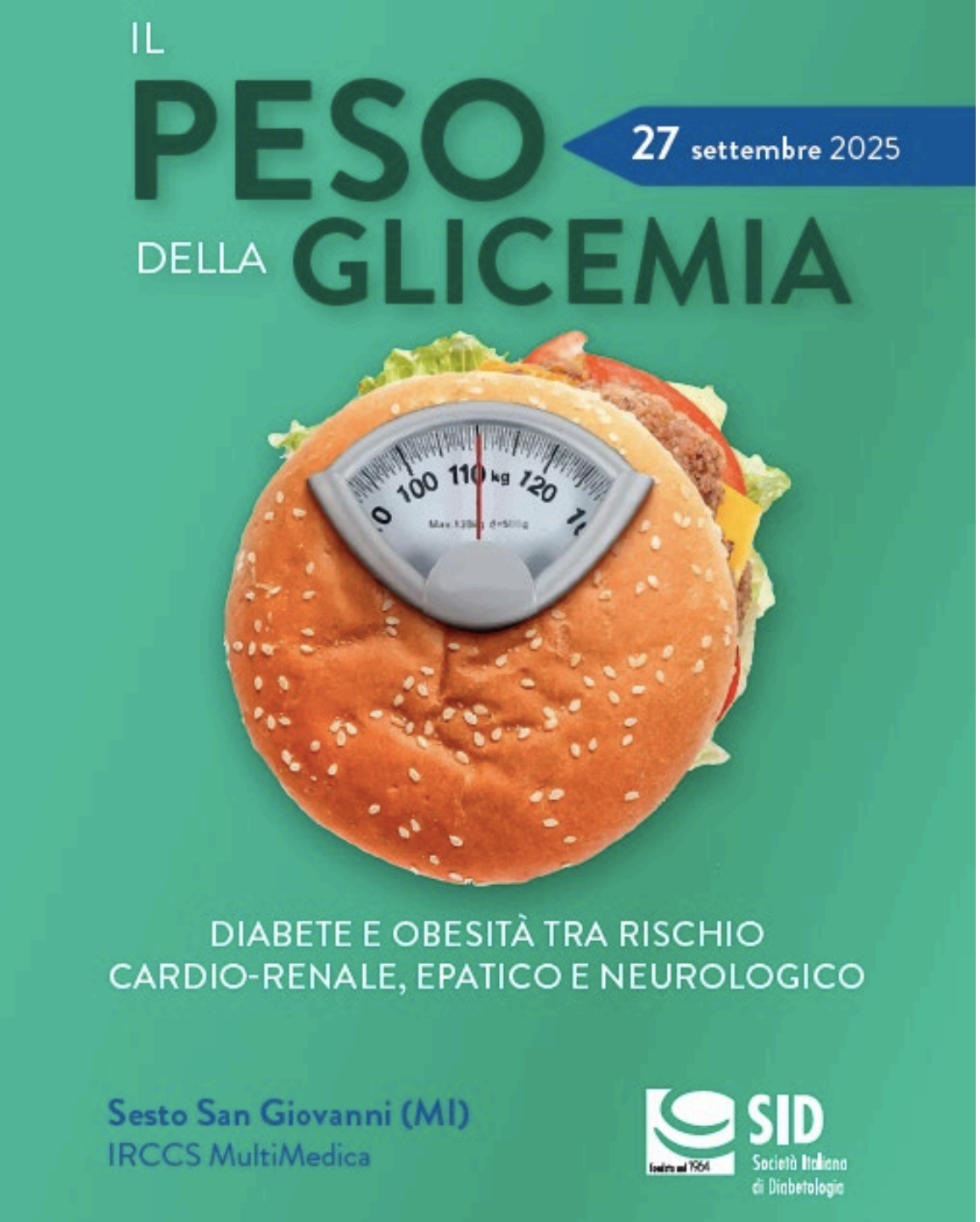


III SESSIONE

Diabete tipo 2, il punto sulle complicanze "emergenti"

Moderatori: Antonio Ceriello, Alessandro R. Dodesini

Diabete e cancro: quali, quanto e perché?

Antonio C. Bossi, Humanitas Bergamo

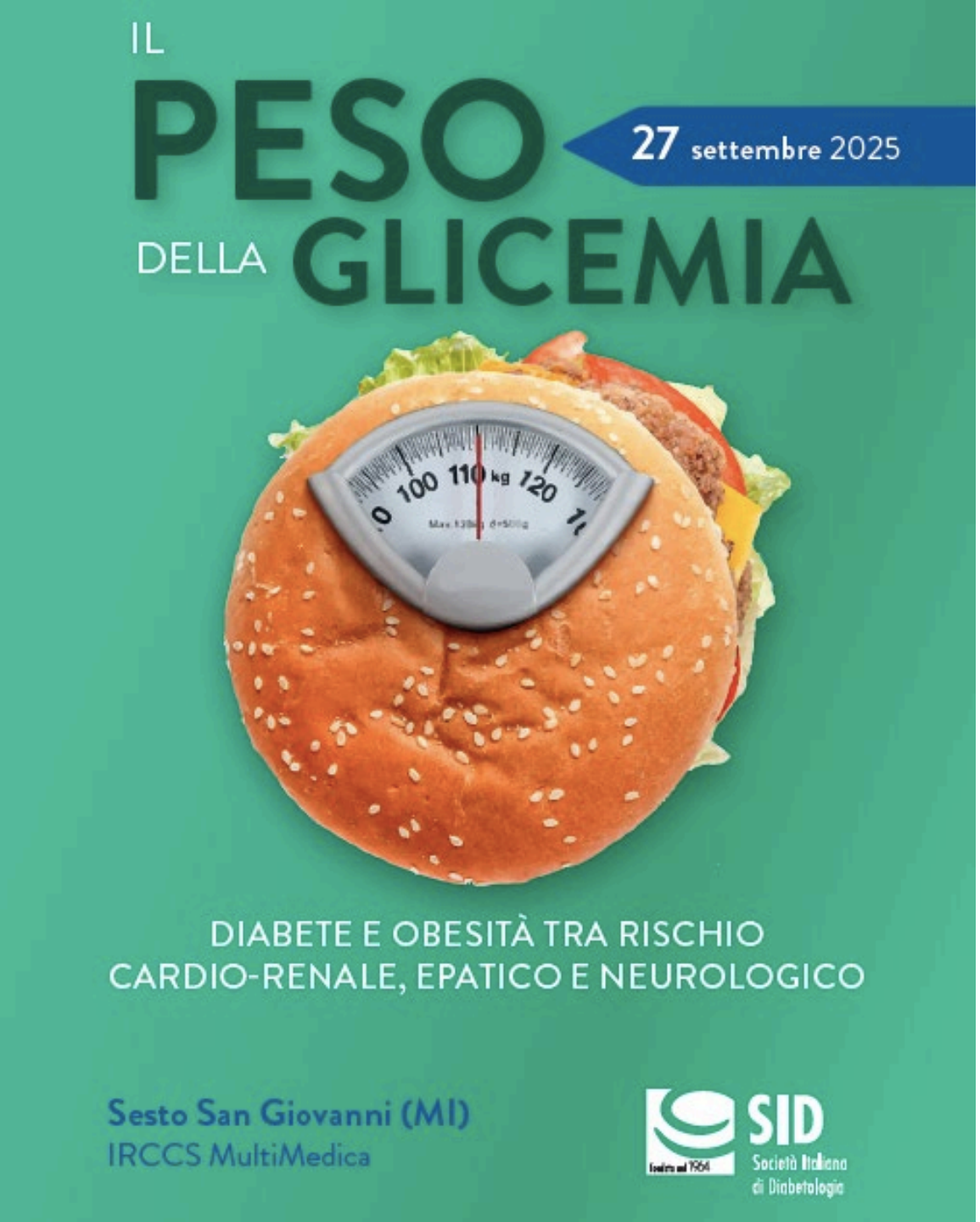
DISCLOSURES

In the last ten years, ACB reports:

- Research Grants from: Novo-Nordisk Dk
  Eli Lilly USA
  Bayer SA D
  Sanofi Italia SpA
  Pikdare Italia SpA
- Advisory Board and Personal Fees from: MSD Int. USA
  Alfasigma Italia SpA
  Johnson & Johnson Italia SpA
  Boehringer Ingelheim Italia SpA
  Astra Zeneca Italia SpA
  Takeda Italia SpA
  Mundipharma Italia SpA
  Pfizer Italia SpA

I acknowledge the Italian Diabetes Society (SID) for its contribution to my scientific and clinical continuous education.

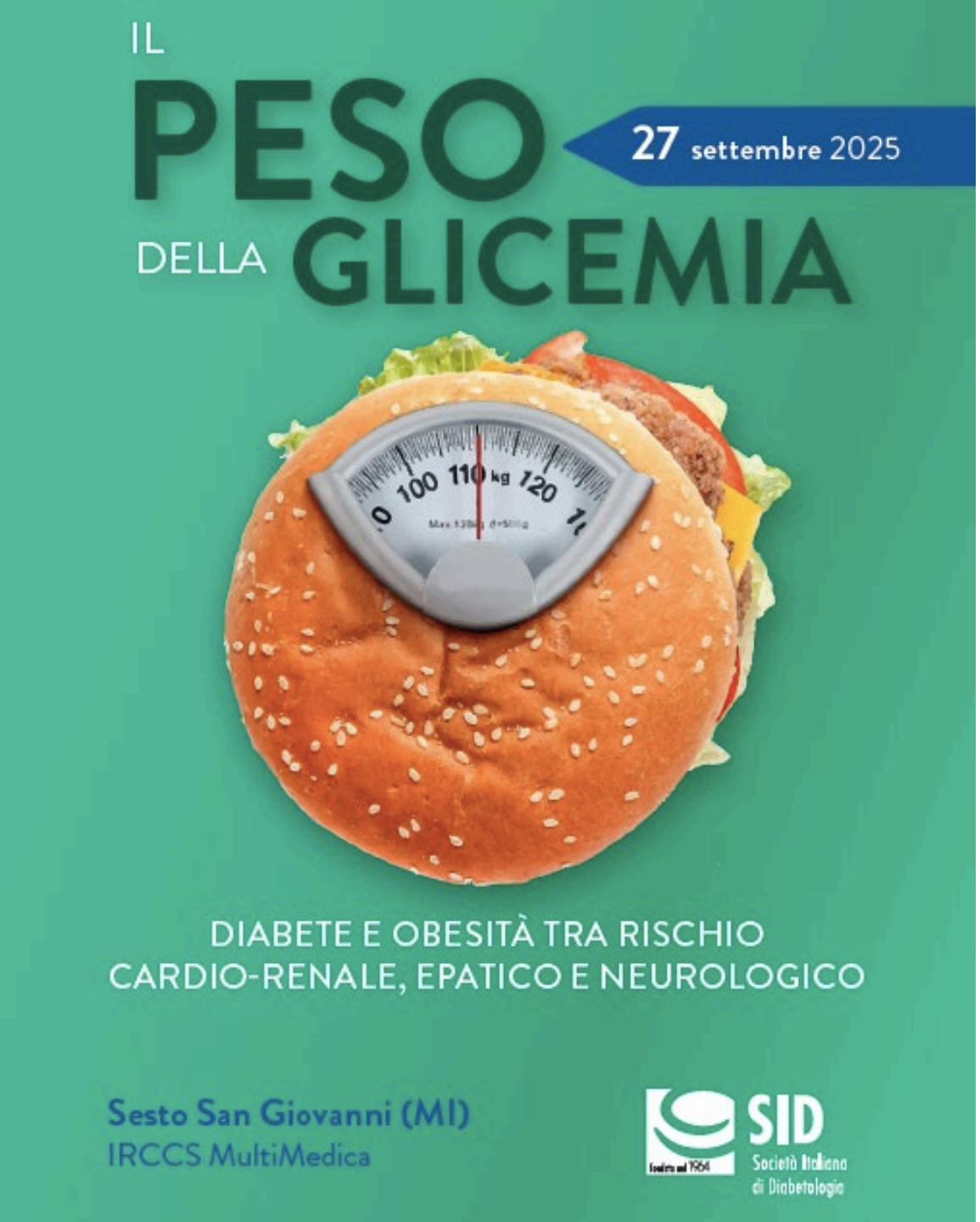
www.siditalia.it



Diabete e cancro: quali, quanto e perché?

AGENDA

- Introduzione
- Quali
- Quanto
- Perché
- Conclusioni

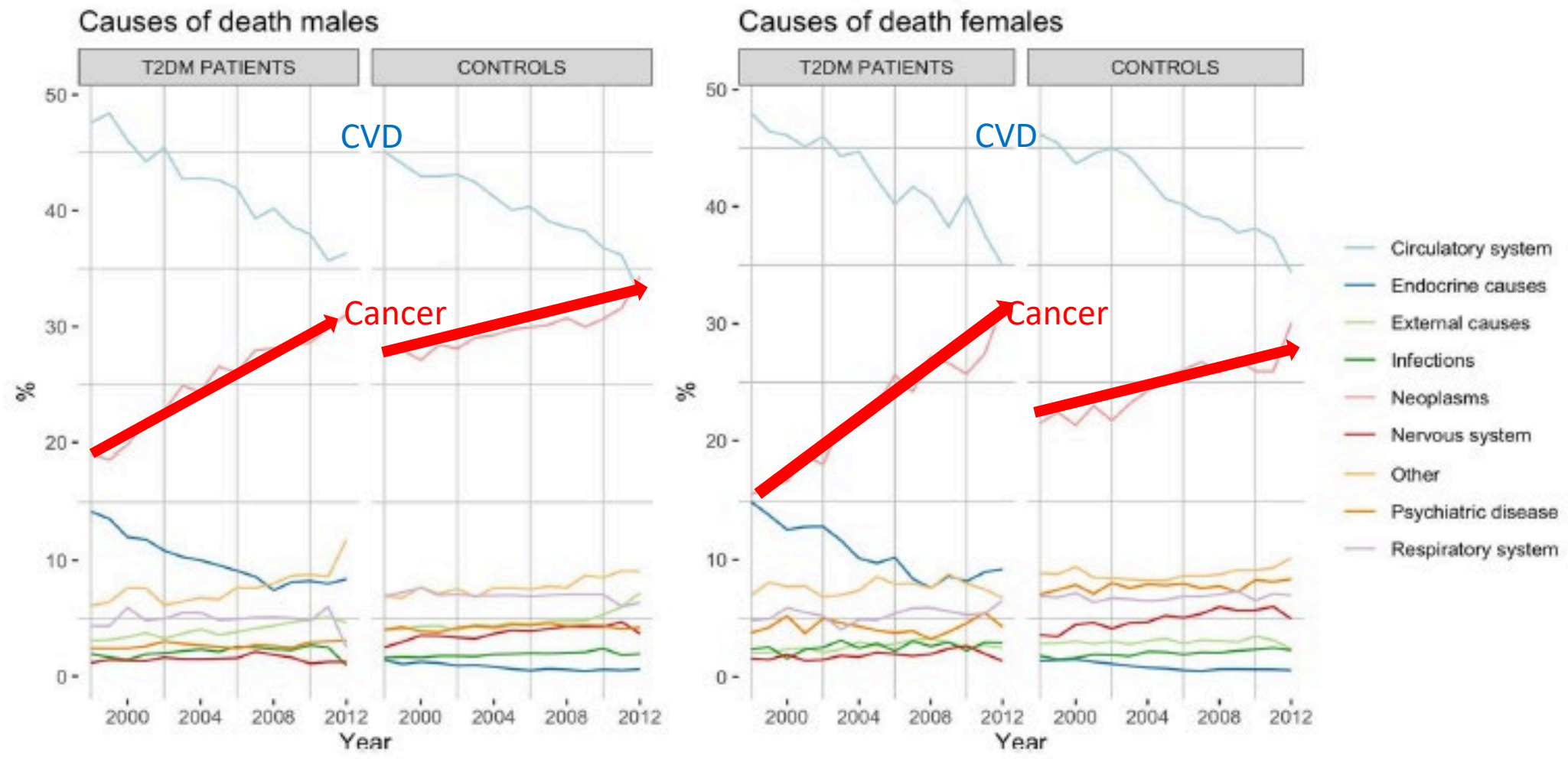


Diabete e cancro: quali, quanto e perché?

AGENDA

- **Introduzione**
- Quali
- Quanto
- Perché
- Conclusioni

A national observation study of cancer incidence and mortality risks in type 2 diabetes compared to the background population over time.



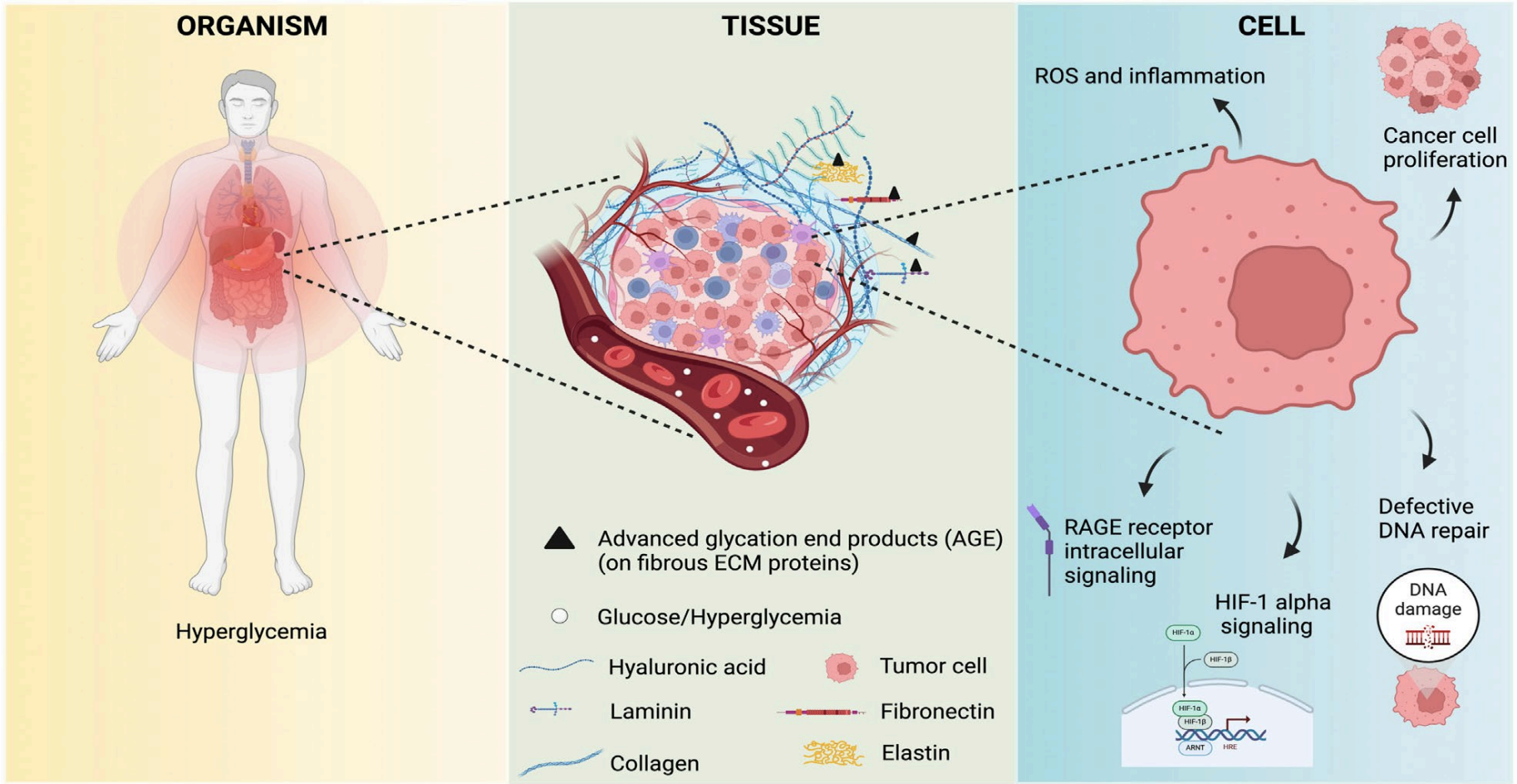
Björnsdottir H et al. Scientific Reports, 10, 17376. (doi: 10.1038/s41598-020-73668-y)

Diabetes and Cancer: A Twisted Bond

Oncology Reviews

HUMANITAS GAVAZZENI

Mihai Cosmin Stan [1,2] and Doru Paul [3]**



Organism levels impinges by hyperglycemia related to oncogenesis.

published: 21 May 2024. doi: 10.3389/or.2024.1354549

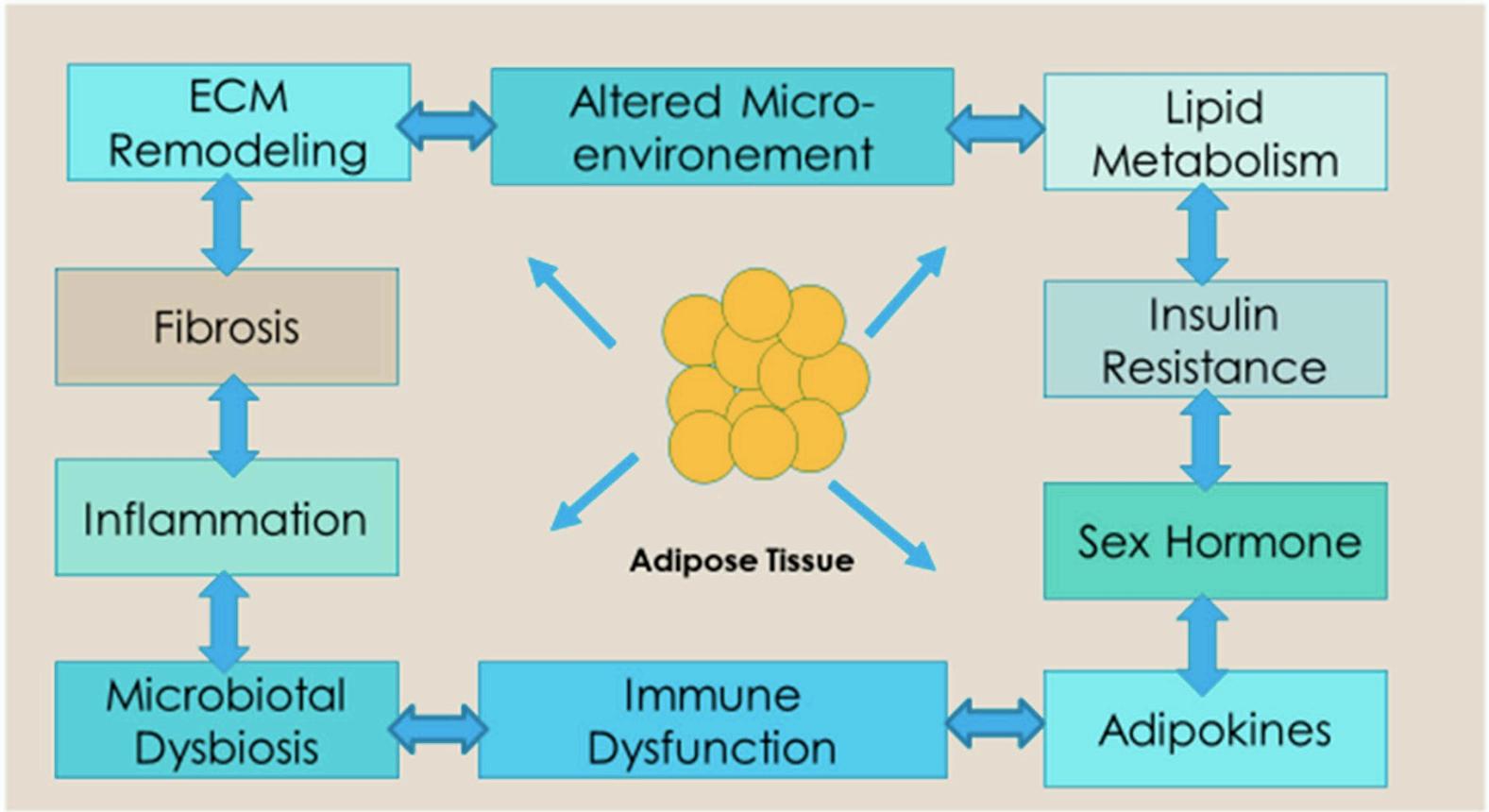
cancers

Review

Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management

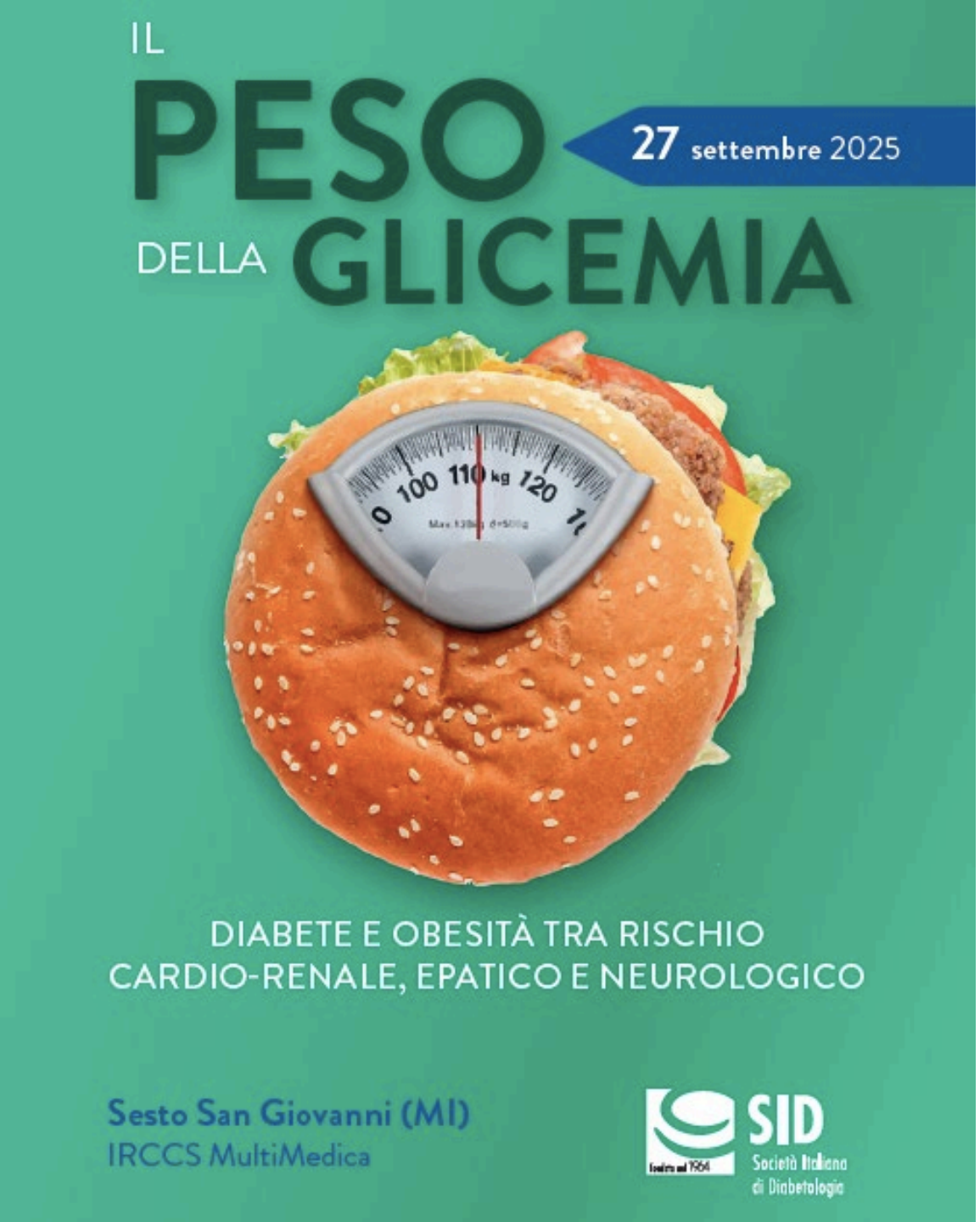
Sukanya Pati [1], Wadeed Irfan [2], Ahmad Jameel [1], Shahid Ahmed [1,3,*] and Rabia K. Shahid [1,*]

HUMANITAS GAVAZZENI



Potential mechanism of obesity-induced dysfunction of adipose tissue on tumor initiation, progression, and recurrence. ECM: Extra Cellular Matrix

Cancers. 2023, 15, 485. https://doi.org/10.3390/cancers15020485



Diabete e cancro: quali, quanto e perché?

AGENDA

- Introduzione
- Quali
- Quanto
- Perché
- Conclusioni

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Associations between diabetes and cancer: A 10-year national population-based retrospective cohort study

Heléna Safadi [a,b,*,1], Ágnes Balogh [c,2], Judit Lám [a,b,d,3], Attila Nagy [a,e,4], Éva Belicza [a,b,d,5]

Results of the Cox proportional hazard regression analysis.[a]

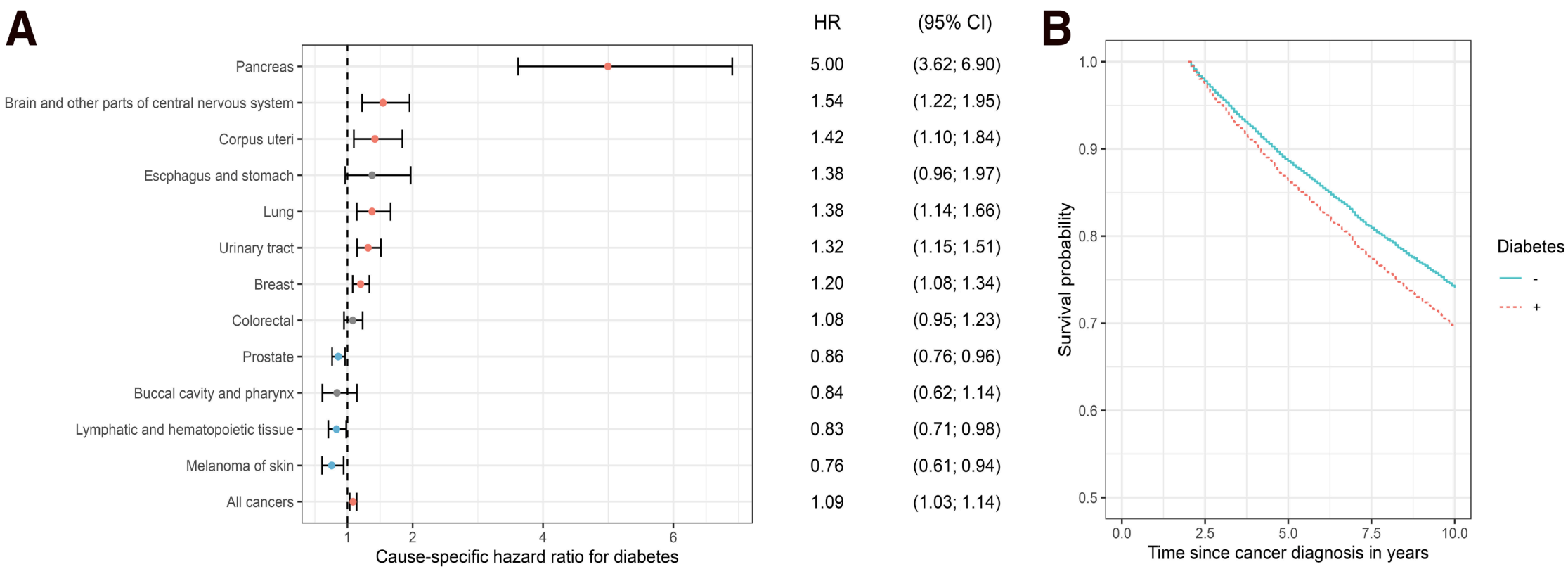
Cancer site	Independent variables											
	Sex (ref: male)				Age (continuous)				Presence of diabetes (ref: control)			
	Hazard ratio	Sig.	Conf.int (99 %)		Hazard ratio	Sig.	Conf.int (99 %)		Hazard ratio	Sig.	Conf.int (99 %)	
			lower	upper			lower	upper			lower	upper
All sites	0.697	***	0.690	0.703	1.045	***	1.045	1.045	1.223	***	1.189	1.258
Colorectal	0.568	***	0.557	0.579	1.059	***	1.058	1.060	1.300	***	1.229	1.375
Liver	0.503	***	0.479	0.527	1.048	***	1.046	1.050	1.830	***	1.631	2.054
Pancreatic	0.718	***	0.690	0.748	1.055	***	1.053	1.057	2.294	***	2.099	2.507
Breast (female)		NA			1.017	***	1.016	1.018	1.137	***	1.055	1.227
Prostate		NA			1.083	***	1.082	1.084	1.171	***	1.071	1.280
Kidney	0.470	***	0.451	0.491	1.043	***	1.041	1.044	1.442	***	1.287	1.616

[a] Based on multivariate Cox regression separately for each cancer site; modelled time to cancer diagnosis with independent variables of diabetes status, age (as continuous variable), and sex (where applicable).

*** $p < 0{,}001$.

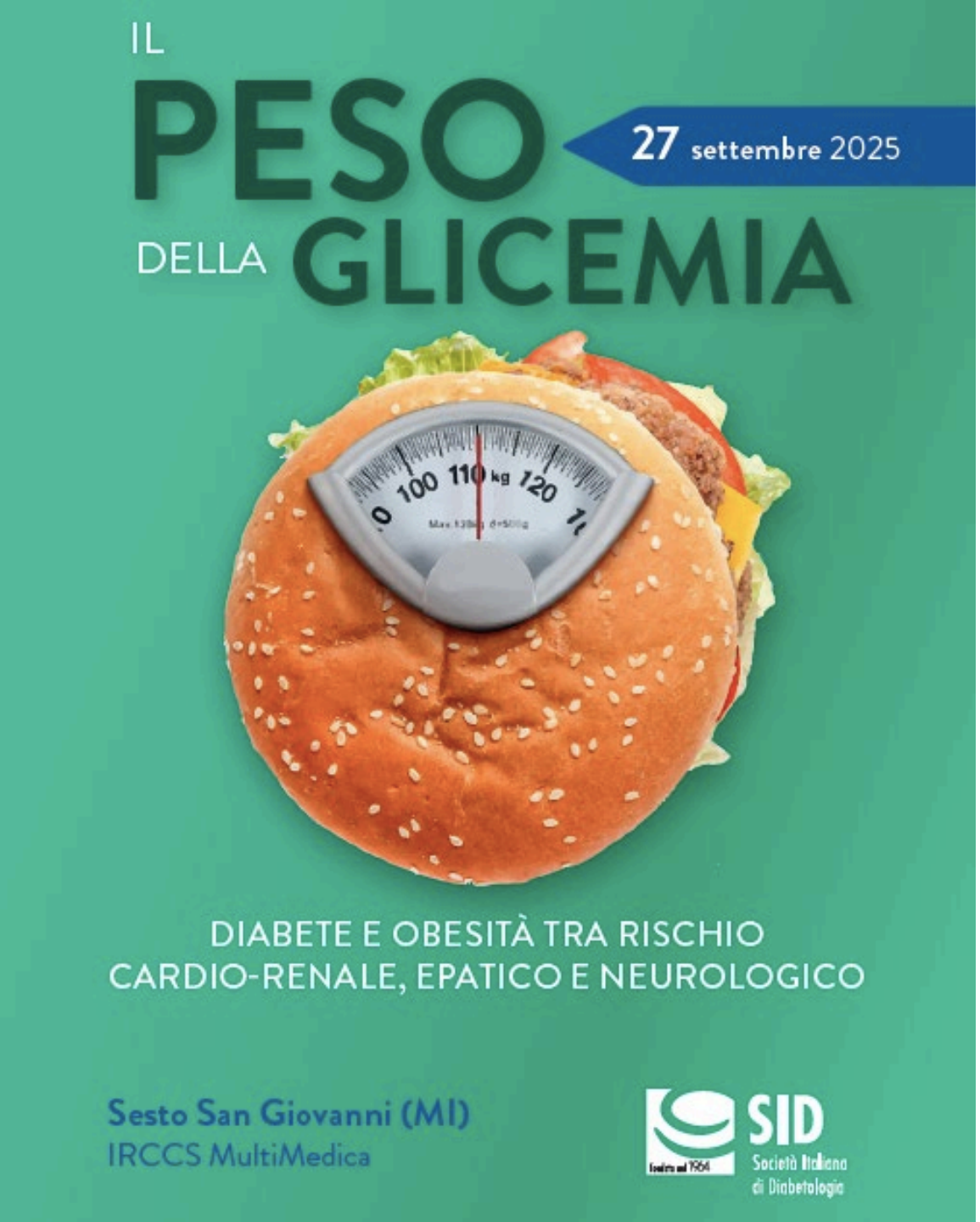
Safadi H et al. Diab Res Clin Pract 2024 May:211:111665. doi: 10.1016/j.diabres.2024.111665. Epub 2024 Apr 9.

Incidence of New-Onset Type 2 Diabetes After Cancer: A Danish Cohort Study



Cause-specific HRs for incident type 2 diabetes for cancer case subjects vs. control subjects by type of cancer and all cancers, with adjustment for age and, when applicable, sex. Error bars indicate 95% CIs.

Sylow L. et al. Diabetes Care 2022;45:e105–e106 | https://doi.org/10.2337/dc22-0232



Diabete e cancro: quali, quanto e perché?

AGENDA

- Introduzione
- Quali
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- Conclusioni

cancers

Review

Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management

Sukanya Pati [1], Wadeed Irfan [2], Ahmad Jameel [1], Shahid Ahmed [1,3,*] and Rabia K. Shahid [1,*]

HUMANITAS GAVAZZENI

Type of Cancer	Number of Cohorts	Relative Risk (95% Confidence Interval)	
		Women	Men
Endometrial cancer [4]	19	1.59 (1.50–1.68)	NA
Gallbladder cancer [4]	4	1.59 (1.02–2.47)	1.09 (0.99–1.21)
Esophageal adenocarcinoma [4]	5	1.51 (1.31–1.74)	1.52 (1.33–1.74)
Kidney cancer [4]	12	1.34 (1.25–1.43)	1.24 (1.15–1.34)
Postmenopausal breast cancer [4]	34	1.12 (1.08–1.16)	NA
Hpatocellular cancer [19]	9	1.12 (1.03–1.22)	1.19 (1.09–1.29)
Pancreatic adenocarcinoma [23]	23	1.10 (1.04–1.16)	1.13 (1.04–1.22)
Colon cancer [4]	29	1.09 (1.05–1.13)	1.24 (1.20–1.28)
Ovarian cancer [77]	34	1.06 (1.00–1.12)	NA
Stomach cancer [4]	8	1.04 (0.90–1.20)	0.97 (0.88–1.06)
Rectal cancer [4]	29	1.02 (1.00–1.05)	1.09 (1.06–1.12)
Later stage prostate cancer [73]	23	NA	1.08 (1.04–1.12)

Gender-specific summary of cancer risk for each 5 kg per m^2 increase in BMI for major cancers with strong evidence of relationship with obesity.

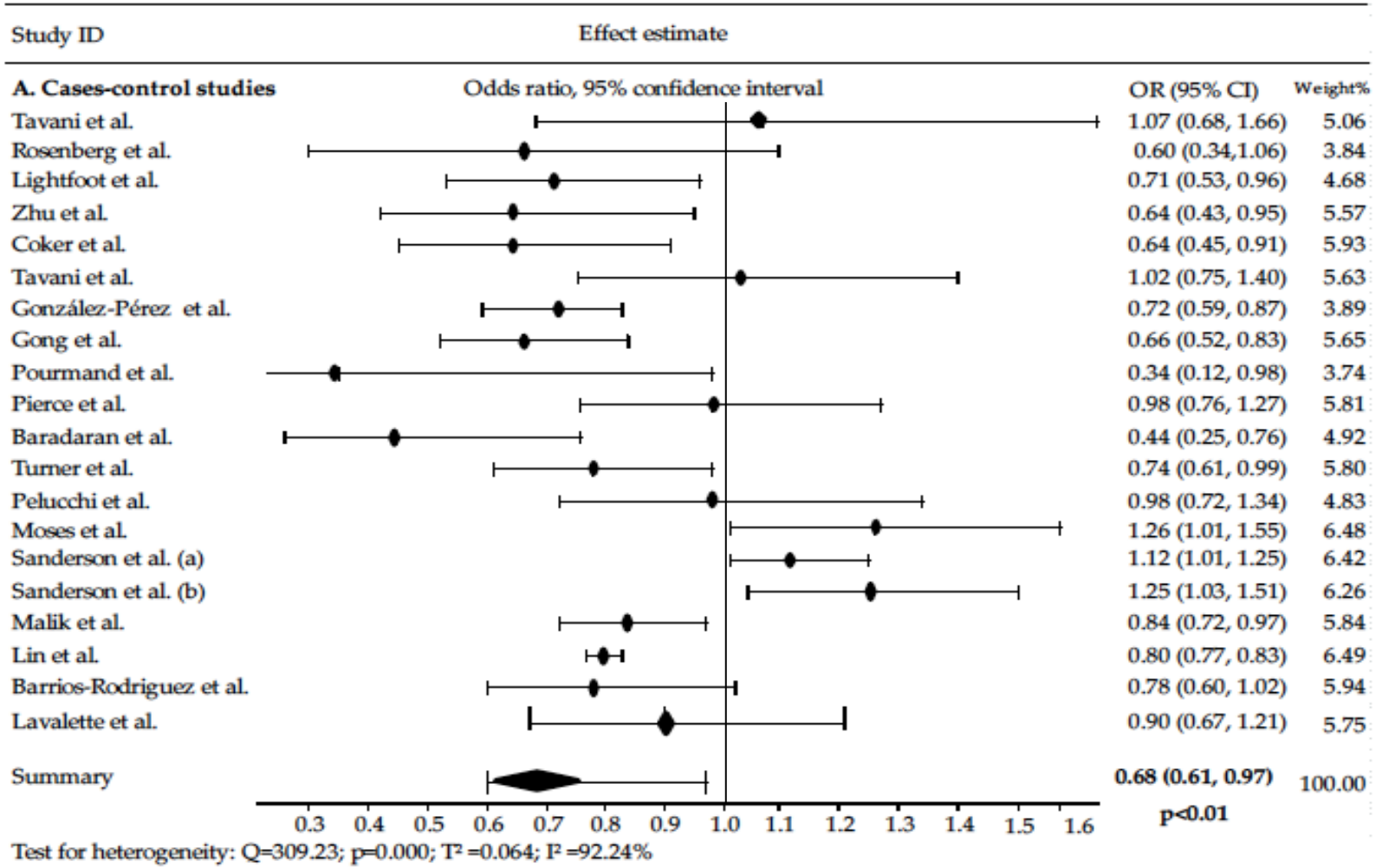
Cancers. 2023, 15, 485. https://doi.org/10.3390/cancers15020485

cancers

Systematic Review

Diabetes Mellitus and Prostate Cancer Risk—A Systematic Review and Meta-Analysis

Agnieszka Drab [1], Krystian Wdowiak [2,*], Wiesław Kanadys [2], Krzysztof Zajączkowski [3], Paweł Koczkodaj [4], Urszula Religioni [5], Mariola Borowska [4], Magdalena Łoś [6] and Macarena Lozano-Lorca [7,8,9]



Cancers 2024, 16, 4010. https://doi.org/10.3390/cancers16234010

Diabetes medications and cancer risk associations: a systematic review and meta-analysis of evidence over the past 10 years

A total of 92 studies were identified, involving **171 million participants**.

BIGUANIDES:

Inverse relationships with **colorectal** (RR = 0.85) and **liver** cancers (RR = 0.55)

THIAZOLIDINEDIONES:

Lower risks of **breast** (RR = 0.87), **lung** (RR = 0.77) and **liver** (RR = 0.83) cancers.

INSULINS:

Negatively associated with **breast** (RR = 0.90) and **prostate cancer** risks (RR = 0.74).
Positive associations between insulin **secretagogues** and **pancreatic cancer** (RR = 1.26), and between **insulins** and **liver** (RR = 1.74) and **pancreatic cancers** (RR = 2.41).

Chen Y, et al. Scientific Reports | (2023) 13:11844 | https://doi.org/10.1038/s41598-023-38431-z

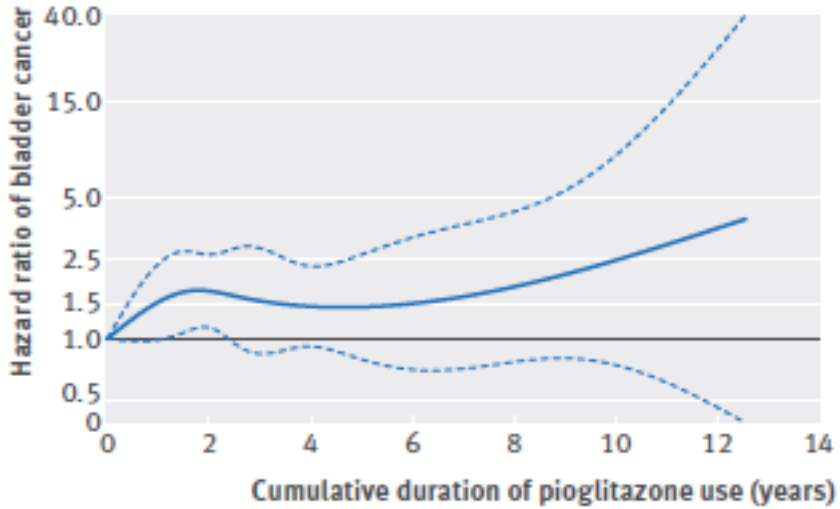
BMJ 2016;352:i1541

HUMANITAS GAVAZZENI

Pioglitazone use and risk of bladder cancer: population based cohort study

Marco Tuccori,[1,2] Kristian B Filion,[1,2,3] Hui Yin,[1] Oriana H Yu,[1,4] Robert W Platt,[1,2,5,6] Laurent Azoulay[1,7]

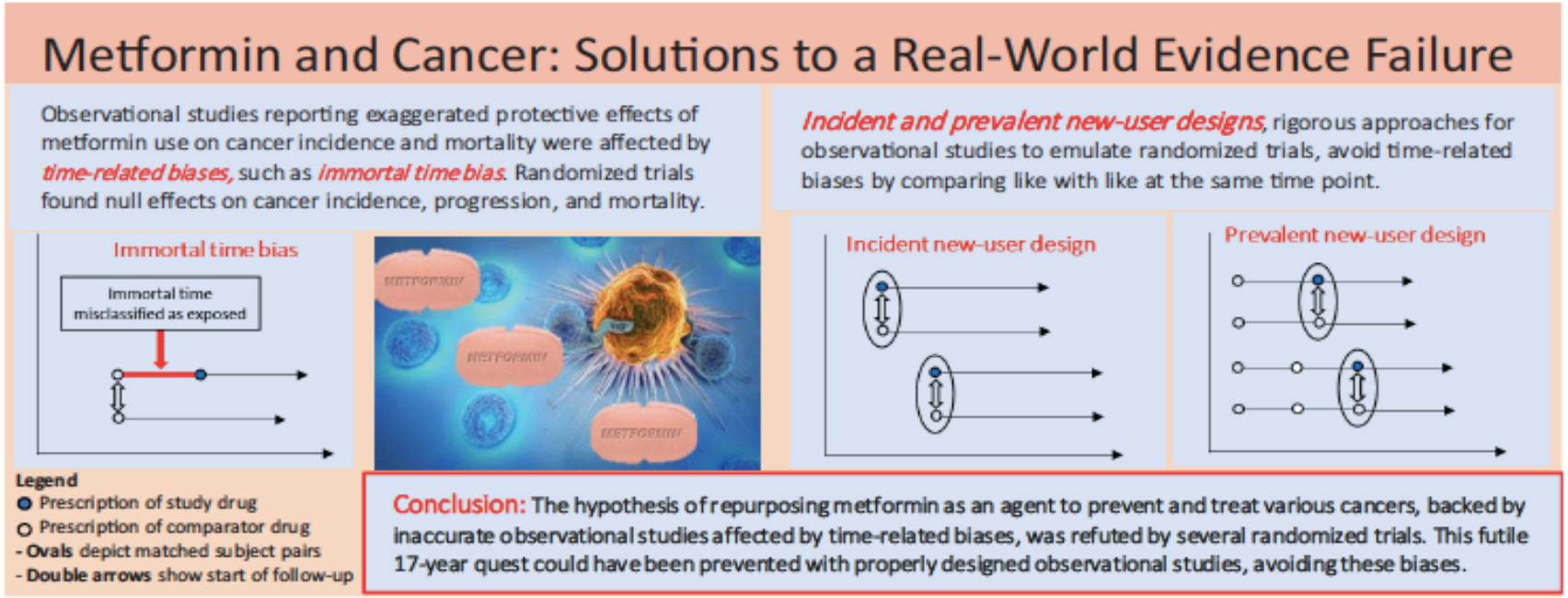
Design: Population based cohort study.

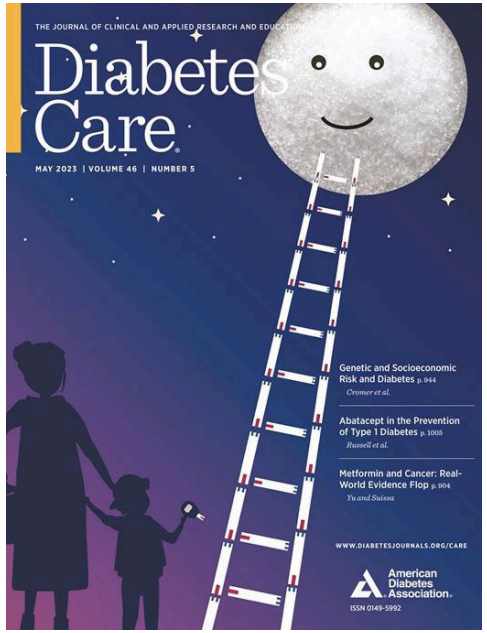


Metformin and Cancer: Solutions to a Real-World Evidence Failure

Oriana Hoi Yun Yu [1,2,3] *and Samy Suissa* [1,3,4]

Diabetes Care 2023;46:904–912 | https://doi.org/10.2337/dci22-0047





- The quest to repurpose metformin as an agent for cancer prevention and treatment, initiated in 2005, generated observational studies that reported remarkably reduced risks of cancer incidence and mortality with metformin.
- These observational studies were shown in 2012 to be **affected by time-related biases that exaggerate the benefit of a drug.**
- To date, **the randomized trials of metformin as a treatment for various cancers have not found reductions in disease-free survival or overall survival.**

OXFORD

Association of metformin use and cancer incidence: a systematic review and meta-analysis

Lauren O'Connor, PhD, MPH,[1] Maeve Bailey-Whyte, PhD, MPH,[2] Manami Bhattacharya, PhD, MS,[3] Gisela Butera, MLIS, MA,[4] Kaitlyn N. Lewis Hardell, PhD, MPH,[1,5] Andrew B. Seidenberg, PhD, MPH,[6,7] Philip E. Castle, PhD, MPH,[8] Holli A. Loomans-Kropp, PhD, MPH[9,10,11,*]

HUMANITAS GAVAZZENI

Metformin may be associated with a decreased risk of many cancer types, but high heterogeneity and risk of publication bias limit confidence in these results.

Bile duct or biliary tract	4	0.82 (0.54 to 1.11)
Bladder	5	0.70 (0.56 to 0.83)
Bone	3	0.90 (0.74 to 1.06)
Cervical	3	0.68 (0.49 to 0.87)
Endometrial	6	1.12 (0.89 to 1.35)
Esophageal	12	0.68 (0.50 to 0.86)
Gastric	15	0.76 (0.63 to 0.89)
Head and neck or oral	8	0.58 (0.45 to 0.72)
Kidney	3	0.66 (0.12 to 1.19)
Lung	19	0.88 (0.76 to 0.99)
Ovarian	2	0.53 (0.21 to 0.85)
Pancreatic	15	1.13 (0.86 to 1.40)
Skin	5	0.86 (0.63 to 1.09)
Thyroid	6	0.74 (0.51 to 0.97)

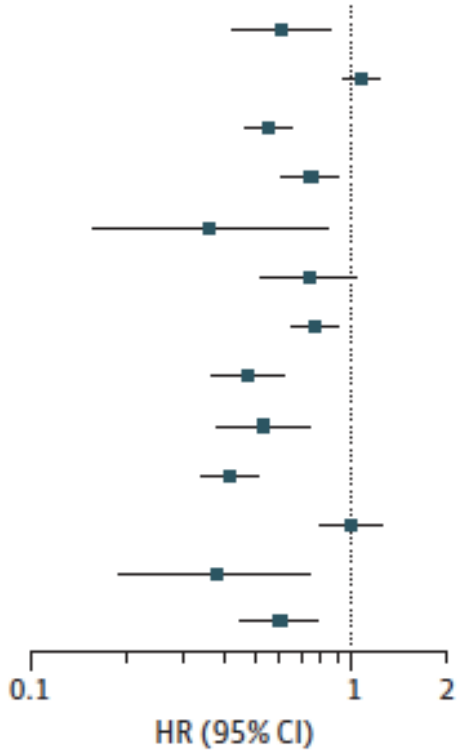
JNCI: Journal of the National Cancer Institute, 2024, 116(4), 518–529 https://doi.org/10.1093/jnci/djae021

Original Investigation | Oncology

JAMA Network Open

Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes

Outcome (N = 1651452)	Group prescribed GLP-IRAs but not insulin, No (%) (n = 48983)	Group prescribed insulin but not GLP-IRAs, No (%) (n = 1044745)	HR (95% CI)
Esophageal cancer (n = 48437)	49 (0.10)	77 (0.16)	0.60 (0.42-0.86)
Breast cancer (n = 13768)	427 (3.08)	379 (2.94)	1.07 (0.93-1.23)
Colorectal cancer (n = 48443)	223 (0.46)	391 (0.81)	0.54 (0.46-0.64)
Endometrial cancer (n = 25750)	160 (0.62)	210 (0.82)	0.74 (0.60-0.91)
Gallbladder cancer (n = 48587)	<10 (<0.02)	19 (0.04)	0.35 (0.15-0.83)
Stomach cancer (n = 48449)	56 (0.12)	75 (0.16)	0.73 (0.51-1.03)
Kidney cancer (n = 48322)	223 (0.46)	284 (0.59)	0.76 (0.64-0.91)
Hepatocellular carcinoma (n = 48397)	79 (0.16)	167 (0.35)	0.47 (0.36-0.61)
Ovarian cancer (n = 25739)	51 (0.20)	94 (0.37)	0.52 (0.37-0.74)
Pancreatic cancer (n = 48490)	123 (0.25)	290 (0.60)	0.41 (0.33-0.50)
Thyroid cancer (n = 48527)	154 (0.32)	149 (0.31)	0.99 (0.79-1.24)
Meningioma (n = 48518)	11 (0.02)	29 (0.06)	0.37 (0.18-0.74)
Multiple myeloma (n = 48527)	80 (0.17)	131 (0.27)	0.59 (0.44-0.77)



Risk of 13 Obesity-Associated Cancers Among Patients Receiving GLP-1RAs vs Those Receiving Insulins

Wang L, et al. JAMA Network Open. 2024;7(7):e2421305. doi:10.1001/jamanetworkopen.2024.21305

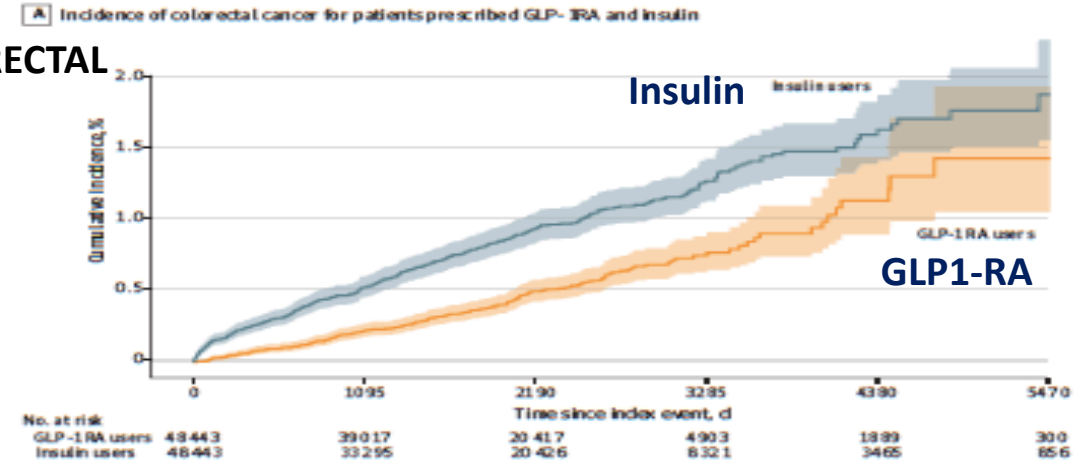
JAMA Network Open

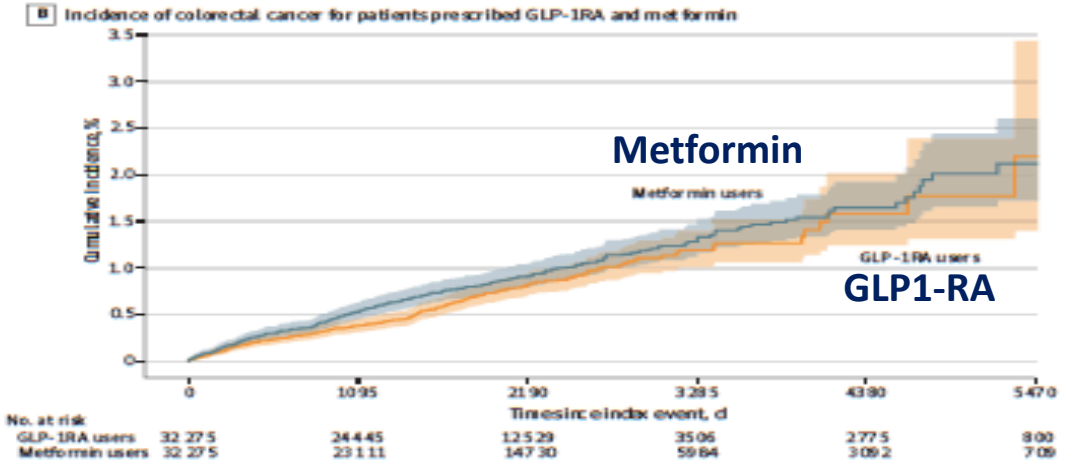
Original Investigation | Oncology

Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes

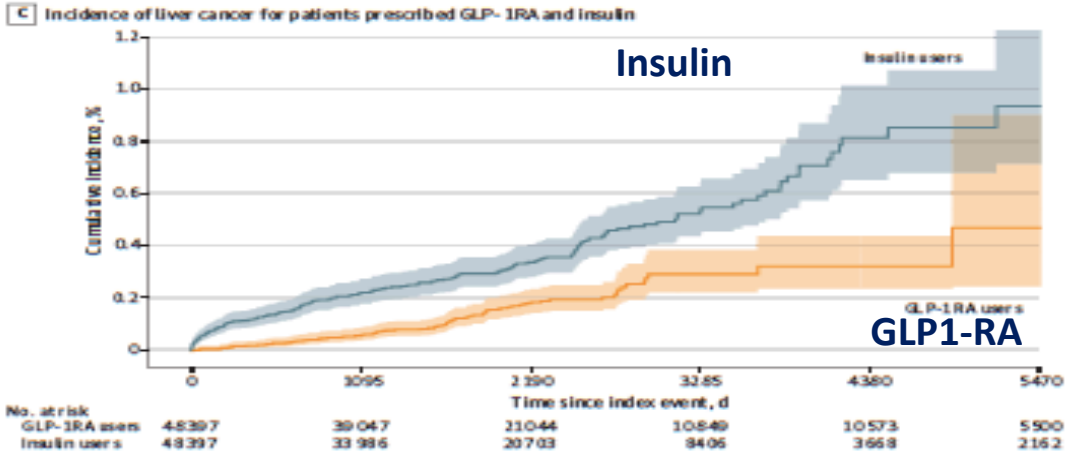
HUMANITAS GAVAZZENI

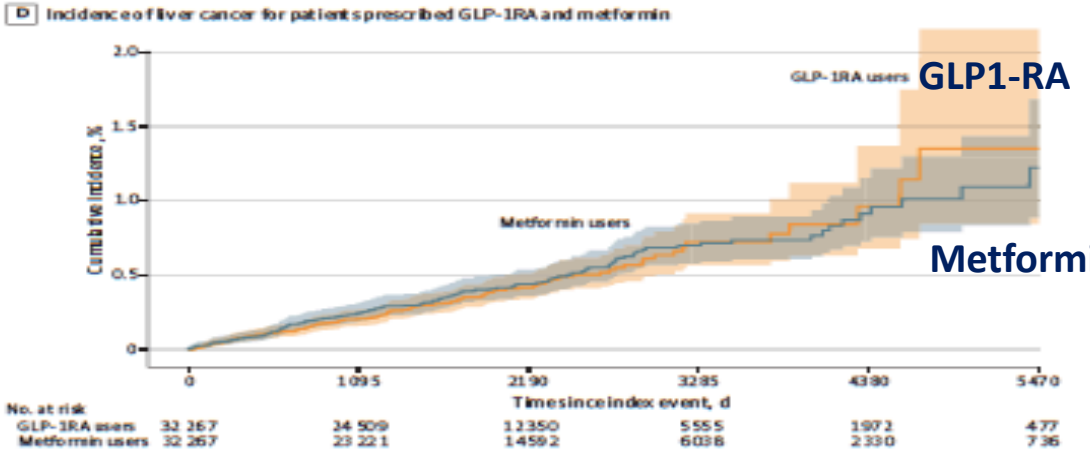
COLORECTAL





LIVER





Kaplan-Meier survival analysis was used. Each eligible individual was followed up from the index event until the occurrence of the outcomes, death, loss to follow-up, or 15 years after the index event, whichever occurred first.

Cumulative Incidences of Colorectal Cancer and Liver Cancer Among Patients Receiving GLP-1RAs vs Those Receiving Insulins or Metformin During a 15-Year Follow-Up

Wang L, et al. JAMA Network Open. 2024;7(7):e2421305. doi:10.1001/jamanetworkopen.2024.21305

Diabetes Care
American Diabetes Association
2023 Feb 1;46(2):384-390.
doi: 10.2337/dc22-1148.

HUMANITAS GAVAZZENI

The use of GLP-1 receptor agonists is associated with an increased risk of thyroid cancer

GLP-1 receptor agonists and the risk of thyroid cancer

Bezin J., Gouverneur A., Pénichon M., Mathieu C., Garrel R., Hillaire-Buys D., Pariente A., Faillie J-L.

Clinicians should be aware of this potential risk in initiating a GLP-1 RA and carefully monitor exposed patients, especially in the presence of other risk factors for thyroid cancer.

	Case subjects *n* = 2,572	Control subjects *n* = 45,184	Adjusted hazard ratio (95%CI)*
GLP-1 receptor agonists			
No use	2,255 (88.0)	40,836 (90.4)	Reference
Cumulative use ≤1 year	117 (4.6)	1,767 (3.9)	1.22 (0.99 to 1.50)
Cumulative use 1-3 years	112 (4.4)	1,419 (3.1)	1.58 (1.27 to 1.95)
Cumulative use >3 years	78 (3.0)	1,162 (2.6)	1.36 (1.05 to 1.74)
DPP-4 inhibitors			
No use	1,522 (59.4)	27,406 (60.7)	Reference
Cumulative use ≤1 year	333 (13.0)	5,209 (11.5)	1.12 (0.99 to 1.28)
Cumulative use 1-3 years	310 (12.1)	5,918 (13.1)	0.96 (0.84 to 1.10)
Cumulative use >3 years	397 (15.5)	6,651 (14.7)	1.19 (1.04 to 1.35)

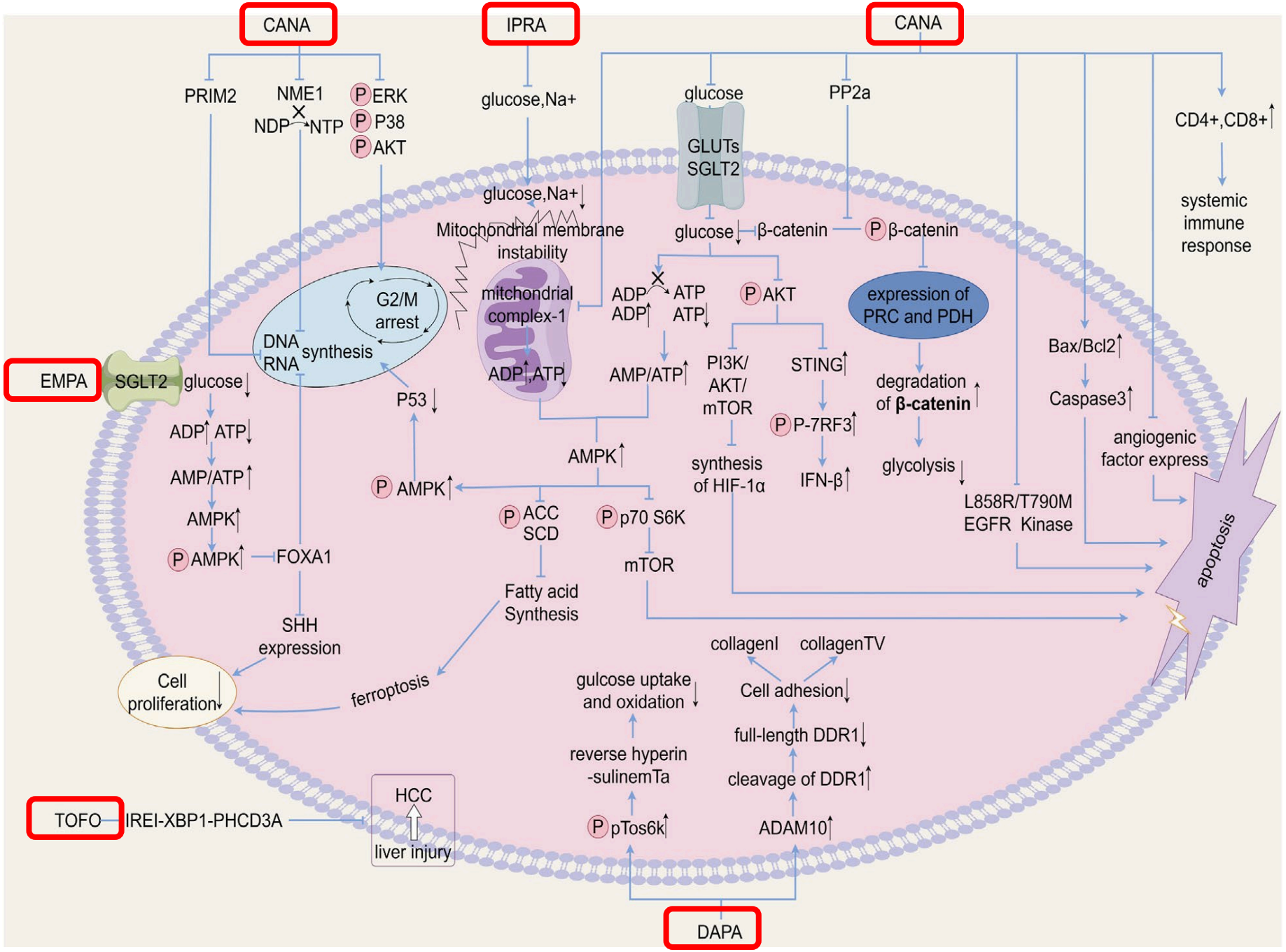
*Adjusted for social deprivation index, goiter, hypo- and hyperthyroidism in the last year, and use of other antidiabetes drugs in the last 6 years considered in therapeutic class.

SGLT2 Inhibitors as Potential Anticancer Agents

HUMANITAS GAVAZZENI

Tumor Site	Cancer Model	SGLT2i for Intervention	Study Type	Results
Breast	MCF-7 (human)	Canagliflozin	in vitro	Inhibition of cell proliferation, clonogenic survival, and colony formation
	MCF-7 (human)	Canagliflozin and Dapagliflozin	in vitro/in vivo	Significant reduction in tumor volume; Potently inhibited cell proliferation; Induced cell cycle arrest and apoptosis
	MCF-7 (human)	Ipragliflozin	in vitro	Inhibition of glucose and sodium influx; Alteration in mitochondrial membrane potential
	SKBR3, BT-474, MCF-7 (human)	Canagliflozin	in vitro	Inhibition of oxygen consumption and glutamine metabolism
Liver	Huh7, HepG2 (human)	Canagliflozin	in vitro	Inhibition of glucose uptake
	Huh7, Hep3B	Canagliflozin	in vitro/in vivo	Inhibition of β-catenin pathway
	Humans	Canagliflozin	*Patient sample*	suppression of angiogenesis
	Huh7, Hep3B	Canagliflozin	in vitro	Downregulation of ATP synthase F1 subunit alpha (mitochondrial electron transport system protein)
Pancreas	Capan-1, PANC-1	Canagliflozin	in vitro/in vivo	Suppression of glucose transporter-1 and lactate dehydrogenase A
Thyroid	TPC-1, BCPAP, Nthy-ori-3–1	Canagliflozin	in vitro/in vivo	Inhibition of glucose uptake, glycolysis, and AKT/mTOR signaling activation; increased AMPK activation
Bone	MNNG/HOS, MG-63, 143B, U2OS, K7M2	Canagliflozin	in vitro/in vivo	Activation of STING/IRF3/IFN-β pathway and suppression of AKT phosphorylation
Lung	A549 (human)	Canagliflozin	in vitro	Inhibition of cell cycle progression
	HCC827, H1975	Canagliflozin	in vitro	Inhibition of EGFR kinase
Prostate	PC3	Canagliflozin	in vitro	Inhibition of complex I supported mitochondrial respiration

Basak D, Gamez D, Deb S. Biomedicines 2023, 11, 1867. https://doi.org/10.3390/biomedicines11071867



Sun M, et al. Unveiling the anticancer effects of SGLT-2i: mechanisms and therapeutic potential. Front. Pharmacol. 2024;15:1369352.

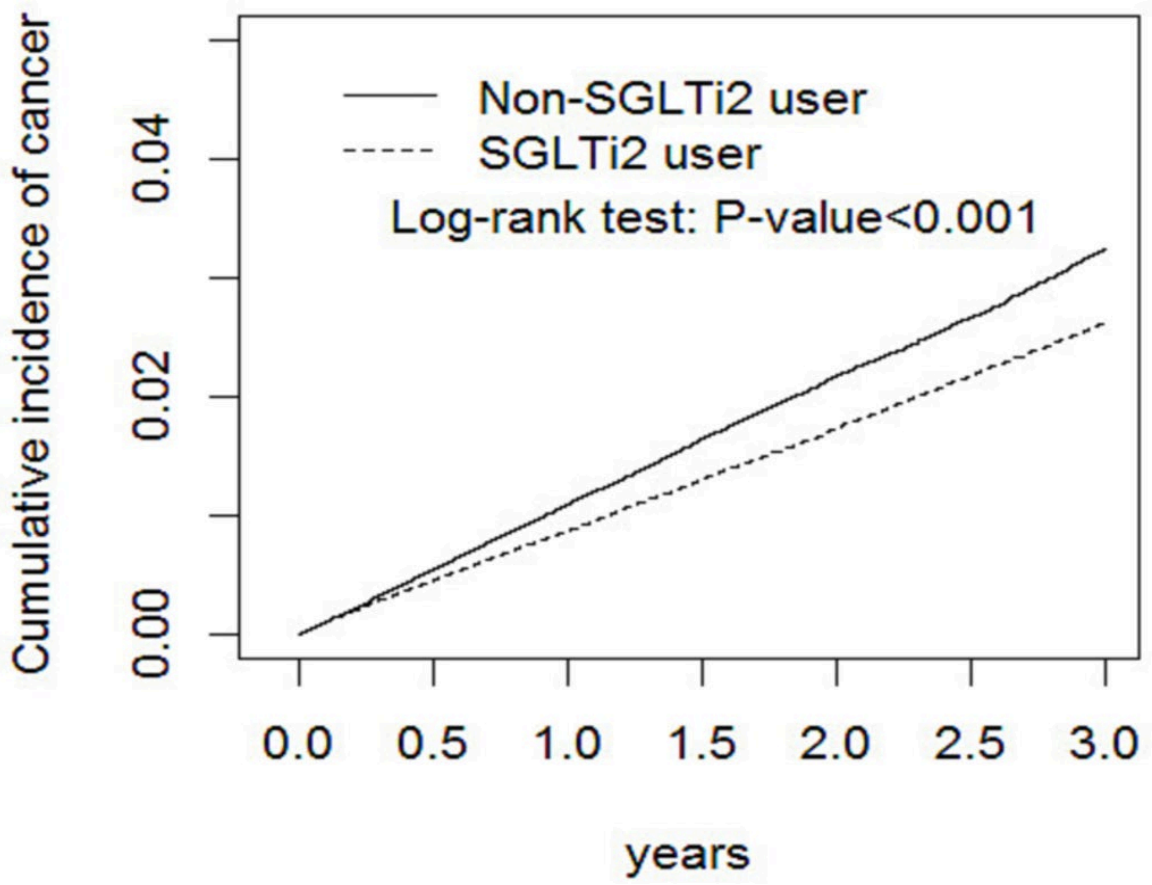
Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

Hu WS, Lin CL. 37 (2023) 108468

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

Patients with diabetes with and without SGLT2-inhibitors use with incident cancer risk.

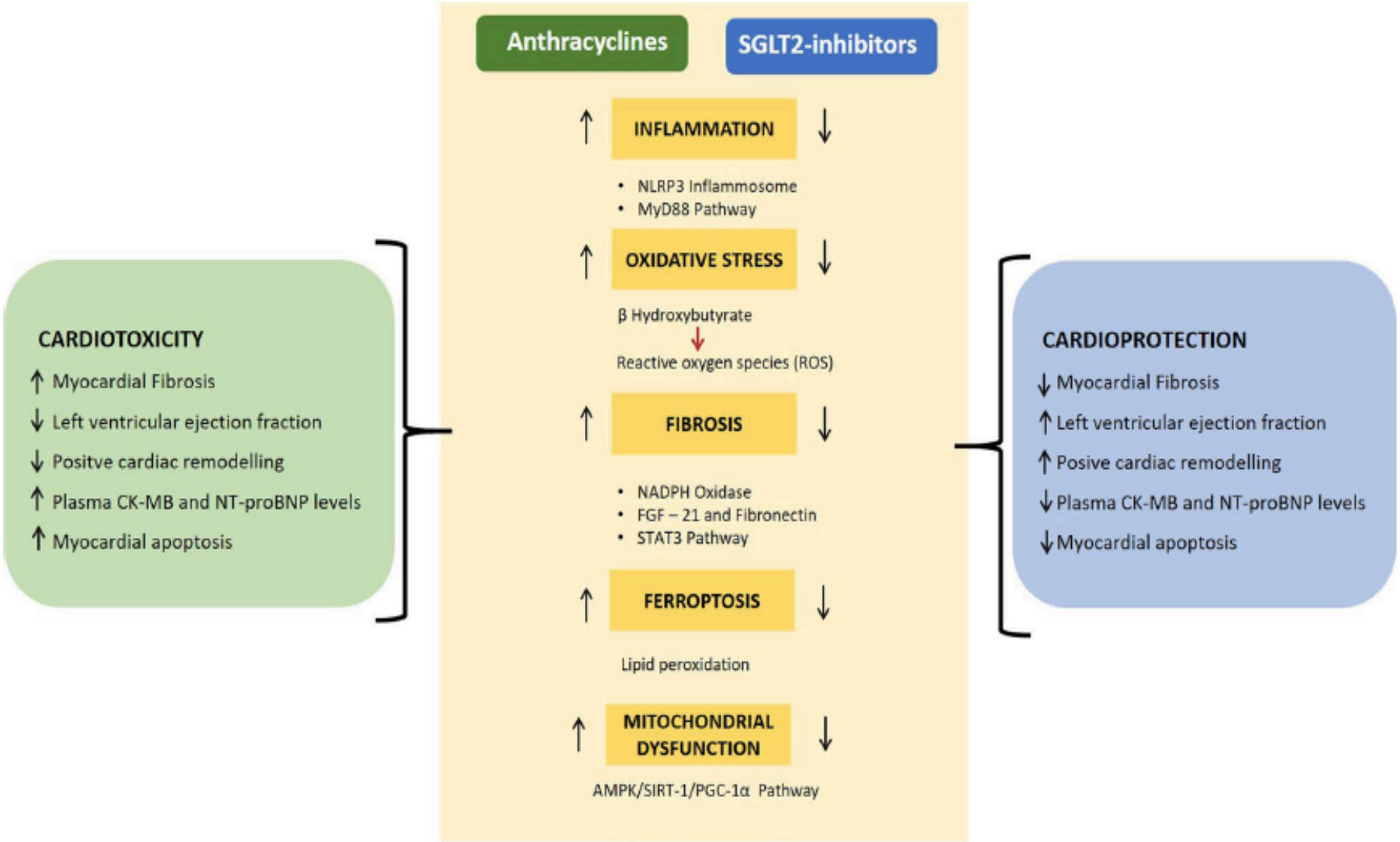


Adj HR: 0,79 p<0.001

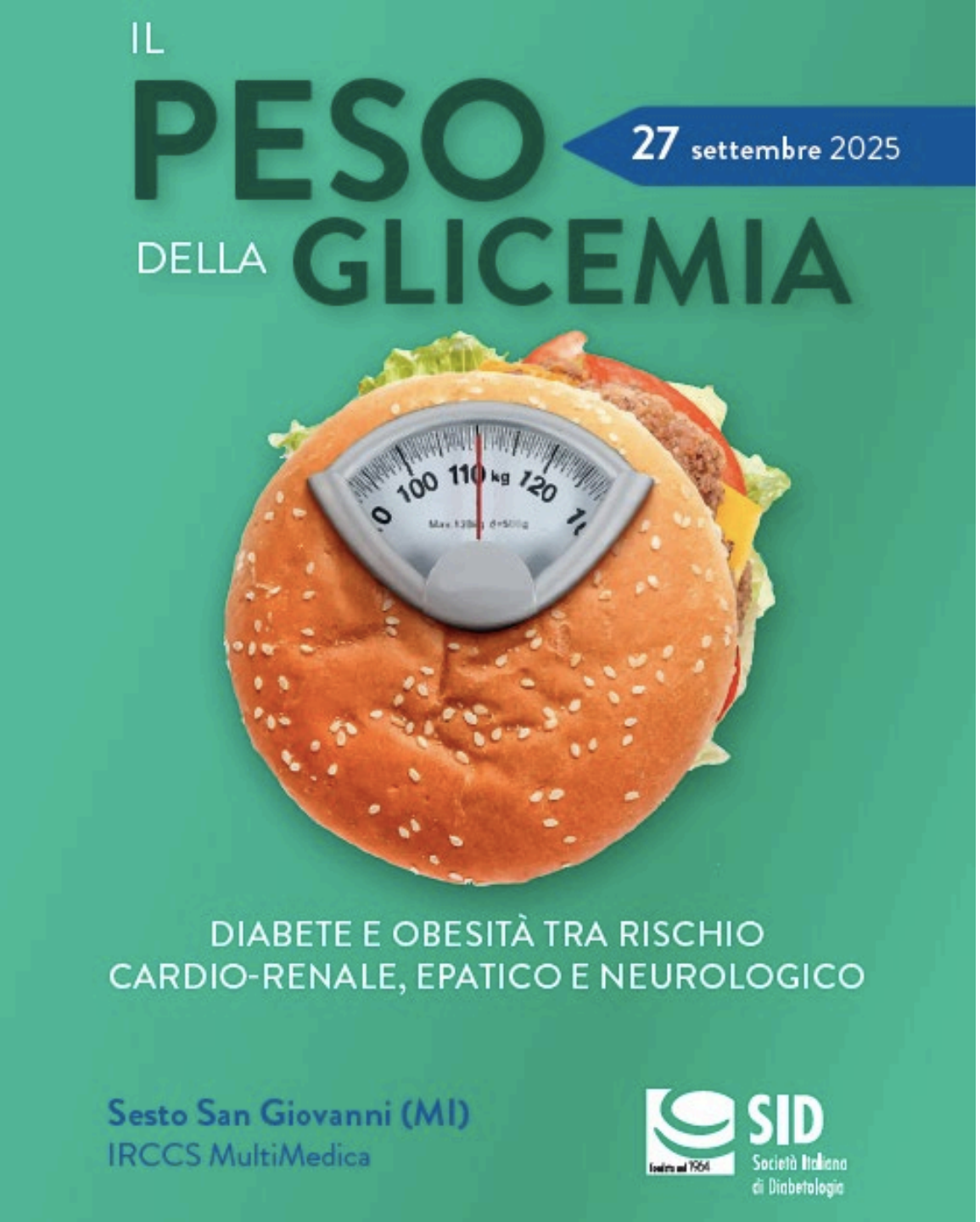
Cumulative incidence of cancer in SGLT2 inhibitor users compared to non-SGLT2 inhibitor users.

Sodium–glucose cotransporter 2 inhibitors and the cancer patient: from diabetes to cardioprotection and beyond

HUMANITAS GAVAZZENI



Camilli M, et al. Basic Research in Cardiology, 2024 - https://doi.org/10.1007/s00395-024-01059-9



Diabete e cancro: quali, quanto e perché?

AGENDA

- Introduzione
- Quali
- Quanto
- Perché
- Conclusioni

World Journal of Diabetes

Diabetes and cancer: Epidemiological and biological links

Characteristic of diabetes	Consequences which promote cancer
High blood sugar level	DNA damage
	ROS production
	Chronic inflammation
	Promote cancer cell proliferation
	Promote cancer cell growth
	Promote cancer cell metastasis
	Provide alternative energy source for cancer cell survival
High blood insulin level (as in T2DM)	Increase level of IGF-1
	Promote cancer cell proliferation
	Promote cancer cell differentiation
	Promote cancer cell survival
	Promote cancer cell migration
	Promote cancer cell growth
	Promote cancer cell metastasis
Inflammation	Promote cancer cell proliferation
	Accelerate cancer cell growth
	Accelerate cancer cell metastasis
	Promote EMT
	Promote cancer cell survival
	Inhibit certain immune responses

Wang M, Yang Y, Liao Z. World J Diabetes 2020; 11(6): 227-238 - DOI: https://dx.doi.org/10.4239/wjd.v11.i6.227

cancers

Review

Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management

Sukanya Pati [1], Wadeed Irfan [2], Ahmad Jameel [1], Shahid Ahmed [1,3,*] and Rabia K. Shahid [1,*]

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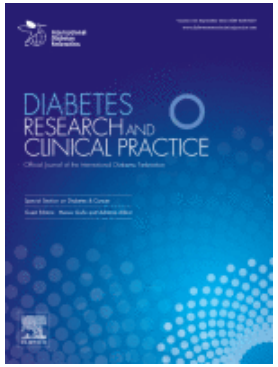
1) Increased synthesis of estradiol from androgens due to the presence of aromatase found in peripheral adipose tissue, that has been linked to an **increased risk of developing breast, endometrial, ovarian,** and other **cancers**.

2) **Hyperinsulinemia and Insulin-resistance** due to increased BMI, which stimulates the normal growth function of insulin as well as prolonging the duration of the **action of insulin-like growth factor-1 (IGF-1)**. The development of **colon, renal, prostate, and endometrial cancer** may be aided by this point.

3) **Proinflammatory environment** cultivated by the altered secretion of many **adipokines** by adipose tissue, specifically increased levels of **leptin, which is a potent inflammatory, proliferative, and antiapoptotic agent**. Excess fat tissue leads to adipocyte hypertrophy and cell death resulting in the **chronic, subclinical inflammation of adipose tissue.**

Cancers. 2023, 15, 485. https://doi.org/10.3390/cancers15020485



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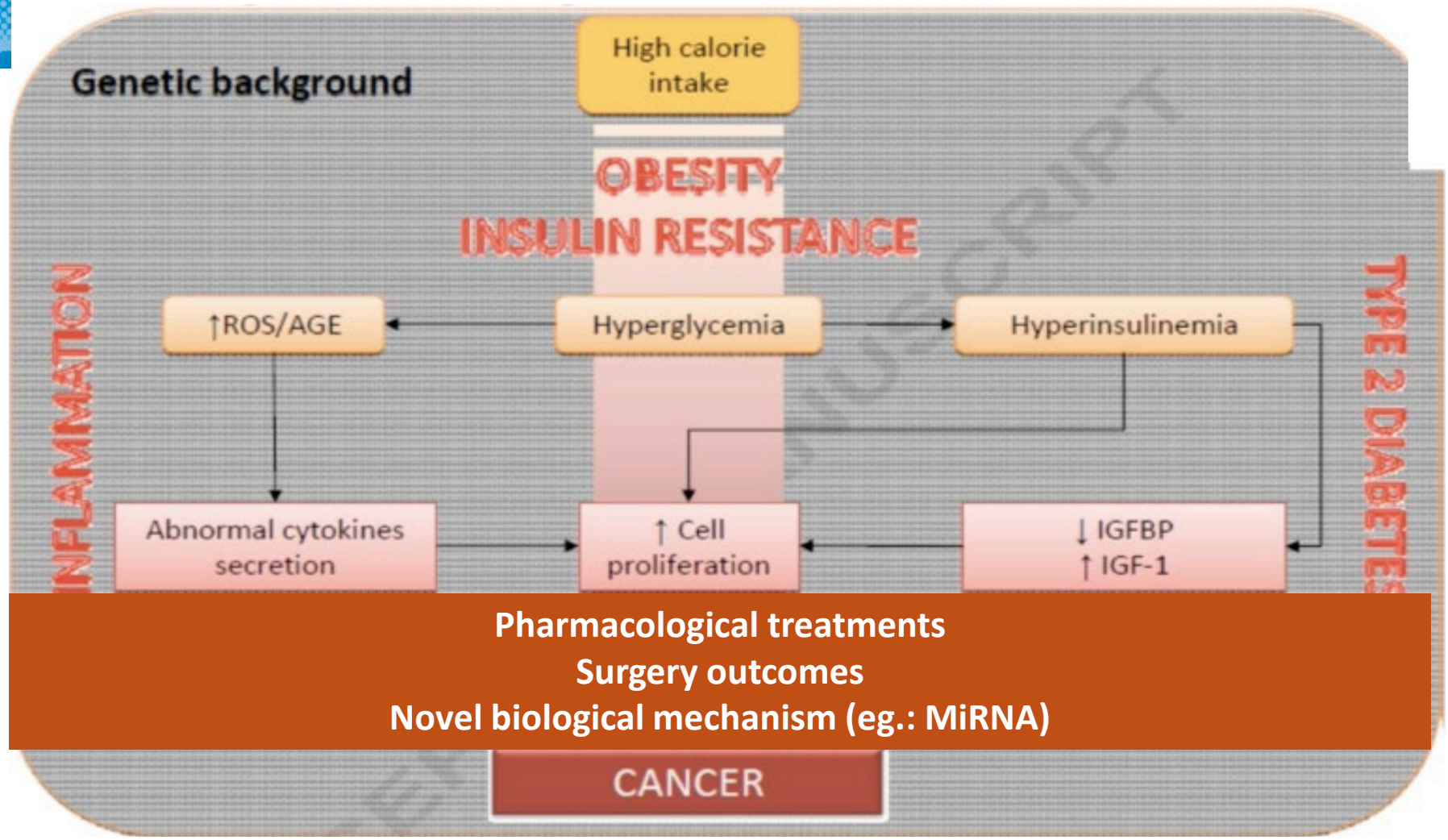
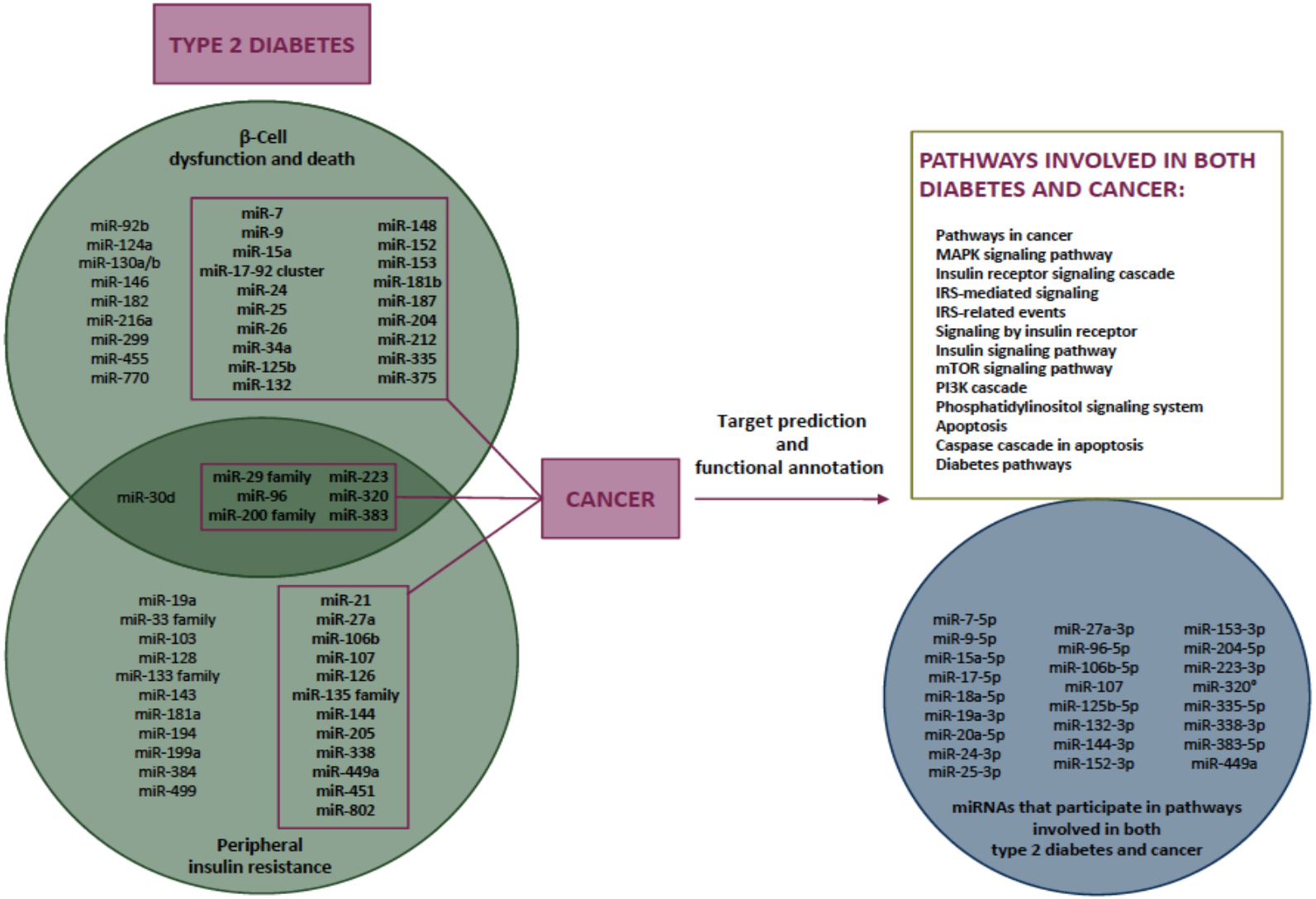
Diabetes and cancer:
Pathophysiological fundamentals of a 'dangerous affair'

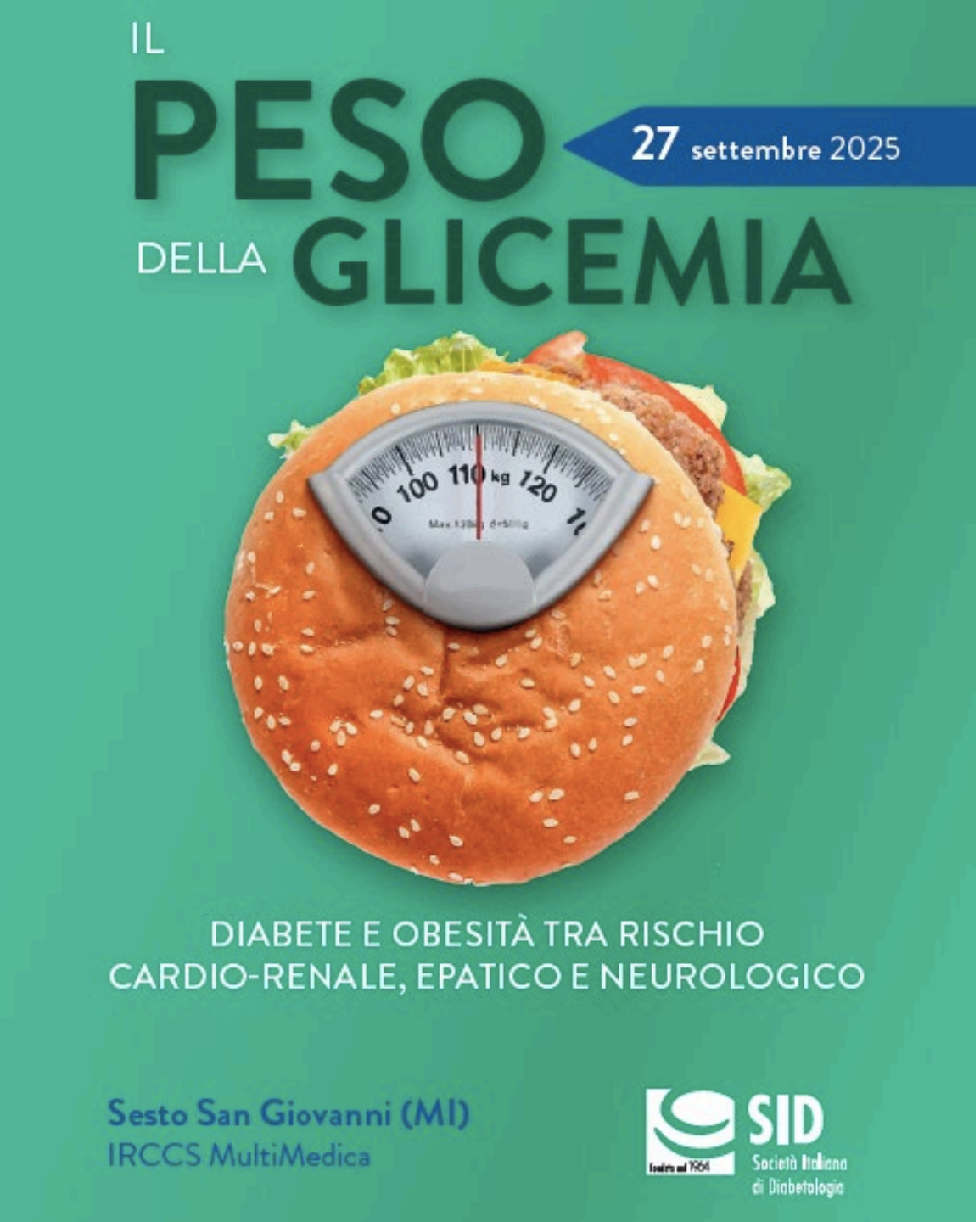


Cignarelli A, et al. Diabetes Research and Clinical Practice, 2018, Volume 143, 378 - 388

MiRNA dysregulation underlying common pathways in type 2 diabetes and cancer development: an Italian Association of Medical Oncology (AIOM)/ Italian Association of Medical Diabetologists (AMD)/Italian Society of Diabetology (SID)/Italian Society of Endocrinology (SIE)/Italian Society of Pharmacology (SIF) multidisciplinary critical view



Natalicchio A, et al. ESMO Open Volume 8 - Issue 3 - 2023 https://doi.org/10.1016/j.esmoop.2023.101573



Diabete e cancro: quali, quanto e perché?

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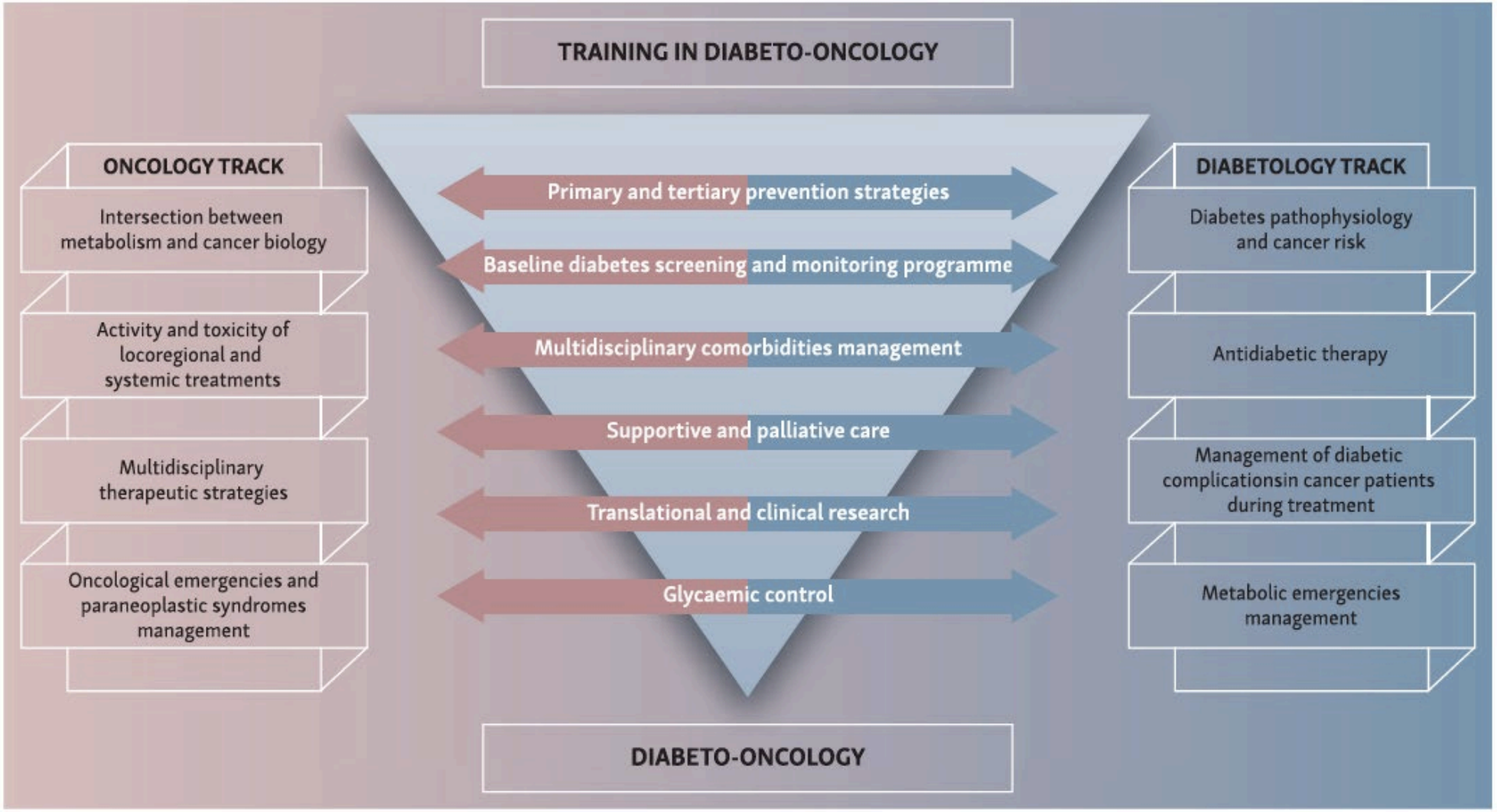
Diabetes management in cancer patients. An Italian Association of Medical Oncology, Italian Association of Medical Diabetologists, Italian Society of Diabetology, Italian Society of Endocrinology and Italian Society of Pharmacology multidisciplinary consensus position paper



Silvestris N, et al. ESMO Open Volume 8 - Issue 6 - 2023 https://doi.org/10.1016/j.esmoop.2023.102062

Glycemic control and cancer outcomes in oncologic patients with diabetes: an Italian Association of Medical Oncology (AIOM), Italian Association of Medical Diabetologists (AMD), Italian Society of Diabetology (SID), Italian Society of Endocrinology (SIE), Italian Society of Pharmacology (SIF) multidisciplinary critical view

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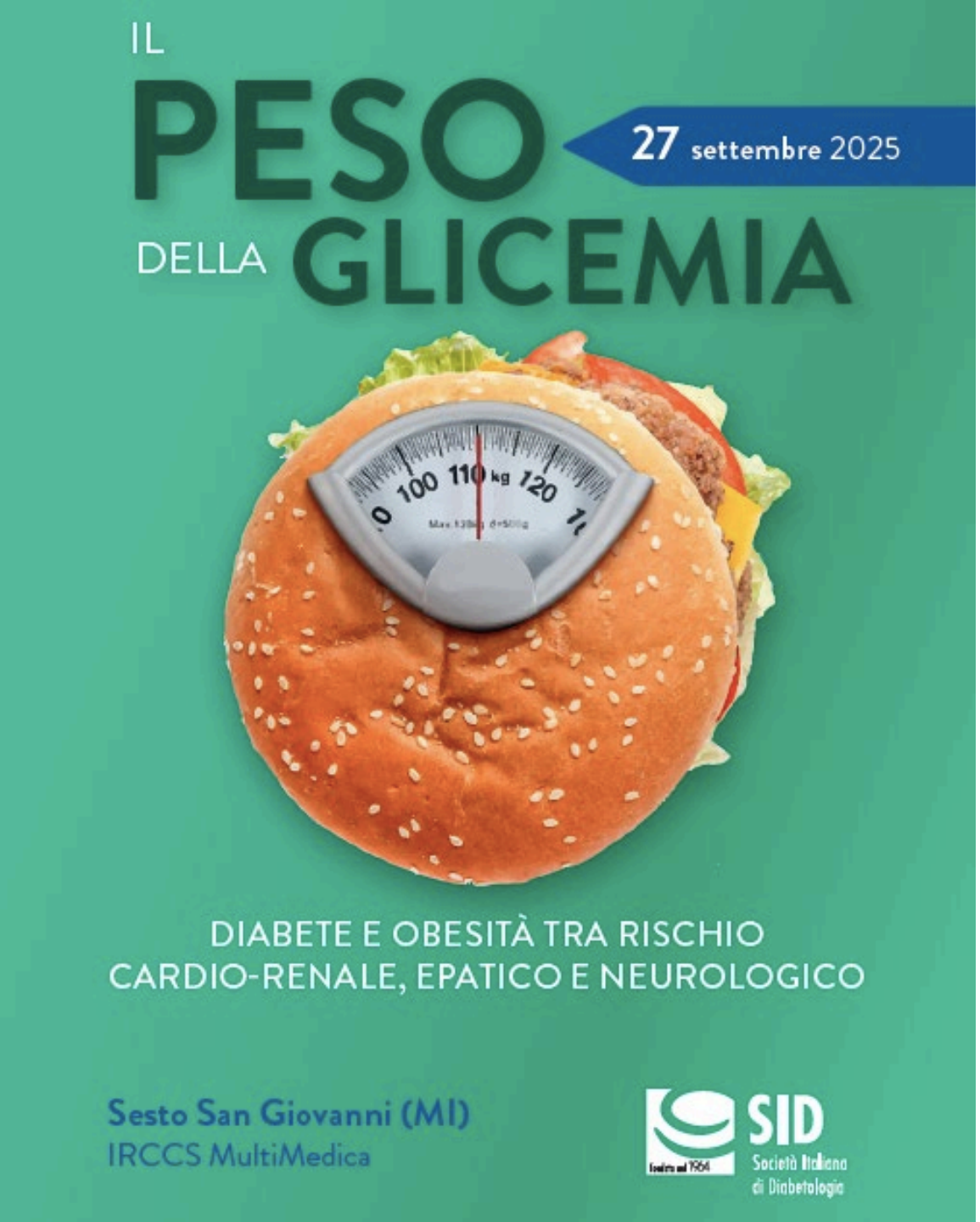
Evidence on the association between glycemic control and cancer outcomes in oncologic patients with diabetes

Cancer	Type of study	Glycemic control (evaluation method)	Cancer outcome
Various cancers	Review and meta-analysis	Various methods	↑ Survival and DFS, = PFS
Various cancers	Prospective	HbA1c	↓ Adverse events, reduction or interruption of chemo-therapy
Various cancers	Prospective	FG	↓ Mortality
Various cancers	Analysis of 97 retrospective studies	FG	↓ Cancer death
Various cancers	Retrospective	HbA1c 6 months before cancer diagnosis	= OS; ↓ survival in patients with bladder cancer and treated with insulin
Various cancers	Cross-sectional	HbA1c during chemotherapy	= Severity of symptoms
Various cancers	Prospective	HbA1c	↓ Mortality

↑ adequate glycemic control increases the probability of the indicated outcome, ↓ adequate glycemic control reduces the probability of the indicated outcome, = adequate glycemic control has no effect on the indicated outcome, DFS disease-free survival, FG fasting glucose levels, HbA1c glycated hemoglobin, OS overall survival, PFS progression-free survival

Natalicchio A, et al. Journal of Endocrinological Investigation (2024) 47:2915–2928 https://doi.org/10.1007/s40618-024-02417-z



III SESSIONE
Diabete tipo 2, il punto sulle complicanze "emergenti"
Moderatori: Antonio Ceriello, Alessandro R. Dodesini

Diabete e cancro: quali, quanto e perché?

Antonio C. Bossi, Humanitas Bergamo

GRAZIE per la Vostra ATTENZIONE!