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PER UNA DIABETOLOGIA PREDITTIVA, PREVENTIVA, PERSONALIZZATA E PARTECIPATIVA

La terapia oncologica nel paziente diabetico: problematiche ed efficacia

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Il problema cancro nel paziente diabetico: epidemiologia e biologia

- Epidemiological studies have detected a higher incidence of various tumour entities in diabetic patients.

- However, the underlying mechanisms remain insufficiently understood.

Twarock S, Int J Cancer 2017

DM come fattore di rischio

Table 1 – Meta-analyses: diabetes as a risk factor for cancer.

Author	Tumour type	Case–control studies		Prospective cohort studies	
		#	RR (95% CI)	#	RR (95% CI)
Larsson et al.[78]	Bladder	7	1.4 (1.0–1.8)	3	1.4 (1.2–1.7)
Larsson et al.[79]	Breast	5	1.2 (1.1–1.3)	15	1.2 (1.1–1.3)
Wolf et al[80]	Breast	4	1.1 (1.0–1.3)	6	1.3 (1.2–1.3)
Larsson et al.[81]	Colorectal	6	1.4 (1.2–1.5)	9	1.3 (1.2–1.4)
Friberg et al.[82]	Endometrium	13	2.2 (1.8–2.7)	3	1.6 (1.2–2.2)
El-Serag *et a*[83]	HCC	13	2.5 (1.9–3.2)	12	2.5 (1.9–3.2)
Chao et al.[84]	NHL	10	1.2 (1.0–1.4)	3	1.8 (1.3–2.5)
Mitri et al.[85]	NHL	11	1.1 (0.9–1.3)	5	1.4 (1.1–1.9)
Everhart et al.[86]	Pancreatic	11	1.8 (1.1–2.7)	9	2.6 (1.6–4.1)
Huxley et al.[87]	Pancreatic	17	1.9 (1.5–2.5)	19	1.7 (1.6–1.9)
Bonovas et al.[88]	Prostate	5	0.9 (0.7–1.2)	9	0.9 (0.9–1.0)
Kasper et al.[89]	Prostate	7	0.9 (0.7–1.1)	12	0.8 (0.7–0.9)

RR: pooled relative risk. CI: confidence interval. HCC: hepatocellular carcinoma. NHL: non-Hodgkin's lymphoma. *Number of studies.

Jalving M et al, *Eur J Cancer 2010*

Il problema cancro nel paziente diabetico: epidemiologia e biologia

- However, the underlying mechanisms remain insufficiently understood.

- Glucose-derived pericellular and extracellular hyaluronan (HA) promotes tumour progression and development.

Twarock S, Int J Cancer 2017

Quali problemi osserva l'oncologo medico?

- ***"Scompenso" glicemico*** (iperglicemia e/o iperinsulinemia) in pazienti sottoposti ad alcuni trattamenti antineoplastici, indipendentemente dal pregresso stato metabolico.

Ariaans G et al, *Cancer Treatment Reviews 2015*

Table 1
Consequences of cancer treatment for insulin resistance and efficacy of cancer treatment.

	Plasma glucose	Plasma insulin	Working mechanism of cancer treatment	Possible mechanism of insulin resistance development	Effect of insulin resistance on cancer therapy
Glucocorticoids					
Dexamethasone [7,32–35,95]	↑	Not measured	Anti-inflammatory, immunosupressant	Down-regulation of IRS protein Down-regulation of GLUT1 Reduced pancreatic β-cell mass	Reduced efficacy
Prednisone [7,32,96]	↑	(↓)	Anti-inflammatory, immunosupressant	Down-regulation of IRS protein	
Chemotherapy					
5-Fluorouracil [38]	↑	Not measured	Pyrimidine analogue		
Doxorubicin [10]	No studies	No studies	DNA intercalating agent		Reduced efficacy in combination with hyperglycaemia
Platinum-based [10,97]	↑	Not measured	DNA cross-linking agent		Reduced efficacy in combination with hyperglycaemia
Paclitaxel [10]	No studies	No studies	Mitotic inhibitor		Reduced efficacy in combination with hyperglycaemia
Androgen deprivation [98]	↑	↑	Reduction of androgen hormones	Interrelation between testosterone and insulin	No specific studies
IR and IGF1R inhibition					
MK-0646 [99]	↑	Not measured	IGF1R inhibiting antibody		
BMS-536924 [47]	–	↑	ATP-competitive IGF1R/IR inhibitor	Higher accumulation in tumour than in muscle tissue	
PI3K/AKT inhibition					
NVP-BEZ235 [48–51]	↑	Not measured	Dual PI3K-mTOR inhibitor	Decreased levels of IRS Decreased secretion of insulin	
NVP-BKM120 [48,49,51]	↑↑	Not measured	Specific PI3K inhibitor	Decreased levels of IRS Decreased secretion of insulin	
PI-103 [48–50]	↑	Not measured	PI3K/AKT/mTOR inhibitor	Decreased levels of IRS Decreased secretion of insulin	
IC87114 [48–50]	–	–	p110δ-selective inhibitor		
mTOR inhibition					
Everolimus [8,54,55,100]	↑	↓	mTORC1 inihibitor	Altered activation of AKT and IRS Differential inhibition of mTORC1 and mTORC2 Reduced pancreatic β-cell mass	No specific studies

Ariaans G et al, *Cancer Treatment Reviews 2015*

Vorrei invece un controllo glicemico, perché…

Evidenze sul ruolo di iperglicemia e/o iperinsulinemia:

- ↓ **Sopravvivenza**[1,2,4,7]
- ↑ Rischio di recidiva/ripresa di malattia[2,4,5,6,8]
- ↓ Efficacia della terapia oncologica[2]
- ↑ Tossicità dalla terapia oncologica[3]

*Gerards MC et al, Crit Rev Oncol Hematol 2017*10.1016/j.critrevonc.2017.03.00

1. Villarreal-Garza C et al, *Exp Diabetes Res 2012*
2. Barba M et al, *Ann Oncol 2012*
3. Carroll J et al, *Breast Cancer Res Treat 2012*
4. Cai Q et al, *Br J Cancer 2013*
5. Wright JL et al, *Prostate Cancer Prostatic Dis 2013*
6. Hosokawa T et al, *World J Gastroenterol 2013*
7. Xu H et al, *J Cancer Res Clin Oncol 2013*
8. Pantano F et al, *Cancer Biol Ther 2013*

In effetti, è abbastanza logico…

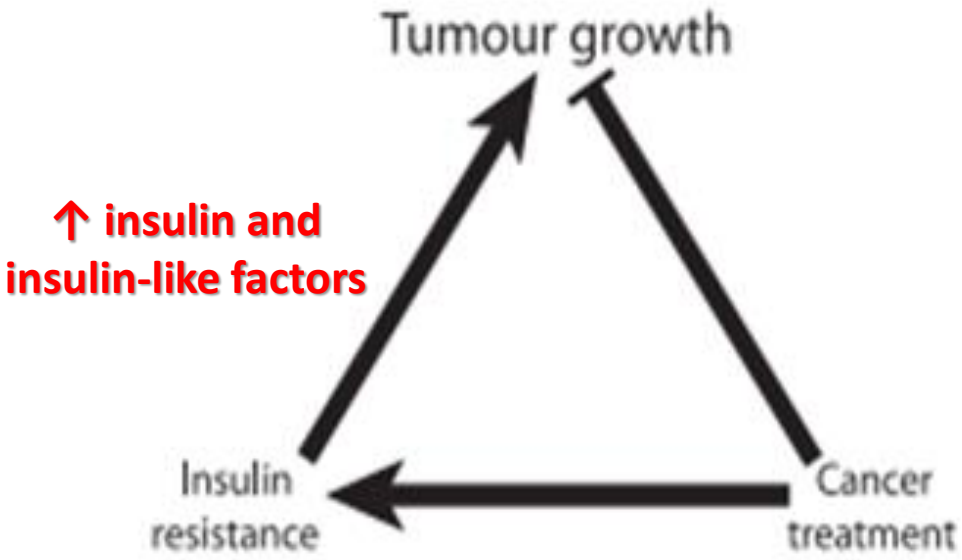


Fig. 2. Interrelation between cancer treatment, insulin resistance and tumour growth. Cancer treatments have the potential to induce insulin resistance, which may promote tumour growth and progression and also may reduce treatment efficacy.

Adapted from Ariaans G et al, *Cancer Treatment Reviews 2015*

Ma i meccanismi molecolari potrebbero essere molto difficili e coinvolgere direttamente anche l'iperglicemia

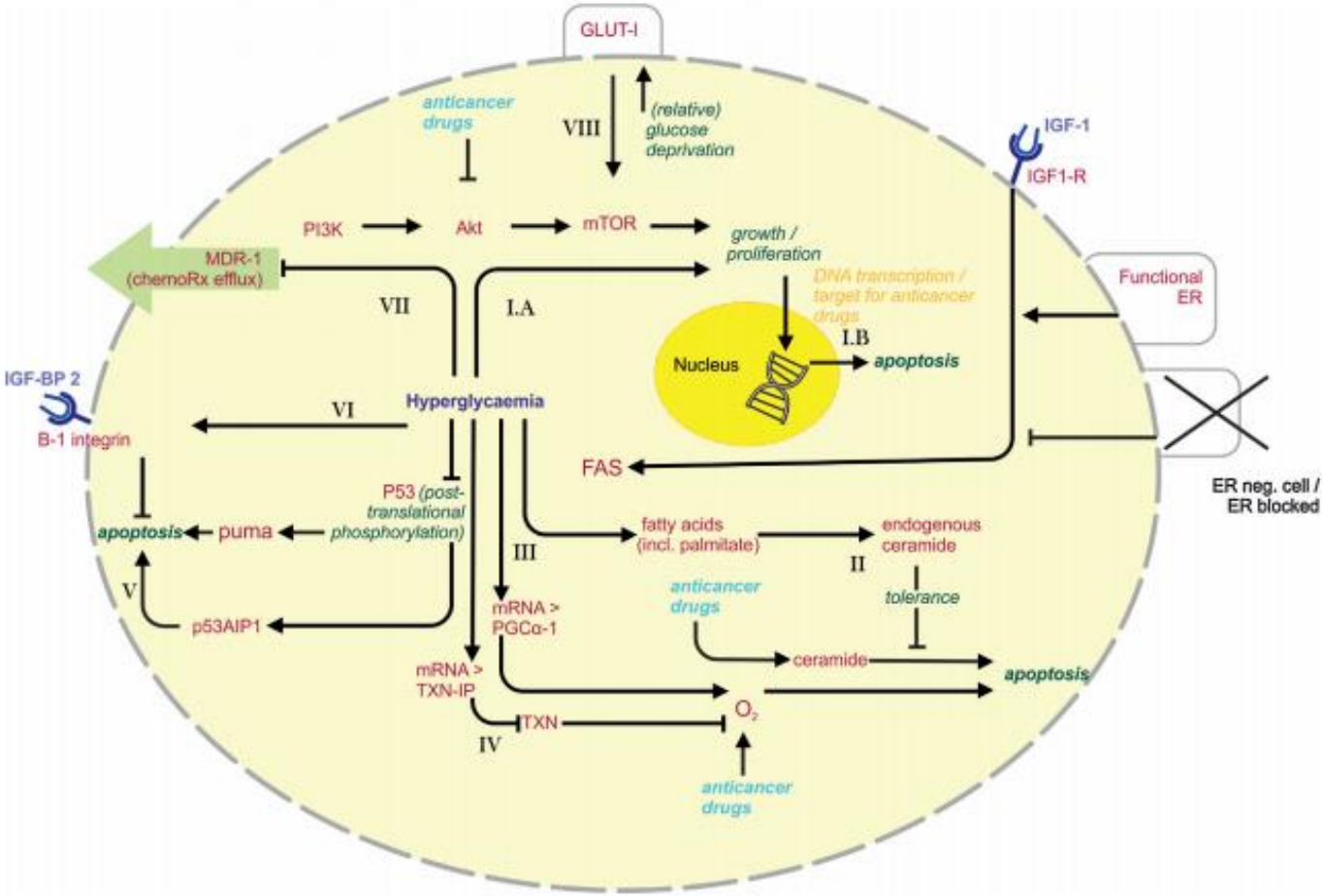


Fig. 1. Simplified pathways of the mechanisms described in the included studies. T-lines depict an inhibitory effect and arrows depict a stimulatory effect.
Abbreviations: ER = Estrogen receptor. FAS = Fatty acid synthase. GLUT-1 = glucose uptake transporter 1. IGF-BP2 = Insulin growth factor binding protein-2. IGF-1(R) = insulin growth factor 1(-receptor). IR = insulin receptor. MDR-1 = multidrug resistance protein-1. PGC-1a = Peroxisome proliferator-activated receptor γ coactivator-1alpha. P53AIP1 = p53-regulated apoptosis-inducing protein-1. PUMA = P53 Upregulated Modulator of Apoptosis. ROS = reactive oxygen species. TXN = Thioredoxin. TXN-IP = TXN interacting protein.

Gerards MC et al, *Crit Rev Oncol Hematol 2017*

Iperinsulinemia ed iperglicemia non sono, poi, i soli colpevoli

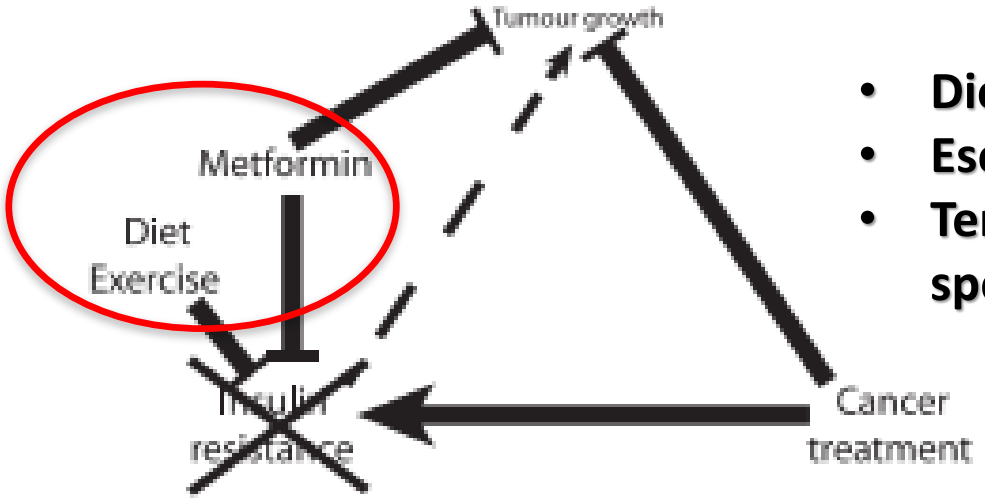
Table 3
Overview of mechanisms that may play a role in the association between diabetes mellitus and hyperglycemia on the one hand, and chemotherapy response on the other hand.

Mechanism	Effect
Hyperglycemia	Glucose can serve as fuel for growth of cancer. There are hypotheses on indirect effects of glucose concentration on cancer progression, which are explained in Fig. 1.
Hyperinsulinemia	Insulin is an anabolic hormone and can stimulate growth of tissues, including malignant cells.
Diabetes-associated comorbidities	Diabetes associated comorbidities such as nephropathy, vasculopathy and neuropathy limit the dosages of chemotherapy tolerated by patients and increase risk of toxicity
Diabetes treatment	Exogenous insulin use is associated with increased incidence and progression of cancer. Metformin is associated with favorable outcomes in cancer treatment. For neither of these treatment modalities, a causal relationship has been established.

Gerards MC et al, *Crit Rev Oncol Hematol 2017*

Allora vorrei proprio tanto un controllo glicemico!!!

Dobbiamo quindi incentivare i classici sistemi di controllo…

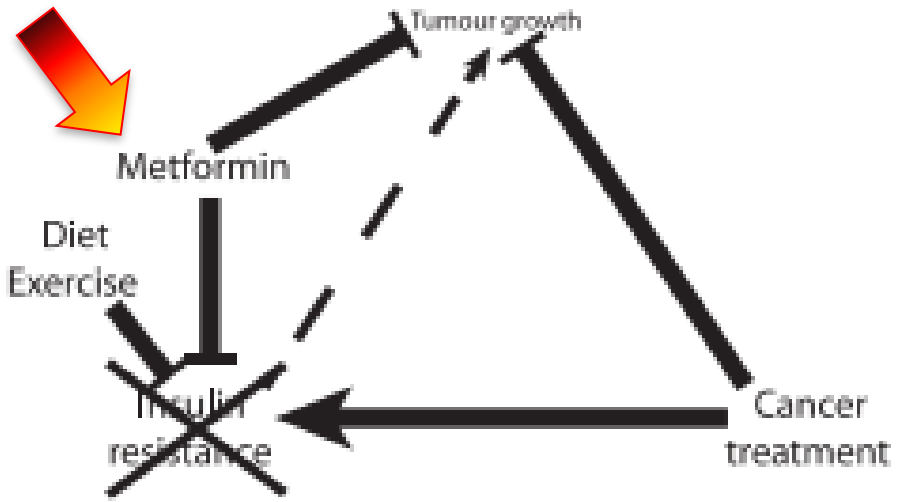


- **Dieta**
- **Esercizio fisico**
- **Terapia ipoglicemizzante specifica**

Inhibition of insulin resistance by diabetes medications, fasting regimes and exercise could diminish insulin resistance, thereby increasing efficacy of cancer treatments.

Adapted from Ariaans G et al, *Cancer Treatment Reviews 2015*

Terapia ipoglicemizzante orale o normoglicemizzante orale?

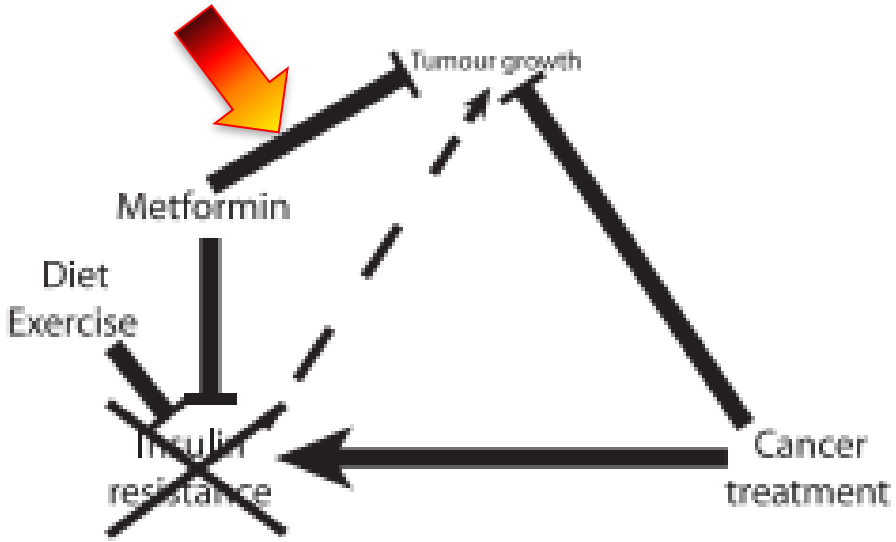


Inhibition of insulin resistance by diabetes medications, fasting regimes and exercise could diminish insulin resistance, thereby increasing efficacy of cancer treatments.

Essendo centrale il ruolo dell'insulina in qualità di fattore di crescita, appare logico che "colpire" con farmaci che agiscono sull'insulina e sul sistema dell'insulino-resistenza è più ragionevole che utilizzare farmaci ipoglicemizzanti che incrementano i valori di insulina (es. sulfaniluree, insulina esogena…)

Adapted from Ariaans G et al, *Cancer Treatment Reviews 2015*

Però c'è qualcosa di più…



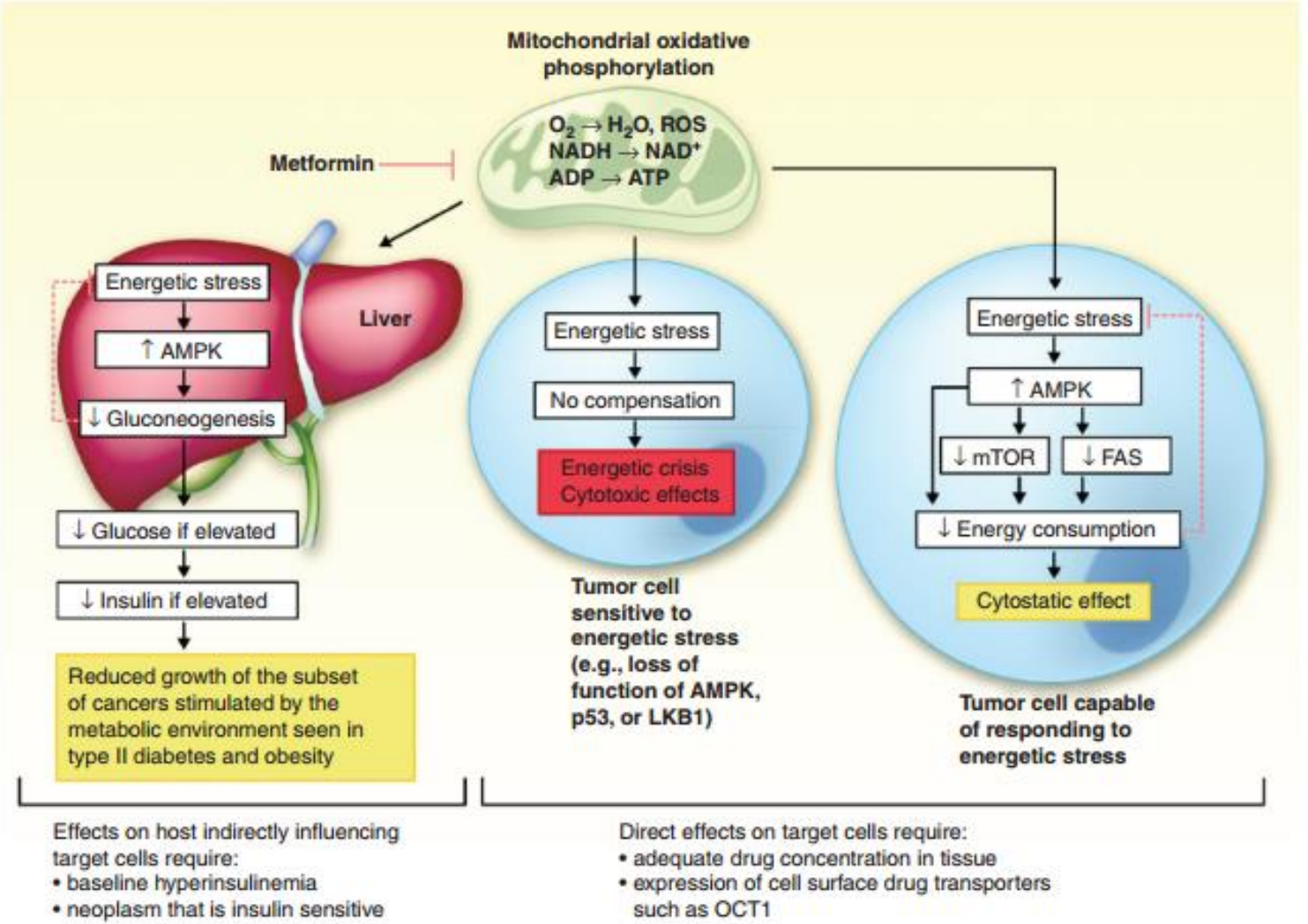
Inhibition of insulin resistance by diabetes medications, fasting regimes and exercise could diminish insulin resistance, thereby increasing efficacy of cancer treatments.

La **metformina** ha proprietà antitumorali intrinseche

Adapted from Ariaans G et al, *Cancer Treatment Reviews 2015*

Metformina

(A simplified view of proposed antineoplastic mechanisms of action of biguanides)



Pollak MN, *Cancer Discovery 2012*

Metformina

(A simplified view of proposed antineoplastic mechanisms of action of biguanides)

- These mechanisms suggest opportunities for rational combination therapies of biguanides with other agents.

- Metformin is a suitable agent for clinical trials related to the “insulin reduction” mechanism, but biologically significant declines may be confined to patients with hyperinsulinemia at baseline.

Metformina

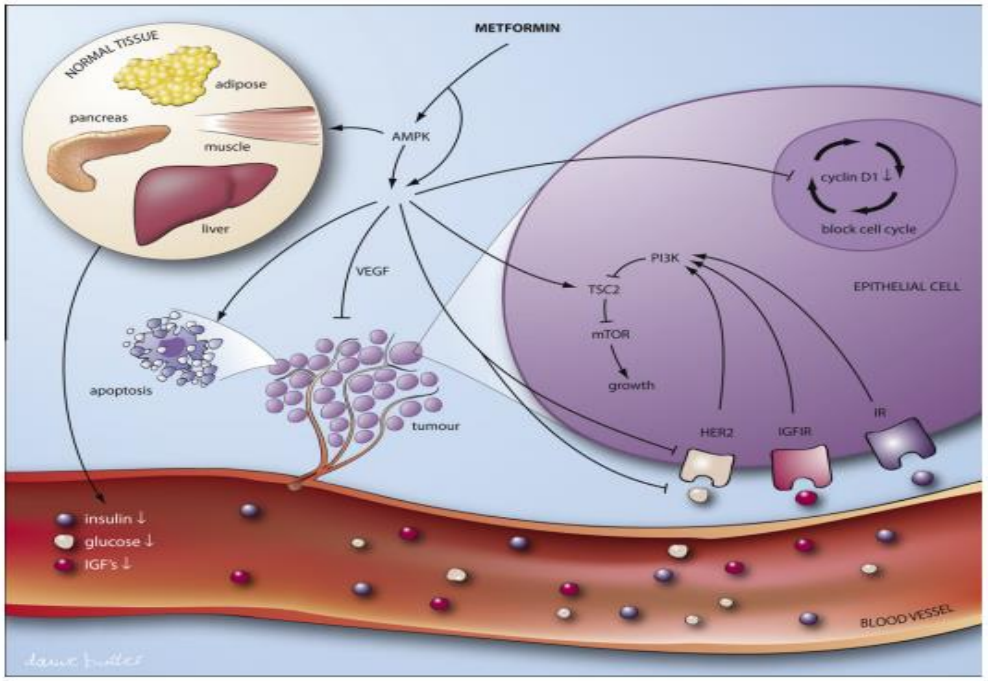
(A simplified view of proposed antineoplastic mechanisms of action of biguanides)

It remains to be determined if :

orally administered metformin at ***conventional*** antidiabetic doses achieves sufficient drug levels in neoplastic tissue to allow for clinical evaluation of the proposed "direct" mechanisms of action, or if this will require the development of ***novel biguanide*** formulations designed to minimize adverse effects (at least for short-term administration) while achieving adequate neoplastic tissue exposure

Anti-cancer effects of metformin

Jalving M et al, *Eur J Cancer 2010*



1. M. can inhibit mTOR signalling through phosphorylation and stabilisation of TSC2.

2. M. can suppress HER-2 protein expression and also inhibit HER-2 protein kinase activation resulting in reduced signalling through downstream pathways.

3. M. can decrease levels of VEGF resulting in inhibition of angiogenesis.

4. M. can induce apoptosis through p53-dependent or independent mechanisms.

5. M. can block cell cycle arrest at least partially mediated through reduced cyclin D1 expression

Prospettive future…

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A TUTTI I LIVELLI!!

		Study
	…ruiting	Phase I/II Study OF Metformin in Combination With Cisplatin and Radiation in Head and Neck Squamous Cell Carcinoma **Condition:** Head and Neck Squamous Cell Carcinoma **Intervention:** Drug: Metformin
2	Withdrawn	Study of Metformin With Simvastatin for Men With Prostate Carcinoma **Condition:** Prostate Carcinoma **Interventions:** Drug: Metformin; Drug: Simvastatin
		Study of Paclitaxel, Carboplatin and Oral Metformin in the Treatment of Advanced Stage Ovarian Carcinoma **Condition:** Epithelial Ovarian Carcinoma **Interventions:** Drug: Metformin; Drug: Paclitaxel; Drug: Carboplatin
4	Recruiting	Vandetanib in Combination With Metformin in People With HLRCC or SDH-Associated Kidney Cancer or Sporadic Papillary Renal Cell Carcinoma **Conditions:** Renal Cell Carcinoma; Hereditary Leiomyomatosis and Re… Papillary Renal Cell Carcinoma, Sporadic **Interventions:** Drug: Vandetanib; Drug: Metformin
		Primary Prevention Hepatocellular Carcinoma by Metformin

TRATTAMENTO NELLA MALATTIA LOCALIZZATA A SCOPO CURATIVO O ADIUVANTE

TRATTAMENTO NELLA MALATTIA AVANZATA

TRATTAMENTO IN SOTTOGRUPPI SPECIFICI

PREVENZIONE TUMORALE

Screenshot from *clinicaltrials.gov*

… ma non solo!

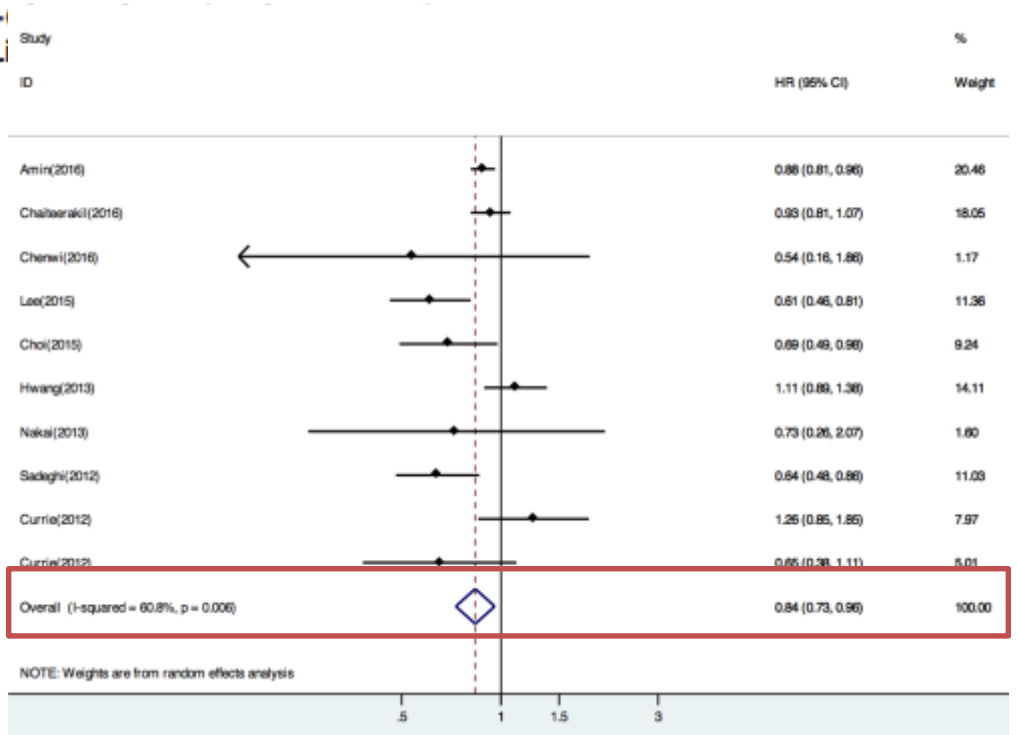
www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 15), pp: 25242-25250

Research Paper

Metformin is associated with survival benefit in pancreatic cancer patients with diabetes: a systematic review and meta-analysis

Ping-Ting Zhou[1,*], Bo Li[2,*], Fu-Rao Liu[1], Mei-
Li[1], Ci Xu[1], Yuan-Hua Liu[3], Yuan Yao[4], Dong Li

We found that there was a relative **survival benefit associated with metformin** treatment compared with non-metformin treatment in both overall survival (OS) (**[HR] 0.84**; 95% confidence interval [CI]: 0.73 – 0.96). These associations were also observed in subgroups of Asian countries and high quality articles.



Sato E et al, *Mol Clin Oncol 2017*

Review Article

Metformin Use Is Associated with Reduced Incidence and Improved Survival of Endometrial Cancer: A Meta-Analysis

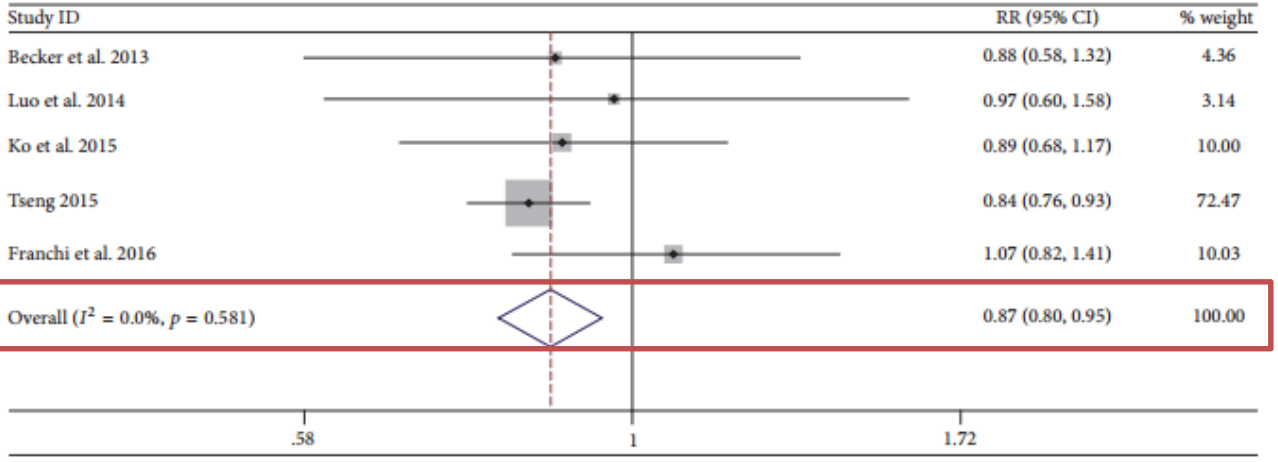


FIGURE 2: Forest plot of the association between metformin use and incidence of endometrial cancer.

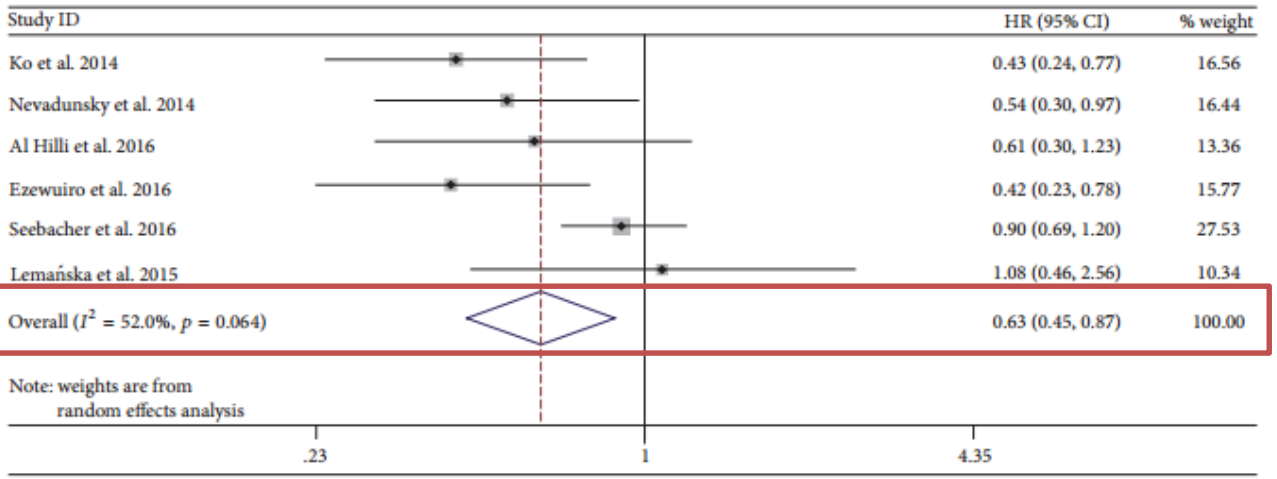


FIGURE 3: Forest plot of the association between metformin use and survival of endometrial cancer.

In the pooled analysis of six retrospective cohort studies evaluating the effect of metformin on the survival of EC patients, we found that, relative to nonuse, **metformin use significantly improved the survival of EC patients (HR = 0.63**, 95% CI: 0.45–0.87; p = 0.006).

Tang YL et al, *BioMed Res Internat 2017*

ARTICLE IN PRESS

Original Study

Effect of Metformin Use on Survival Outcomes in Patients With Metastatic Renal Cell Carcinoma

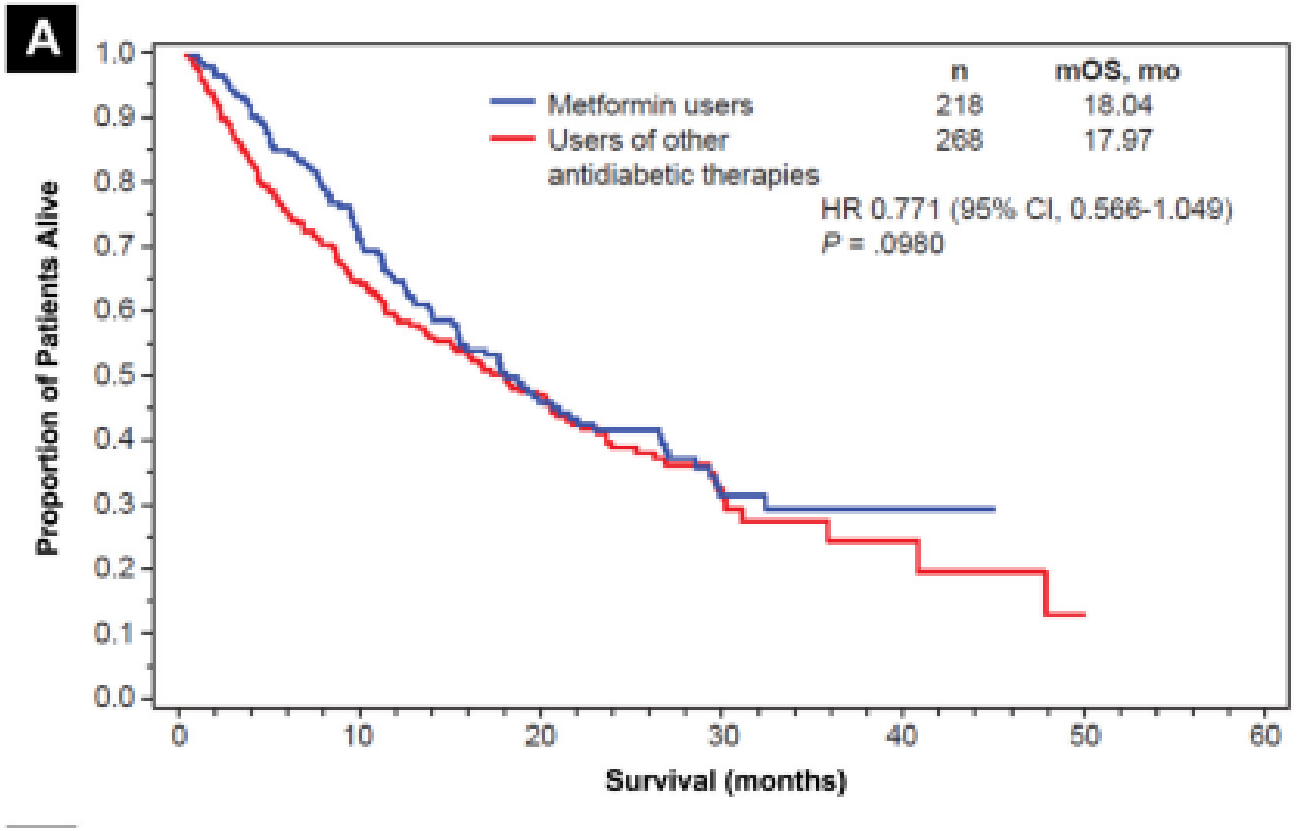
Lana Hamieh,[1] Rana R. McKay,[1] Xun Lin,[2] Raphael B. Moreira,[1] Ronit Simantov,[2] Toni K. Choueiri[1]

Abstract

In light of the emerging evidence of the antineoplastic potential of metformin, we investigated its effect on survival outcomes in metastatic renal cell carcinoma using a large clinical trial database. Although metformin did not affect survival in the overall cohort, it conferred a survival advantage in diabetic metastatic renal cell carcinoma patients treated with sunitinib.

Introduction: Observational studies have suggested that metformin use is associated with favorable outcomes in several cancers. For renal cell carcinoma (RCC), data have been limited. Therefore, we investigated the effect of metformin on survival in metastatic RCC (mRCC) using a large clinical trial database. **Patients and Methods:** We conducted a retrospective analysis of patients with mRCC in phase II and III clinical trials. The overall survival (OS) in metformin users was compared with that of users of other antidiabetic agents and those not using antidiabetic agents. Progression-free survival, objective response rate, and adverse events were secondary endpoints. Subgroup analyses were conducted after stratifying by class of therapy, type of vascular endothelial growth factor tyrosine kinase inhibitors, and International Metastatic RCC Database Consortium (IMDC) risk groups. **Results:** We identified 4736 patients with mRCC, including 486 with diabetes, of whom 218 (4.6%) were taking metformin. Metformin use did not affect OS when compared with users of other antidiabetic agents or those without diabetes. Furthermore, metformin use did not confer an OS advantage when stratified by class of therapy and IMDC risk group. However, in diabetic patients receiving sunitinib ($n = 128$), metformin use was associated with an improvement in OS compared with users of other antidiabetic agents (29.3 vs. 20.9 months, respectively; hazard ratio, 0.051; 95% confidence interval, 0.009-0.292; $P = .0008$). **Conclusion:** In the present study, we found a survival benefit for metformin use in mRCC patients treated with sunitinib. Clinical and preclinical studies are warranted to validate our results and guide the use of metformin in the clinic.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■
Keywords: Diabetes, Kidney cancer, Prognosis, Sunitinib, Targeted therapy


A
Proportion of Patients Alive
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
Survival (months)
n
mOS, mo
Metformin users
218
18.04
Users of other antidiabetic therapies
268
17.97
HR 0.771 (95% CI, 0.566-1.049)
P = .0980

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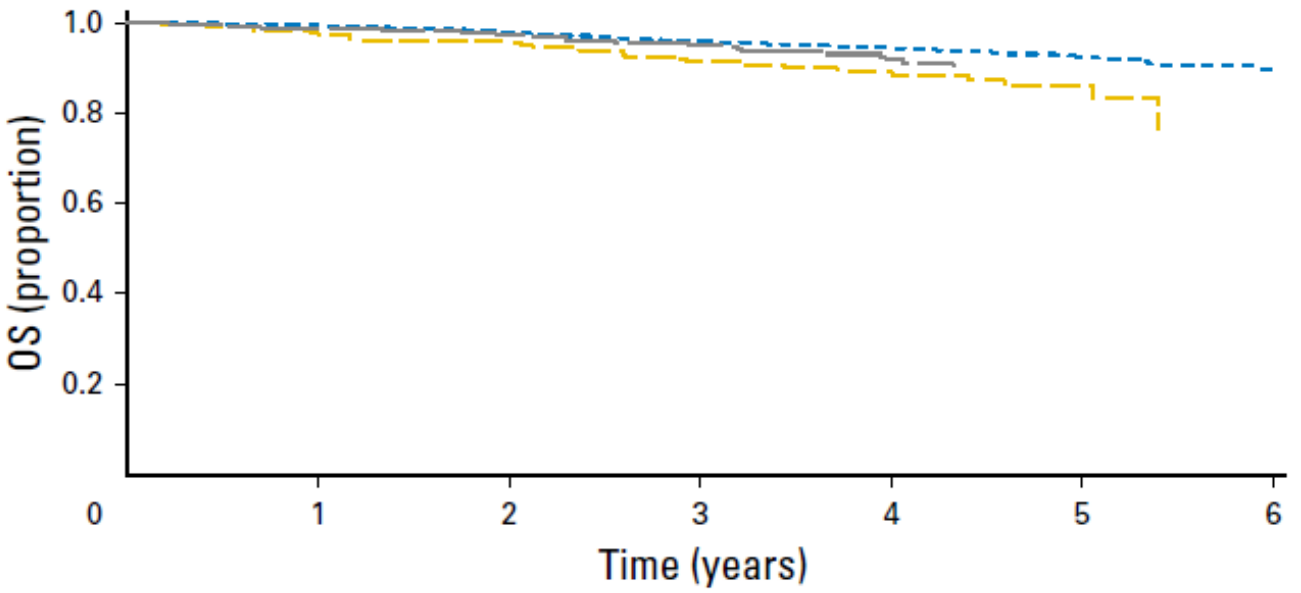
ORIGINAL REPORT

C



No. at risk:							
Nondiabetic	7,935	7,511	7,256	6,751	5,124	1,953	105
Diabetes nonmetformin	186	171	163	143	107	46	5
Diabetes metformin	260	243	232	200	145	53	2

Patients with diabetes who had not been treated with metformin experienced worse DFS (multivariable hazard ratio [HR], 1.40; 95% CI, 1.01 to 1.94; P = .043), DDFS (multivariable HR, 1.56; 95% CI, 1.10 to 2.22; P = .013), and OS (multivariable HR, 1.87; 95% CI, 1.23 to 2.85; P = .004).

Conclusioni

Obiettivo: controllo glicemico

Metodi:

- Stile di vita (dieta, esercizio fisico)
- Terapia normoglicemizzante e normoinsulinemizzante

Possibili *steps forward*: metformina come trattamento antitumorale specifico (probabilmente in combinazione ai trattamenti oncologici standard) ???

NETWORK ITALIANO CURE DI SUPPORTO IN ONCOLOGIA

Grazie per l'attenzione!