Type II Diabetes and Metformin Use Does Not Affect Colorectal Cancer Prognosis

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Table of Contents

S TABLE 1 Frequencies and proportions of baseline clinical and tumour characteristics among 33,028 Swedish CRC patients stratified by diabetes status

		Total cohort n (col%)	Non-diabetic CRC patients n (col%)	CRC patients with T2DM n (col%)
Overall		33,028	28,489	4,539
Year of diagnosis	2007-2011	15,327 (46.4)	13,427 (47.1)	1,900 (41.9)
	2012-2016	17,701 (53.6)	15,062 (52.9)	2,639 (58.1)
Age	18-49	1,557 (4.7)	1,515 (5.3)	42 (0.9)
	50-59	3,337 (10.1)	3,084 (10.8)	253 (5.6)
	60-69	8,775 (26.6)	7,637 (26.8)	1,138 (25.1)
	70-79	11,715 (35.5)	9,726 (34.1)	1,989 (43.8)
	80-89	7,038 (21.3)	5,984 (21.0)	1,054 (23.2)
	> 90	606 (1.8)	543 (1.9)	63 (1.4)
	Median (IQR)	*72.1 (64-79)*	*72.0 (64-79)*	*74.1 (68-79)*
Sex	Male	17,249 (52.2)	14,476 (50.8)	2,773 (61.1)
	Female	15,779 (47.8)	14,013 (49.2)	1,766 (38.9)
Education level	<10 yrs.	12,215 (37.0)	10,250 (35.8)	2,010 (44.3)
	10-12 yrs.	12,967 (39.3)	11,245 (39.5)	1,722 (37.9)
	>12 yrs.	7,478 (22.6)	6,761 (23.7)	717 (15.8)
	Missing	368 (1.1)	278 (1.0)	90 (2.0)
CCI	0	21,045 (63.7)	18,692 (65.6)	2,353 (51.8)
	1	4,296 (13.0)	3,495 (12.3)	801 (17.7)
	2	5,054 (15.3)	4,281 (15.0)	773 (17.0)
	≥ 3	2,633 (8.0)	2,021 (7.1)	612 (13.5)
ASA score	1	5,369 (16.3)	5,312 (18.7)	57 (1.3)
	II	17,475 (52.9)	15,460 (54.3)	2,015 (44.4)
	III	8,576 (26.0)	6,418 (22.5)	2,158 (47.5)
	IV+	592 (1.8)	398 (1.4)	194 (4.3)
	Missing	1,016 (3.1)	901 (3.2)	115 (2.5)
BMI (kg/m2)	<18,5	703 (2.1)	672 (2.4)	31 (0.7)
	18.5- <25	12,997 (39.4)	11,870 (41.7)	1,127 (24.8)
	25- <30	11,301 (34.2)	9,605 (33.7)	1,696 (37.4)
	30- <35	3,778 (11.4)	2,862 (10.1)	916 (20.2)
	≥35	1,108 (3.4)	742 (2.6)	366 (8.1)
	Missing	3,141 (9.5)	2,738 (9.6)	403 (8.9)
	Median (IQR)	*25.4 (23.0-28.4)*	*25.1 (22.8-27.9)*	*27.5 (24.7-30.9)*
Aspirin use	No	25,766 (78.0)	23,124 (81.2)	2,642 (58.2)
	Yes	7,262 (22.0)	5,365 (18.8)	1,897 (41.8)
Tumor location	Colon, right	12,644 (38.3)	10,710 (37.6)	1,934 (42.6)
	Colon, left	9,640 (20.2)	8,298 (29.1)	1,342 (29.6)
	Colon, UNS	5 (0.02)	5 (0.02)	0
	Rectum	10,739 (32.5)	9,476 (33.3)	1,263 (27.8)
Disease stage	Stage I	8,017 (24.3)	6,921 (24.3)	1,096 (24.2)
	Stage II	12,923 (39.1)	11,133 (39.1)	1,790 (39.4)
	Stage III	12,088 (36.6)	10,435 (36.6)	1,653 (36.4)
Type of surgery	Elective	29,688 (89.9)	25,527 (89.6)	4,161 (91.7)
	Emergency	2,840 (8.6)	2,517 (8.8)	323 (7.1)
	Missing	500 (1.5)	445 (1.6)	55 (1.2)
Neoadjuvant treatment	Colon cancer	279 (1.3)	242 (1.3)	37 (1.1)
	Rectal cancer	6,942 (64.6)	6,182 (65.2)	760 (60.2)
Adjuvant treatment	Colon cancer	5,459 (24.5)	4,810 (25.3)	649 (19.8)
	Rectal cancer	2,231 (20.8)	2,026 (21.4)	205 (16.2)

Abbreviations: ASA score; American society of Anaesthesiologists score, BMI; body mass index, CCI; charlson comorbidity, col; column, CRC; colorectal cancer, IQR; interquartile, n; number, UNS; unspecified

S TABLE 2 Time to recurrence, CRC-specific mortality and all-cause mortality among 4,539 T2DM patients with CRC patients, stratified by T2DM treatment group using T2DM non-metformin users as reference

Event and T2DM treatment group	No. of Events/ Total No.	HR[a] (95% CI)	HR[b] (95% CI)	HR[c] (95% CI)
Time to recurrence				
T2DM non-metformin user	182 / 1,098	1.00	1.00	1.00
T2DM metformin user	272 / 1,745	0.93 (0.77-1.22)	1.01 (0.82-1.25)	1.01 (0.82-1.25)
T2DM diet-only	270 / 1,696	0.96 (0.81-1.13)	1.05 (0.85-1.29)	1.07 (0.85-1.34)
CRC-specific mortality				
T2DM non-metformin user	147 / 1,098	1.00	1.00	1.00
T2DM metformin user	243 / 1,745	1.04 (0.84-1.27)	1.11 (0.88-1.39)	1.10 (0.88-1.39)
T2DM diet-only	238 / 1,696	1.05 (0.85-1.29)	1.12 (0.90-1.40)	1.12 (0.88-1.43)
All-cause mortality				
T2DM non-metformin user	503 / 1,098	1.00	1.00	1.00
T2DM metformin user	557 / 1,745	0.63 (0.55-0.71)	0.86 (0.75-0.99)	0.88 (0.76-1.00)
T2DM diet-only	678 / 1,696	0.84 (0.74-0.94)	0.93 (0.82-1.06)	1.01 (0.88-1.16)

Abbreviations: CI; confidence interval, CRC; colorectal cancer, HR; hazard ratio, No.; number, T2DM; type 2 diabetes mellitus.

[a] Estimated from an unadjusted Cox regression model restricted to metformin users.
[b] Estimated from a model as in (a) also adjusting for age at surgery, sex, education level, year of diagnosis, CCI, ASA score and BMI.
[c] Estimated from a model as in (b) also adjusting for duration of diabetes.

S TABLE 3 Time-to recurrence, CRC-specific mortality and all-cause mortality among 33,028 Swedish CRC patients, stage I-III, stratified by T2DM treatment groups. In these analyses the results have been stratified by additional T2DM treatment groups, metformin monotherapy users and insulin therapy users

Event and T2DM treatment group	No. of Events/ Total No.	HR[a] (95% CI)	HR[b] (95% CI)
Time to recurrence			
Non-diabetic CRC	4,219 / 28,489	1.00	1.00
T2DM			
T2DM diet-only	270 / 1,696	1.09 (0.96-1.23)	0.97 (0.85-1.11)
T2DM monotherapy metformin user*	85 / 580	0.99 (0.80-1.30)	0.92 (0.73-1.16)
T2DM metformin user (+ other ADD/insulin)	187 / 1,165	1.09 (0.94-1.26)	1.01 (0.86-1.18)
T2DM non-metformin user (other ADD/insulin)	148 / 859	1.19 (1.01-1.40)	1.00 (0.83-1.19)
T2DM monotherapy insulin user**	34 / 239	0.97 (0.69-1.35)	0.83 (0.58-1.19)
CRC-specific mortality			
Non-diabetic CRC	3,789 / 28,489	1.00	1.00
T2DM			
T2DM diet-only	238 / 1,696	1.06 (0.93-1.21)	0.97 (0.84-1.12)
T2DM monotherapy metformin user*	78 / 580	1.01 (0.81-1.27)	0.95 (0.74-1.21)
T2DM metformin user (+ other ADD/insulin)	165 / 1,165	1.07 (0.92-1.25)	1.00 (0.84-1.18)
T2DM non-metformin user (other ADD/insulin)	119 / 859	1.05 (0.88-1.27)	0.92 (0.75-1.23)
T2DM monotherapy insulin user**	28 / 239	0.88 (0.61-1.28)	0.78 (0.52-1.16)
All-cause mortality			
Non-diabetic CRC	7,933 / 28,489	1.00	1.00
T2DM			
T2DM diet-only	678 / 1,696	1.57 (1.45-1.70)	1.16 (1.07-1.27)
T2DM monotherapy metformin user*	181 /580	1.15 (0.99-1.33)	1.07 (0.91-1.26)
T2DM metformin user (+ other ADD/insulin)	376 / 1,165	1.19 (1.07-1.32)	1.07 (0.96-1.20)
T2DM non-metformin user (other ADD/insulin)	383 / 859	1.81 (1.63-2.00)	1.25 (1.12-1.40)
T2DM monotherapy insulin user**	120 /239	2.14 (1.79-2.56)	1.29 (1.06-1.58)

Abbreviations: ADD; antidiabetic drugs, CRC; colorectal cancer, CI; confidence interval, HR; hazard ratio, No.; number, T2DM; type 2 diabetes mellitus

*T2DM patients who have only been using metformin. No dispensation of any other antidiabetic treatment ever.

** T2DM patients who have only been using insulin. No dispensation of any other antidiabetic treatment ever.

[a] Estimated from an unadjusted Cox regression model restricted to metformin users.
[b] Estimated from a model as in (a) also adjusting for age at surgery, sex, education level, year of diagnosis, CCI, ASA score and BMI

S TABLE 4 Time to recurrence, CRC-specific mortality and all-cause mortality among 22,857 Swedish CRC patients, stage I-III, stratified by T2DM treatment groups and metformin users are additionally stratified by cumulative metformin pills dispensed. The analysis includes CRC patients diagnosed on or after July 1, 2010, ensuring at least 5 years of dispensation data

Event and T2DM treatment group and metformin users stratified by cumulative use	No. of Events/ Total No.	HR[a] (95% CI)	HR[b] (95% CI)
Time to recurrence			
Non-diabetic CRC	2,787 / 19,491	1.00	1.00
T2DM			
T2DM diet-only	210 / 1,274	1.17 (1.02-1.35)	1.01 (1.18)
T2DM metformin user: < 365	12 / 58	1.49 (0.85-2.63)	1.48 (0.82-2.28)
T2DM metformin user: 365-<1095	33 / 264	0.87 (0.62-1.23)	0.81 (0.56-1.18)
T2DM metformin user: 1095-<1825	43 / 311	0.97 (0.72-1.31)	0.89 (0.64-1.23)
T2DM metformin user: ≥ 1825	101 / 675	1.05 (0.86-1.28)	0.97 (0.79-1.20)
T2DM non-metformin user	132 / 784	1.21 (1.01-1.44)	0.98 (0.81-1.18)
CRC-specific mortality			
Non-diabetic CRC	2,488 / 19,491	1.00	1.00
T2DM			
T2DM diet-only	187 / 1,274	1.17 (1.01-1.35)	1.03 (0.88-1.20)
T2DM metformin user: < 365	11 / 58	1.52 (0.84-2.75)	1.49 (0.80-2.78)
T2DM metformin user: 365-<1095	29 / 264	0.85 (0.59-1.23)	0.82 (0.55-1.21)
T2DM metformin user: 1095-<1825	39 /311	0.98 (0.71-1.35)	0.89 (0.64-1.26)
T2DM metformin user: ≥ 1825	88 /675	1.03 (0.82-1.27)	0.95 (0.76-1.19)
T2DM non-metformin user	110 / 784	1.12 (0.92-1.35)	0.91 (0.74-1.12)
All-cause mortality			
Non-diabetic CRC	5,231 / 19,491	1.00	1.00
T2DM			
T2DM diet-only	516 / 1,274	1.67 (1.52-1.82)	1.21 (1.10-1.33)
T2DM metformin user: < 365	14 / 58	0.87 (0.52-1.48)	0.86 (0.50-1.48)
T2DM metformin user: 365-<1095	78 / 264	1.10 (0.88-1.38)	1.04 (0.81-1.33)
T2DM metformin user: 1095-<1825	98 / 311	1.20 (0.99-1.47)	1.11 (0.90-1.37)
T2DM metformin user: ≥ 1825	211 / 675	1.21 (1.05-1.39)	1.08 (0.94-1.25)
T2DM non-metformin user	348 / 784	1.87 (1.68-2.09)	1.23 (1.09-1.39)

Abbreviations: CRC; colorectal cancer, CI; confidence interval, HR; hazard ratio, No.; number, T2DM; type 2 diabetes mellitus

[a] Estimated from an unadjusted Cox regression model restricted to metformin users.

[b] Estimated from a model as in (a) also adjusting for age at surgery, sex, education level, year of diagnosis, CCI, ASA score and BMI.