Review Article
Circulating adiponectin level and risk of colorectal cancer: evidence from a dose-response meta-analysis

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Abstract: Background: Experimental researches shows that adiponectin may have some regulatory roles in the mechanism of colorectal cancer, but epidemiological studies on the association between circulating adiponectin level and colorectal cancer reported inconsistent findings. A dose-response meta-analysis was thus performed to assess the evidence on the association between adiponectin and colorectal cancer. Methods: A systematic search of Pubmed and Embase was performed up to December 20, 2016. Relative risks (RR) and 95% confidence intervals (95% CI) were pooled to assess the risk of colorectal cancer associated with higher adiponectin level. In the dose-response meta-analysis, a two-stage generalized least-square trend method was used to calculate RR of colorectal cancer per 5 µg/mL increase in circulating adiponectin level. Results: Eight prospective studies were identified. All those 8 studies were nested case-control studies, and they included a total of 4,076 colorectal cancer cases and 5,509 matched non-cancer controls. When compared with lower adiponectin level, higher adiponectin level was significantly associated with lower level of colorectal cancer (RR = 0.81, 95% CI 0.71-0.93; P = 0.002). Besides, dose-response meta-analysis suggested that the pooled RR of colorectal cancer per 5 µg/mL increase in circulating adiponectin level was 0.86 (95% CI 0.77-0.95; P = 0.005). The pooled outcomes were not obviously influenced by the between-study heterogeneity. Conclusion: There is an obvious dose-response association between circulating adiponectin level and colorectal cancer risk, suggesting that adiponectin is an important protective mediator in the development of colorectal cancer.

Keywords: Adiponectin, colorectal cancer, meta-analysis, dose-response

Introduction

Colorectal cancer remains one of the main causes of cancer-related mortality world [1]. There were about 72,000 men and 65,000 women diagnosed with colorectal cancer in 2014 in United States, and it's the second leading cause of cancer death [2, 3]. Though the incidence rate of colorectal cancer has declined in some developed countries, it incidence rate in some other countries is still increasing [2, 4]. Screening for colorectal cancer is an effective method to reduce the incidence rate of colorectal cancer, especially among those with risk factors of colorectal cancer [1]. Therefore, the finding of risk factors of colorectal cancer not only leads to a better understanding of the mechanism of colorectal cancer, but is also helpful for the screening for colorectal cancer [1, 5, 6].

Previous studies have shown strong epidemiological evidence for the impact of obesity on colorectal cancer, and obesity substantially adds colorectal cancer risk [7-10]. Besides, obesity is linked to increased risk of mortality in colorectal cancer patients [6, 11, 12]. Previous studies have proposed that the dysfunction of adipokines secreted by the adipose tissues in obese individuals may mediate the adverse influence of obesity on human health [13, 14]. Adiponectin is one of the most commonly studied adipocyte-secreted hormones [15]. Adiponectin has been suggested to have several important actions, such as insulin-sensitizing effect and anti-inflammatory action [16-19]. Obese individuals have decreased level of circulating adiponectin, which may result in insulin resistance and inflammatory response and thus further result in increased risks of obesity-related diseases [16-19]. Considering the

Figure 1. Study selection in the meta-analysis.

records were identified through checking the references lists of eligible studies.

Included studies should meet the following eligible criteria: 1) Prospective cohort studies or nested case-control studies; 2) Participants were healthy individuals at baseline, and cases had histologically confirmed colorectal cancer; 3) Controls were non-cancer or healthy individuals; 4) Assessing the risk of colorectal cancer in individuals with different categories of circulating adiponectin level and sufficient data for the dose-response meta-analysis; 5) Reporting risk estimates with 95% confidence intervals (95% CI), such as relative risk (RR). Nonhuman studies, case-reports, or reviews were all excluded. Studies with overlapping data were also excluded.

Data extraction and quality assessment

We used a standardized form to extract data. The following data were extracted: name of first author, study design, country, sources of the participants, adjusted factors, adjusted RRs of colorectal cancer in individuals with different categories of circulating adiponectin level. The study quality was measured using Newcastle-Ottawa Scale (NOS) proposed for meta-analysis of observational studies [36].

Statistical analysis

Study-specific RRs were firstly pooled to assess the risk of colorectal cancer associated with higher adiponectin level. The I^2 indicating the percentage of variation attributable to heterogeneity was used to measure heterogeneity across included studies [37]. I^2 more than 50% suggested obvious heterogeneity across included studies and random-effect meta-analysis was performed [38]. I^2 less than 50% suggested low heterogeneity across included studies and fixed-effect meta-analysis was performed [39]. In the dose-response meta-analysis, a two-stage generalized least-square trend meth-
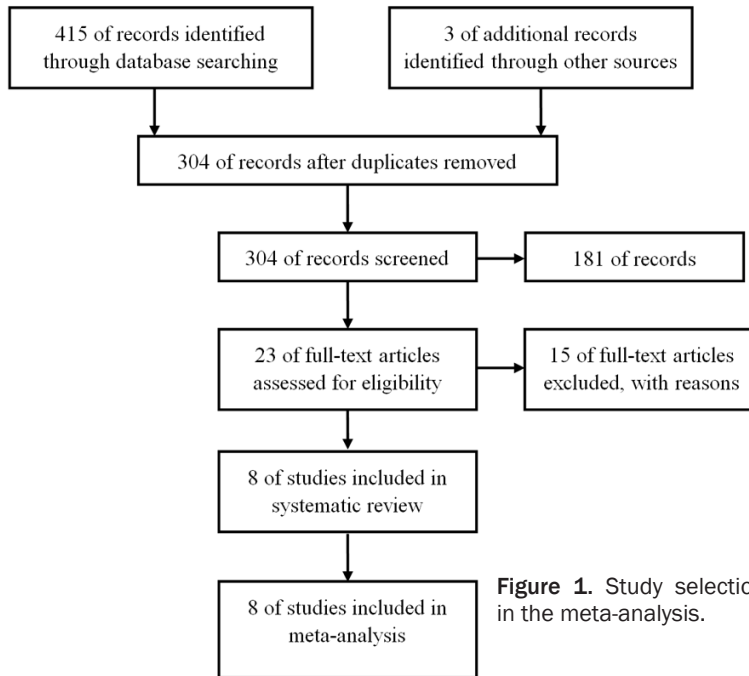
crucial roles of adiponectin, it has been investigated as a disease biomarkers or risk factor in many diseases including diabetes, cancer and cardiovascular diseases [20-23]. Numerous in vitro and animal studies have suggested an important role of adiponectin in the mechanism of colorectal cancer [18, 24-27]. Epidemiological studies on the association between circulating adiponectin level and colorectal cancer have reported inconsistent findings [28-35], and a dose-response relationship has not been established. In this systematic review, a dose-response meta-analysis was thus performed to assess the evidence on the association between adiponectin and colorectal cancer.

Materials and methods

Systematic search and eligibility criteria

To identify prospective cohort studies or nested case-control studies that reported the relation of circulating adiponectin level with colorectal cancer, a systematic search of Pubmed and Embase was performed up to December 20, 2016. We used the following keywords: (adiponectin) AND (colorectal carcinoma OR colorectal cancer OR rectum carcinoma OR rectum cancer OR colon carcinoma OR colon cancer). There was no language limitation. Additional

Table 1. Characteristics of prospective studies on circulating adiponectin levels and colorectal cancer risk

Study	Study design	Country	Participants	Adjusted factors	Quality
Wei E 2005 [28]	Nested case-control	USA	179 incident colorectal cancer cases and 358 matched controls from Health Professionals Follow-up Study	Hours since last meal, family history, physical activity, multivitamin use, folate, calcium, vitamin D, current smoking, vitamin E, alcohol intake, aspirin use, and endoscopy before 1994.	8
Lukanova A 2006 [29]	Nested case-control	Norway	381 colorectal cancer cases, and 381 matched controls from Janus Project	Levels of leptin and C-peptide (after ln-transformation).	8
Fukumoto J 2008 [30]	Nested case-control	Japan	656 cases of colorectal adenomas and 648 controls from Self Defense Forces (SDF) Health Study	Hospital, plasma/serum status, rank in the Self Defense Forces (SDF), cigarette smoking, alcohol use, physical activity, and parental colorectal cancer.	9
Stocks T 2008 [31]	Nested case-control	Sweden	306 colorectal cancer cases and 595 matched controls nested in the Northern Sweden Health and Disease Cohort	Sex, age, smoking status and fasting time before blood draw.	8
Ho G 2012 [33]	Nested case-control	USA	457 colorectal cancer cases and 841 subcohort subjects from Women's Health Initiative cohort	Age, race, smoking status, ever had colonoscopy, and estrogen level.	8
Aleksandrova K 2012 [32]	Nested case-control	Europe	1206 incident colorectal cancer cases and 1206 matched controls from the European Prospective Investigation into Cancer and Nutrition Study	Smoking status, education, alcohol intake, physical activity, fiber intake and consumption of red and processed meat, fish and shellfish and fruits and vegetables.	9
Song M 2013 [34]	Nested case-control	USA	616 incident colorectal cancer cases and 1,205 controls within the Nurses' Health Study (1990-2008) and the Health Professionals Follow-up Study (1994-2008)	Matching factors, BMI, fasting status of blood collection, colorectal cancer in parent or sibling, prior lower gastrointestinal endoscopy, history of polyp, regular use of multivitamins, pack-years of smoking, alcohol consumption, physical activity, regular aspirin/NSAID use, plasma 25(OH)D, and DASH score, menopausal status and current postmenopausal hormone use.	9
Chandler P 2015 [35]	Nested case-control	USA	275 colorectal cancer cases and 275 matched controls from Women's Health Study	Randomized treatment assignment to aspirin and vitamin E, BMI, physical activity, family history of colorectal cancer, smoking status, alcohol consumption, menopausal status and hormone therapy use, month of blood draw, and multivitamin use.	8

Note: The study quality was assessed using NOS scale proposed for meta-analysis of observational studies.
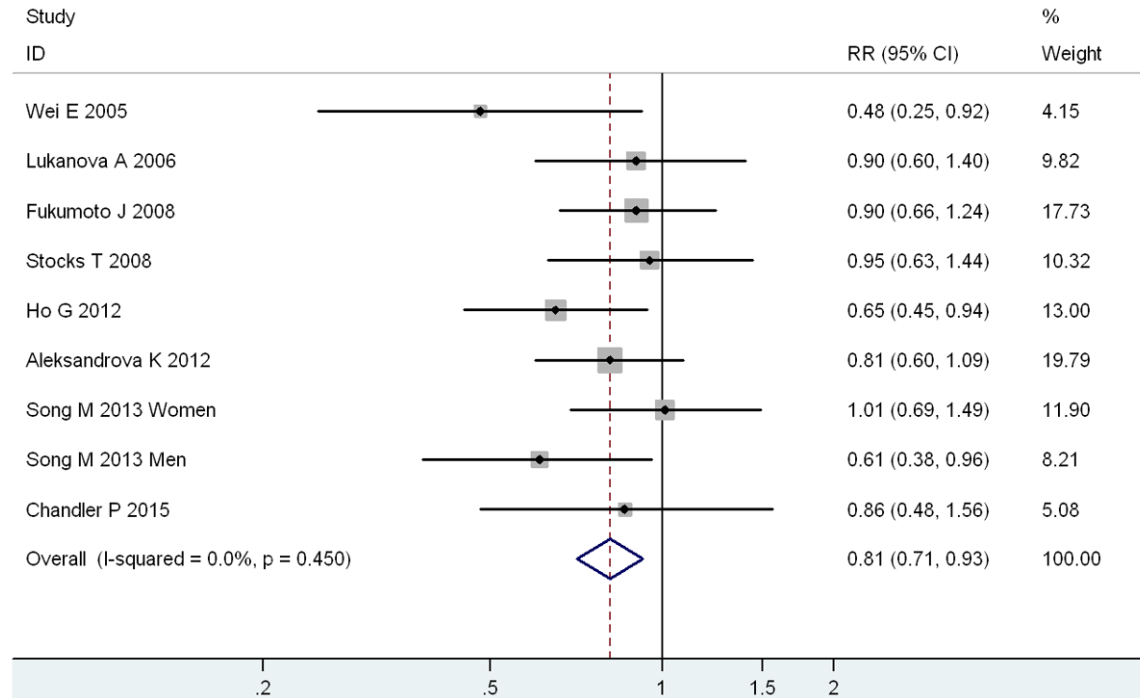
Figure 2. Higher adiponectin level was significantly associated with lower risk of colorectal cancer.

od was used to calculate RRs of colorectal cancer per 5 µg/mL increase in circulating adiponectin level. The study-specific RRs per 5 µg/mL were calculated using the random-effect generalized least-squares trend method [40, 41]. Sensitivity analysis was done by examining changes in the pooled RRs after sequential omission of individual study. Publication bias was firstly graphically assessed by the funnel plot, and then further assessed by Egger's test [42]. All analyses were performed in Stata version 11.2. *P* value <0.05 indicated a significant finding.

Results

Study search and characteristics

Our systematic search identified 304 studies (**Figure 1**). Twenty-three studies were assessed by reviewing full-text articles [28-35, 43-57]. Fifteen studies were then excluded [43-57] and 8 studies finally met the eligible criteria [28-35]. All those 8 studies were nested case-control studies, and they included a total of 4,076 colorectal cancer cases and 5,509 matched non-cancer controls (**Table 1**). All studies were from developed countries, and most studies were done in Caucasian populations (**Table 1**). Adiponectin levels were measured either enzy-

me-linked immunosorbent assay (ELISA) or by radioimmunoassay. All included studies reported adjusted RRs, but the adjusted factors were obviously different across those eligible studies (**Table 1**). The study quality by NOS was used in **Table 1**, and all studies had high quality with more than 7 points.

Meta-analysis

Heterogeneity of those eligible studies was relatively small. In the meta-analysis of data comparing the high category of adiponectin level with lower category of adiponectin level, the I^2 was 0%. In the dose-response meta-analysis, the I^2 was 6.1%.

When compared with lower adiponectin level, higher adiponectin level decreased the risk of colorectal cancer (RR = 0.81, 95% CI 0.71-0.93; P = 0.002), indicating a 19% reduction in colorectal cancer risk in individuals with higher category of adiponectin level (**Figure 2**). In the sensitivity analysis by excluding one study at a time, the pooled RRs were not materially changed.

Dose-response meta-analysis suggested that the pooled RR of colorectal cancer per 5 µg/mL increase in adiponectin was 0.86 (95% CI 0.77-
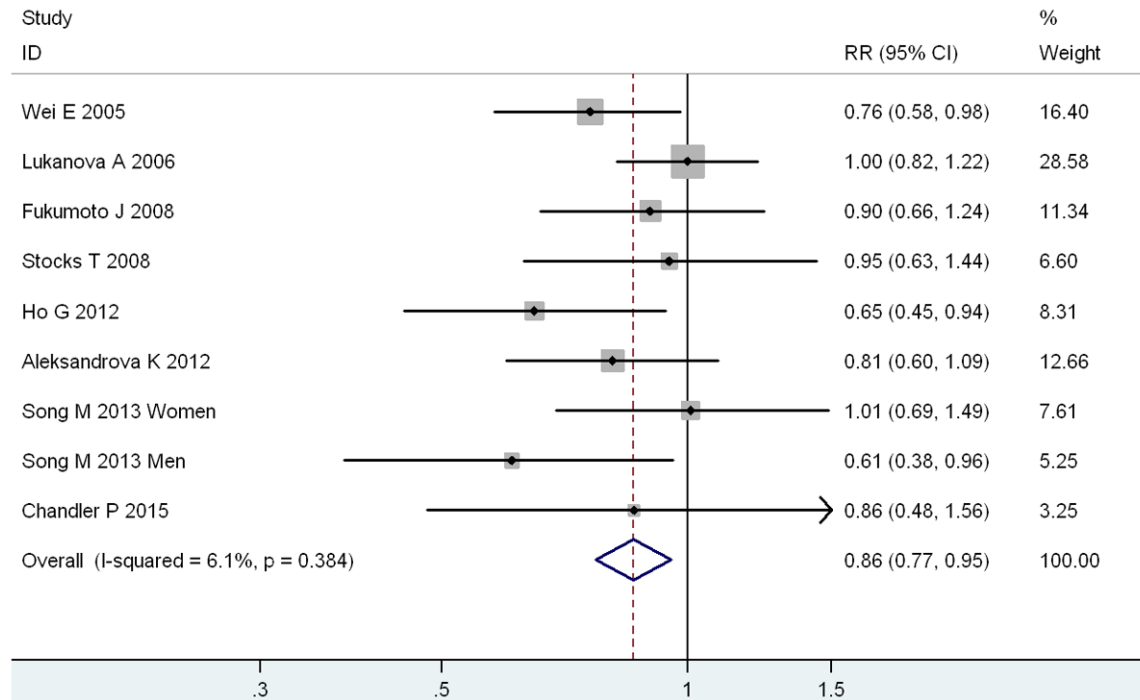
Figure 3. Dose-response meta-analysis suggested an obvious reduction in colorectal cancer risk associated with per 5 µg/mL increase in circulating adiponectin level.

0.95; P = 0.005), suggesting an inverse dose-response relationship existed (**Figure 3**). In the sensitivity analysis by excluding one study at a time, the pooled RRs were also not materially changed.

The symmetry of funnel plots in the meta-analysis didn't suggest risk of publication bias (**Figure 4**). Besides, Egger's test also showed that no obvious risk of publication bias (P > 0.05).

Discussion

Epidemiological studies on the association between circulating adiponectin level and colorectal cancer risk reported inconsistent findings, and a dose-response relationship has not been established. We therefore performed a dose-response meta-analysis to assess the evidence for the dose-response relationship between adiponectin and colorectal cancer. Eight nested case-control studies including a total of 4,076 colorectal cancer cases and 5,509 matched non-cancer controls were identified. When compared with lower adiponectin level, higher adiponectin level was significantly associated with lower level of colorectal cancer

(RR = 0.81; P = 0.002) (**Figure 1**). Besides, dose-response meta-analysis suggested that the pooled RR of colorectal cancer per 5 µg/mL increase in adiponectin was 0.86 (95% CI 0.77-0.95; P = 0.005), suggesting an inverse dose-response relationship existed (**Figure 3**). Therefore, there is an obvious dose-response association between adiponectin and colorectal cancer, suggesting that adiponectin is an important protective mediator in the development of colorectal cancer.

The association between obesity and colorectal cancer has been well established, numerous epidemiological researches have shown strong evidence for the causal relationship between obesity and colorectal cancer [7, 8, 10]. Adipokines secreted by the adipose tissues in obese individuals are regarded as important mediators involved in the causal relationship between obesity and colorectal cancer. The abnormally levels of adipokines observed in colorectal cancer patients provided some evidence for the roles of adipokines in the development of colorectal cancer. There were also some other prospectively epidemiological studies proving the roles of adipokines in colorectal cancer. Some studies explored the
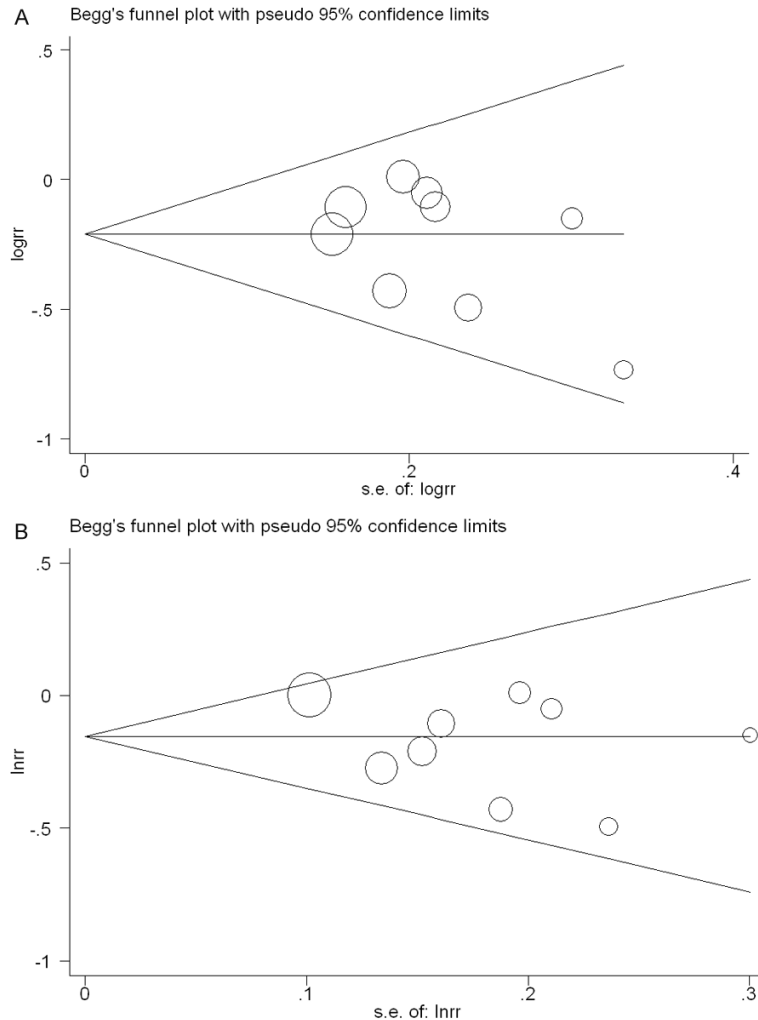
Figure 4. A. Funnel plot in the meta-analysis of the association between higher adiponectin level and colorectal cancer risk; B. Funnel plot in the dose-response meta-analysis.

factors [52]. Compared with those two studies, we included prospective studies, and used adjusted risk estimates, which could lead to a precise evaluation of the association between adiponectin and colorectal cancer. Besides, the dose-response meta-analysis proved a dose-response association between adiponectin and colorectal cancer, which was not studied in previous meta-analyses.

There were obvious differences across those included studies in the measurement of circulating adiponectin, matched factors and the ascertainment of outcome (**Table 1**). Those differences could result in considerable heterogeneity and biased the original measurement of the association between adiponectin and colorectal cancer. However, the heterogeneity of those eligible studies was relatively small, and the values of I^2 were all less more than 10%, which suggested that those differences were unable to cause risk of bias. Besides, all included studies were nested case-control studies and had high quality, which further decreased risk of bias in the meta-analysis and could help to a appropriate evaluation of the association between circulating adiponectin level and colorectal cancer risk.

The findings of experimental studies and the present meta-analysis prove that adiponectin is an important protective factor in the development of colorectal cancer [25, 26, 59]. Another critical question is whether adiponectin is an effective target for both the prevention and treatment of colorectal cancer. Some lifestyle interventions can increase adiponectin levels, and some compounds can induce the secretion of adiponectin [16, 60-62]. Whether these methods can become possible preventive or

roles of adiponectin in the development of colorectal cancer, but there were no conclusive findings. The findings from this meta-analysis suggest that adiponectin is an important mediator involved in the causal relationship between obesity and colorectal cancer.

A previous meta-analysis was published to compare the circulating level of adiponectin between colorectal cancer patients and controls, and found that patients with colorectal cancer had markedly decreased adiponectin level than controls [58]. Another meta-analysis suggested that an inverse association between adiponectin and colorectal cancer, but it used unadjusted risk estimates and was thus unable to exclude the influence of confounding

therapeutic methods for colorectal cancer are still unclear. More studies are needed to evaluate the effects of interventions specifically targeting adiponectin in preventing colorectal cancer.

Several limitations existed in the meta-analysis. Firstly, few of those included studies reported data on the associations of adiponectin with colon cancer and rectum cancer separately. The present meta-analysis was thus unable to perform dose-response meta-analyses by sites of colorectal cancer. More studies are needed to confirm the dose-response relationship in the associations of adiponectin with colon cancer and rectum cancer. Secondly, the role of adiponectin on colorectal cancer risk in non-obese individuals was not studied. Those included studies didn't assess the association between circulating adiponectin level and colorectal cancer risk in nonobese individuals. The roles of adiponectin on colorectal cancer risk remain to be elucidated in future studies. Thirdly, all those included studies were from developed countries, and the findings in the meta-analysis were limited to certain populations. The association between circulating adiponectin level and colorectal cancer risk in other populations need to be elucidated in future studies. Finally, the influence of other important confounders, such as diets and leptin, was not excluded in some studies. More studies with careful measurements of those important confounders are needed. Considering the above limitations, the findings of the meta-analysis may be interpreted with caution.

In summary, there is an obvious dose-response association between circulating adiponectin level and colorectal cancer risk, suggesting that adiponectin is an important protective mediator in the pathogenesis of colorectal cancer. However, more studies are needed to validate the findings of the meta-analysis and to explore the interventions specifically targeting adiponectin in preventing colorectal cancer.

Disclosure of conflict interest

None.

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