Chemotherapy: Open Access
ISSN: 2167-7700

Su et al., Chemotherapy 2017, 6:2
DOI: 10.4172/2167-7700.1000233

Research Article OMICS International

The Effect of Metformin on Colorectal Carcinoma in Type 2 Diabetes Mellitus Patients: A Markov Model Analysis

Tianhong Su[1], Yihao Liu[2], Weifeng Liu[3], Shuling Chen[4], Qian Zhou[5], Zhenwei Peng[5], Sui Peng[1,5]* and Haipeng Xiao[2]*

[1]*Department of Gastroenterology and Hepatology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, PR China*
[2]*Department of Endocrinology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, PR China*
[3]*Department of Anesthesiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, PR China*
[4]*Division of Interventional Ultrasound, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, PR China*
[5]*Clinical Trial Unit, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, PR China*

Abstract

Objective: Morbidity and mortality of colorectal cancer (CRC) in type 2 diabetes mellitus (T2DM) patients are higher than that of general population, the mechanism of which remains undetermined. Some studies found that metformin could lower the risk of cancer, including CRC, in T2DM patients, but others demonstrated different results. Therefore, we target to evaluate the CRC prevention effect of metformin in comparison with that of other T2DM medications from a Markov model perspective.

Methods: A Markov model simulating a randomized trial comparing metformin with non-metformin treatment in T2DM patients without CRC over 11-year time horizon was constructed based on data from 8 literatures. CRC morbidity was selected as endpoint. Monte Carlo analysis with 10,000 patients allocated for each arm was performed to assess CRC morbidity and cumulative tumor-free survival in each group.

Results: In contrast with non-metformin group, T2DM patients treated with metformin had a lower rate of CRC (1.670% *vs*. 2.146%). Moreover, cumulative tumor-free survival of metformin group was, slightly but significantly, better than that of non-metformin group (10.91 years *vs*. 10.88 years, p<0.001). Monte Carlo Strategy Selection analysis showed that metformin group had a better optimal frequency than the other one.

Conclusion: T2DM patients treated with meformin have a lower morbidity of CRC and a better cumulative tumor-free survival than that of the non-metformin group. Large scale, randomized, double blind clinical trials are needed to illustrate the role of metformin in the prevention of CRC.

Keywords: Colorectal carcinoma; Type 2 diabetes mellitus; Metformin; Non-metformin medications; Morbidity; Cumulative tumor-free survival; Markov model

Introduction

Colorectal carcinoma (CRC) is the third most common cancer and the third leading cause of cancer death in America. Adoption of colonoscopy screening and new treatments declined the rate by 3.9% per year among adults aged 50 years and older in the USA. However, the incidence in America increased by 1.1% per year among men and women aged younger than 50 years, in which the increased prevalence in obesity prevalence and the emergence of unfavorable dietary patterns have been implicated [1]. While in Asia-Pacific region, CRC incidence has increased since the last decades and is the third most prevalent cancers, which is also attributed to such environmental factors as obesity and the adoption of the Western lifestyle [2].

Many researches demonstrate that Western dietary habits and increasing incidence of metabolic syndrome result in more and more CRC cases [3,4]. Morbidity and mortality of CRC in type 2 diabetes mellitus (T2DM) patients are higher than that in the general population [5], since they have such risk factors in common as obesity, alcohol consumption and Western diet pattern and so on [6]. On exploring chemopreventive drugs against cancer, many studies, but not all, found that metformin, the typical first-line treatment for T2DM, reduced the incidence of many cancers, including CRC [7,8]. Nevertheless, some studies illustrated that metformin provided no protective effect against cancers, including CRC in T2DM patients [9,10]. Therefore, the role of metformin on CRC remains obscure and large scale, randomized, controlled trials (RCTs) are needed to unveil their relationship.

Nevertheless, it is difficult to conduct those large trials due to tremendous difficulties in patient enrollment and treatment allocations. By emulating disease process where patients progress through different health states over the preset cycles, Markov model can be applied to assess disease's outcomes. Generally, Markov models are applied in describing stochastic processes, which are random processes evolving over time [11]. Since its first introduction in predicting medical prognosis in 1983, Markov models have been more and more prevalent in the field of clinical evaluations [12]. By dividing a disease into distinct states and assigning transitions probabilities for movement between those states, then attaching estimates of costs and health outcomes to the states and running the model over many cycles, the model is able to estimate the long-term costs and outcomes associated with that disease and the related healthcare interventions [11]. The advantage of Markov model by taking into accounts both costs and outcomes over a period of time makes it particularly suitable to model the progression

***Corresponding author:** Sui Peng, Department of Gastroenterology and Hepatology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, PR China, Tel: +86-20-87755766; E-mail: pengsui2002@vip.sina.com

Haipeng Xiao, Department of Endocrinology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, PR China, Tel: +86-20-87755766; E-mail: xiaohp@mail.sysu.edu.cn

Received March 18, 2017; **Accepted** May 22, 2017; **Published** May 29, 2017

Citation: Su T, Liu Y, Liu W, Chen S, Zhou Q, et al. (2017) The Effect of Metformin on Colorectal Carcinoma in Type 2 Diabetes Mellitus Patients: A Markov Model Analysis. Chemotherapy 6: 233. doi:10.4172/2167-7700.1000233

of chronic disease. Up to date, Markov model has been widely adopted in the evaluation of disease screening or treatments around the world [13-15]. It has been successfully used in the simulation of head–to–head comparison of the treatment efficacy of two modalities [16,17]. Therefore, we attempted to simulate a RCT which compared metformin with non-metformin treatment in terms of CRC incidence for T2DM patients without CRC by building a Markov model.

Methods and Materials

Model construction

A multi-state Markov analyzing model, which emulated a RCT with a follow-up period of 11 years, was constructed to compare the CRC prophylaxis effect of metformin with that of other T2DM medications in T2DM patients. Thus, in this model, the two therapeutic decisions to be analyzed were metformin and other antidiabetic agents. The end point was defined as CRC morbidity. Diagram of this model was represented in Figure 1. As was showed in this model, a total of 6 Markov states were developed including three states in metformin group and the remaining in another group. The cycle length was set to be one year, which was the pertinent interval to observe the treatment response of tumor episodes. Further, in consideration of obtaining sustained outcomes and the actual life expectancy of T2DM patients, we assumed the patients to be observed for 11 years [18]. Then, the half-cycle correction was used [19]. The annual mortality or morbidity was derived from the median survival or cumulative probability of survival using the declining exponential approximation of life expectancy (DEALE) method [20].

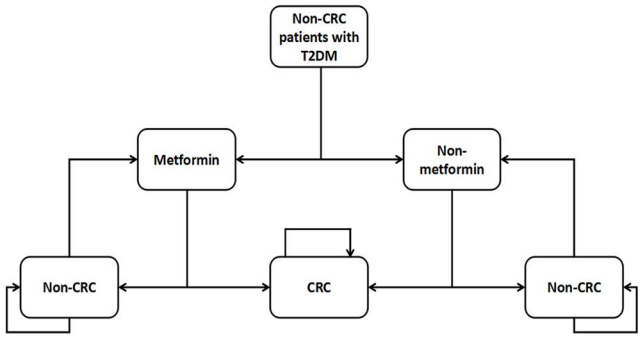

Figure 1: Flow diagram of Markov analyzing model. Each pane represents a health State; Straight lines with arrows indicate transition from one state to another one while circular arrows suggest that some patients may stay at the same state for more than one cycle. Two therapy strategies were compared in this model with initial treatments being metformin and non-metformin medications.

The TreeAge-Pro-2008 software (TreeAge Software Inc., Williamstown, MA, USA) was applied to build up such a Markov model.

Furthermore, sensitivity analyses were also performed to evaluate the contribution of certain variable to the CRC morbidity and the robustness of our results [21]. One-way and two-way sensitivity analysis was performed to assess the extent to which an endpoint was influenced by respectively changing the value of one and two estimates with the other parameters remaining constant. Last, a second-order Monte Carlo probabilistic sensitivity analysis was performed to evaluate the total impact of parameter uncertainties on the model results, with 10,000 patients allocated into each group respectively.

Literature selection

Transition probabilities between each state in this model were extracted from the included literatures published in English that investigated the therapeutic efficacy of metformin and/or other T2DM medications on CRC for T2DM patients without CRC (Table 1) [18,22-30]. Literatures were retrieved from two databases of PubMed and Cochrane Library with the latest searching on September 27, 2016. The following search terms were used: colorectal carcinoma, colorectal cancer, colorectal malignancies, CRC, metformin, type 2 diabetes mellitus, T2DM, morbidity, prevalence, mortality, death. Reference lists of the included studies were hand-searched to identify further relevant trials. If more than one article was published in the same data subset, only the most recent article was employed. Besides, two investigators independently searched all the eligible studies and a third party was consulted when the two searchers' opinions differed. Studies were to be recruited if they met the following criteria:

(i) The entire population or subpopulation were adult patients with T2DM but without CRC.

(ii) Any of the parameter estimates applied in our model was reported.

(iii) RCTs, quasi-randomized trials, prospective or retrospective cohort studies were included whereas reviews, letters, case reports, editorials or comments and meeting abstracts were excluded.

Parameter estimation

Before pooling the extracted transition probabilities, double arcsine transformations on them were performed for variances stabilization [31]. The Wilson score method was also used to estimate the 95% confidence intervals (CIs) of these probabilities [32]. Then, STATA software (Stata Corp., College Station, TX, USA) was applied to pool the above mentioned rates using random-effect model. Further, SAS 9.2

Author	Sample size	Age	Region	M[a] users	NM[b] users	CRC[c] cases	
						M users	NM users
Meei-Shyuan Lee [22]	480, 984	>20	Taiwan	11,221	4213	30	26
Home [23]	4351	60 (mean)	UK	1454	2897	7	14
Rikje Rutter [24]	85, 289	>18	Netherlands	52,698	32,591	228	299
Bernd Kowall [25]	60571 (UK); 19692 (GER)	30-89	German and UK	55,988	17,704	281	150
Ramjeesingh [26]	277	24-98	Canada	133	144	133	144
Jin Ha Lee [27]	595	30-88	Korea	258	337	258	337
Ming Chia Hsieh [28]	61777	61.44 ± 13.23 (mean)	Taiwan	3963	6823	46	163

Table 1: Detailed characteristics of studies included in this model. A: Metformin; B: Non metformin (other diabetic medications); C: Colorectal carcinoma.

(SAS Institute Inc., Cary, NC, USA) was employed to apply the Wilson score method and calculate the 95% CIs.

Summary of transition probabilities and assumptions

The transition probabilities retrieved from the literatures were summarized in Table 2. For T2DM patients without CRC, the estimated annual mortality was derived by excluding CRC-specified mortality from that of the whole T2DM population [33]. The average age of patients in the included studies ranged from 25 years to 79 years, then we assumed the mean age of this cohort to be 60–65 years with the annual age-related mortality being 0.055 [34].

Results

Morbidity and cumulative tumor-free survival outcome of the model

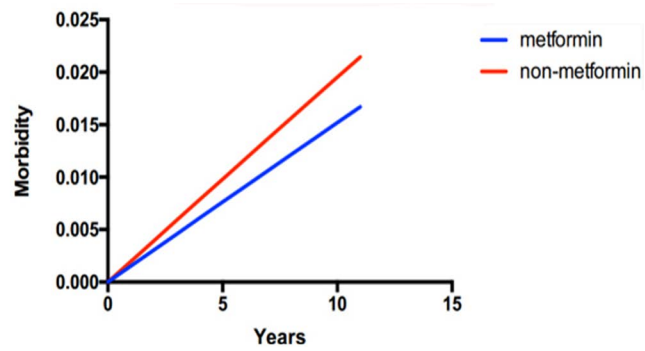

Figure 2: CRC morbidity curves for metformin and non-metformin groups in the treatment of T2DM patients. The CRC morbidity of metformin group was lower than that of non-metformin group.

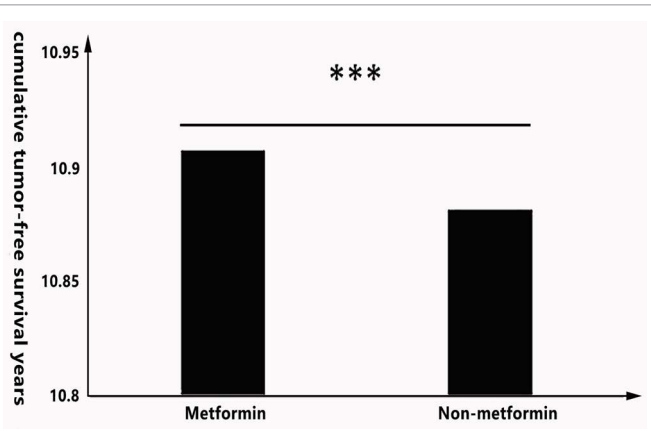

Figure 3: Cumulative tumor-free survival curves for metformin and non-metformin groups in the treatment of T2DM. Curves of metformin group showed a better result than that of non-metformin group.

Based on the data from literature review, the CRC morbidity of metformin group and non-metformin group were 1.670% and 2.146% respectively (Figure 2). The expected cumulative tumor-free survivals were 10.908 years and 10.882 years for metformin and non-metformin groups, respectively ($p<0.001$, Figure 3).

One-way and two-way sensitivity analysis

One-way sensitivity analyses for all the variables demonstrated that the curves of expected cumulative tumor-free survival representing metformin treatment were always above those representing non-metformin until the CRC morbidity of metformin group was higher than 0.197%, which suggested that metformin treatment had better tumor-free survival benefit than non-metformin therapy in most cases (Figure 4). Similar result could be observed in two-way sensitivity analysis (Figure 5). For any of the two variables, there was no point of intersection between these two therapies as showed in the Figure even when comparing the most sensitive factors in both groups and assuming the best scenario for non-metformin treatment.

Second-order Monte carlo simulation

The probability distributions of cumulative tumor-free survival using Monte Carlo Simulation demonstrated that the estimated CRC-free survival in metformin group (95% CI: 10.906–10.908 years) was better than that in non-metformin group (95% CI: 10.881–10.882 years) (Figures 6A and 6B). The 95% CIs of the difference in overall survival between these two groups were 0.0258-0.0264 years. The difference was statistically significant ($p<0.001$). This result further validated our model by suggesting that the superiority of metformin to non-metformin would not be altered by the uncertainties of parametric estimations.

Discussion

Anti-malignancies effect of metformin is not well determined. Some previous observational and mechanistic studies show positive results [35-37]. However, no demonstrable protective effect of metformin against malignancy is shown in the RCT (OR=0.69, 95% CI: 0.26–1.82) [23]. Yet, this may be due to the fact that these two RCTs and others were not primarily launched to collect data on CRC and the numbers of malignancy cases are small, in the case of which bases could be expected. By simulating RCT, Markov model can be applied to predict disease outcomes, compare treatment efficacy of various therapies and evaluate the cost-effectiveness of treatment modalities [38,39]. Thus, it may help to provide informative data in the comparison of metformin and other anti-diabetes medications for the prevention of CRC in T2DM patients when RCTs are unavailable.

Based on 7 observational and 1 RCT researches recruited in this study, we constructed a Markov model to simulate a RCT analyzing the CRC prophylaxis effect of metformin in CRC-free T2DM patients and found that metformin, in comparison with other diabetes medications, had a lower risk of CRC. This finding is in accordance with the results of some previous observational studies and meta-analysis [38,39]. A

Variable	Metformin	Non-metformin
Annual mortality rate of general population(60-65 years old)	5.5% [33]	
Mortality of T2DM[a] patients without CRC[b]	0.154 [24]	
CRC morbidity	0.153% (0.068%-0.201%) [22-25,28]	0.197% (0.197%-0.242) [22,24,28]
CRC specific mortality	5% (1.56%-10.248%) [26,27,33]	11.3% (4.21%-18.82%) [26,27,33]
Non-CRC mortality	1.3% (0.335%-2.667%) [29,30]	3.3% (2.536%-4.397%) [26,33]

Table 2: Estimated transition probabilities extracted from literatures for the Markov Model. [a]: Type 2 diabetes mellitus; [b]: Colorectal carcinoma.

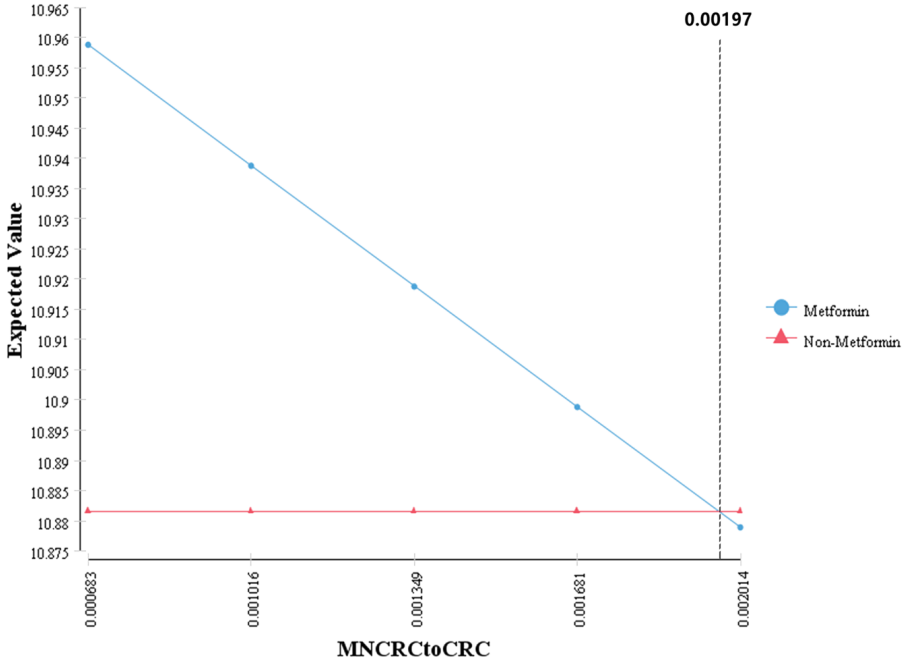

Figure 4: One-way sensitivity analysis for CRC morbidity. The effects of CRC rate on cumulative tumor-free survival for metformin group and non-metformin group were analysed. Note the incremental difference between these two groups.MNCRC to CRC: CRC morbidity of CRC-free T2DM patients in metformin group.

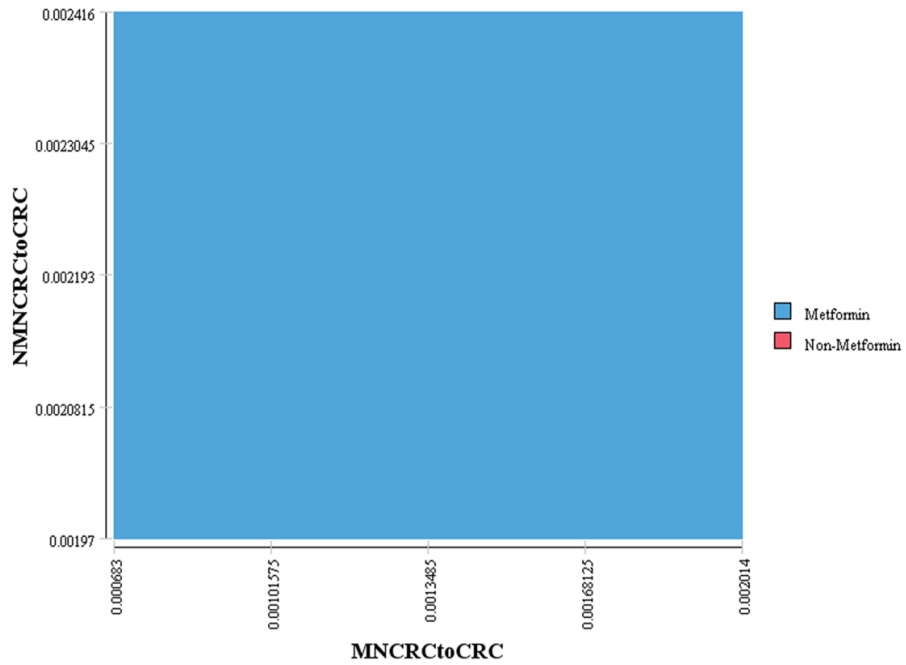

Figure 5: Two-way sensitivity analysis for CRC rate in each group. Whichever scenario it was, metformin treatment was always the optimal decision.
MNCRC to CRC: CRC morbidity of CRC-free T2DM patients in metformin group.
NMNCRC to CRC: CRC morbidity of CRC-free T2DM patients in non-metformin Group.

growing body of evidence could back up the protective effect against CRC of metformin from *in vivo* and *in vitro* studies. More and more studies demonstrate a systemic and cellular-targeted effect by which metformin suppresses carcinogenesis. Systemic (insulin-dependent) effect of metformin can indirectly suppress tumorigenesis by improving hyperglycemia to neutralize the Warburg effect, which characterizes the metabolic feature of cancer cells through facilitating bypass senescence [40,41]. While targeting at cancer cells, metformin can directly exert

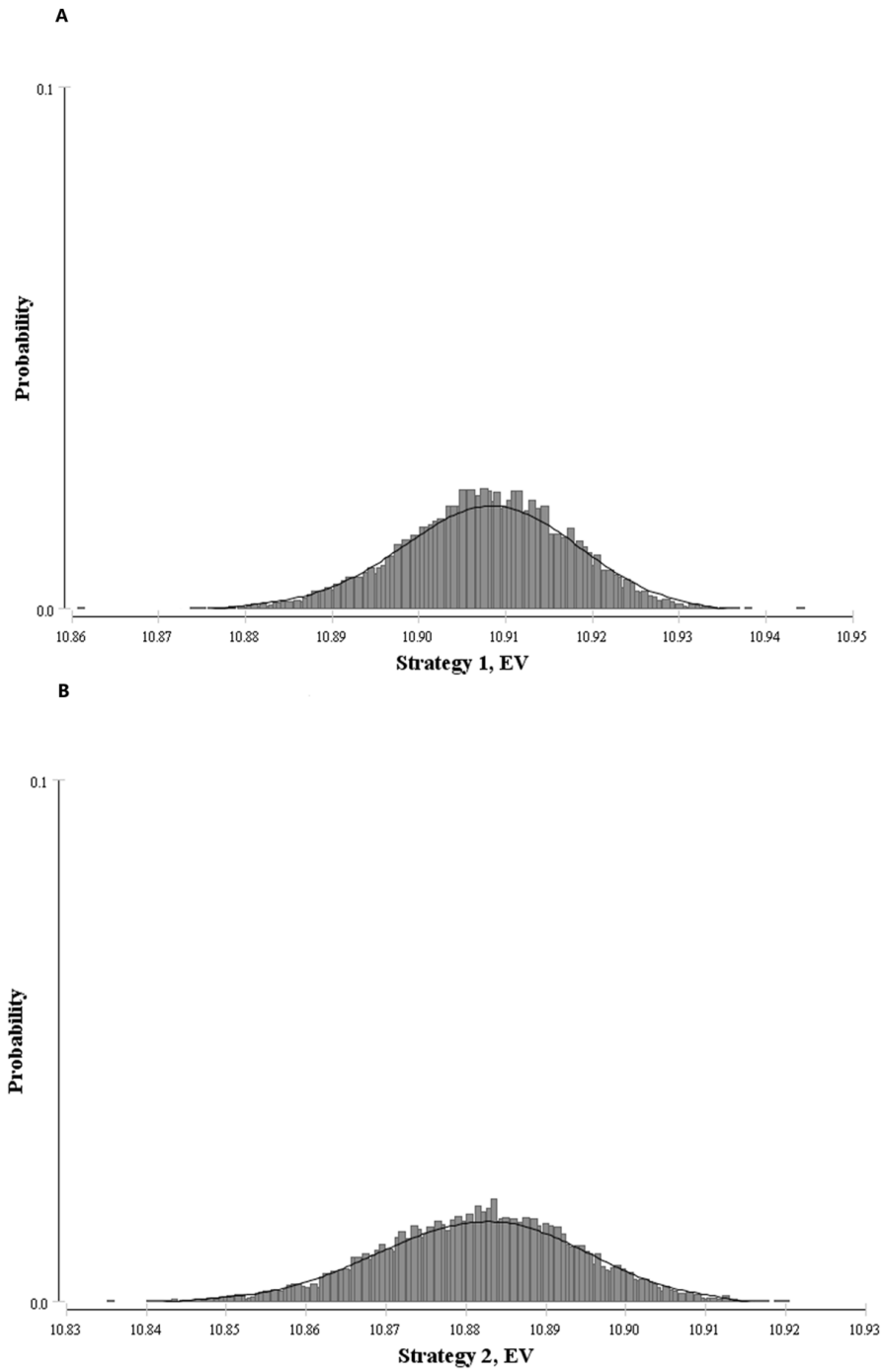

Figure 6: The second-order Monte Carlo probability distribution of the cumulative tumor-free survival (EV) in strategy 1 (metformin group) (A) and strategy 2 (non-metformin group) (B). Note that the difference of distribution between these two therapy strategies was significant.

pleiotropic inhibitory effects on various signalings involved in the process of survival and metastasis [42], including mTOR pathway, which plays a key role in proliferation and carcinogenesis in various cancers [43]. Furthermore, metformin can regulate the number and/or the maintenance of cancer stem cells by down regulating systemic metabolic markers including IGF-1 and insulin, which is essential for the generation and/or maintenance of mammal stem cells [44-46]. Anticancer effect of metformin also works in animal model. Zaafar DK et al. found that metformin protected against DMH-induced colon cancer in non-diabetic and diabetic mice, the therapeutic effect of which may be, at least in part, attributed to its anti-angiogenic and anti-proliferative mechanisms [47]. Abovementioned evidence from *in vivo* and *in vitro* supports the protective effect of metformin as one of the promising candidates for cancer therapeutics. Further, our model presented, slightly but significantly, an encouraging cumulative tumor-free survival outcome for patients treated with metformin. This may

be due to the fact that the Markov cycle was set to repeat 11 times, which ensured a long enough follow-up period to obtain data from patients as much as possible. However, the effect of metformin on CRC survival warrants further demonstration by RCTs which stratify CRC patients. The process of CRC progression and its various corresponding therapy regimen need to be taken into account, because these variables could also impact patients' survival benefit, which may bias the effect of metformin and other diabetes medications.

Limitations of this study were demonstrated as follow. Firstly, the non-metformin group consisted of multiple treatment regimens, including the mono-application or combination of rosiglitazone, glibenclamide, sulfonylurea and insulin and so on. This would inevitably cause biases. Then, limited information about the survival benefit generated by metformin on CRC patients could be attained. Secondly, in spite of detailed systematic review of all the eligible RCTs and observational studies were performed to retrieve data as accurate as possible, the paucity of RCTs included might influence the results to some extent. Moreover, our pooled parameters were based on data from observational studies, while just one RCT is applicable. It is acknowledged that observational studies had such methodical drawbacks as a tendency to time-related biases, including immortal time bias and time-lagging issues. Thirdly, covariates of included studies were incomplete and inconsistent even after statistical adjustment. Finally, literatures pooled were confined to English language researches, which might potentially evoke publication bias. Notwithstanding, it is impractical to expect a model simulating exactly the real clinical scenario because of too many uncertainties regarding the treatment selection during a patient's whole disease course. Our model is a simplified, practical mathematical model aiming to provide some insight for these controversial research hotspots, but not to replace RCTs completely.

Therefore, based on this Markov model with enormous sample size and long follow-up period, our findings may help the future investigations and management of T2DM with regards of CRC. Validation for our findings will merit further high-quality studies.

Acknowledgement

The manuscript does not contain clinical studies or patient data. For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors. The authors declare that they have no conflict of interest.

References

1. Siegel R, Desantis C, Jemal A (2014) Colorectal Cancer Statistics. CA Cancer J Clin 64: 104-117.
2. Pourhoseingholi AM (2014) Epidemiology and burden of colorectal cancer in Asia-Pacific region: what shall we do now. Transl Gastrointest Cancer 3: 169-173.
3. Feakins RM (2016) Obesity and metabolic syndrome: pathological effects on the gastrointestinal tract. Histopathology 68: 630-640.
4. Mendonça FM, de Sousa FR, Barbosa AL, Martins SC, Araújo RL, et al. (2015) Metabolic syndrome and risk of cancer: Which link? Metabolism 64: 182-189.
5. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R (2009) Diabetes and cancer. Endocr Relat Cancer 16: 1103-1123.
6. Giovannucci E1, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, et al. (2010) Diabetes and cancer: a consensus report. CA Cancer J Clin 60: 207-221.
7. Wang SY, Chuang CS, Muo CH, Tu ST, Lin MC, et al. (2013) Metformin and the incidence of cancer in patients with diabetes: a nested case-control study. Diabetes Care 36: e155-156.
8. Tseng CH (2012) Diabetes, metformin use, and colon cancer: a population-based cohort study in Taiwan. Eur J Endocrinol 16: 409-416.
9. Tsilidis KK, Capothanassi D, Allen NE, Rizos EC, Lopez DS, et al. (2014) Metformin does not affect cancer risk: a cohort study in the U.K. Clinical Practice Research Datalink analyzed like an intention-to-treat trial. Diabetes Care 37: 2522-2532.
10. Kowall B, Stang A Rathmann W, Kostev K (2015) No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. Pharmacoepidemiol Drug Saf 24: 865-874.
11. Briggs MA, Sculpher M (1998) An introduction to Markov modelling for economic evaluation. Pharmacoeconomics 13: 397-409.
12. Sonnenberg FA, Beck JR (1993) Markov models in medical decision making a practical guide. Med Decis Making 13: 322-338.
13. Parsonnet J, Harris RA, Hack HM, Owens DK (1996) Modelling cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer: a mandate for clinical trials. Lancet 348: 150-154.
14. Nayagam S, Conteh L, Sicuri E, Shimakawa Y, Suso P, et al. (2016) Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in The Gambia: an economic modelling analysis. Lancet Glob Health 4: e568-e78.
15. Hillner BE, Smith TJ (1991) Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. A decision-analysis model. N Engl J Med 324: 160-168.
16. Briggs A, Claxton K, Sculpher M (2006) Decision modeling for health economic evaluation. Oxford University press Inc., New York, USA.
17. Lee WC, Samyshkin Y, Langer J, Palmer JL (2012) Long-term clinical and economic outcomes associated with liraglutide versus sitagliptin therapy when added to metformin in the treatment of type 2 diabetes: a CORE Diabetes Model analysis. J Med Econ 2: 28-37.
18. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, et al. (2011) Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol 26: 863-876.
19. Naimark DM, Bott M, Krahn M (2008) The half-cycle correction explained: two alternative pedagogical approaches. Med Decis Making 28: 706-712.
20. Beck JR, Kassirer JP, Pauker SG.(1982) A convenient approximation of life expectancy (the "DEALE").I. Validation of the method. Am J Med 73: 883-888.
21. Brown ST, Grima DG, Sauriol L (2014) Cost-effectiveness of insulin glargine versus sitagliptin in insulin-naïve patients with type 2 diabetes mellitus. Clin Ther 36: 1576-1587.
22. Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, et al. (2011) Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. BMC Cancer 11: 20.
23. Home PD, Kahn SE, Jones NP, Noronha D, Beck-Nielsen H, et al. (2010) Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. Diabetologia 53: 1838-1845.
24. Ruiter R, Visser LE, van Herk-Sukel MP, Coebergh JW, Haak HR, et al. (2012) Lower Risk of Cancer in Patients on Metformin in Comparison With Those on Sulfonylurea Derivatives. Diabetes Care 35: 119-124.
25. Kowall B, Stang A, Rathmann W, Kostev K (2015) No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. Pharmacoepidemiol Drug Saf 24: 865-874.
26. Ramjeesingh R, Orr C, Bricks CS, Hopman WM, Hammad N (2016) A retrospective study on the role of diabetes and metformin in colorectal cancer disease survival. Curr Oncol 23: 1-4.
27. Lee JH, Kim TI, Jeon SM, Hong SP, Cheon JH, et al. (2012) The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. Int J Cancer 131: 752-759.
28. Hsieh MC, Lee TC, Cheng SM, Tu ST, Yen MH, et al. (2012) The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. Exp Diabetes Res 2012: 413782.
29. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008) 10-Year

Follow-up of Intensive Glucose Control in Type 2 Diabetes. N Engl J Med 359: 1577-1589.

30. Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P, et al. (2004) Efficacy and Safety of Pioglitazone Versus Metformin in Patients with Type 2 Diabetes Mellitus: A Double-Blind, Randomized Trial. J Clin Endocrinol Metab 89: 6068-6076.
31. Freeman MF, Tukey JW (1950) Transformations related to the angular and the square root. Ann Math Statist 21: 607-611.
32. Newcombe RG (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 17: 857-872.
33. Mc Menamin ÚC, Murray LJ, Hughes CM, Cardwell CR (2016) Metformin use and survival after colorectal cancer: A population-based cohort study. Int J Cancer 138: 369-79.
34. Department Of Health And Human Services NCFH, Statistics (2006) National Vital Statistics Reports 57(14).
35. Tseng CH (2012) Diabetes, metformin use, and colon cancer: a population-based cohort study in Taiwan. Eur J Endocrinol 167: 409-416.
36. Singh S, Singh H, Singh PP, Murad MH, Limburg PJ (2013) Antidiabetic Medications and the Risk of Colorectal Cancer in Patients with Diabetes Mellitus: A Systematic Review and Meta-analysis. Cancer Epidemiol Biomarkers Prev 22: 2258-2268.
37. Sehdev A, Shih YC, Vekhter B, Bissonnette MB, Olopade OI, et al. (2015) Metformin for Primary Colorectal Cancer Prevention in Patients With Diabetes: A Case-Control Study in a US Population. Cancer 121: 1071-1078.
38. Eddy DM, Schlessinger L, Kahn R (2005) Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med 143: 251-264.
39. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, et al. (2005) The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med 142: 323-332.
40. Del Barco S, Vazquez-Martin A, Cufí S, Oliveras-Ferraros C, Bosch-Barrera J, et al. (2011) Metformin: multifaceted protection against cancer. Oncotarget 2: 896-917.
41. Kondoh H, Lleonart ME, Gil J, Wang J, Degan P, et al. (2005) Glycolytic enzymes can modulate cellular life span. Cancer Res 65: 177-185.
42. Martin-Castillo B, Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA (2010) Metformin and cancer: doses, mechanisms and the dandelion and hormetic phenomena. Cell Cycle 9: 1057-1064.
43. Klümpen HJ, Beijnen JH, Gurney H, Schellens JH (2010) Inhibitors of mTOR. Oncologist 15: 1262-1269.
44. Bendall SC, Stewart MH, Menendez P, George D, Vijayaragavan K, et al. (2007) IGF and FGF cooperatively establish the regulatory stem cell niche of pluripotent human cells in vitro. Nature 448: 1015-2021.
45. Korkaya H, Wicha MS (2007) Selective targeting of cancer stem cells (2007) a new concept in cancer therapeutics. BioDrugs 21: 299-231.
46. Liu S, Wicha MS (2010) Targeting breast cancer stem cells. J Clin Oncol 28: 4006-4012.
47. Zaafar DK, Zaitone SA, Moustafa YM (2014) Role of metformin in suppressing 1,2-dimethylhydrazine-induced colon cancer in diabetic and non-diabetic mice: effect on tumor angiogenesis and cell proliferation. PLoS One 9: e100562.

Citation: Su T, Liu Y, Liu W, Chen S, Zhou Q, et al. (2017) The Effect of Metformin on Colorectal Carcinoma in Type 2 Diabetes Mellitus Patients: A Markov Model Analysis. Chemotherapy 6: 233. doi:10.4172/2167-7700.1000233