

Serum C-peptide concentration and prostate cancer

A meta-analysis of observational studies

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Abstract

Background: The association between serum C-peptide concentration and prostate cancer remains unexplored. Therefore, we conducted a meta-analysis to assess whether C-peptide serum concentrations are associated with increased prostate cancer risk.

Methods: Several databases were searched to identify relevant original research articles published before November 2017. Random-effects models were used to summarize the overall estimate of the multivariable-adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Nine observational studies involving 11,796 participants were identified. The findings of the meta-analysis indicated that the association between serum C-peptide concentration and prostate cancer was not significant (OR: 1.15, 95% CI: 0.85–1.54; for highest versus lowest category C-peptide concentrations, $P = .376$). The associations were inconsistent, as indicated by subgroup analyses.

Conclusion: Although our findings provided no support for the hypothesis that serum C-peptide concentration is associated with excess risk of prostate cancer, people must pay attention to this aspect and increase physical activity or modify dietary habits to constrain insulin secretion, which possibly lead to decreased incidence of prostate cancer. Hence, well-designed observational studies involving different ethnic populations are still needed.

Abbreviations: CIs = confidence intervals, HR = hazard ratio, MeSH = medical subject headings, NOS = Newcastle–Ottawa scale, OR = odds ratio, RR = risk ratio.

Keywords: C-peptide, meta-analysis, prostate cancer

1. Introduction

Prostate cancer is gradually becoming a major problem and is a leading cause of morbidity and mortality in men worldwide.^[1,2] Higher prostate cancer incidence rate is found in the United States and Europe compared with other countries, but the incidence has

markedly increased in historically low-incidence regions, including Asia and Spain.^[3] To reduce the number of men who suffer from prostate cancer, scholars must determine the associated risk factors.

C-peptide is a protein secreted by the pancreas and insulin—a widely used in the production of biomarkers.^[4,5] Metabolic syndrome, including elevated serum insulin and C-peptide levels, is regarded as a link between Western lifestyle and prostate cancer and is largely caused by obesity.^[6,7] Moreover, hyperinsulinemia is considered as the underlying biological mechanism of such associations.^[8,9] The direct markers of hyperinsulinemia, including serum C-peptide concentration and insulin, may be associated with the elevated risk of prostate cancer.^[10–12]

Several observational studies reported that high plasma C-peptide levels may be a predictive factor for increased colorectal carcinoma susceptibility.^[13,14] However, in their meta-analysis, Autier et al^[15] found no strong evidence for any association between serum C-peptide concentration and breast cancer risk. The associations between serum C-peptide concentration and prostate cancer risk were inconsistent, with several findings being positive,^[16–18] negative,^[19] and null.^[20–24] The same inconsistency is observed for advanced versus localized prostate cancer.^[19,22] To our knowledge, no review or meta-analysis has synthesized evidence to explore the influence of serum C-peptide levels on prostate cancer among men globally. Hence, our study aimed to examine this relation. A broad systematic review and meta-analysis of published studies were performed to precisely evaluate the relationship between serum C-peptide

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concentration and prostate cancer and help healthcare professionals in making related clinical decisions.

2. Methods

2.1. Search strategies

The methods in this meta-analysis were performed in accordance with the Cochrane Collaboration criterion.^[25] We reported our meta-analysis according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.^[26] All analyses were based on previous studies. Thus, no ethical approval and patient consent are required.

Eligible studies were found by searching the electronic databases of PubMed, Embase, and Cochrane Library for relevant original research articles published until November 2017 regarding the association between serum C-peptide concentration and prostate cancer risk. We did not apply any restrictions to the regions, publication types, or language. We used a combination of Medical Subject Headings (MeSH) and non-MeSH terms. For instance, “prostatic neoplasms” or “prostate cancer” was combined with “C-peptide” (see “Appendix” for search algorithms, <http://links.lww.com/MD/C380>). Moreover, gray literature retrieval and manual searches of reference lists were conducted to identify appropriate studies. The main search was completed independently by 2 investigators (Z-LG and XW). For studies with insufficient information, we contacted the primary authors to acquire and verify the data. Any discrepancy was resolved by consulting an investigator (SW) who was not involved in the initial procedure.

2.2. Eligibility criteria and study selection

Two authors (Z-LG and F-LC) independently selected eligible studies without limitations on regions, gender, or age and in compliance with the inclusion criteria. We resolved any disagreements through discussion. Studies had to fulfill the following criteria for inclusion: outcome was prostate cancer risk; measurements of serum concentrations of C-peptide were reported; study design included case control, retrospective, prospective cohorts, and cross-sectional studies; high level of serum concentrations of C-peptide is defined as 1.13 ng/mL and low level is defined as 2.23 ng/mL^[16]; and the odds ratio (OR), relative risk (RR), or hazard risk (HR) of prostate cancer related to serum C-peptide concentration were reported, and crude HR, OR, or RR with corresponding 95% CIs were calculated.

2.3. Data extraction and methodological quality assessment

Data from the included studies were extracted and independently summarized by 2 authors (L-LG and S-TX). Any disagreement was resolved by the adjudicating senior authors (S-SW). Two authors (Z-LG and X-TW) independently summarized the first author, publication year, country, study design, study period, and baseline population characteristics, such as mean age and sample size. The risk estimates were obtained with 95% CIs from all included studies into a standardized evidence table. Finally, 2 authors (L-LG and S-TX) cross-checked these data for accuracy. For studies with insufficient information, the reviewers contacted the primary authors to acquire and verify the data when possible.

The methodological qualities of the included studies were assessed by 2 independent reviewers (C-MG and SG) using the

original Newcastle–Ottawa scale (NOS),^[27] which consists of 3 factors, namely, patient selection, comparability of the study groups, and assessment of outcome. A score of 0 to 9 (awarded as stars) was allocated to each study. All included studies with 6 or more stars were considered to be of high quality. Disagreements were also settled through discussion.

2.4. Statistical analyses

We calculated the overall estimate to assess the association between serum C-peptide concentration and prostate cancer risk. The aggregated results and 95% CIs for effect size were calculated through inverse-variance weighted random-effect meta-analysis, which could provide an average estimate and the variability of the risk estimates represented by this average may have clinical implications.^[28] Subsequently, we performed the *I*-square (*I*²) test to assess heterogeneity across the studies, and *I*² values of 0%, 25%, 50%, and 75% represented no, low, moderate, and high heterogeneity, respectively. Along with the overall results, the *I*² test results were presented in the form of a forest plot—a graphical display of estimated results from a number of scientific studies addressing the same question. Furthermore, statistical significance was set at *P* < .05. Sensitivity analysis was conducted by examining the exclusion of each study in a stepwise manner to evaluate the quality and consistency of the results. Subgroup analyses were performed according to geographical region and study design. A meta-regression analysis was conducted on 5 variables through the restricted maximum likelihood method. However, the use of Egger regression asymmetry test was limited because of the small number of studies evaluated.^[29]

3. Results

3.1. Study characteristics and methodological quality

The process for filtering the relevant original research articles through our search of 3 major electronic databases was summarized after comprehensive screening (Fig. 1). A total of 389 records were initially identified, and only 354 studies remained after 35 duplicates were removed. Then, we read the titles and abstracts of 354 articles in detail, among which, 43 articles were further evaluated via full texts. Finally, 34 full-text articles were excluded for the following causes: 20 studies did not meet the inclusion criteria; 12 studies did not regard prostate cancer risk as its outcome; and 2 studies reported no sufficient data for extraction. Among these studies, 9^[16–24] were selected and subsequently included for review in accordance with the inclusion criteria.

The overall basic participant characteristics from the included studies,^[16–24] which includes 6 prospective cohort studies^[16,19,21–24] and 3 case-control studies,^[17,18,20] are summarized in Table 1. The eligible studies were published between 2007 and 2017, comprising 11,796 participants and sample sizes with the number of participants ranging between 263 and 3600. Seven studies were based in the USA,^[16–18,20,22–24] 1 in Japan,^[21] and 1 in Sweden.^[19] Various confounding factors in prostate cancer, particularly age, ethnicity, body mass index, and smoking, were adjusted in all studies.^[16–24]

Furthermore, the methodological quality of the 7 studies was considered to be of high quality,^[16,18,20–24] and 2 studies^[17,19] were regarded to be of low quality on the basis of NOS. The main deficiency of the low-quality studies was the selection bias related

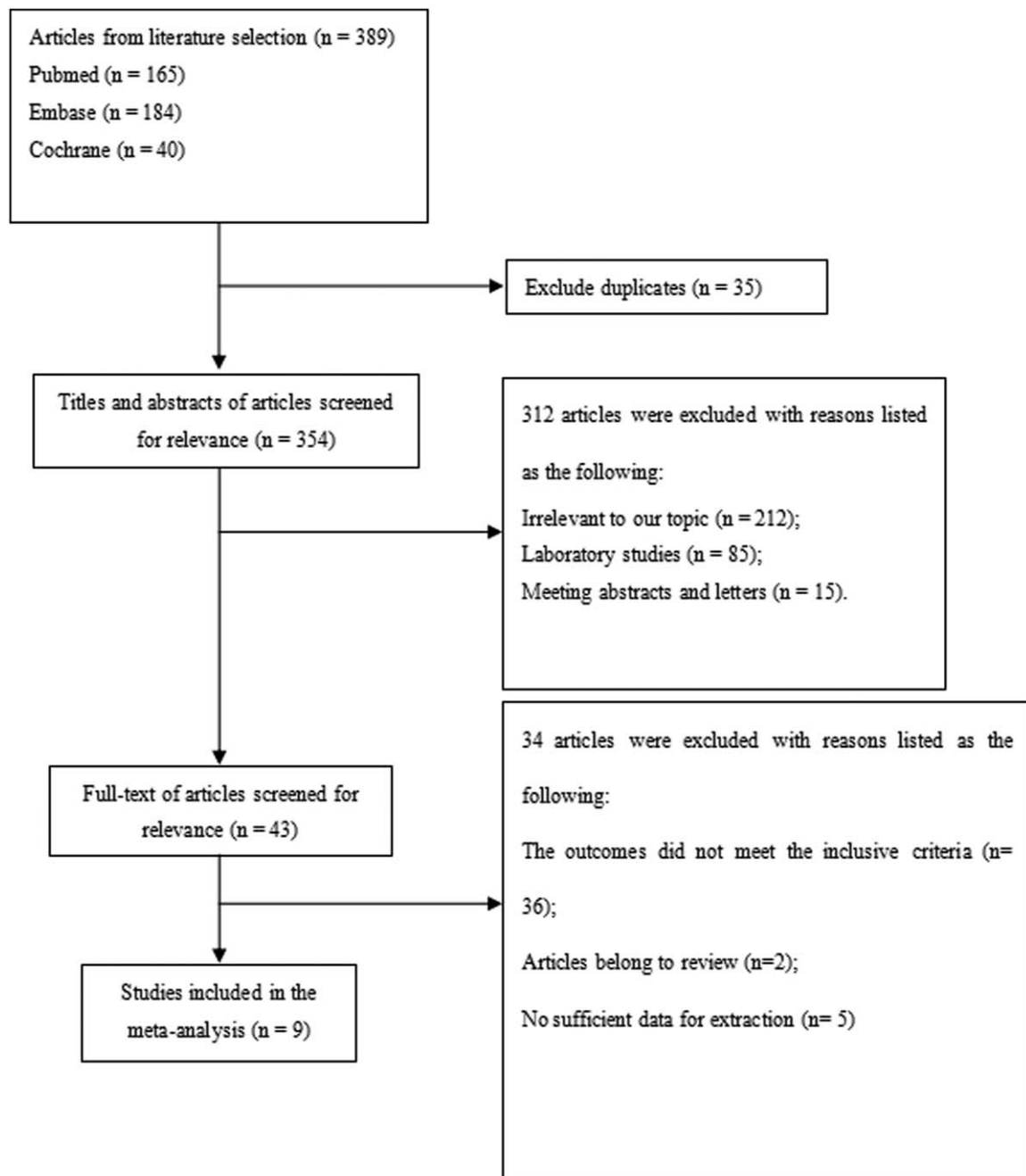


Figure 1. Flow diagram of study selection.

to patient selection and insufficient adjustment of core factors.^[17,19]

3.2. Meta-analysis

The meta-analysis of nine studies^[16–24] (Fig. 2) showed that the association between serum C-peptide concentration and prostate cancer was not significant (OR: 1.15, 95% CI: 0.85–1.54; for highest vs lowest category C-peptide concentrations, $P=.376$), whereas heterogeneity was significant ($I^2=72.6\%$, $P=.000$). Thus, subgroup analyses were conducted to investigate the potential factors that may substantially affect between-study heterogeneity.

3.3. Subgroup analyses

Subgroup analysis was conducted, and the results are shown in Fig. 3. Geographical region and study design were considered influencing factors. When the studies were stratified by different geographical regions, significant association was observed among the studies performed in Europe (OR=0.59; 95% CI=0.40–0.88) but not among those conducted in North America and Asia (Fig. 3A). Moreover, a significant association was observed among case-control studies (OR=1.77; 95% CI=1.21–2.60) but not in prospective cohort studies. However, all subgroups exhibited no considerable contributions to heterogeneity (Fig. 3B).

Table 1
Basic characteristics of the included studies.

Author, y	Study design	Country	Number of participants case/control	Age (y)	Study period	Adjustments	OR (95% CI)
Borugian et al 2007 ^[20]	Case-control	USA	57/243	69	1990–2003	Age, ethnicity, time since last meal, BMI, waist circumference, caloric intake, and dietary vitamin D intake	1.12 (0.59–2.29)
Giovannucci et al 2004 ^[16]	Prospective cohort	USA	263	40–75	1986–1998	Age, racial group, smoking history, and alcohol intake	1.55 (1.07–2.25)
Kiyabu et al 2017 ^[21]	Prospective cohort	Japan	201/402	40–69	1990–1995	Smoking status, alcohol intake, marital status, BMI, previous history of diabetes, and intake of green tea and miso soup	0.81 (0.43–1.56)
Lai et al 2010 ^[22]	Prospective cohort	USA	264/264	70.2 (46.1–92.3)	1989–2002	BMI, and family history of prostate cancer	0.65 (0.37–1.14)
Lai et al 2014 ^[23]	Prospective cohort	USA	1314/1314	64.2	1993–1995	Height, family history of prostate cancer, vasectomy, vigorous physical activity, smoking in the past 10 years, intakes of total energy, alcohol, lycopene, red meat, fish, calcium, alpha-linolenic acid, fructose, use of a vitamin E, and selenium supplement	1.05 (0.82–1.34)
Ma et al 2008 ^[17]	Case-control	USA	2546	40–84	1982–2007	Age at diagnosis, smoking status, time between BMI measurement, plasma C-peptide measurement, and cancer diagnosis	2.38 (1.31–4.30)
Neuhouser et al 2010 ^[18]	Case-control	USA	1803/1797	63.6	2005–2010	Age, race, BMI, body circumferences, family history of prostate cancer, current smoking status, or alcohol habits	1.88 (1.19–2.97)
Stevens et al 2014 ^[24]	Prospective cohort	USA	272/272	65–76	1992–2007	BMI, family history of prostate cancer, physical activity, total calcium intake, and energy intake	1.41 (0.72–2.78)
Stocks et al 2007 ^[19]	Prospective cohort	Sweden	392/392	< 59	1985–1996	BMI, leptin, and smoking status	0.59 (0.40–0.89)

95% CI=confidence interval, BMI=body mass index, OR=odds ratio.

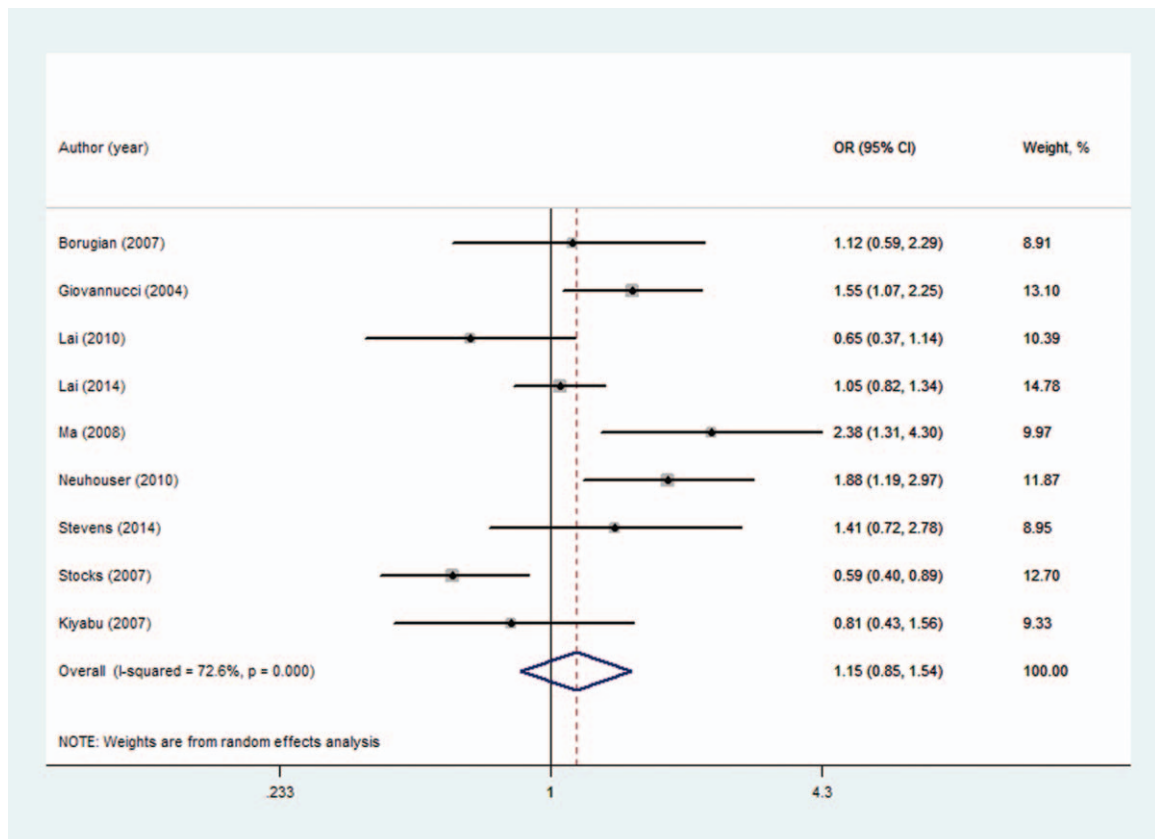


Figure 2. Overall meta-analysis results.

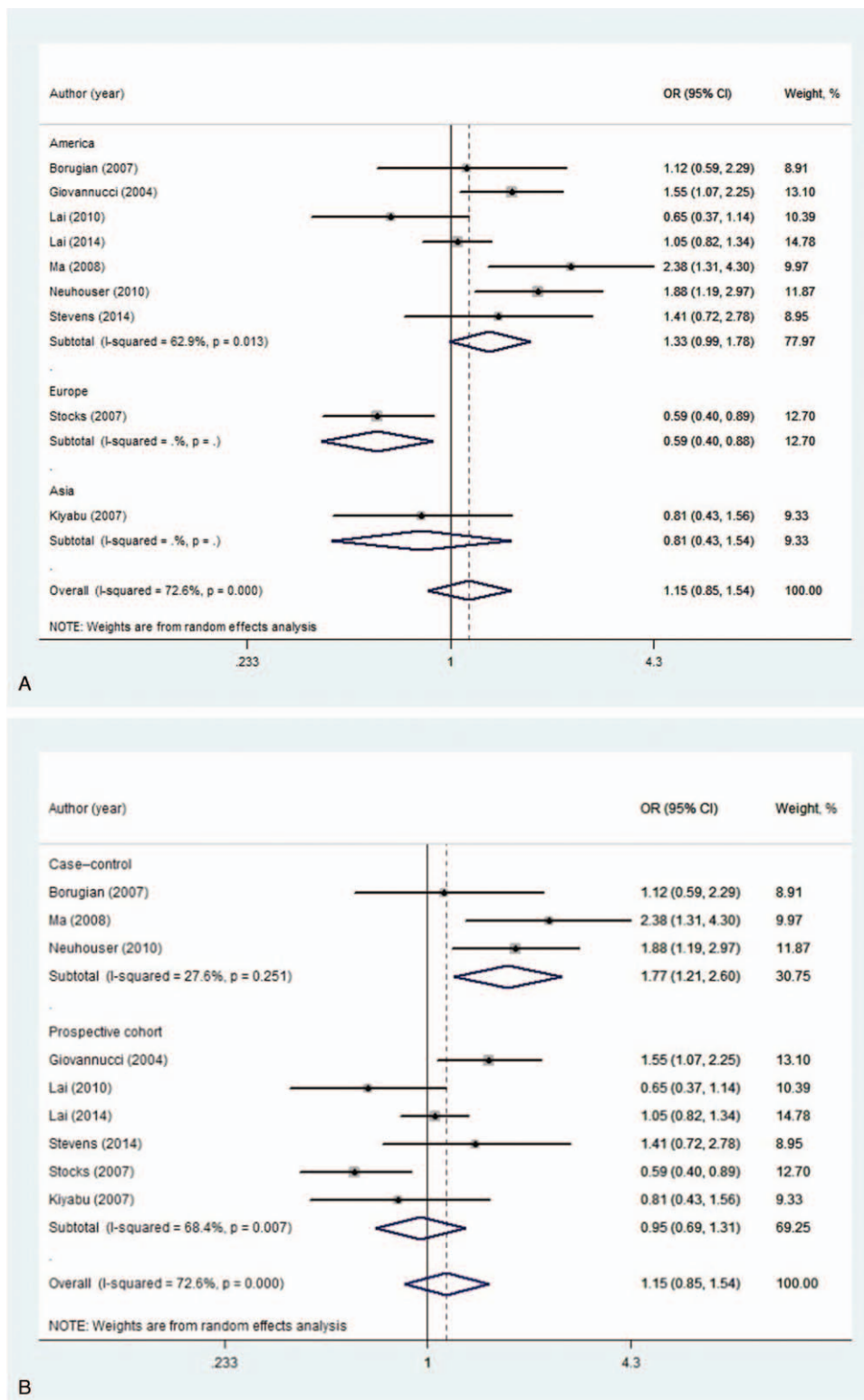


Figure 3. Subgroup analyses.

3.4. Sensitivity analyses

Sensitivity analysis was performed to determine whether certain studies strongly influenced the overall risk estimates or the final heterogeneity. We evaluated the effect of each study on the summary results by sequentially excluding a single study (Fig. 4).

The omission of any single study did not prominently affect the overall combined OR, which ranged from 1.06 (95% CI=0.79–1.42) to 1.26 (95% CI=0.96–1.66). The rationality and reliability of our meta-analysis was validated through sensitivity analysis.

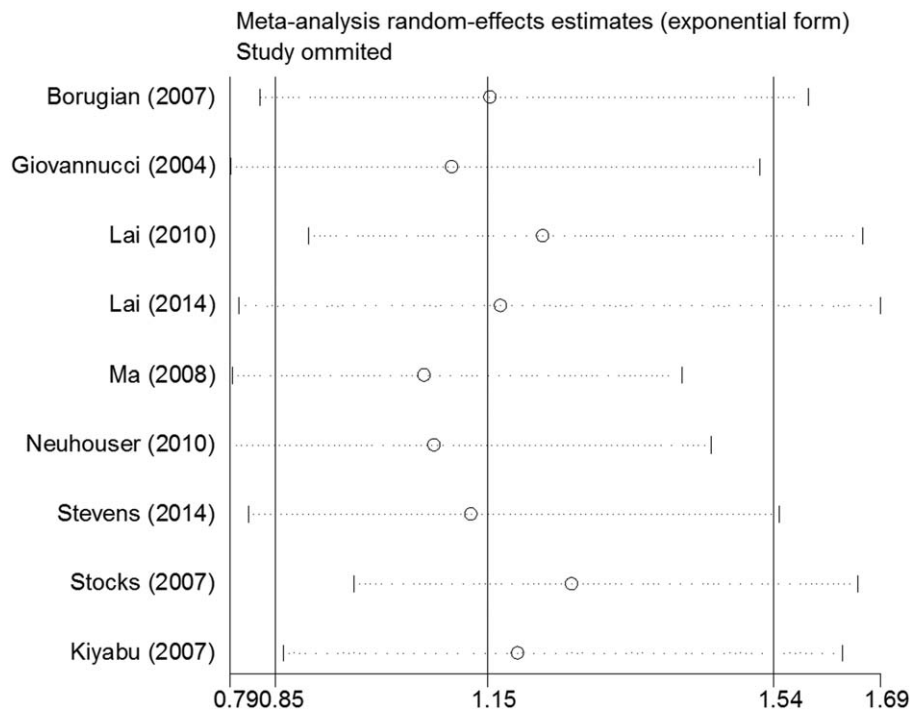


Figure 4. Plot showing the influence of excluding each individual study on the summary estimate on the association between serum C-peptide concentration and risk of prostate cancer.

3.5. Meta-regression analysis

To control heterogeneity among studies, we conducted a meta-regression analysis on 2 variables. Restricted maximum likelihood method was used for the analysis. The meta-regression analysis results showed that none of the covariates (continent, $P = .145$; study design, $P = .073$) resulted in heterogeneity among the included studies. Therefore, the adjusted R-squared values of 28.60% to 41.77% indicate that the regressors contribute little to the explanation of the response variables (Table 2).

4. Discussion

In this study, we analyzed the association between serum C-peptide concentration and prostate cancer by performing a systematic and comprehensive meta-analysis of 9 cross-sectional studies^[16–24] to obtain a powerful conclusion given that individual studies are too small to yield a valid conclusion. To our knowledge, this study is the first that provides comprehensive insight into this association through meta-analysis. Our findings provided no support for the hypothesis that serum C-peptide concentration is associated with increased risk of prostate cancer. Notably, the subgroup and sensitivity analyses validated the reliability of our meta-analysis. Meta-regression analysis could not determine the risk factors related to the significant

heterogeneity. However, publication bias was not observed because of the limited number of included studies.

Most of the included studies suggested no association between serum C-peptide concentration and prostate cancer risk,^[20–24] whereas 1 study reported negative results.^[19] Stocks et al^[19] considered that Swede patients with higher serum C-peptide concentration are associated with decreased risk of developing prostate cancer, and the multivariable OR is 0.59 (95% CI: 0.40–0.89). Moreover, 3 studies conducted in the USA found increased risk of prostate cancer in men with elevated serum C-peptide concentration,^[16–18] but this finding has not been confirmed in other investigations.^[19–24] Giovannucci et al^[16] demonstrated that higher serum C-peptide concentration is statistically associated with increased risk of prostate cancer incidence, and the multivariable OR is 1.55 (95% CI: 1.07–2.25). Ma et al and Neuhouser et al also noted the absence of a statistically significant association between serum C-peptide concentration and the risk of prostate cancer in the case-control studies in the USA.^[17,18] Furthermore, we discovered a potential positive effect of serum C-peptide concentration on prostate cancer incidence. The majority of multivariable HR points were >1, and a potential trend toward the right in the meta-analysis of elevated serum C-peptide concentration was observed. However, this trend may not be obvious. Thus, more high-quality research must be conducted to validate this trend.

Table 2
Results of meta-regression.

Logor	Exp(b)	Standard error	t	P> t	95% CI	R-squared	
Geographical region	0.6876209	0.1568247	−1.64	.145	0.4009919	1.179132	28.60%
Study design	0.5424305	0.1576211	−2.11	.073	0.272855	1.078342	41.77%

Geographical region (1 = USA, 2 = Europe, 3 = Asia). Study design (1 = case-control study, 2 = prospective cohort study).

When the studies were stratified by different study designs, we found inconsistent findings on the association between serum C-peptide concentration and prostate cancer risk. The case-control studies showed a positive association (OR = 1.77; 95% CI = 1.21–2.60) in this regard, whereas prospective cohort studies did not. In the stratification of different geographical regions, a significant association was observed among the studies performed in Europe (OR = 0.59; 95% CI = 0.40–0.88) but not among those conducted in North America and Asia. However, all subgroups exerted no considerable contributions to heterogeneity.

Although we measured C-peptide instead of insulin, C-peptide and predictors of C-peptide have been examined in place of insulin in studies on breast and colorectal cancers.^[13,30] Our findings are consistent with an earlier prospective study, in which prostate cancer was not associated with levels of insulin in the Northern Sweden Health and Disease Cohort.^[31,32] This finding may explain the absence of an association between serum C-peptide concentration and prostate cancer risk. We recognize that despite us and other researchers not finding a strong relationship with the risk of prostate cancer, C-peptide or other indicators of insulin resistance may act as negative prognostic markers among men with prostate cancer. The mechanisms involved in the influence of C-peptide on prostate cancer are explored. Several experimental studies indicated that metabolic abnormalities are associated with prostate cancer risk, but the mechanism apparently occurs through insulin resistance and not via adipokines, such as leptin.^[33,34] Given their steady increase worldwide, obesity and diabetes, which are related to hyperinsulinemia, can be important influencing factors for prostate cancer incidence.^[35] An increase in physical activity, overweight and obesity management, or modification of dietary habits to constrain insulin secretion are expected to be beneficial to populations and possibly lead to reduced incidence of prostate cancer.

In general, our meta-analysis exhibited several crucial strengths. First, our meta-analysis was the first to investigate worldwide data on the association between serum C-peptide concentration and prostate cancer through thorough systematic search and rigorous analytical approaches. This work contributed important clinical and epidemiological evidence for policy-makers and health professionals. Second, the rationality and reliability of our meta-analysis was evidently improved because the overall combined estimates were based on a large sample size. Furthermore, we performed subgroup, sensitivity, and meta-regression analyses to explore the risk factors related to the significant heterogeneity and ensure the reliability of this study. Finally, confounding factors that possibly influenced serum C-peptide concentration were minimized because multivariable-adjusted risk estimates were applied.

However, several limitations in our meta-analysis should be mentioned before the results of this study are accepted. First, despite our rigorous methodology, the number of studies included in the meta-analysis was limited, especially in terms of subgroup analyses and studies that used the same range of serum C-peptide concentration. Second, heterogeneity is another possible critical issue due to several design differences among the studies. However, we could not determine the risk factors related to the significant heterogeneity through subgroup and meta-regression analyses. Third, the included studies were only distributed in Europe, North America, and Asia. Therefore, well-designed studies conducted among additional regions on other continents with different doses of serum C-peptide levels are necessary. The dose–response relationship between serum C-

peptide concentration and prostate cancer risk was limited because of insufficient data from the included studies.

5. Conclusions

Our findings provide no support for the hypothesis that serum C-peptide concentration is associated with increased risk of prostate cancer. However, despite our rigorous methodology, the inherent limitations of the included studies prevent us from reaching definitive conclusions. Therefore, further large-volume, well-designed cross-sectional studies of different ethnic populations with extensive follow-up and low risk of bias are necessary to confirm and update the findings of this analysis.

Author contributions

S-SW conceived the study idea. Z-LG and X-TW performed the literature search. Z-LG, X-TW, F-LC, L-LG, S-TX, C-MG, and SG performed the study selection, data extraction, and methodological quality assessment. Z-LG and L-LG performed the statistical analyses and interpretation of corresponding results. Z-LG drafted the initial manuscript. C-MG, SG, and Z-LG modified the initial manuscript. S-SW was primarily responsible for the final content. All authors made critical comments for the initial manuscript.

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