chiave e deve essere attivamente portata avanti nel corso del follow-up dei *CS.*
- Le **linee guida** attualmente disponibili, pur riconoscendo l'importanza della prevenzione della sindrome metabolica nei *CS*, **forniscono indicazioni ancora poco specifiche** sulle strategie adottabili per contrastarla.

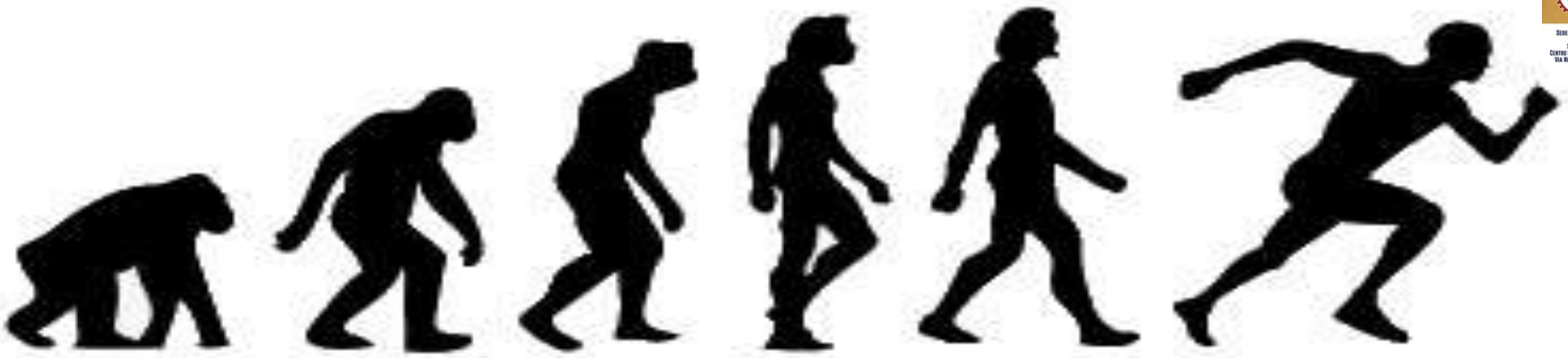


It doesn't stop at cure: monitoring childhood cancer survivors

Childhood cancer survivors are at **long-term risk of substantial adverse events**. Follow-up should be centred on the **individual, and information should be provided to survivors to help them understand how regular checkups can improve their long-term wellbeing and quality of life.** Ultimately, what is required is a more comprehensive, proactive, and integrated follow-up care pathway for survivors of childhood cancer. **Treating the patient doesn't stop with their last cycle of therapy.**

www.thelancet.com/oncology Vol 14 July 2013





TO BE CONTINUED...