

**n references for each site-specific cancer**

*Gastrointestinal tract*

- 13 Liver
- 10 Hepatocellular Carcinoma (HCC)
- 6 Biliary tract
- 25 Pancreas
- 17 Stomach
- 7 Oesophagus
- 27 Colorectal
- 2 Pharynx

*Urinary System*

- 19 Bladder
- 12 Kidney
- 1 Urinary tract

*Skin*

- 4 Squamous Cell Carcinoma (SCC)
- 5 Melanoma

*Respiratory Tract*

- 12 Lung

*Reproductive System (Sex-specific)*

- 14 Endometrial
- 21 Breast
- 10 Ovarian
- 4 Cervix
- 1 Vulvar
- 3 Uterus
- 20 Prostate

*Blood*

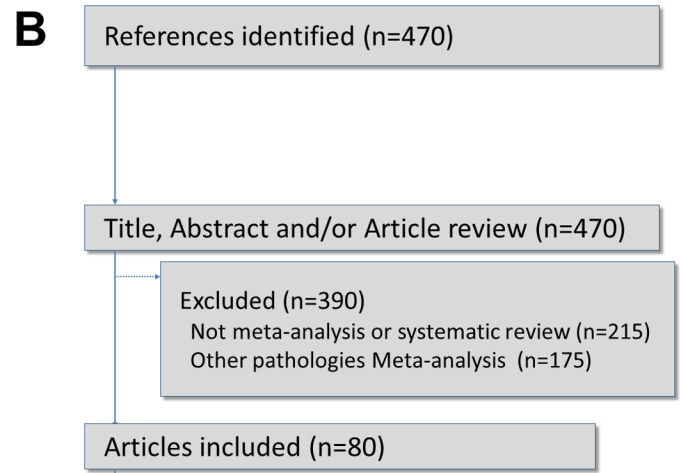
- 10 Non-Hodgkin Lymphoma (NHL)
- 7 Leukaemia
- 4 Myeloma

*Others*

- 5 Thyroid
- 5 Neuroendocrine
- 1 Nervous system
- 2 Connective tissue
- 17 All type of Cancer

**n Studies per type of diabetes**

- 8 Diabetes Type I
- 13 Diabetes Type II
- 78 Diabetes Type I and II
- 3 Gestational Diabetes



**n references for each site-specific cancer**

*Gastrointestinal tract*

- 7 Liver
- 2 Hepatocellular Carcinoma (HCC)
- 3 Biliary tract
- 7 Pancreas
- 6 Stomach
- 5 Oesophagus
- 19 Colorectal

*Urinary System*

- 1 Bladder
- 6 Kidney

*Skin*

- 2 Melanoma

*Respiratory Tract*

- 2 Lung

*Reproductive System (Sex-specific)*

- 4 Endometrial
- 12 Breast
- 9 Ovarian
- 4 Cervix
- 8 Prostate

*Blood*

- 3 Non-Hodgkin Lymphoma (NHL)
- 1 Lymphoma
- 3 Leukaemia
- 3 Myeloma

*Others*

- 3 Thyroid

**Figure S1** - Flow diagram of selection process of meta-analyses on association between **diabetes (A) or obesity (B) and cancer**. Two researches independently search PubMed database using the following algorithm: “(diabetes/obesity) AND (cancer OR carcinoma OR neoplasia OR tumor OR tumour OR neoplasm OR malign\*) AND (meta analysis OR systematic review)”. The titles, abstracts and full texts were examined and selection or not was as indicated. Period Jan 2004-Sep 2015.

**A**

Site	References identified	Included					Excluded			
		Total	Metformin	Insulin	Incretins	Glitazones	Total	Not specific Cancer site	Not specific treatment	Unrelated review
Liver	13	4	1	2	1	0	9	6	1	2
Pancreas	36	15	8	6	0	1	21	11	4	6
Stomach	9	7	2	4	0	1	2	1	1	0
Colorectal	29	15	3	11	0	1	14	3	5	6
Endometrial	14	8	4	2	1	1	6	4	1	1
Breast or Mammary	75	41	21	18	0	2	34	23	5	6
Ovarian	12	7	6	0	0	1	4	2	1	1
Bladder	44	34	3	4	0	27	10	6	1	3
Kidney	27	4	1	2	1	0	9	6	1	2
Blood	9	0	0	0	0	0	9	2	1	6
Non-Hodgkin-Lymphoma	6	3	0	1	0	2	3	1	1	1
Leukaemia	4	0	0	0	0	0	4	2	1	1
Myeloma	2	0	0	0	0	0	2	1	1	0
Prostate	12	10	4	5	0	1	2	1	1	0

**B**

Treatment	References identified	Included After title review	Included After article review
Antineoplastic	39	3	3
Chemotherapy	70	9	9
Corticoids	38	9	4
mTOR inhibitors	26	9	2
Tyrosin Kinase inhibitors	13	3	1
Androgen Deprivation Ther	98	41	3
5-Fluorouracil	72	5	2
Cisplatin	40	2	2
Radiotherapy	62	6	1

**Figure S2** - Flow diagram of selection process of meta-analyses on association between **anti-diabetic (A)** or **anti-neoplastic (B) treatment** and site-specific cancer. The searching algorithm in PubMed was: “site-specific AND antidiabetic AND cancer AND epidemiology” or “site-specific AND anti-neoplastic AND cancer AND epidemiology”, respectively. Period Jan 2009-Sep 2015. Included references are classified according to the treatment.

## Supplementary Table S1

Epidemiological links between obesity, diabetes and site-specific cancers.

Cancer Site	Relative Risk (95% CI) associated to											
	Obesity		[Ref]	T2D		[Ref]	T1/2D		[Ref]	T1D		[Ref]
Liver	RR	1.35 (1.24 - 1.47)	[1]	RR	2.31 (1.87 - 2.84)	[2]	RR	2.01 (1.61 - 2.51)	[3]	SMR	1.59 (0.30 - 4.71)	[4]
Melanoma	RR	1.31 (1.19 - 1.44)	[5]				RR	2.16 (1.14 - 4.35)	[6]	SIR	0.80 (0.50 - 1.10)	[3]
Endometrium	RR	2.54 (2.11 - 3.06)	[7]	RR	1.97 (1.71 - 2.27)	[2]	RR	2.10 (1.75 - 2.53)	[3]	SIR	2.70 (1.40 - 4.70)	[3]
Pancreas	RR	1.48 (1.15 - 1.92)	[8]	RR	1.95 (1.66 - 2.28)	[2]	RR	1.94 (1.66 - 2.27)	[3]	SIR	2.00 (1.37 - 3.01)	[3]
Biliary Tract	RR	1.66 (1.47 - 1.88)	[9]	RR	1.52 (1.26 - 1.84)	[2]	RR	1.43 (1.18 - 1.72)	[3]			
Kidney	RR	1.77 (1.68 - 1.87)	[10]	RR	1.38 (1.10 - 1.72)	[2]	RR	1.42 (1.06 - 1.91)	[3]	SIR	0.80 (0.20 - 2.10)	[3]
Bladder	RR	1.10 (1.06 - 1.42)	[11]	RR	1.35 (1.17 - 1.56)	[2]	RR	1.24 (1.08 - 1.42)	[3]	SIR	1.60 (0.70 - 3.10)	[3]
Leukaemia	RR	1.26 (1.17 - 1.37)	[12]	RR	1.28 (1.05 - 1.57)	[2]	OR	1.22 (1.03 - 1.44)	[13]	SIR	1.30 (0.70 - 2.20)	[3]
NHL	RR	1.20 (1.07 - 1.34)	[14]	RR	1.27 (1.09 - 1.48)	[2]	RR	1.22 (1.07 - 1.39)	[13]	SIR	1.40 (0.74 - 2.40)	[4]
CRC	OR	1.32 (1.18 - 1.48)	[15]	RR	1.27 (1.21 - 1.34)	[2]	RR	1.27 (1.21 - 1.34)	[3]	SIR	1.10 (0.60 - 1.70)	[3]
Breast	RR	1.42 (1.30 - 1.45)	[16]	RR	1.20 (1.12 - 1.28)	[2]	RR	1.20 (1.12 - 1.28)	[3]	SIR	1.00 (0.80 - 1.30)	[3]
Ovary	OR	1.30 (1.10 - 1.50)	[17]	RR	1.17 (1.02 - 1.34)	[2]	RR	2.42 (0.96 - 6.09)	[6]	SIR	0.80 (0.40 - 1.50)	[3]
Thyroid	RR	1.29 (1.18 - 1.41)	[18]	RR	1.16 (0.97 - 1.39)	[2]	RR	1.34 (1.11 - 1.63)	[19]	SIR	1.20 (0.60 - 2.20)	[3]
Stomach	OR	1.13 (1.03 - 1.24)	[20]	RR	1.09 (0.98 - 1.22)	[2]	RR	0.97 (0.64 - 1.46)	[3]	SIR	2.30 (1.10 - 4.10)	[3]
Lung	RR	0.79 (0.73 - 0.85)	[21]	RR	1.03 (0.94 - 1.13)	[2]	HR	1.00 (0.85 - 1.17)	[22]	SIR	1.10 (0.50 - 1.90)	[3]
Prostate	RR	1.16 (1.08 - 1.24)	[23]	RR	0.91 (0.82 - 1.01)	[2]	RR	0.84 (0.76 - 0.93)	[3]	SIR	0.33 (0.01 - 1.89)	[4]

**Supplementary Table S1.** Summary of random effects estimated with 95% confidence from meta-analysis on incidence of cancer and obesity, type 2 diabetes (T2D), type 1 or 2 diabetes (T1/2D) or type 1 diabetes (T1D). Values correspond to the Relative Risk (RR), Standardized Incidence Ratio (SIR), Odds Ratio (OR) or Hazard Ratio (HR) as indicated on the left according to availability. Obesity data correspond to BMI  $\geq$  30 Kg/m<sup>2</sup>, except # that correspond to the BMI increase of 5 kg/m<sup>2</sup>. References (in brackets on the right) were selected according to the following criteria: meta-analysis most recent, with largest number of patients, by the same author (if possible to allow better comparison).

## Supplementary Table S2

### Epidemiological links between antidiabetic treatments and site-specific cancers

Cancer Site	Relative Risk (95% CI) associated to antidiabetic treatment			
	Insulin [Ref]	Metformin [Ref]	Sulfonylureas [Ref]	TZD [Ref]
Pancreas	RR 2.58 (2.05 - 3.25) [24]	OR 0.56 (0.36 - 0.86) [25]	RR 1.34 (0.87 - 2.06) [26]	RR 1.55 (0.78 - 3.07) [27]
Liver	RR 1.84 (1.32 - 2.58) [24]	OR 0.34 (0.19 - 0.60) [25]	RR 1.17 (0.60 - 2.29) [26]	RR 0.56 (0.37- 0.84) [27]
Colorectal	RR 1.69 (1.25 - 2.27) [28]	RR 0.70 (0.59 - 0.87) [29]	RR 0.95 (0.76 - 1.17) [26]	RR 1.08 (0,86 - 1.36) [27]
Stomach	RR 1.65 (1.02 - 2.68) [24]	OR 0.83 (0.76 - 0.91) [25]		
Kidney	RR 1.38 (1.06 - 1.79) [24]	OR 1.30 (1.00 - 1.60) [25]		RR 1.30 (0.70 - 2.30) [27]
Lung	RR 1.30 (1.14 - 1.47) [24]	OR 0.83 (0.64 - 1.06) [25]	RR 0.67 (0.51 - 0.87) [27]	RR 0.55 (0.32 - 0.94) [27]
Thyroid	OR 1.14 (0.62 - 2.09) [30]	OR 1.48 (0.86 - 2.54) [30]	OR 1.42 (0.82 - 2.46) [30]	OR 0.82 (0.36 - 1.84) [30]
Bladder	RR 1.09 (0.93 - 1.28) [23]	RR 0.99 (0.70 - 1.39) [26]	RR 0.64 (0.47 - 1.90) [26]	RR 0.94 (0.66 - 1.34) [27]
Melanoma	RR 0.99 (0.80 - 1.22) [24]	OR 0.80 (0.60 - 1.10) [25]		RR 1.00 (0.50 - 1.80) [27]
Breast	RR 0.90 (0.81 - 1.00) [24]	OR 0.97 (0.88 - 1.08) [25]	RR 0.85 (0.58 - 1.24) [26]	RR 0.92 (0.70 - 1.19) [27]
Endometrial	OR 0.88 (0.56 - 1.36) [31]	OR 0.88 (0.58 - 1.32) [31]	OR 1.09 (0.73 - 1.62) [31]	OR 1.10 (0.62 - 1.95) [31]
Prostate	RR 0.80 (0.73 - 0.88) [24]	OR 1.18 (0.69 - 2.04) [25]	RR 1.07 (0.78 - 1.46)[26]	RR 0.86 (0.64 - 1.14) [27]

**Supplementary Table S2.** Summary of random effects of antidiabetic treatments on site-specific cancer incidence estimated with 95% confidence. The effect of antidiabetics are expressed as: Insulin versus no prior use of insulin, Metformin vs. no prior use, Sulfonylureas vs. no prior use or thiazolidinediones (TZD) vs. no prior use. Values correspond to the Relative Risk (RR) or Odds Ratio (OR) according to data availability. Meta-analysis (cited in brackets on the right) were selected according to the following criteria: most recent, with largest number of patients, by the same author (when possible) to allow better comparisons.

## Supplementary Table S3

Epidemiological links between antineoplastic treatments and development of hyperglycaemia

Cancer Site	Type of Treatment	Drug	% Patients develop HG		Relative Risk (95% CI) of developing HG	Ref	
			All Grade	Grade 3-4 or Db			
<b>Chronic Myeloid Leukaemia</b>	Tyrosine Kinase Inhibitor	Nilotinib	38.0	5.0		[34]	
		Imatinib	20.0	-			
<b>Renal cell carcinoma</b>	mTOR Inhibitor	Everolimus	50.0	12.0	RR 2.18 ( 1.56 – 3.03)	[34]	
		Placebo	23.0	1.0			
		Temsirolimus	26.0	11.0	RR 2.36 ( 1.50 – 3.73)	[35]	
		Interferon	11.0	2.0			
	Tyrosine Kinase Inhibitor	Tems+Interferon	17.0	6.0	RR 1.53 ( 0.93 – 2.51)	[34]	
		Pazopanib	41.0	2.0			
<b>Metastatic renal cell carcinoma</b>	mTOR Inhibitor	Placebo	33.0	1.0	RR 1.24 ( 0.95 – 1.62)	[34]	
		Sunitinib	15.0	6.0			
		Tems + Bevac	22.0	6.0			RR 4.30 ( 2.70 – 6.85)
Interferon + Bevac	5.0	1.0					
<b>Pancreatic NETs</b>	mTOR Inhibitor	Everolimus	13.0	5.0	RR 3.36 ( 1.52 – 7.22)	[34]	
		Placebo	4.0	2.0			
<b>Breast</b>	mTOR Inhibitor	Everolimus	13.0	4.0	RR 6.22 ( 2.54 –15.26)	[34]	
		Placebo	2.0	0.5			
		#Ever+Transt+Paclit	13.0	6.0			
		#Placebo+Transt+Paclit	5.0	1.0			
		Tems+Letrozole	13.0	4.0			RR 2.58 ( 1.70 – 3.93)
		Placebo+Letrozole	5.0	1.0			
<b>Gastrointestinal NETs</b>	mTOR Inhibitor	Everolimus+Octreotide	12.0	5.0	RR 6.38 ( 2.27 –17.97)	[34]	
		Placebo+Octreotide	2.0	0.5			
<b>Prostate</b>	Androgen Deprivation Therapy	PADT	12.5	2.9*	RR 1.37 ( 1.21 – 1.54)	[36]	
		No PADT	9.1	2.1*			
<b>CRC</b>	Pyrimidine analogues	##5-FU	26.1	13.2*		[37]	
<b>Undefined/ Several</b>	IR/IGF1R Inhibitor	AVE1642	4.0	4.0		[32]	
		Cixutumumab	53.0	10.0			
		Dalatumumab	38.1	0.8			
		Pigitumumab	38.9	10.6			
		Ganitumab	25.0	9.1			
		R1507	15.8	2.3			
	PI3K/Akt Inhibitor	BKM120	30.1	8.4		[32]	
		MK-2206	30.0	3.0			
		Perilosine	9.6	2.7			
		XL147	7.0	0.0			
	mTOR Inhibitor	CCI-779	20.0	1.0		[32]	
		Deforolimus	28.0	6.0			
		Everolimus	25.7	6.3			
		Ridifirolimus	18.0	18.0			
	Glucocorticoids	Temsirolimus	8.0	5.0		[33]	
Prednisone or Dexamethasone**		58.9	13.3*				

**Supplementary Table S3.** Relative Risk with 95% CI of developing hyperglycaemia (HG) was calculated for each regime containing the indicated drug (3<sup>rd</sup> column) vs. the same regime substituting the drug for placebo or interferon. Common terminology criteria for hyperglycaemia based on fasting blood glucose (FBG) values. Hyperglycaemia all grades, FBG >126 mg/dl (> 7.0 mmol/l); grade 3: FBG between 252-500 mg/dl (13.9-27.8 mmol/l), grade 4: FBG > 500 mg/dl (>27.8 mmol/l). Everolimus (Ever), trabstuzumag (Transt), paclitaxel (Paclit), Temsirolimus (Tems), Bevacizumab (Bevac). \*\*Prednisone or Dexamethasone also received radiotherapy or other chemotherapy drugs. #This group of breast cancer patients also have Her2 mutation. ""5-FU alone or in combination with oxaliplatin, irinotecan or mitomycin. References in brackets are indicated on the right column

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