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Review

Serum insulin level, HOMA-IR and prostate cancer risk: A systematic review and meta-analysis

Somayeh Saboori [a], Esmaeil Yousefi Rad [a], Mehdi Birjandi [a], Sara Mohiti [b, c], Ebrahim Falahi [a, *]

[a] Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
[b] Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran
[c] Department of Nutrition, Qazvin University of Medical Sciences, Qazvin, Iran

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ABSTRACT

Aims: This meta-analysis study was performed to assess serum insulin level and insulin resistance status in prostate cancer patients in observational studies.
Materials and methods: A systematic literature search was performed for observational studies in Scopus, PubMed, Ovid and ISI Web of Science up to July 2017.
Results: From 2070 publication were searched firstly, only 10 studies with 9 and 6 arms included for the meta-analysis assessing serum insulin level and HOMA-IR status in prostate cancer patients, respectively. Pooled effects analysis showed that the Fasting insulin level was significantly higher in men with prostate cancer compared to control group (WMD = 2.12 μ IU/ml, 95%CI; 0.26, 3.99; P = 0.02). Sub-group analysis showed that the elevation in serum insulin level takes place only in patients with ages more than 65 years old (WMD = 3.88 μ IU/ml, 95%CI; 2.28, 5.48; P < 0.001). HOMA-IR was no significantly different between study groups. However, the difference got statistically significant after sub-grouping patients based on their age (WMD = 1.37, 95% CI; 0.61, 2.12; P < 0.001).
Conclusion: In conclusion, the results of this meta-analysis study showed higher fasting serum insulin and HOMA-IR levels especially in patients with ages more than 65 years..
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1. Introduction

Prostate cancer is the second most common non-skin malignancies and after lung and colon cancer, it is the third common cause of cancer related deaths in men [1,2]. Besides common risk factors of prostate cancer including inheritance, age, race and dietary factors [3], hormonal status can profoundly affect the development of prostate cancer [4]. Epidemiological studies confirmed an increased risk of several cancer including breast, colorectal and pancreatic cancers in patients with insulin resistance conditions [5]. It has been shown that serum insulin level has a critical role in prostate cancer through stimulating cell proliferation and apoptosis inhibition [6]. Several studies evaluating the association between diabetes or insulin level with prostate cancer risk got conflicting results. Albanes et al. in one case-cohort study showed that increasing serum insulin level, even in normal ranges could exposure people at higher risk of prostate cancer [7]. Other studies confirmed increased insulin levels in prostate cancer patients at higher tumor grade [8,9]. However, a nationwide case-control study in Sweden concluded reduced risk of prostate cancer in type 2 diabetes patients. The risk was reduced by increasing HbA1c concentration [10]. Other cohort studies did not show any association between prostate cancer risk and serum insulin level [11,12]. Previously, one meta-analysis assessing results of 19 studies in 2006 suggested reduced prostate cancer risk in diabetic patients [13]. However, the relationship between serum insulin and insulin resistance levels with prostate cancer risk is poorly understood. We conducted this meta-analysis to evaluate serum insulin and insulin resistance levels in patients with prostate cancer.

2. Materials and methods

2.1. Search strategy and study selection

The systematic literature search of this meta-analysis performed via PubMed, Scopus, Ovid and ISI Web of Science databases from

* Corresponding author.
E-mail address: fahahi.e@lums.ac.ir (E. Falahi).

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inception due to July 2017. The search was done independently by two authors with the use of following search terms: (insulin OR insulin resistance OR hyper-insulinemia OR HOMA-IR) AND (prostate cancer OR prostatic cancer OR prostate neoplasm OR prostatic neoplasm) AND (cohort OR prospective OR follow-up OR longitudinal OR case-control OR cross-sectional) in the titles, abstracts and keywords. Conference papers were searched in Scopus and ISI Web of Science databases. No restriction was done for language and the reference lists of eligible article also checked manually for relevance to the topic. The protocol of this systematic review registered at PROSPERO [CRD42018087310].

2.2. Inclusion and exclusion criteria

The inclusion criteria for selecting articles were: 1) observational studies assessing the association between insulin and insulin resistance with prostate cancer risk and 2) Reported mean or median values of serum insulin level and HOMA-IR in prostate cancer and the control groups with SD, SEM or 95% CI. The exclusion criteria were: 1) No control group 2) Data of insulin level and HOMA-IR were not available or could not be extracted. Control group was defined as patients without prostate cancer.

2.3. Study selection and data extraction

Two independent reviewers (SS, SM) screened the title and abstracts of articles to choose more relevant articles on the topic. Any disagreements solved by the third investigator (EY). After this stage, data extraction was done. The following information from selected articles were extracted: first author's name, publication year, journal name, origin of country, sample size in case and control groups, serum PSA level in case and control groups, mean age and BMI of subjects in case and control groups, mean insulin and HOMA-IR values in case and control groups. For quality assessment of included studies, Newcastle-Ottawa scale (NOS) [14] was used. This scale with two different tools for case-control and

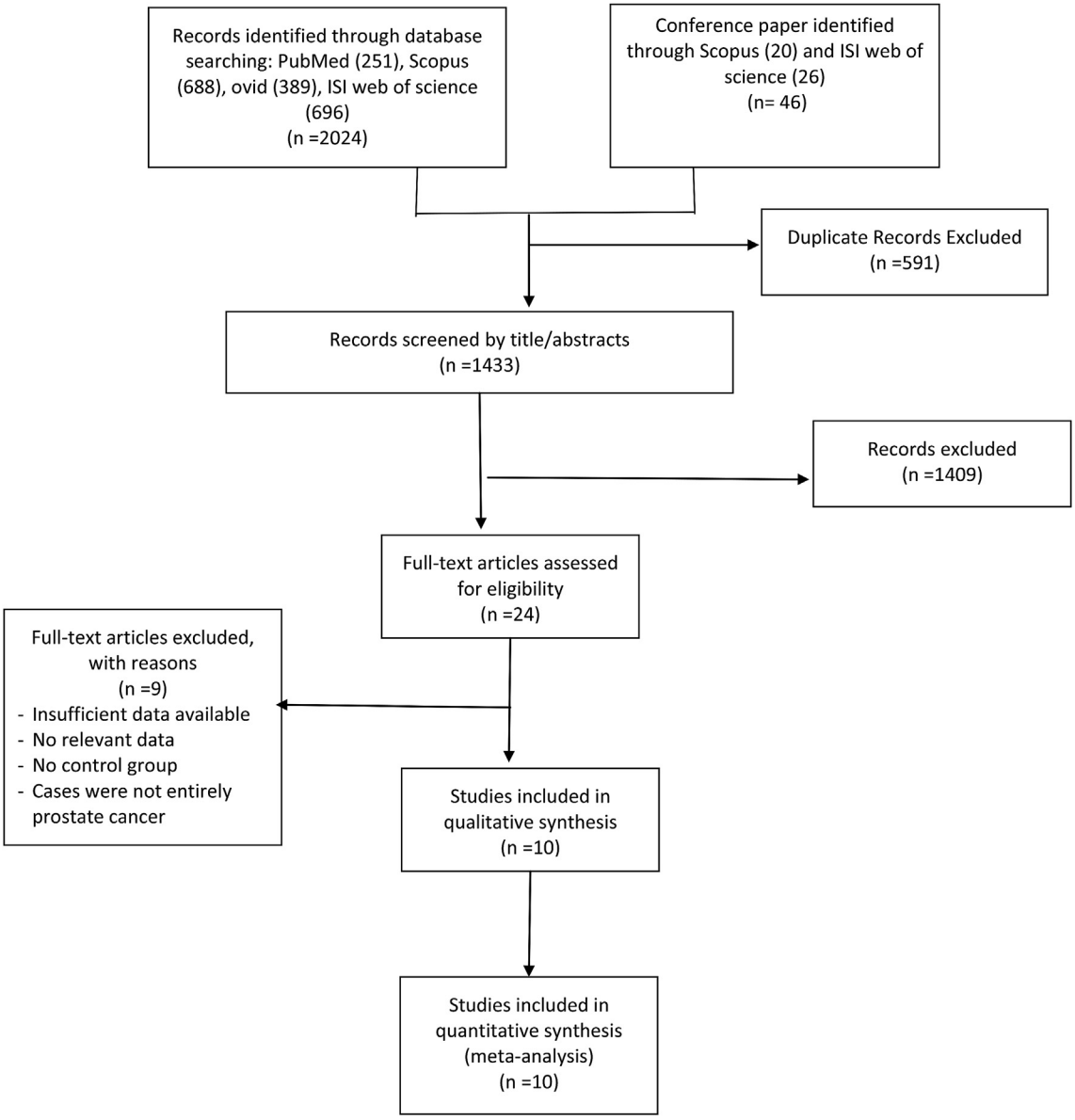

Fig. 1. Flowchart of study selection for inclusion studies in the systematic review.

cohort studies scores articles for selection, comparison and exposure/outcome assessments.

2.4. Data synthesis and statistical analysis

Our systematic review and meta-analysis was done according to PRISMA guidelines and all analyses performed by STATA12 (College Station, TX, USA). Mean and SD of values in the case and control groups were used and mean difference was adopted to calculate summary statistics. Using Hozo et al. method [15], median values with confidence interval or range converted to mean and SD. Existence of heterogeneity was tested by Cochrane's Q-test at $P < 0.05$ level of significance and the percentage of heterogeneity among studies was calculated by using I^2 test. The random effect model analysis was used for estimating pooled effect size. Publication bias was evaluated by using funnel plot, beg and Egger's regression test.

3. Results

3.1. Search results and study selection

In the systematic search of the literature, 2070 publications were found firstly; after removing of duplicates, 1433 articles remained for title/abstracts screening for more relevant to the

Table 1
Basic characteristics of included studies.

First author	Year	Origin of country	Study design	Mean age in case/control group	Mean BMI in case/control group	Biochemical assay	Insulin resistance definition	Matched or adjusted confounders
Stattin. P	2000	Sweden	Nested Case-control	NR	26.3/26.27	RIA	–	age, date after completing the survey, town or village of residency
Chen. Ch	2004	USA	Case-control	NR	NR	RIA	–	age at enrollment (within 3 years), race, year of entry, and year of blood draw
Goktas. S	2005	Turkey	Case-control	65.8/62.2	25.1/26.3	RIA	HOMA-IR: fasting plasma glucose (in milligrams per deciliter)/immunoreactive insulin (in microunits per milliliter)/405	Adjustment for age, BMI, fasting plasma glucose, or lipid parameters
Stocks. T	2007	Sweden	Nested Case-control	NR	26/26.5	NR	HOMA-IR (-)	Matched for age (±6 months) and date at recruitment (±2 months)
Michalakis.K	2007	Greece	Case-control	74/64	26.2/27.6	RIA	–	Adjustment for age and BMI
Nandeesha.H	2007	India	Case-control	61.89/58.85	20.49/20.34		HOMA-IS (22.5/fasting insulin X fasting glucose)	Matched for age
Albanes.D	2009	Finland	Case-cohort	59/56.4	26.5/26.6	RIA	HOMA-IS (22.5/fasting insulin X fasting glucose)	Adjustment for age and BMI
Grosman.H	2010	Argentina	Case-control	60/60	28/27	RIA	–	Matched for age and BMI
Grosman.H	2015	Argentina	Case-control	65/62	27.4/26.2	RIA	HOMA-IS (22.5/fasting insulin X fasting glucose)	Matched for age and BMI
Zhang.J-Q	2015	China	Case-control	73/74	25.65/22.09	NR	HOMA-IS (22.5/fasting insulin X fasting glucose)	Matched for age

Table 2
Study Quality assessment using Newcastle-Ottawa scale for case-control studies.

Study, Year	Selection				Comparability of cases and controls (matched for)	Exposure			Total Score
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Stattin. P, 2000	–	*	*	*	**(age, date after completing the survey, town or village of residency)	*	*	–	7
Chen. Ch, 2004	*	–	–	*	**(age at enrollment (within 3 years), race, year of entry, and year of blood draw)	*	*	–	6
Goktas. S, 2005	*	*	–	*	**(Adjustment for age, BMI, fasting plasma glucose, or lipid parameters)	*	*	–	7
Stocks. T, 2007	*	*	*	*	**(age and date at recruitment (±2 months))	*	*	–	8
Michalakis.K, 2007	*	*	–	*	–	*	*	–	5
Nandeesha.H, 2007	*	*	–	*	*(age)	*	*	–	6
Albanes.D, 2009	*	–	*	*	–	*	*	–	5
Grosman.H, 2010	*	*	–	*	**(Matched for age and BMI)	*	*	*	7
Grosman.H, 2015	*	*	–	*	**(Matched for age and BMI)	*	*	–	7
Zhang.J-Q, 2015	*	*	–	*	*(Matched for age)	*	*	–	6

topic. From 24 articles assessed for eligibility, 14 of them removed and 10 articles remained for qualitative synthesis and all of them included in the meta-analysis. A manual search of the reference lists added no more articles in this meta-analysis. Flowchart of study selection for inclusion is shown in Fig. 1.

3.2. Study characteristic

Included studies in this Meta-analysis were performed from 2000-2015, in the different countries (Sweden [16,17], USA [11], Turkey [18], Greece [19], India [20], Finland [7], Argentina [21,22] and

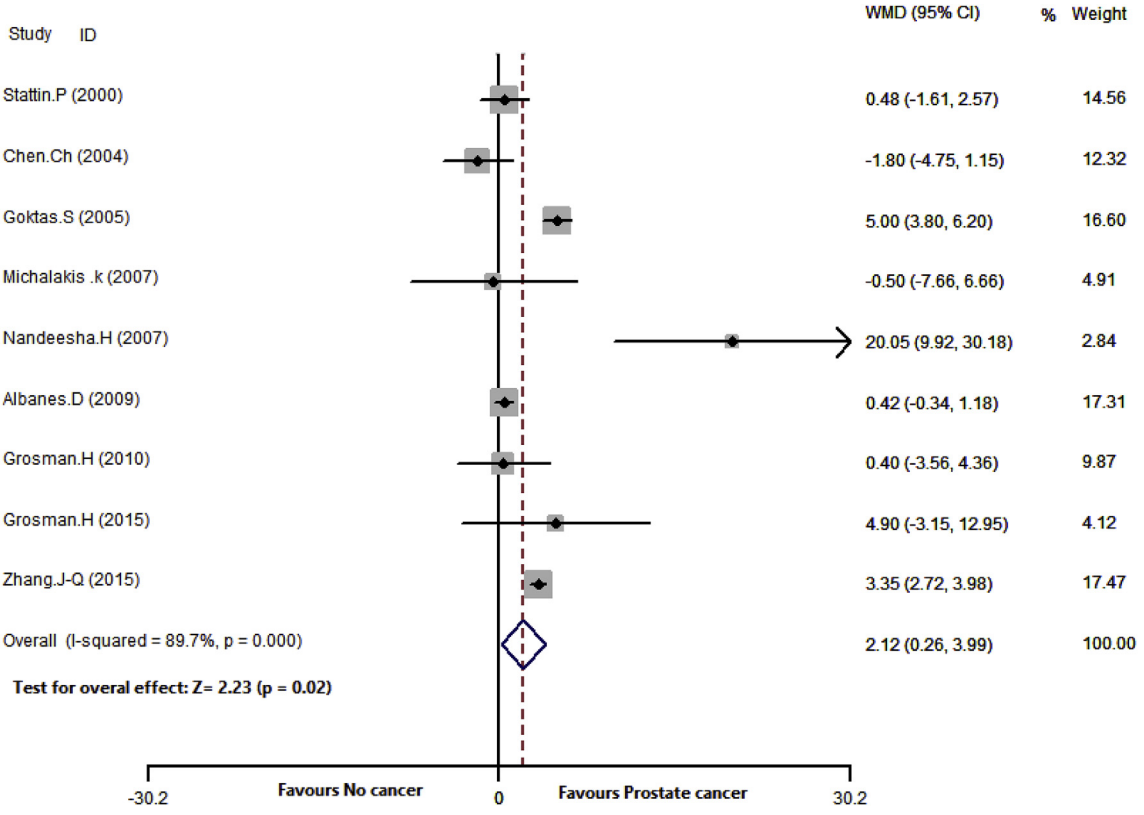

Fig. 2. Pooled random effect size of the association between serum insulin level and prostate cancer (μ IU/ml) WMD, weighted mean difference.

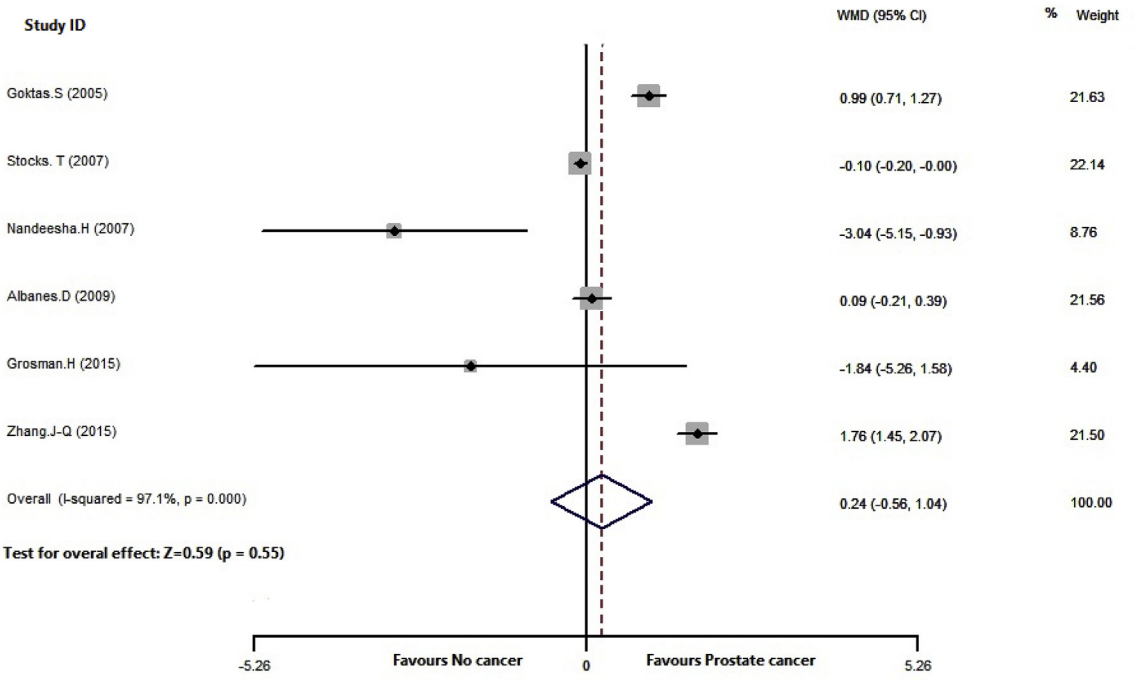

Fig. 3. Pooled random effect size of the association between HOMA-IR level and prostate cancer. WMD, weighted mean difference.

China [23]) with 1143 participants in prostate cancer group and 1692 participants in the control group. All of the included studies were in the design of different case-control studies. Mean age of participants in the prostate cancer group was in the range of 61. 9 to 73 and in control group 58.9 to 74. Mean BMI of participants in the case group were in the range of 20.5–28 and in the control group 20.3 to 27.6. Characteristics of included studies are shown in Table 1. The quality of included studies assessed by Newcastle-Ottawa quality assessment scale was in the range of 5–8 stars (Table 2).

3.3. Meta-analysis and sub-group meta-analysis

Fasting insulin level were significantly higher in men with prostate cancer compared to men without prostate cancer (WMD = 2.12 μ IU/ml, 95%CI; 0.26, 3.99; P = 0.02) with a significant heterogeneity between the included studies (test for heterogeneity: $P < 0.001$ and $I^2 = 89.7\%$, Fig. 2). Sub-group analysis showed that this elevation in serum insulin level takes place only in patients with ages more than 65 years old (WMD = 3.88 μ IU/ml, 95%CI; 2.28, 5.48; $P < 0.001$). There was no significant difference between prostate cancer group and control group in the case of mean HOMA-IR (WMD = 0.24, 95%CI; −0.56, 1.04; P = 0.055) with a significant heterogeneity between the included studies (test for heterogeneity: $P < 0.001$ and $I^2 = 97.1\%$) (Fig. 3). However, this difference got statistically significant after sub-grouping patients based on their age like in the case of insulin level (WMD = 1.37, 95% CI; 0.61, 2.12; $P < 0.001$). Results of sub-group analysis are shown in Table 3.

3.4. Publication bias

The beg test (P = 0.85) and egger's regression test (P = 0.5) did not show any publication bias. Funnel plots are shown in Fig. 4.

4. Discussion

Results of current meta-analysis showed that fasting serum insulin level was significantly higher in prostate cancer patients in compared to control group. Because of significant heterogeneity between studies included in this meta-analysis, sub-group analysis was performed. The results have shown that the increase in serum insulin level takes place only in patients with age more than 65 years old. The mean HOMA-IR was not significantly different between two study groups. Interestingly, sub-group analysis based on age also showed that HOMA-IR level was significantly higher in prostate cancer patients with age more than 65 years old. Age is one of the established risk factors for prostate cancer and studies revealed that the incidence of this disease increases rapidly after 55 years and most patients diagnosed after the age of 65 years old [24]. Because of increasing life expectancy in recent decades, the incidence of prostate cancer had risen increasingly and the age of more than 64% of newly diagnosed prostate cancer patients in the United States was more than 65 years [25].

Insulin could act as growth factor and hyper-insulinemia is associated with increased risk of several cancers including prostate cancer [26,27]. The action of insulin in increasing prostate cancer risk probably involves its effects on sex hormones and insulin like growth factor (IGF) axis. Hyper-insulinemia and insulin resistance could increase the entrance of testosterone into the prostatic cells through its reducing effect on steroid hormone binding globulin (SHBG) which can influence prostate cancer through hormonal changes [28]. Insulin resistance could also increase the prostate cancer risk via reducing the production of IGF-binding protein-1(IGFBP-1) which can increase the bioavailability of IGF-1 [29]. Results of one meta-analysis study confirmed that higher IGF-1 levels are associated with increased risk of prostate cancer [30]. IGF-1 can affect cell proliferation and prostate growth by its mitogenic and anti-apoptotic properties [17,31]. Several studies confirmed a strong association between increased serum insulin level and also insulin resistance with prostate cancer risk. In the Albanes et al. study both HOMA-IR and the ratio of insulin to glucose were significantly associated with increased risk of prostate cancer, especially in patients with early stage prostate malignancies [7]. In the study of Stocks et al. the level of HOMA-IR

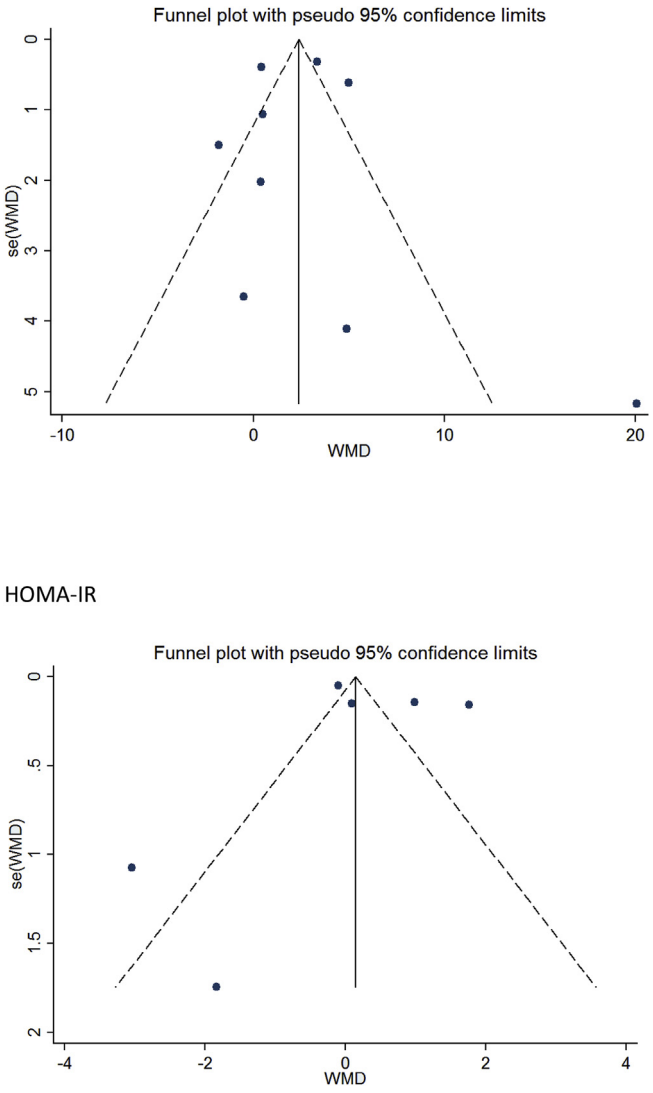

Fig. 4. Funnel plot of studies measured serum insulin and HOMA-IR levels.

Table 3
Subgroup analyses of serum insulin and HOMA-IR levels in prostate cancer.

	NO	MD (95% CI)	P within group	P heterogeneity	I^2
Serum insulin					
Mean age (years)					
≤65	4	4.22 (−0.91, 9.36)	0.10	0.001	80.6%
>65	3	3.88 (2.28,5.48)	<**0.001**	0.03	71.5%
HOMA-IR					
Mean age (years)					
≤65	3	−1.37 (−3.71,0.96)	0.24	0.009	78.8%
>65	2	1.37 (0.61,2.12)	<**0.001**	<0.001	92.3%

AbbreviationsCI, confidence interval; MD, mean differences.

was inversely associated with prostate cancer risk. However, unlike our study, this association was stronger among younger aged men [16]. Another nationwide register study by Fall et al. demonstrated a reduced risk of prostate cancer among diabetic type 2 patients specially whom receiving insulin or having a longer duration of this disease [10]. In line with this results, Gong et al. in Prostate Cancer Prevention Trial (PCPT) study concluded 28% and 47% reduced risk of high-grade cancer and low-grade cancer, respectively [32]. It seems that alterations in shape and size of intra-prostatic micro-vascularization could explain the reduced risk of prostate cancer in diabetic patients [33]. Other mechanisms include protective effects of some drugs using for diabetes treatment and decreased levels of cancer-related growth factors among these patients [34,35].

Some meta-analysis studies confirmed a positive association between obesity and BMI status with prostate cancer risk [36,37]. Obesity could increase prostate tumor proliferation and reduce its apoptosis via elevation of insulin and IGF-1 level [38,39]. Unfortunately, because of limited ranges of BMI in the participants of the studies included in this meta-analysis, we could not be able to do sub-group meta-analysis for assessing the effect of obesity status on prostate cancer risk in relation to insulin resistance status and it is one limitation of this study.

5. Conclusions

In conclusion, the results of this meta-analysis study have shown higher fasting insulin level and increased HOMA-IR levels especially in patients with ages more than 65 years. It seems that adopting strategies for improving insulin sensitivity such as lifestyle changes or using some drugs including insulin sensitizers could affect prostate cancer risk in coming years.

Conflicts of interest

The authors declare that they have no conflict of interest.

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This work had no source of funding.

Author contributions

SS and EF designed and searched systematically for the study. SM and SS reviewed and selected the articles and extracted data from articles under the supervision of EY. SS and MB performed data analysis and interpretation. EY and SS drafted the manuscript. EF revised the article for important intellectual content.

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