

LA GESTIONE DEL PAZIENTE ONCOLOGICO CON DIABETE MELLITO - PRESSO AO S. CROCE E CARLE CUNEO

Introduzione

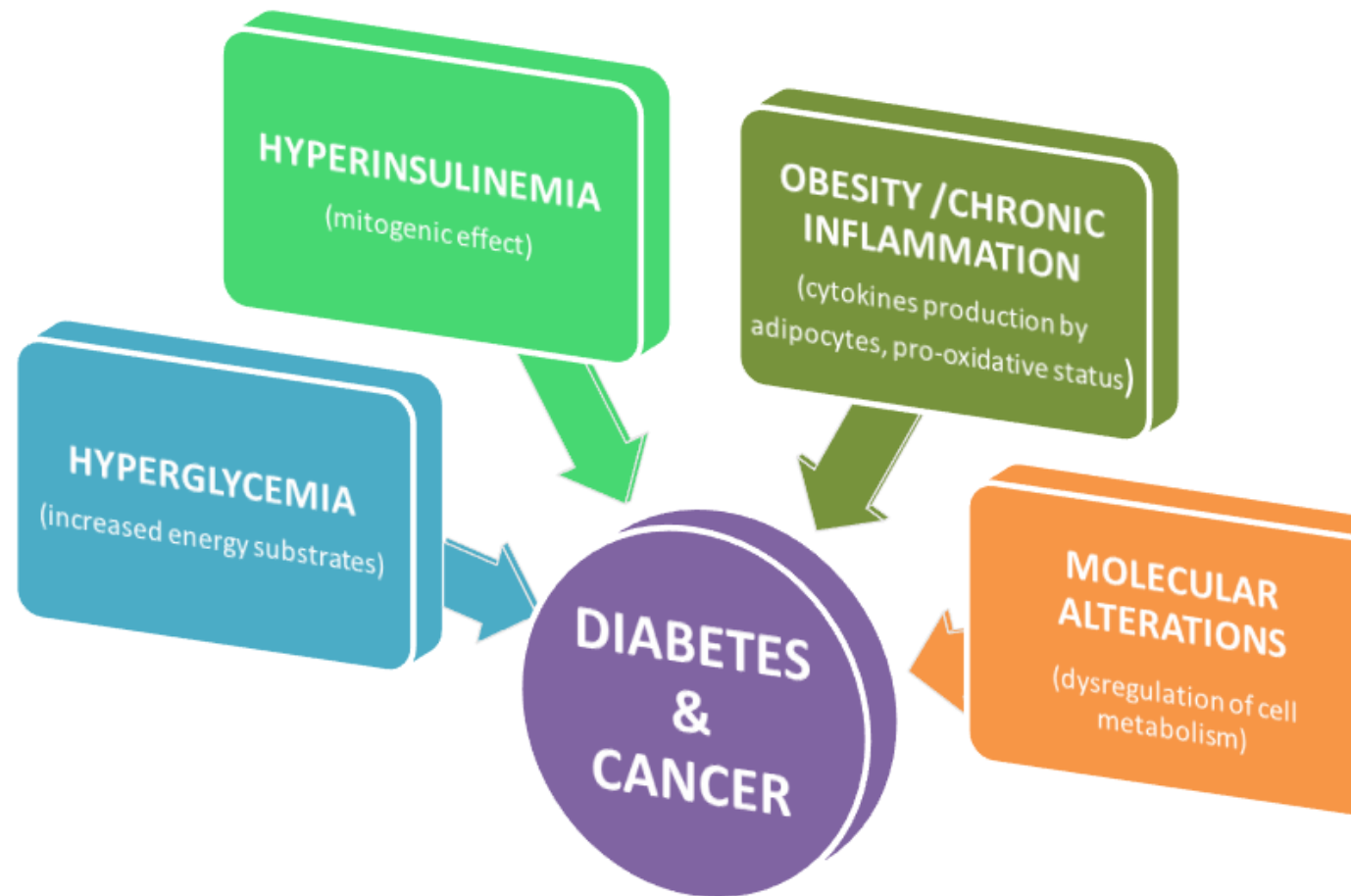
Marco Gallo – Giorgio Grassi

AOU Città della Salute e della Scienza di Torino

Molinette - COES

24 maggio 2018

diabete & cancro



Cignarelli A. et al., *Diab Res Clin Pract* 2017

Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment

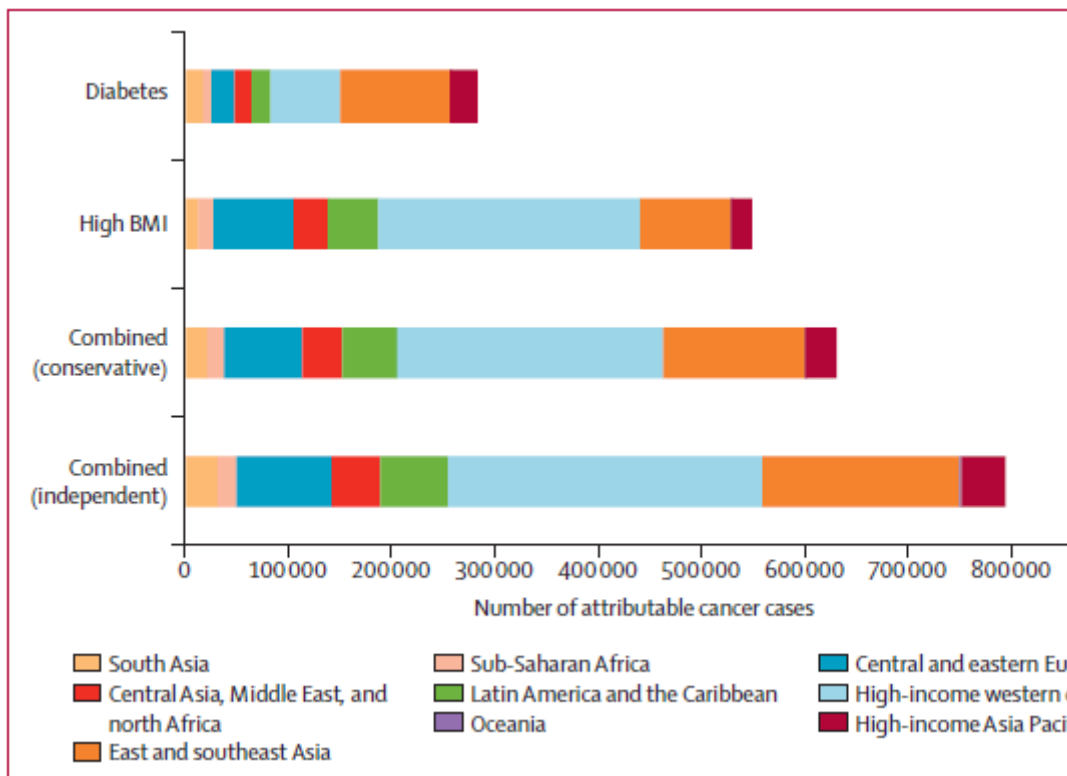
Nathan Pearson-Stuttard, Bin Zhou, Vasilis Kontis, James Bentham, Marc J Gunter, Majid Ezzati

Lancet Diabetes Endocrinol 2017



Methods We estimated population attributable fractions for 12 cancers by age and sex for 175 countries in 2012. We defined high BMI as a BMI greater than or equal to 25 kg/m². We used comprehensive prevalence estimates of diabetes and BMI categories in 2002, assuming a 10-year lag between exposure to diabetes or high BMI and incidence of cancer, combined with relative risks from published estimates, to quantify contribution of diabetes and high BMI to site-specific cancers, individually and combined as independent risk factors and in a conservative scenario in which we assumed full overlap of risk of diabetes and high BMI. We then used GLOBOCAN cancer incidence data to estimate the number of cancer cases attributable to the two risk factors. We also estimated the number of cancer cases in 2012 that were attributable to increases in the prevalence of diabetes and high BMI from 1980 to 2002. All analyses were done at individual country level and grouped by region for reporting.

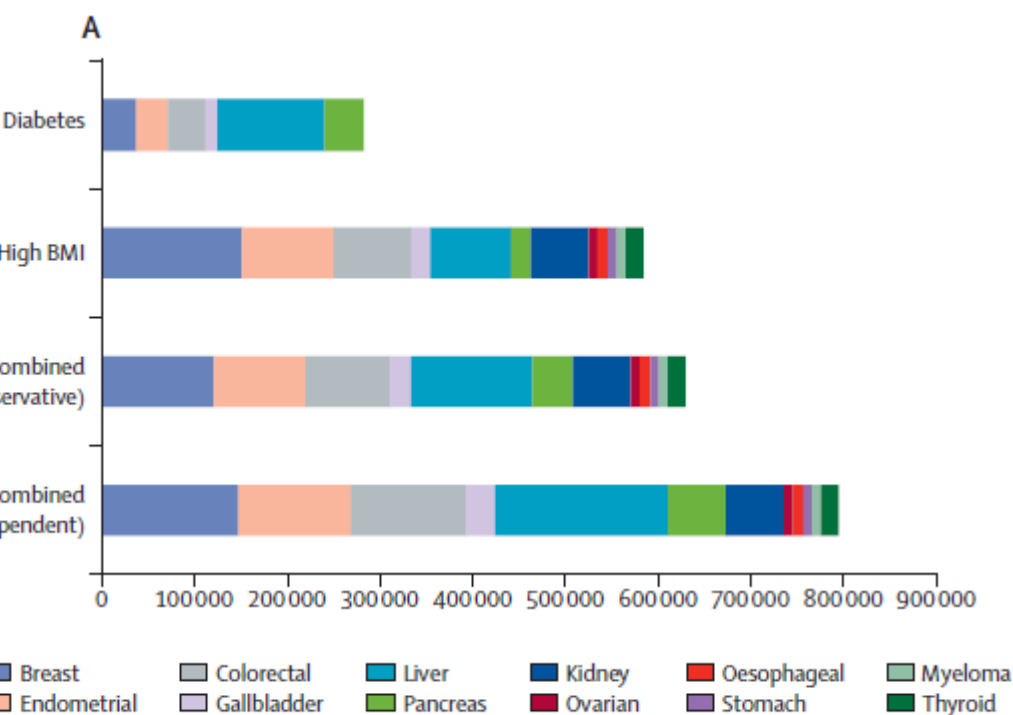
Findings We estimated that 5·6% of all incident cancers in 2012 were attributable to the combined effects of diabetes and high BMI as independent risk factors, corresponding to 792 600 new cases. 187 600 (24·5%) of 766 000 cases of colorectal cancer and 121 700 (38·4%) of 317 000 cases of endometrial cancer were attributable to these risk factors. In the conservative scenario, about 4·5% (626 900 new cases) of all incident cancers assessed were attributable to diabetes and high BMI combined. Individually, high BMI (544 300 cases) was responsible for twice as many cancer cases as diabetes (280 100 cases). 26·1% of diabetes-related cancers (equating to 77 000 new cases) and 31·9% of high BMI-related cancers (174 040 new cases) were attributable to increases in the prevalence of these risk factors from 1980 to 2002.



Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment

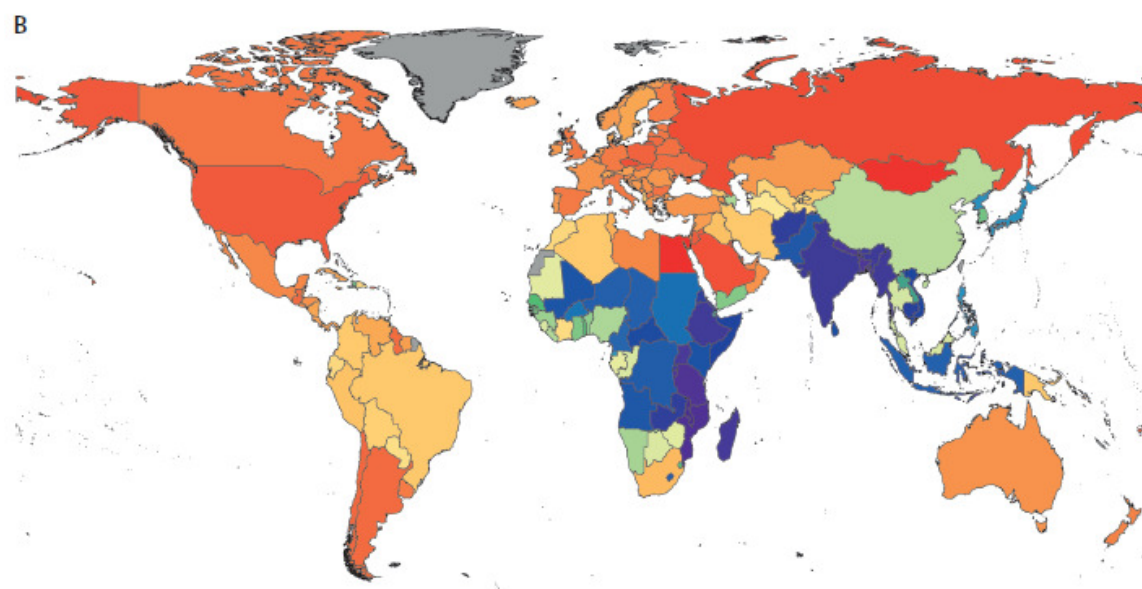
Nathan Pearson-Stuttard, Bin Zhou, Vasilis Kontis, James Benthall, Marc J Gunter, Majid Ezzati

Lancet Diabetes Endocrinol 2017



Discussion

We estimated that approximately 6% of cancer cases worldwide in 2012 were attributable to diabetes and high BMI, with high BMI being responsible for almost twice as many cases as diabetes. About a third of cancer cases attributable to diabetes and a quarter of cases attributable to high BMI were due to increases in the prevalence of these risk factors from 1980 to 2002. Given the continued rise in the prevalence of these risk factors since 2002,²³ the attributable cancer burden is likely to continue to increase in coming decades. Approximately one in four liver and oesophageal adenocarcinomas and 38.4% of endometrial cancers worldwide in 2012 were estimated to be attributable to diabetes and high BMI.



diabete nel mondo

Type 2 Diabetes: Why We Are
Winning the Battle but Losing
the War? 2015 Kelly West Award
Lecture

K.M. Venkat Narayan

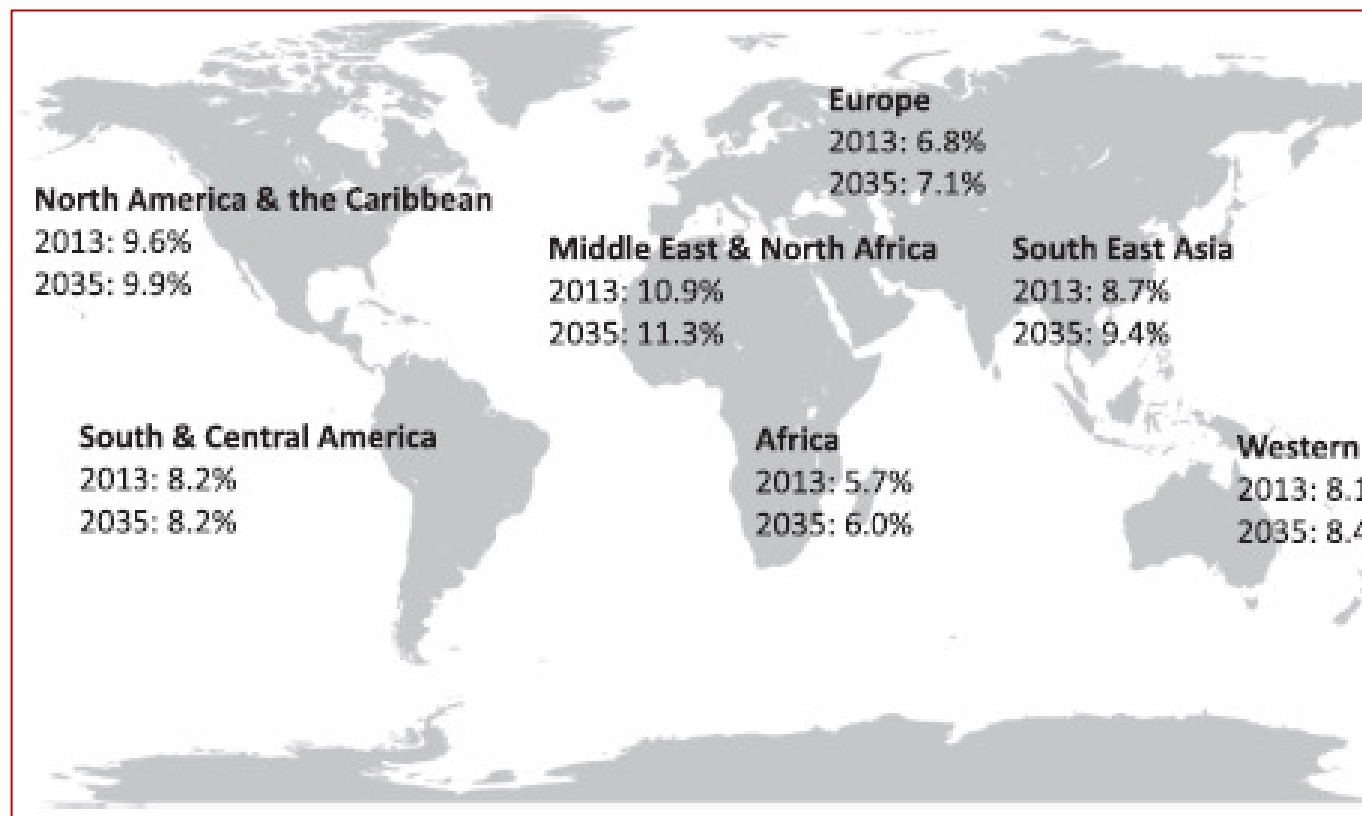
Diabetes Care 2016;39:653–663 | DOI: 10.2337/dc16-0205



IDF, stime prevalenza:

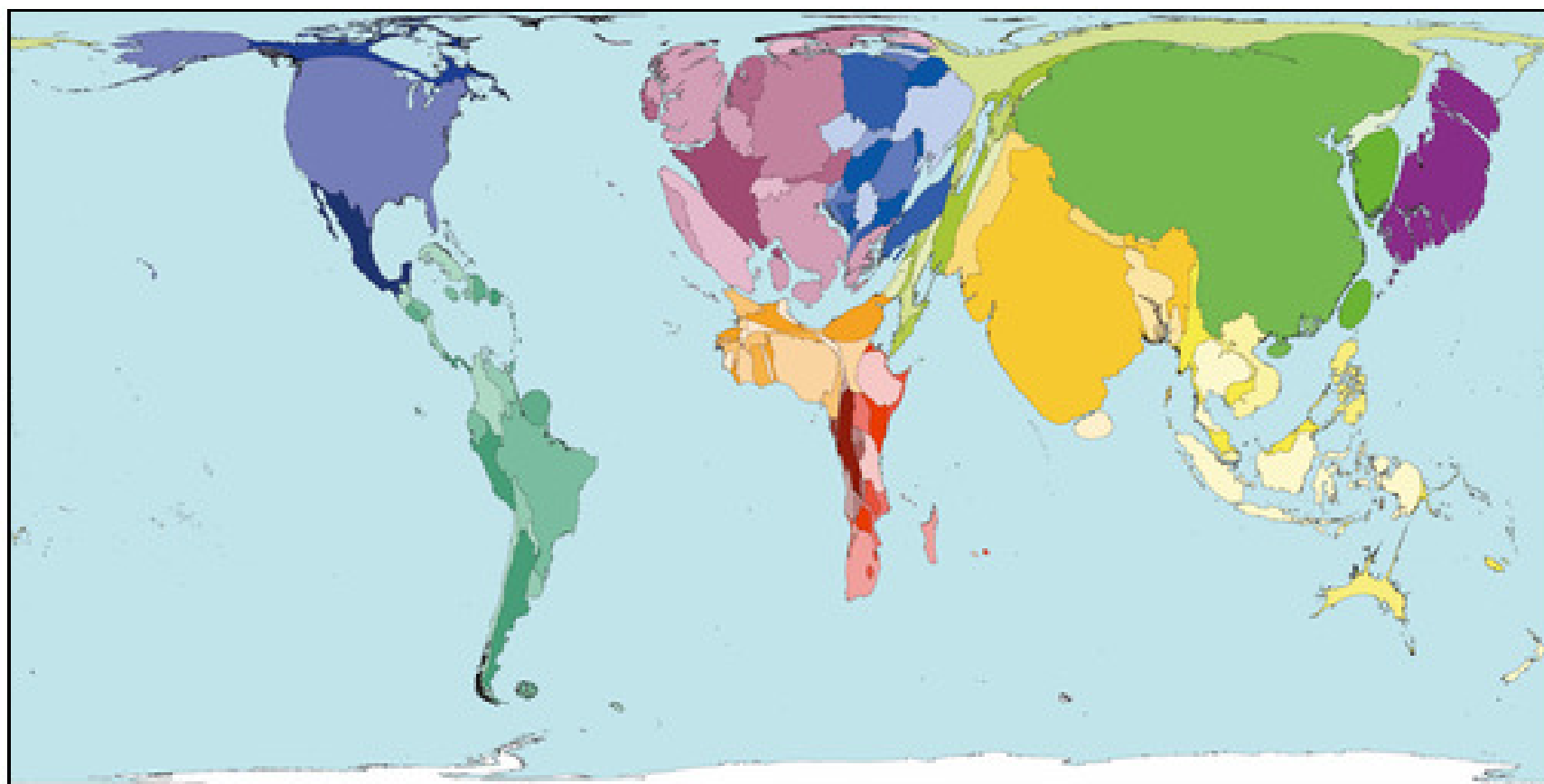
2015: 415 milioni

2040: 642 milioni



mortalità per tumori nel mondo

All Cancer Deaths



Diabete in Italia

Numero assoluto per genere e fascia d'età

2000							
	Maschi	Femmine	Totale		Maschi	Femmine	Totale
	Numero di diabetici (valori in migliaia)				Distribuzione percentuale		
0-54	10	7	18		1	1	1
55-64	222	225	447		22	19	21
65-74	488	508	996		49	44	46
75 e più	233	401	634		23	35	30
Totale	995	1.155	2.149		100	100	100
2011							
	Maschi	Femmine	Totale		Maschi	Femmine	Totale
	Numero di diabetici (valori in migliaia)				Distribuzione percentuale		
0-54	6	13	20		0	1	1
55-64	310	247	557		22	16	19
65-74	633	570	1.205		46	37	41
75 e più	400	733	1.133		29	47	39
Totale	1.383	1.556	2.939		100	100	100

Diabete in Italia

ASPETTO 2. IL DIABETE IN ITALIA, TASSI DI PREVELENZA PER GENERE ED ETÀ.
2000 e 2011, valori per cento abitanti

2000				2011			
	Maschi	Femmine	Totale		Maschi	Femmine	Totale
Numero di diabetici per cento persone della stessa classe di età							
	0,9	0,8	0,9		1,1	0,8	1,0
4	6,8	6,7	6,7		8,4	6,4	7,4
4	13,2	11,0	11,9		15,3	12,4	13,7
più	14,7	15,0	14,9		17,9	20,6	19,5
o totale	3,6	3,9	3,8		4,7	5,0	4,9
o standardizzato	4,0	3,9	3,9		4,8	4,3	4,6



diabete + tumori: epidemiologia



DIABETE: fattore di rischio

- entrambe patologie dell'età avanzata
- aumento prevalenza DM e aspettativa di vita
- differenze nello stile di vita
- fattori di rischio comuni
- fattori genetici
- minor ricorso ed efficacia degli esami di screening

DIABETE: fattore prognostico sfavorevole

- diagnosi in stadio più avanzato
- riduzione sopravvivenza complessiva
- riduzione sopravvivenza tumore-specifica
- trattamenti meno aggressivi
- aumentata tossicità terapie

Diabetes and cancer are diagnosed within the same individual more frequently than would be expected by chance after adjusting for age

Giovannucci E et al., Diabetes Care 2010

diabete e rischio tumori

DIABETES AND CANCER — AN AACE/ACE CONSENSUS STATEMENT ENDOCRINE PRACTICE Vol 19 No. 4 July/August 2013

Summary of the Association of Diabetes and Cancer Risk			
Study group	Cancer evaluated	Risk	95% CI
Mitri et al 2008 (60)	Non-Hodgkin lymphoma	RR 1.19	1.04-1.35
Friberg et al 2007 (57)	Endometrial	RR 2.10	1.75-2.53
Larsson et al 2007 (55)	Breast	RR 1.20	1.12-1.28
El-Seraq et al 2006 (59)	Hepatic (case-control studies)	OR 2.54	1.82-3.54
	Hepatic (cohort studies)	Risk ratio 2.50	1.93-3.24
Kasper et al 2006 (63)	Prostate	RR 0.84	0.76-0.93
Larsson et al 2006 (61)	Bladder	RR 1.24	1.08-1.42
Huxley et al 2005 (58)	Pancreatic	OR 1.82	1.66-1.89
Larsson et al 2005 (56)	Colorectal	RR 1.30	1.20-1.40
Abbreviations: CI = confidence interval; OR = odds ratio; RR = relative risk.			

reverse causality bias (ca pancreas): iperglicemia da disfunzione secrezione insulinica determinata da neoplasia

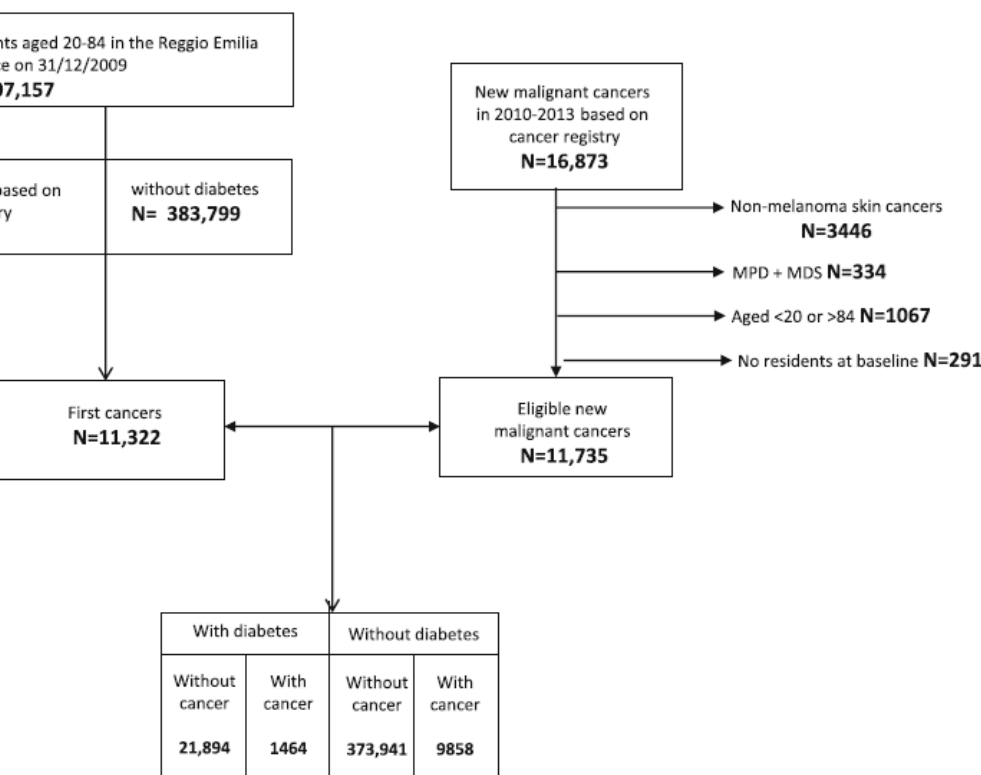
detection bias: aumentata sorveglianza pz diabetici, specie dopo diagnosi di diabete

Diabetes and risk of cancer incidence: results from a population-based cohort study in northern Italy

Paola Ballotari¹, Massimo Vicentini^{1*}, Valeria Manicardi², Marco Gallo³, Sofia Chiatamone Ranieri⁴, Marina Greci⁵ and Paolo Giorgi Rossi¹



BMC Cancer



Background: Aim of this study was to compare cancer incidence in populations with and without diabetes. Furthermore, we aimed at comparing excess risk of cancer according to diabetes type, diabetes duration and treatment, the latter as regards Type 2 diabetes.

Methods: By use of the Reggio Emilia diabetes registry we classified the resident population aged 20–84 on December 31st 2009 into two groups: with and without diabetes. By linking with the cancer registry we computed the 2010–2013 cancer incidence in both groups. The incidence rate ratios (IRR) by cancer site, type of diabetes, diabetes duration, and as concerns Type 2 diabetes, by treatment regimen were computed using Poisson regression model and non-diabetic group as reference.

Many studies and systematic reviews have compared cancer incidence between diabetic patients and general population, but only few analyzed an entire population of subjects with known diabetes. Considering that Reggio Emilia province relies on both cancer and diabetes registry, we could design and conduct a population-based cohort study.

Diabetes and risk of cancer incidence: Results from a population-based cohort study in northern Italy

Ballotari¹, Massimo Vicentini^{1*}, Valeria Manicardi², Marco Gallo³, Sofia Chiatamone Ranieri⁴, Greci⁵ and Paolo Giorgi Rossi¹



BMC Cancer

The cohort included 383,799 subjects without diabetes and 23,358 with diabetes. During follow-up, we had 1464 cancer cases in subjects with diabetes and 9858 in the remaining population. Overall cancer risk was higher in subjects with diabetes than in those without diabetes (IRR = 1.22, 95%CI 1.15–1.29), with results focusing on subjects with at least 2-year diabetes duration. Cancer sites driving overall increased risk were, pancreas, Colon rectum, and bladder in both sexes, corpus uteri for females. There was also suggestion of increased risk for kidney cancer in females and a decreased risk for prostate cancer in males. Among subjects with Type 2 diabetes, more marked among insulin users, especially among those with longer duration. We also observed an increasing risk for diabetes duration up to 10 years from diagnosis, followed by a subsequent decrease to moderate-higher risk (IRR = 1.15, 95%CI 1.04–1.27).

Table 3 Population, No. of cancer, Incidence Rate Ratios (IRR) and 95% Confidence Intervals (95% CI) for type of diabetes, treatment (only for type 2 diabetes), and diabetes duration vs subjects without diabetes

	Person-years	N cancer	IRR	95% CI
Without diabetes	1,499,890	9858	1.00	-
With diabetes	85,953	1464	1.22	1.15–1.29
By type of diabetes:				
Type 1 diabetes	3017	15	0.88	0.53–1.47
Secondary diabetes ^a	393	10	2.04	1.10–3.80
Type 2 diabetes	82,542	1439	1.22	1.15–1.29
By treatment:				
Diet only	22,900	349	1.10	1.00–1.23
OHA only	44,637	792	1.22	1.14–1.32
Insulin only	7738	161	1.32	1.13–1.54
OHA + insulin	7267	137	1.37	1.16–1.62
By diabetes duration (years):				
0–1	24,553	361	1.10	0.99–1.23
2–5	24,710	403	1.23	1.11–1.36
6–10	17,033	337	1.44	1.29–1.61
11+	19,658	363	1.15	1.04–1.30

Table 2 No. of subjects with cancer by diabetes status, Incidence Rate Ratios (IRR) and 95% Confidence Intervals (95%CI) for subjects with diabetes vs subjects without diabetes

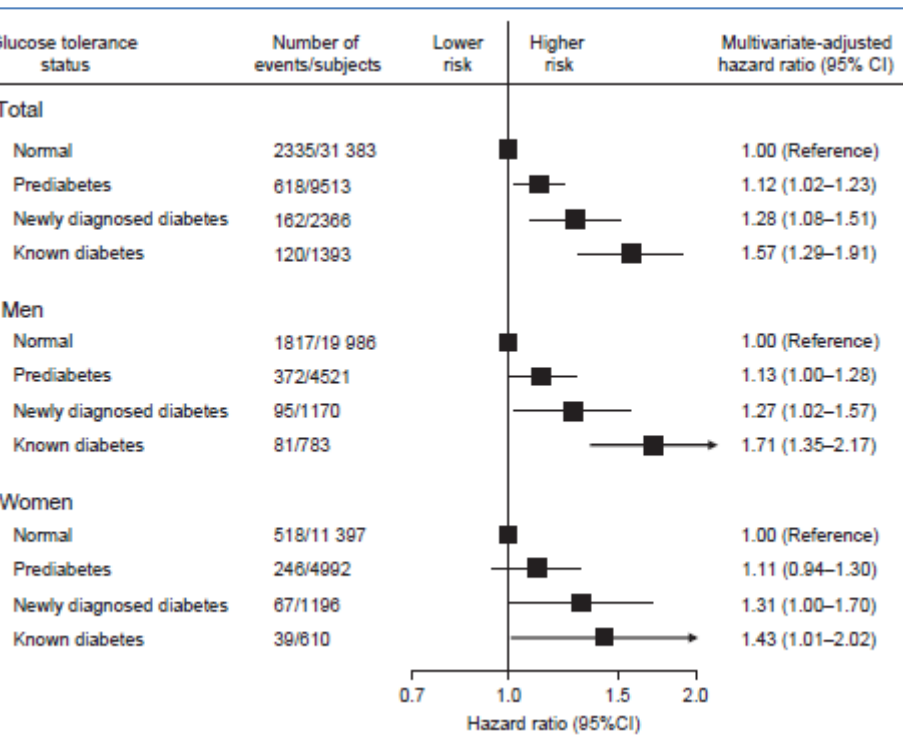
Cancer site ^a	Total				Females				Males			
	No DM	DM	IRR	95% CI	No DM	DM	IRR	95% CI	No DM	DM	IRR	95% CI
All sites	9858	1464	1.22	1.15–1.29	4851	563	1.25	1.15–1.37	5007	901	1.17	1.09–1.25
C16: Stomach	396	58	0.95	0.72–1.26	139	20	1.17	0.72–1.88	257	38	0.87	0.63–1.20
C18–C20: Colon-rectum	956	177	1.32	1.12–1.55	455	59	1.12	0.85–1.49	501	118	1.44	1.21–1.70
C22: Liver	207	99	3.37	2.63–4.32	61	23	3.26	2.00–5.35	146	76	3.40	2.44–4.79
C24: Biliary tract	69	16	1.41	0.81–2.45	28	7	1.76	0.76–4.04	41	9	1.22	0.53–2.81
C25: Pancreas	340	101	2.00	1.60–2.51	155	48	2.49	1.79–3.46	185	53	1.68	0.63–4.46
C33–C34: Lung	1047	177	1.10	0.93–1.29	329	36	1.01	0.71–1.43	718	141	1.11	0.66–1.87
C50: Breast	1643	148	1.05	0.89–1.26	1633	147	1.06	0.89–1.26	10	1	-	-
C54: Corpus uteri	-	-	-	-	249	44	1.84	1.33–2.56	-	-	-	-
C56: Ovary	-	-	-	-	139	21	1.56	0.97–2.49	-	-	-	-
C61: Prostate	-	-	-	-	-	-	-	-	938	134	0.86	0.73–1.00
C64–C66; C68: Kidney	377	60	1.20	0.67–2.14	111	19	1.55	0.94–2.54	266	41	1.02	0.73–1.43
C67; D09: Bladder	627	138	1.39	1.16–1.68	126	25	1.72	1.11–2.66	501	113	1.33	1.00–1.76
C73: Thyroid	504	27	1.00	0.67–1.49	368	18	1.05	0.64–1.70	136	9	0.88	0.44–1.80
C82–C85; C96: NHL ^b	425	56	1.09	0.82–1.44	180	20	1.14	0.71–1.82	245	36	1.05	0.73–1.52
Other sites ^c	2252	277	1.09	0.96–1.23	1001	102	1.11	0.89–1.36	1251	175	1.07	0.93–1.23

Diabete e outcome oncologici

Prognosi a lungo termine più sfavorevole



DECODE 44.655 pz di 17 Paesi Europei



Zhou XH et al. *Diabetologia* 2010

DIABETES AND CANCER – AN AACE/ACE CONSENSUS STATEMENT

ENDOCRINE PRACTICE Vol 19 No. 4 July/August 2013

Summary of the Association of Diabetes and Cancer Mortality			
Study group	Cancer evaluated	Risk	95% CI
Campbell et al 2012 (men) (65)	Breast	RR 4.20 ^a	2.20-8.04
	Hepatic	RR 2.26 ^a	1.89-2.70
	Oropharyngeal	RR 1.44 ^a	1.07-1.94
	Pancreatic	RR 1.40 ^a	1.23-1.59
	Bladder	RR 1.22 ^a	1.01-1.47
	Colon	RR 1.15 ^a	1.03-1.29
	Prostate	RR 0.88 ^a	0.79-0.97
Campbell et al 2012 (women) (65)	Hepatic	RR 1.40 ^a	1.05-1.86
	Endometrial	RR 1.33 ^a	1.08-1.65
	Pancreatic	RR 1.31 ^a	1.14-1.51
	Colon	RR 1.18 ^a	1.04-1.33
Currie et al 2012 (66)	Breast	RR 1.16 ^a	1.03-1.29
	All cancers	HR 1.09 ^b	1.06-1.13
	Breast	HR 1.32 ^b	1.17-1.49
	Prostate	HR 1.19 ^b	1.08-1.31
	Bladder	HR 1.16 ^b	1.02-1.32
	Lung	HR 0.84 ^b	0.77-0.92

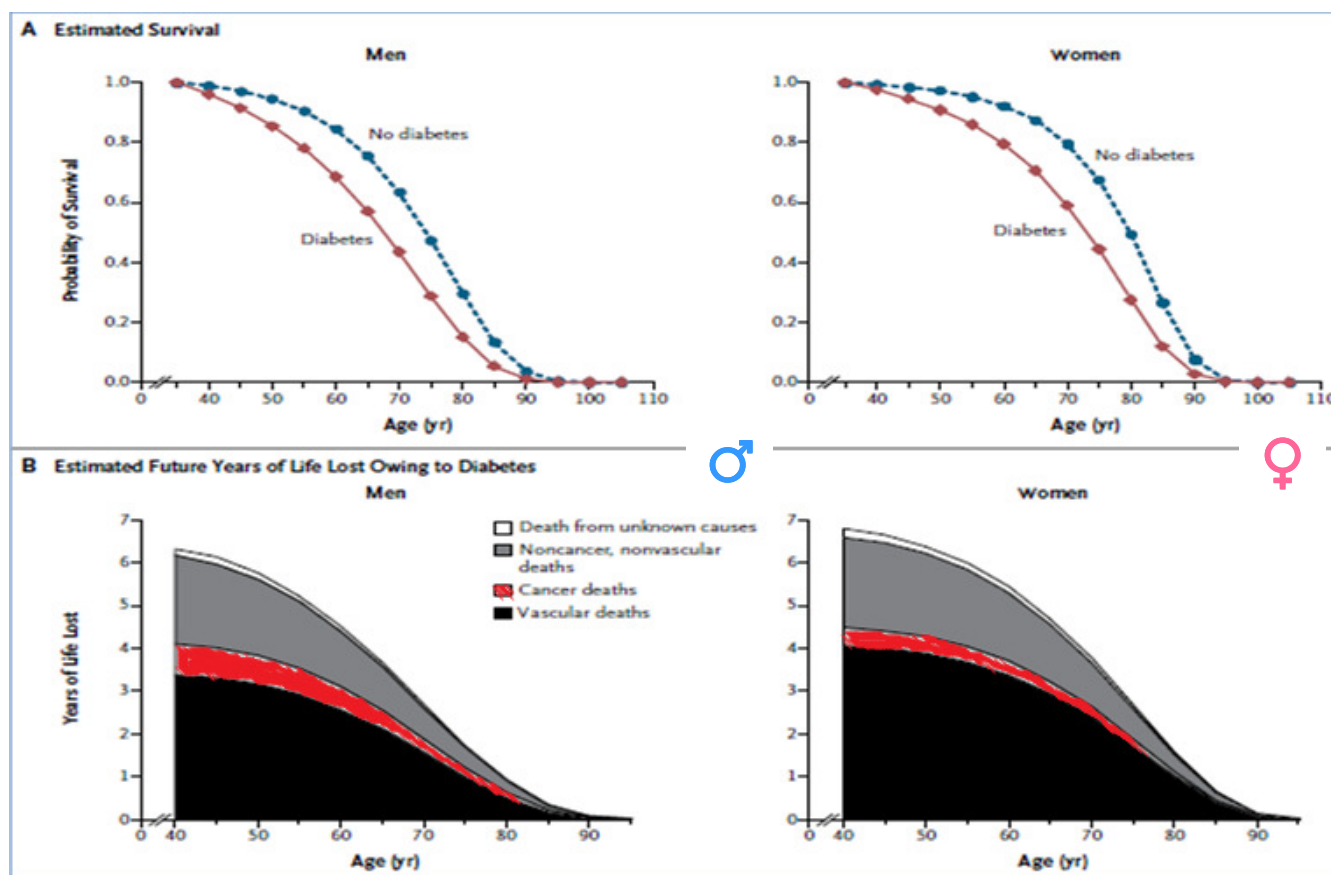
Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death

The Emerging Risk Factors Collaboration*

N ENGL J MED 364;9 NEJM.ORG MARCH 3, 2011

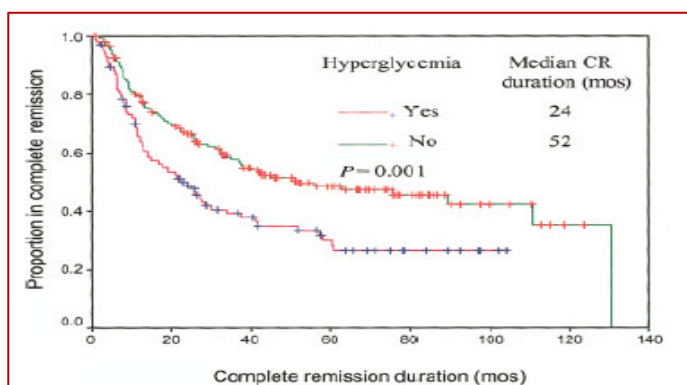


Sopravvivenza e mortalità per diabete



97 studi prospettici
821.000 pz

Correlation between the Duration of Remission and Hyperglycemia during Induction Chemotherapy for Acute Lymphocytic Leukemia with a Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone/Methotrexate–Flutamide Regimen



- Patients with hyperglycemia during induction chemotherapy for ALL
- had a shorter complete remission duration
 - experienced a significant increase in overall mortality
 - were at an increased risk for complicated infections

FIGURE 1. Complete remission (CR) duration survival functions for all patients.

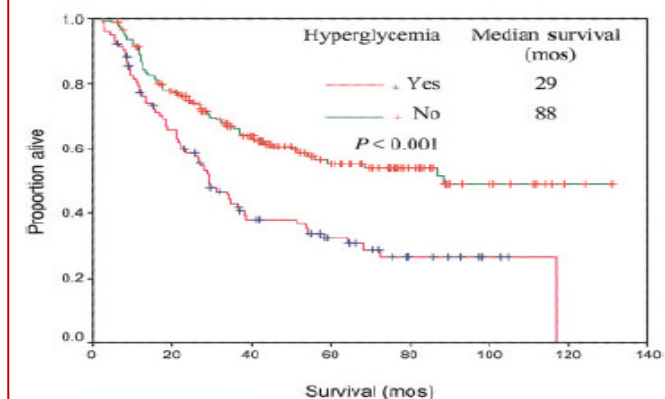


FIGURE 2. Survival functions for all patients.

Rate of Infection during Induction Chemotherapy

	Hyperglycemia, Yes (n = 103)	Hyperglycemia, No (n = 175)	P value
Any infection	74 (72%)	98 (56%)	0.001
Fever of unknown origin	44 (43%)	70 (40%)	0.65
Sepsis	17 (17%)	14 (8%)	0.03
Complicated infection	40 (39%)	44 (25%)	0.01

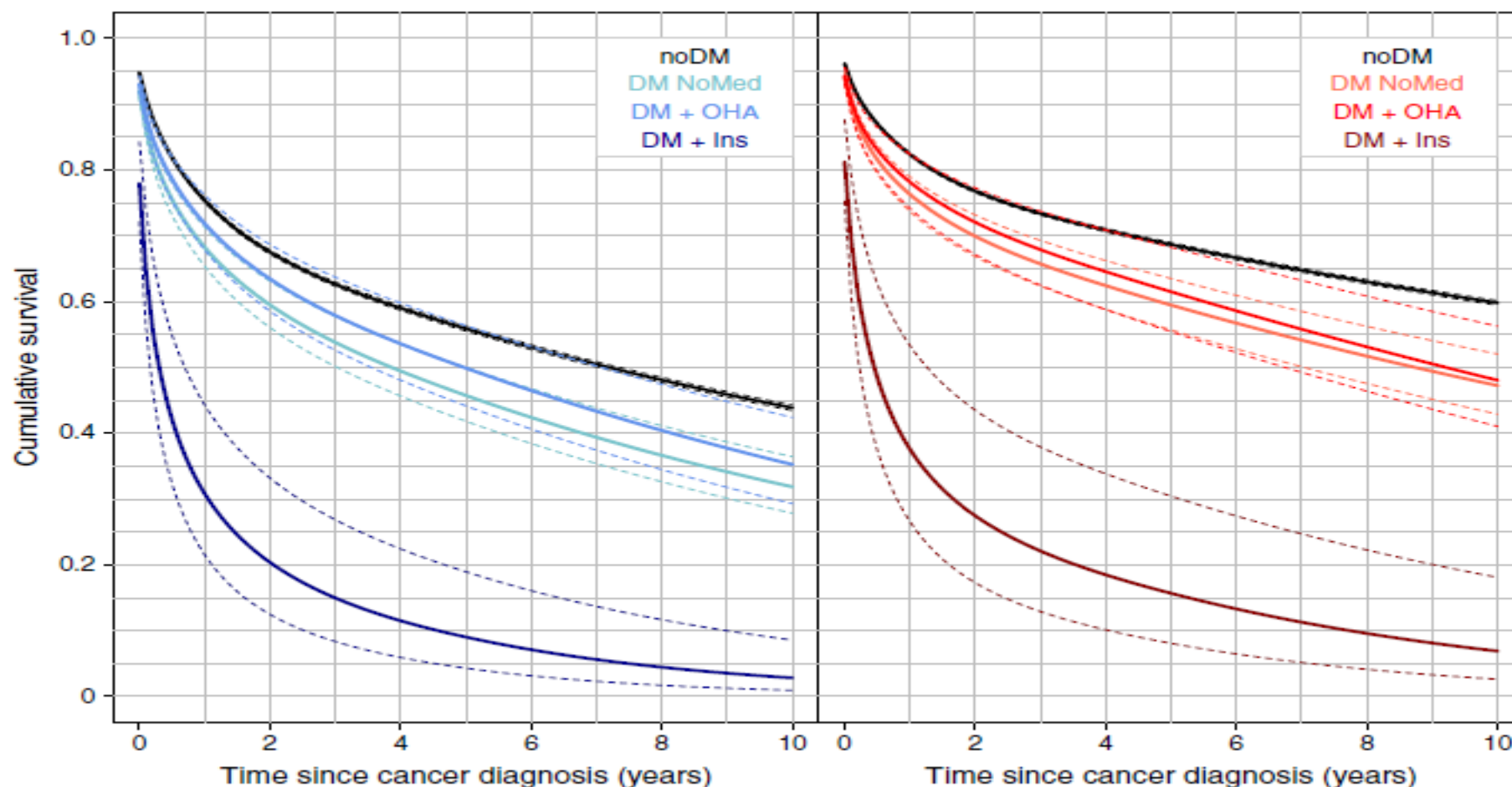
Mortality after cancer among patients with diabetes mellitus: effect of diabetes duration and treatment

Kristina Ranc • Marit E. Jørgensen • Søren Friis •
Lennart Carstensen

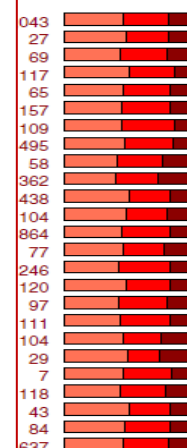
Diabetologia (2014) 57:927–934



All mal. neop.
Oesophagus
Stomach
Ascending colon
Transverse colon
Desc. and sig. colon
Rectum
Colorectal
Liver
Pancreas
Lung
Melanoma of skin
Breast
Prostate
Testis
Kidney
Urinary bladder
Brain
Thyroid
Hodgkin's lymph.
Non-Hodg. lymph.
Multiple myeloma
Leukaemia
Other



Ins



Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death

The Emerging Risk Factors Collaboration*

N Engl J Med 2011;364:829-41. MARCH 3, 2011



Aspettativa di vita per un soggetto di 50 anni

Con DM, senza precedenti vascolari noti

- -6 anni vs soggetto non diabetico
- 40% della differenza per mortalità extravascolare
- 10% per patologie oncologiche



Senza DM, ma con lunga durata di consuetudine al fumo

- -10 anni



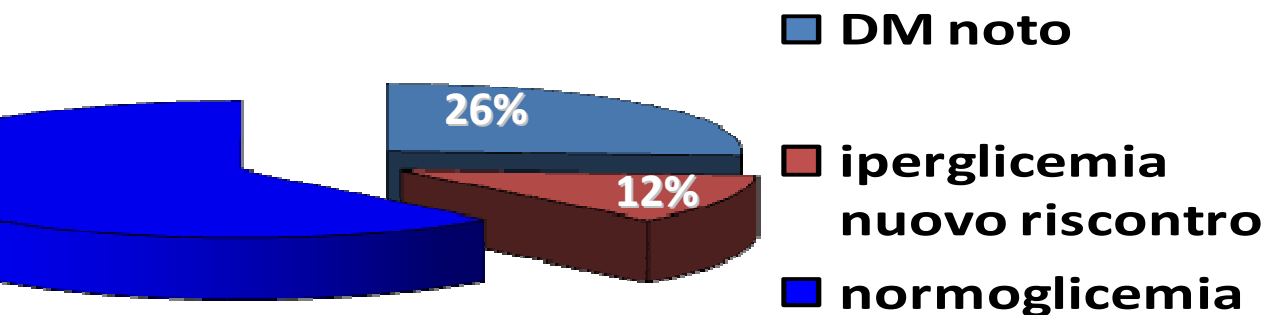
Effects of anti-tumoral therapies on diabetes

- **glucocorticoids**
 - ✓ in combination with cytotoxic agents
 - ✓ as antiemetics, antiemetic, etc.
- **“conventional” chemotherapies**
- **radiotherapy**
- **biotherapies** (somatostatin analogs, IFN α)
- **mTOR inhibitors**
- **tyrosine kinase inhibitors** (nilotinib, ponatinib, pazopanib...)
- **checkpoint inhibitors (anti-PD1 Ab)** (nivolumab, pembrolizumab...)
- **ADT prostate cancer**
- **radionuclide therapy** (ibritumab tiuxetan)
- **pancreasectomy**

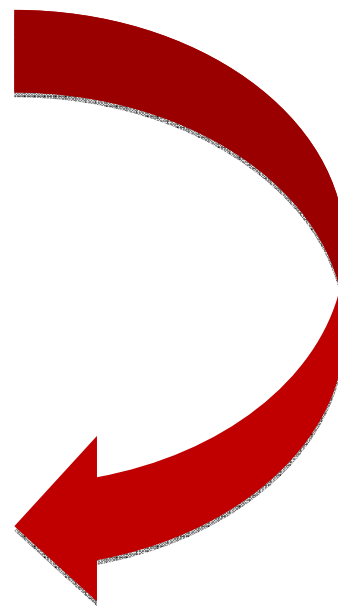
dimensioni del problema

8-18% dei pazienti oncologici è affetto anche da diabete

~38% dei pazienti ricoverati in oncologia ha iperglicemia



- esiti di trattamenti chirurgici
- effetti diretti del tumore
- effetti delle terapie antitumorali
- effetti delle terapie di supporto



DM & tumori

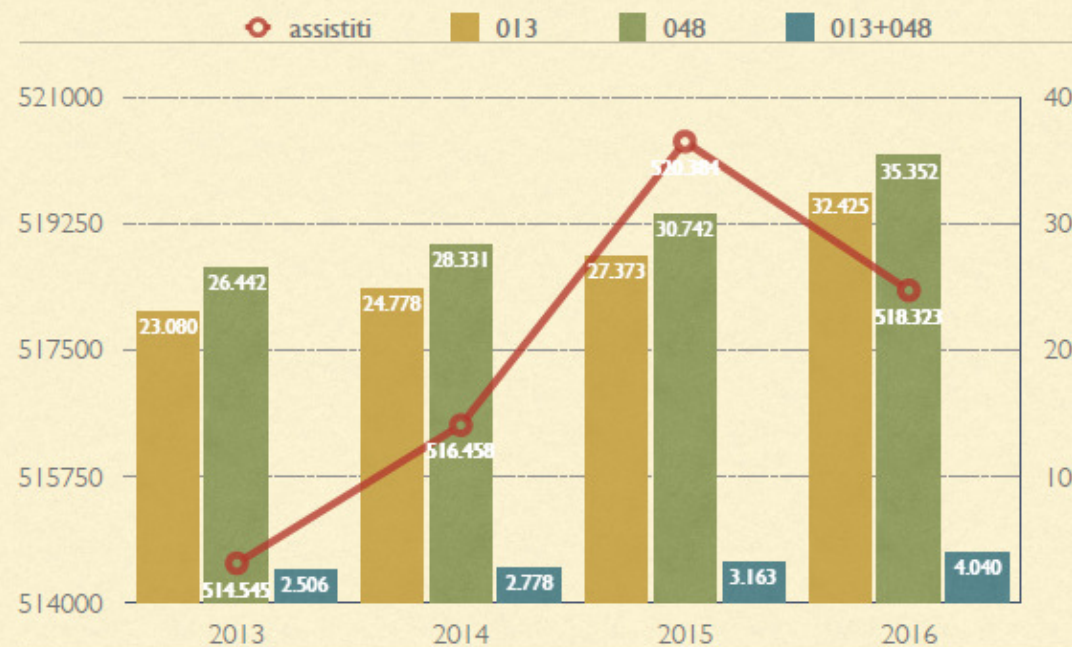
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	2013	2014	2015	2016	
013	23080	24778	27373	32425	6.2%
048	26442	28331	30742	35352	6.8%
013+048	2506	2778	3163	4040	
Assistiti	514545	516458	520384	518323	

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11.4% dei pz oncologici ha esenzione per DM

NUMERI ASLTO4 - 2



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