The Relationship between Prostate Cancer and Metformin Consumption: A Systematic Review and Meta-Analysis study

Abstract

Introduction: ***Prostate cancer is the most common malignant cancer in men worldwide and after lung cancer is the second leading cause of cancer deaths in men. The purpose of this study was to investigate the relationship between prostate cancer and metformin consumption in men.***

Method: ***The current study is a systematic and meta-analysis review based on the PRISMA statement. To access the studies of domestic and foreign databases, Iran Medex, SID, Magiran, Iran Doc, Medlib, ProQuest, Science Direct, PubMed, Scopus, Web of Science and the Google Scholar search engine were searched during the 2009-2018 period for related keywords. In order to evaluate the heterogeneity of the studies, Q test and I^2 indicator were used. The data were analyzed using the STATA 15.1 software.***

Results: ***In 11 studies with a sample size of 877058, the odds ratio of metformin consumption for reducing prostate cancer was estimated 0.89 (95% ~~confidence interval~~CI: 0.67-1.17). Meta-regression also showed there was no significant relationship between the odds ratio and the publication year of the study. However, there was a significant relationship between the odds ratio and the number of research samples.***

Conclusion: ***Using metformin in men reduces the risk of prostate cancer but it is not statistically significant.***

Keywords: metformin, prostate cancer, chronic diseases

Introduction:

Chronic diseases have an impact on the economic, social, welfare and quality of life of patients and their families (1-6). Prostate cancer is the most common malignant cancer in men worldwide and after lung cancer is the second leading cause of cancer deaths in men (7-12). On the other hand, apart from skin cancer, prostate cancer is the most common cancer among men in the Western world (13). Frequent urination , Urinary inability, urinary incontinence , blood in the urine, burning and constant pain in the lower back and abdominal pain are also the clinical symptoms of prostate cancer (14). Various factors including age, race, genetic factors, environmental factors and family history play an important role in the progression of prostate cancer (15, 16). More than 670,000 men with prostate cancer are diagnosed annually. Of these, there are about 225,000 in Europe and 240,000 in the United States (17). The incident rate of prostate cancer varies in different races. For instance, it was varied between 4-7 per 100,000 for Asian countries and 70-100 per 100,000 people for European and North American countries (18, 19). In general, Asian men have a lower prostate cancer risk than the western population (20). The average length of stay in the hospital for patients with prostate cancer is between 5 to 10 days, which costs a lot to the individual and the clinical system (21). In spite of the extensive global difference in mortality rates among prostate cancer patients of different ages, autopsy studies confirmed that in the eighteenth century prostate cancer is present in 42-80 % of men (22, 23). On the other hand, the incidence and mortality rate of prostate cancer in developing countries and less developed countries is increasing (24, 25). The annual global incidence of prostate cancer is about 58.9 per 100,000 (26). This figure also varies between 3.9 in India and 178.8 in black Americans (24, 27). It is estimated that

300,000 new cases are annually known of which 41,000 are deadly (28, 29). Metformin has a variety of mechanisms that can reduce cancer and carcinogenesis: Direct effect (on the tumor and microenvironment) and indirect effects (on the host that may affect the tumor). Generally, metformin is directly and indirectly connected via The AKT-Mtor route (30-33). The pathway activation mechanisms that are most commonly associated with prostate cancer involve: The loss of the repressive PTEN (34), PI3K mutation (35), or activation of growth factor receptors such as insulin (36-38). Metformin is the most widely used anti-diabetic drug in the world, and only in the United States in 2010, 48 million copies were prescribed (39-41). Metformin is a biguanide that is available in most parts of the world, it is also inexpensive and has a low side effect and is well tolerated, since it does not cause hypoglycemia (42-44). The ability of metformin to reduce hyperinsulinemia may also indirectly reduce the risk of prostate cancer (45-47). Elsewhere, laboratory evidence has shown that hyperinsulinemia regulates insulin receptors in PCa cells and increases the growth of tumor (1, 48). Several invitro and invivo studies have shown that metformin acts directly in diminishing the growth specific tumors, decreasing insulin levels in the bloodstream or direct activation of AMP kinase (34, 49-51). The purpose of this study was to investigate the relationship between metformin use and the risk of prostate cancer in men by systematic review and meta-analysis method.

Methods and materials:

Study protocol:

The present study is a systematic review and meta-analysis study that examines the relationship between metformin use and the risk of prostate cancer in men. This study was conducted on the basis of the PRISMA[1] statement (52) which is

concerned with systematic review and meta-analysis studies. Based on this protocol, all stages of the research methodology such as search, selection of studies and qualitative assessment of studies and data extraction from the studies were conducted by two researchers independently. If there was a difference in the report of the researchers, the third researcher investigated and resolved the dispute.

Search Strategy:

First, all articles related to the association between metformin use and the risk of prostate cancer in men were searched without time limits through domestic databases including Iran Medex, SID, Magiran, Iran Doc, Medlib and external databases such as ProQuest, Science Direct, PubMed, Scopus, Web of Science using the keywords "metformin, prostate cancer, systematic review and meta-analysis" and their various combinations with the operators (AND, OR). In the end, in order to complete the search process, related keywords were also searched in the Google Scholar search engine.

Inclusion and Exclusion Criteria:

Inclusion criteria included: a) epidemiologic studies that included case-control or cohort, b) studies that examined the relationship between metformin use and the risk of prostate cancer and c) sufficient information for the evaluation such as the frequency of variables under investigation. Exclusion criteria also included: a) studies that examined the effects of other drugs on prostate cancer, b) studies that examined the effect of metformin on diseases other than the prostate cancer, and c) lack of reporting sufficient information for the analysis.

Quality Evaluations study: Researchers assessed the quality of selected articles from the methodological aspects such as sampling methods, variables measurements, statistical analyses and study objectives using standard STROBE checklist (53). The Strobe checklist contains 22 sections that cover different parts of a report and the maximum score of a report equals 44, so that a score of 1-15 indicates poor quality, 16-30 shows average quality and 31-44 is considered to be excellent.

Data Extraction:

All articles that were of good quality under the Strobe checklist entered the data collection stage. To extract the data from the articles, a checklist was already prepared by researchers to extract the necessary information such as the name of the author, the year of the study, the place where the study took place, the men who had consumed metformin and were afflicted to prostate cancer, the men who had not taken metformin but had prostate cancer, the men who had taken metformin and had no prostate cancer and the men who had not taken metformin and have no prostate cancer.

Statistical Analysis:

To evaluate the effect of metformin on the risk of prostate cancer in men compared to the control group, the odds ratio (OR) index was used. In order to combine the results of the studies, OR logarithms were used in each study and the I^2 index and Cochran Q test were used to check the heterogeneity of the studies. In the context of the index I2, there are three classifications (less than 25% are Low

heterogeneity, between 25% and 75% are moderate heterogeneity, and more than 75% are intense heterogeneity). Considering that the fixed effects model is used for the low heterogeneity, and the random effects model are used for the high heterogeneity, in this study, a random effects model was used (I^2=99.6%). Data analysis was performed using STATA (Ver. 15.1) software. The significance level of the test was considered to be P <0.05.

Results

Characteristics of patients: 399 studies were reviewed and evaluated, of which 11 high-quality studies (with a sample size of 877058 people) entered the meta-analysis process. The specifications of the studies assessed and the study selection stages based on the PRISMA protocol are shown in Figure 1.

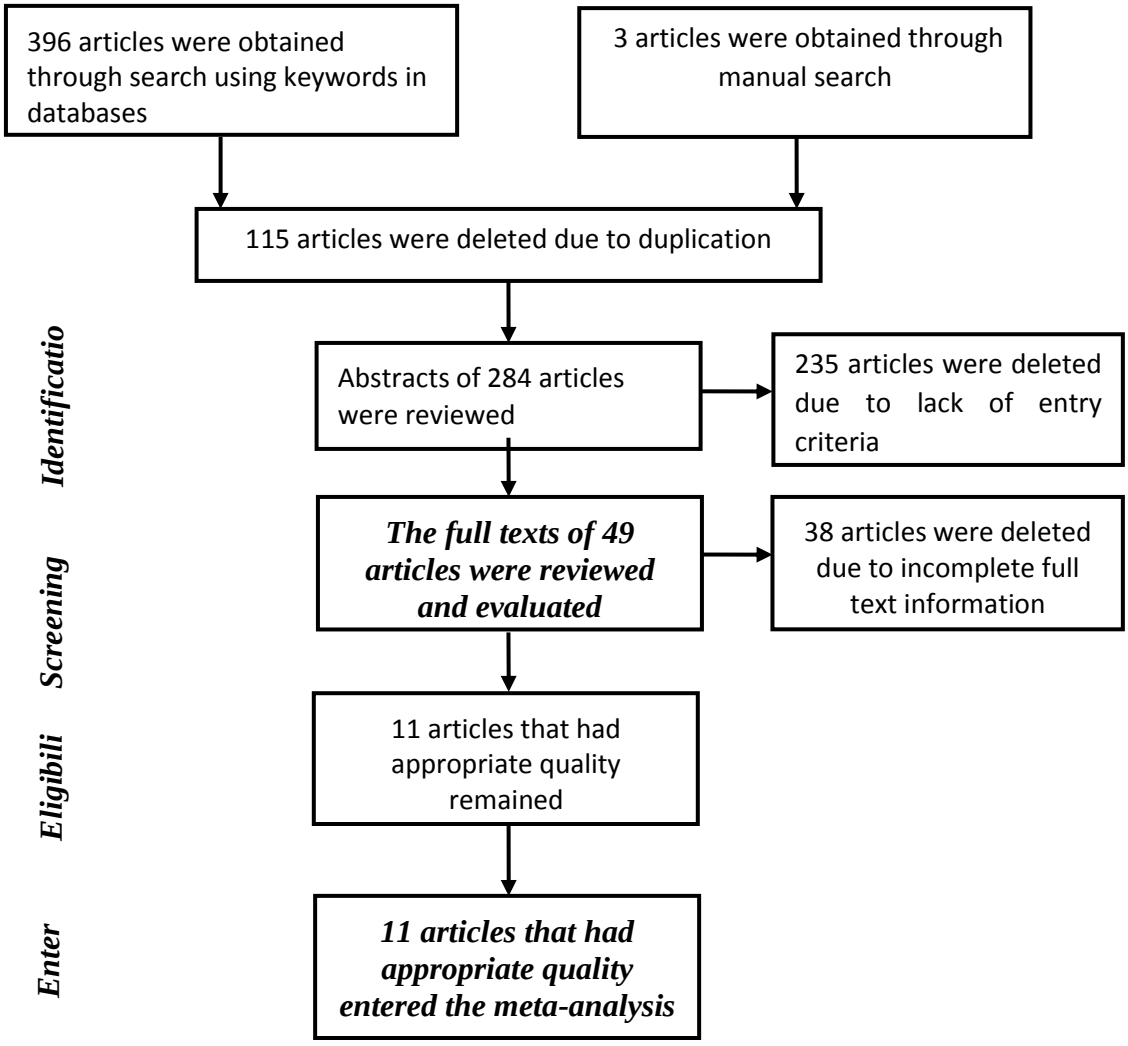

Figure1. PRISMA study selection diagram.

Table 1: Specifications of studies entered into meta-analysis.

Reference	Author's name	Duration of treatment	type of study	country name	Continent name	Year of publication of the article	age average	OR	Lower	Upper	Meaningful
(54)	Chen.CB	9 year	Cohort	Canada	America	2017	64	۷۹.	۶۴.	۹۶.	It is
(55)	Kabarriti.A	---	Case-control	UK	Europe	2015	---	۸۶.	۷۹.	۹۴.	It is
(31)	Margel.D	2.9 year	Cohort	Canada	America	2013	76	۱.۱۵	۱.۰۸	۱.۲۳	It is
(56)	Randazzo.M	7.3 year	Cohort	Switzerland	Europe	2015	65/5	۹۵.	۱.۰۹	۱.۱۳	It is
(57)	Preston.MA	3.2 year	Case-control	Denmark	Europe	2014	71/7	۸۴.	۷۴.	۹۶.	It is
(58)	Tesang.C-H	<180 day	Cohort	Taiwan	Asia	2014	---	۴۷.	۴۵.	۴۹.	It is
(59)	Feng.T	2 and 4 year	Cohort	USA	America	2015	50-75	۱.۱۹	۱.۰۱	۱.۸۳	It is
(60)	Wright.JL	---	Case-control	USA	America	2009	---	۵۶.	۳۲.	۱.۰۰	It is not
(61)	Azoulay.l	10 year	cohort	Uk	Europe	2010	74/1	1.23	.99	1.52	It is not
(62)	Nancy E. Morden	1.3 year	Cohort	Lebanon	Asia	2011	77.4	.97	.76	1.24	It is not
(63)	P.D. Home	4-6 year	Case-control	UK	Europe	2010		1.22	.86	1.74	It is not

In Probing the relationship between metformin use and the prostate cancer risk in men worldwide, the odds ratio of 0.89 (95% ~~confidence interval~~CI: 0.67-1.17) was estimated which is not statistically significant (Figure 1).

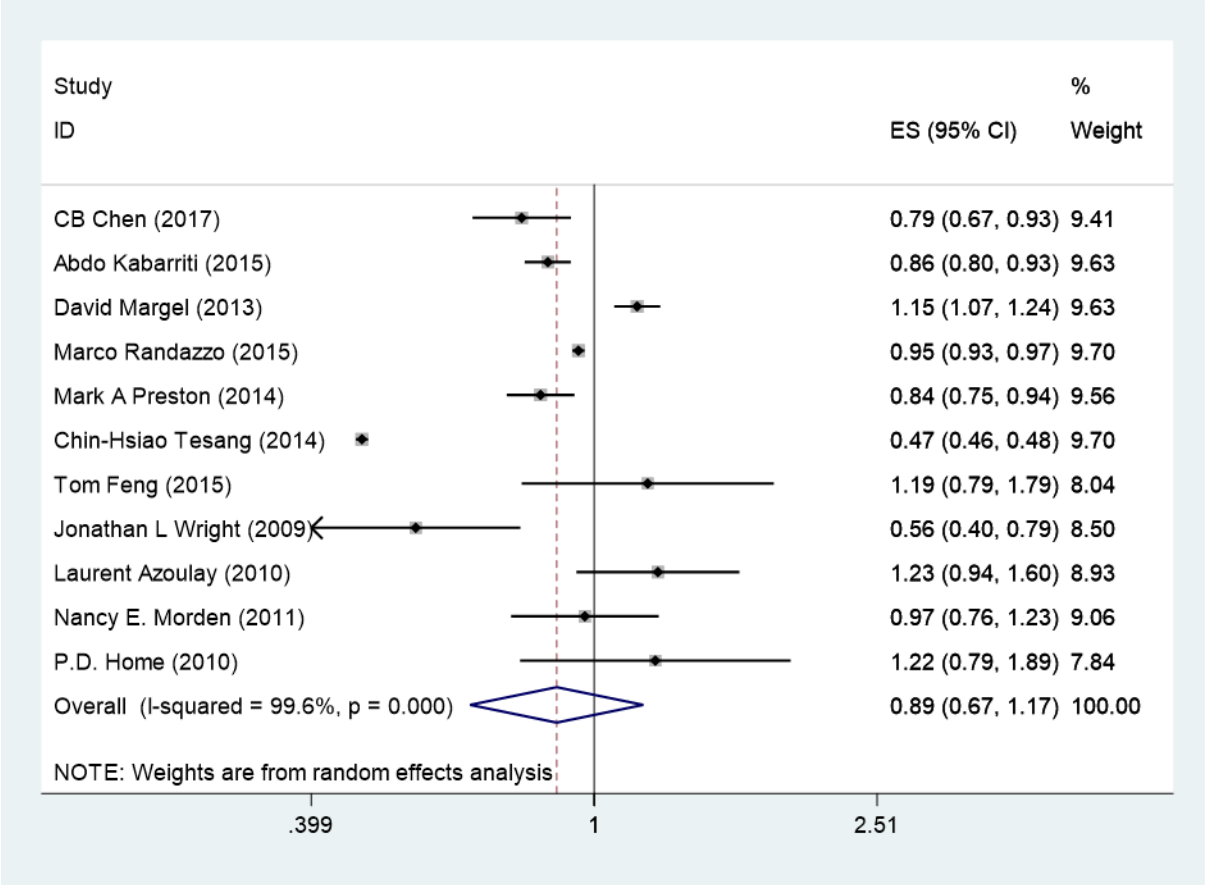

Diagram 1: Relationship between metformin use and the risk of prostate cancer worldwide based on the random effects model. The midpoint of each segment estimates the odds ratio and length of the segment, showing the 95% confidence interval in each study. The diamond sign shows the odds ratio for all studies.

Table 2: The odds ratio of metformin use and the risk of prostate cancer in different subgroups.

Subgroups		Number of study	OR	LOW-OR	UP-OR	P-Value	I^2%
Continent	America	4	0.89	0.65	1.21	0.000	90.4
	Europe	5	0.93	0.85	1.01	0.003	74.6
	Asia	2	0.67	0.33	1.36	0.000	97.1
Country	Canada	2	0.96	0.66	1.39	0.000	94.2
	UK	3	1.05	0.78	1.40	0.014	76.5
	Switzerland	1	0.95	0.93	0.97	---	---
	Denmark	1	0.84	0.75	0.94	---	---
	Taiwan	1	0.47	0.46	0.48	---	---
	USA	2	0.81	0.39	1.69	0.000	87
	Lebanon	1	0.97	0.76	1.23	---	---
Age	64-70 year	2	0.88	0.74	1.05	0.025	80.1
	71-77 year	4	1.03	0.84	1.25	0.000	87.1
	Other	5	0.78	0.52	1.16	0.000	98.5
follow up	<5 year	6	0.92	0.58	1.46	0.000	99.2
	5-10 year	3	0.95	0.80	1.12	0.013	77.1

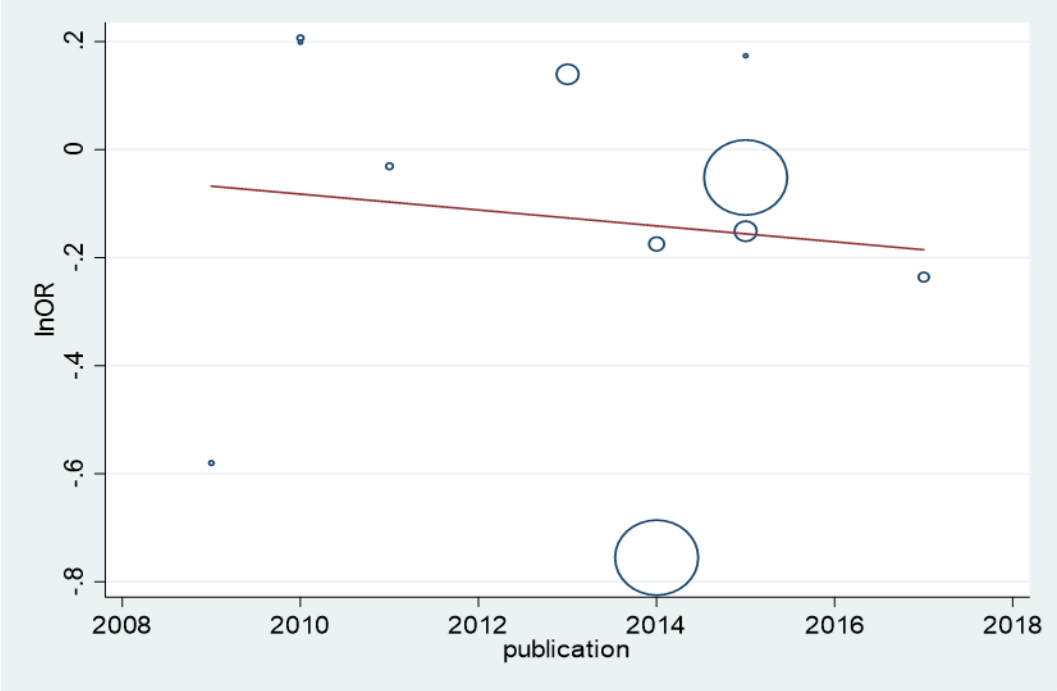

Chart 2: Meta-regression of the relationship between odds ratio and publication year of the study. (P = 0.729)

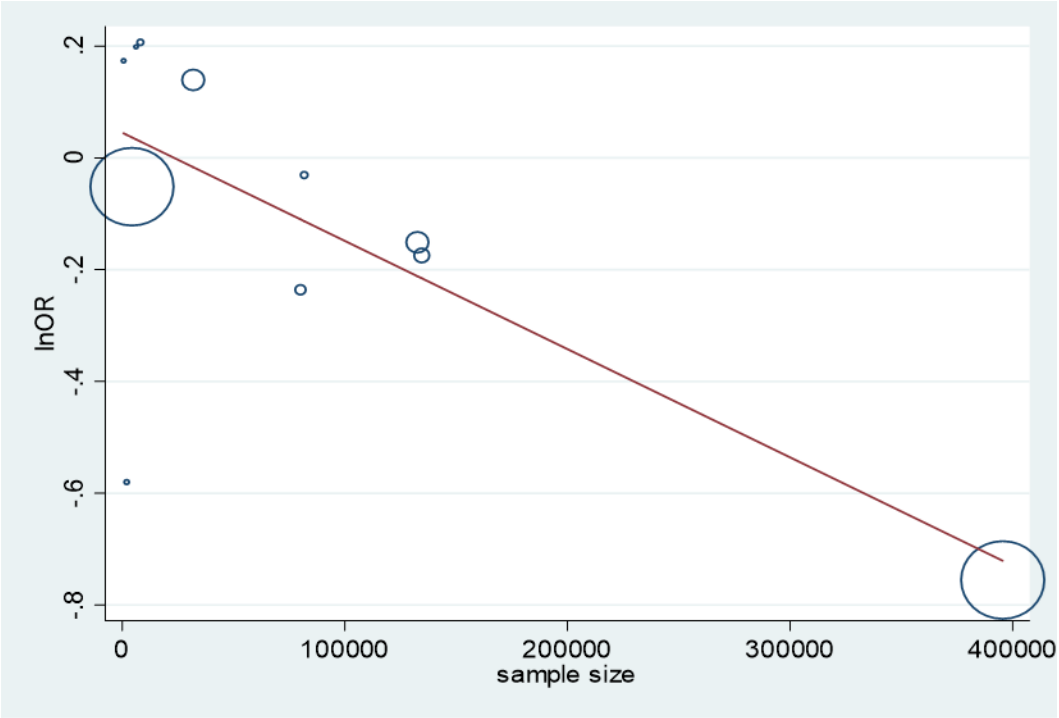

Chart 3: Meta-regression of the relationship between odds ratio and sample size. (P = 0.003)

On the other hand, the odds ratio meta-regression of the metformin use and the risk of prostate cancer with the publication year of study is not statistically significant. That is, during 2009-2018, the risk of prostate cancer in men was reduced by metformin, but this decline is not statistically significant (Figure 2). Meta-regression of the metformin use odds ratio and the risk of prostate cancer with sample size of the studies are statistically significant. By increasing the sample size, the risk of prostate cancer decreased with metformin use and this reflects that more odds ratio was not reported in larger sample sizes (Fig. 3). The analysis of publication bias showed that there was no probable publication bias in the studies because P = 0.524.That is, most of the published studies in

this area were covered as a result of the search for studies, and the article search phase has been completely done.

Discussion:

In the 11 studies we explored, it was concluded that taking metformin would reduce by 0.89 the risk of prostate cancer in men. As we see in Table 1, in four studies, the odds ratio of metformin use to reduce the risk of prostate cancer is not significant, and in the other 7 studies it is significant, and overall the effect of metformin on reducing the risk of prostate cancer is not statistically significant (Table 1). Regarding the conflict in the information reported in previous articles, the present article aimed at systematic review and meta-analyzing the effect of metformin on the reduction of prostate cancer. Meta-regression also showed that there is not a significant relationship between the odds ratio of metformin use and the risk of prostate cancer in men with the print year of study, but there is a significant relationship between the odds ratio of metformin use and the risk of prostate cancer and the research sample size. Also, publication bias showed that there was no probable publication bias in studies.

Various meta-analysis studies have already been published in this area. In one study, Eleven studies were selected for relevance in terms of intervention, population studied, independence, and reporting of cancer incidence or mortality data, reporting 4,042 cancer events and 529 cancer deaths. A 31% reduction in overall summary relative risk (0.69; 95% ~~confidence interval~~CI, 0.61-0.79) was found in subjects taking metformin compared with other antidiabetic drugs(64). In another meta-analysis, Of 25307 citations identified, 12 randomized controlled trials (21,595 patients) and 41 observational studies (1,029,389 patients) met the inclusion criteria. In observational studies there was a significant

association of exposure to metformin with the risk of cancer death [6 studies, 24,410 patients, OR:0.65, 95%CI: 0.53-0.80], all malignancies [18 studies, 561,836 patients, OR:0.73, 95%CI: 0.61-0.88], liver [8 studies, 312,742 patients, OR:0.34; 95%CI: 0.19-0.60] colorectal [12 studies, 871,365 patients, OR:0.83, 95%CI: 0.74–0.92], pancreas [9 studies, 847,248 patients, OR:0.56, 95%CI: 0.36–0.86], stomach [2 studies, 100701 patients, OR:0.83, 95%CI: 0.76–0.91], and esophagus cancer [2 studies, 100694 patients, OR:0.90, 95%CI: 0.83–0.98]. No significant difference of risk was observed in randomized trials. Metformin was not associated with the risk of: breast cancer, lung cancer, ovarian cancer, uterus cancer, prostate cancer, bladder cancer, kidney cancer, and melanoma(65).

In one research, A total of 265 studies (44 cohort studies, 39 case-control studies, and 182 randomized controlled trials (RCT)) were identified, involving approximately 7.6 million and 137,540 patients with diabetes for observational studies and RCTs, respectively. The risk of bias overall was moderate. Meta-analysis demonstrated that the use of metformin or thiazolidinedione's was associated with a lower risk of cancer incidence (RR = 0.86, 95% CI 0.83-0.90, I^2=88.61%; RR= 0.93, 95% CI 0.91-0.96, I^2= 0.00% respectively)(66). The results of another study showed that metformin decreased lung cancer risk by RR: 0.84 in 17997 patients with type 2 diabetes. This drug detected to be act an antioxidant for cell function(67-73). The results of Moradi-Joo's study showed that metformin reduced the risk of breast cancer in 151646 diabetic patients by RR 0.63 (74). In another study, Diana Soffer looked at the connection between the use of metformin and the risk of breast cancer for 66778 patients and HR: 0.85 (75). As we see in the studies above, taking metformin in patients reduces the risk of most cancers.

Recently, epidemiological studies have shown that the risk of colorectal, liver and pancreatic cancer decreases in patients taking metformin (63, 76-80). The results of the Zhi Jiang Zhang study on 108,661 people in the 1966-2011 period showed that metformin reduced the risk of colorectal cancer in patients with type 2 diabetes by RR: 0.63 (81). In meta-analysis, metformin was associated with an estimated 62% reduction in the risk of liver cancer among patients with type 2 diabetes (odds ratio 0.38, 95% CI 0.24, 0.59)(82). In the Shujuan Ma study, by reviewing studies that had used metformin as a liver-cancer risk reducer in diabetic patients, OR was estimated 0.52 (83). In the Hong Hu study, by checking the association between metformin and the risk of pancreatic cancer in patients with type 2 diabetes RR estimated 0.61 (84). The results of studies on the relationship between metformin use and the risk of colorectal, pancreatic and pancreatic cancers, as well as current meta-analysis, have a preventive effect. That is, the results of the above studies are consistent with the current study result.

Although previous systematic studies concluded that there is no relationship between metformin consumption and the risk of prostate cancer, due to differences in populations, statistical analysis, and definitions of high risk, there is a significant heterogeneity (85, 86). In the Hiroshi Noto meta-analysis in 2011, the odds ratio of metformin consumption and prostate cancer was estimated to be 0.89 (95%CI: 0.66-1.19), which is consistent with the outcome of the present study (87). In one study, A total of eight studies fulfilled the eligibility criteria. We found that diabetic PCa patients who did not use metformin were at increased risk of cancer recurrence (RR, 1.20; 95%CI, 1.00-1.44), compared with those who used metformin(88). The results of the Davide Soranna study showed that metformin and sulfonyl in 37632 type 2 diabetic patients decreased the risk of cancer, which RR: 0.61

was for all cancers and for prostate and breast cancer RR was 0.87 (26234 prostate - 1068 breast) (89). The results of studies on the relationship between metformin use and the risk of prostate cancer are consistent with the current study. The odds ratio of metformin and the risk of prostate cancer estimated in the current study was equal to the last meta-analysis performed in this ground, and there were no difference in the outcomes, because in both studies OR <1, and the OR confidence interval interrupted the number one indicating that it was not statistically significant.

Limitations of study:

1- Due to the non-uniformity of the conditions of the studies, sample sizes and screening method, it is not possible to accurately generalize the exact results of the distinct continents and countries. 2- Given that no clinical study was conducted on African countries, we were unable to report the statistics from the African continent. 3-The number of explored studies was limited.

Conclusion:

The odds ratio of metformin use for reducing prostate cancer was 0.89 (95% ~~confidence interval~~CI: 0.67-1.17), which was not statistically significant. Given the variability in the results of various studies and the limited number of studies, more clinical studies are needed to provide a definitive opinion on the metformin intake effect or lack thereof on the decline of prostate cancer. Metformin consumption was a preventive factor in prostate cancer in the continents of Asia, Europe and the United States, although all three were not statistically significant. In studying the results derived from several distinct countries, we also found that metformin was a preventive factor in prostate cancer in Taiwan,

Switzerland and Denmark, which was statistically significant, but the results of other countries were not statistically significant. In the analysis which was conducted based on different treatment durations of the patients, the odds ratio (OR) for the group treated under 5 years was less than the group treated for 5 to 10 years. In both groups, metformin had a preventive role in prostate cancer, but both were not statistically significant. Regarding the age of the patients it can be noted that as the age of the patients increases, the odds ratio (OR) also increases. In other words, in the 64-70 age group, metformin has a preventive role in prostate cancer and is not statistically significant. But in the 71 to 77 age group, metformin is a risk factor for prostate cancer, which is still not statistically significant.

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