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

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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 tumorfree 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

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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-tohead 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	NM⁵ users	CRC [°] 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.

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(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 nonmetformin 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 nonmetformin 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	C 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.

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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 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

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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.

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