Circulating adiponectin levels in various malignancies: an updated meta-analysis of 107 studies

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Keywords: adiponectin, malignancy, biomarker, diagnosis, meta-analysis

Received: December 15, 2015   Accepted: April 16, 2016   Published: April 22, 2016

ABSTRACT

Early detection of cancers is challenging for lack of specific biomarkers. Adiponectin is an adipokine predominantly derived from adipocytes and hypoadiponectinemia has been reported to associate with risk of many types of cancers. However, available evidence is controversial. Some studies show that increased adiponectin levels correlate with cancer risk. Therefore, we performed a meta-analysis of the association between circulating adiponectin levels and cancer development. A systematic search of PubMed, EMBASE, Wiley Online Library and Cochrane Library was conducted for eligible studies involving circulating adiponectin and malignancies from inception to August 8, 2015. Standard mean differences (SMDs) with 95% confidence intervals (95% CIs) were calculated by use of a random-effect model. Funnel plot and Egger’s linear regression test were conducted to examine the risk of publication bias. 107 studies were included with 19,319 cases and 25,675 controls. The pooled analysis indicated that circulating adiponectin levels were lower in patients with various cancers than in controls, with a pooled SMD of -0.334 μg/ml (95% CI, -0.465 to -0.203, \( P = 0.000 \)). No evidence of publication bias was observed. Circulating high molecular weight adiponectin levels were also lower in cancer patients than in controls, with a pooled SMD of -0.502 μg/ml (95% CI, -0.957 to -0.047, \( P = 0.000 \)). This meta-analysis provides further evidence that decreased adiponectin levels is associated with risk of various cancers. Hypoadiponectinemia may represent a useful biomarker for early detection of cancers.

INTRODUCTION

Cancer, a major cause of human mortality, has been a worldwide public health problem. A variety of factors such as genetic lesions, environmental aspect and increasing adoption of unhealthy lifestyle are considered as crucial causes of cancer [1]. Among them, obesity is an important factor contributing to the occurrence and development of malignancies. According to the literature in 2005, 396 and 937 million people suffer from obese and overweight worldwide, respectively [2]. Epidemiological research reveals that obesity increases the risk of cancer with evidence that obese women have 50% higher incidence rate than normal weight women [3]. In the process of obesity, dysregulated circulating hormones and growth factors may play an important role in carcinogenesis [4]. Among them, aberrant adiponectin concentration is reported to be a vital link between obesity and cancer.

Adiponectin, firstly discovered by Scherer et al. in 1995, is an adipokine predominantly produced by adipocytes with the monomeric subunit containing 244 amino-acids in human and circulates abundantly in plasma [5, 6]. Three bioactive forms of adiponectin are produced...
after post-transcriptional process known as trimeric low molecular weight (90 kD, LMW), hexameric medium molecular weight (180 kD, MMW) and oligomeric high molecular weight (> 400 kD, HMW) adiponectin. Among them, HMW-adiponectin is the dominant form in plasma and has the most biological activity than the other two isoforms [7]. Adiponectin mainly acts on two seven-transmembrane adiponectin receptors, AdipoR1 and AdipoR2. Besides, T-cadherin is also responsible for mediating the role of adiponectin in certain tissues [8, 9]. Adiponectin exerts pleiotropic functions in human health such as anti-inflammation, anti-atherosclerosis, and anti-angiogenesis. It also has the properties of insulin-sensitizing and balancing glucose and lipid metabolism in various cells [10]. A number of studies reveal that circulating adiponectin levels decrease in metabolic syndrome, whereas overexpression of it can counteract metabolic dysfunctions [10]. Besides, increased weight reduces the plasma adiponectin level and decreased weight upregulates circulating adiponectin level [11].

It was first reported that circulating adiponectin level was lower in patients with breast cancer in 2003 [12]. Since then, the most clinical studies have indicated that hypoadiponectinemia is associated with risk of various cancers including prostate, endometrial, and colorectal cancers [13-16]. In addition, adiponectin has anti-proliferative and pro-apoptotic effects on cultured cancer cell lines [17, 18]. These results suggest that adiponectin might be an important regulator in carcinogenesis and progression of cancers. However, unchanged or increased circulating adiponectin levels in pancreatic and hepatocellular carcinoma are also reported [19, 20]. Therefore, understanding the exact role of adiponectin in cancer may offer a novel target in tumor diagnosis and therapeutic strategy. In order to gain a more explicit and evidence-based conclusion on the association between circulating adiponectin levels and carcinogenesis, we conducted a comprehensive meta-analysis of current available studies.

RESULTS

Literature selection

The initial comprehensive search yielded 1486 articles, of which 235 articles were excluded for duplication. Then 997 studies were ruled out because of apparent irrelevance after reading titles and/or abstracts.

Figure 1: Flow diagram of the included studies.
| Author         | Year  | Type              | Country             | Ethnicity | Sample       | Mean age (Case/ control) | Number (Case/ control) | Study design | Assay method | Assay source               | Study quality |
|---------------|-------|-------------------|---------------------|-----------|--------------|--------------------------|------------------------|--------------|--------------|----------------------------|---------------|
| Petridou et al. | 2006  | Acute leukemia    | Greece/ USA         | Caucasian | Serum        | NR                       | 201/201                | Case-control | RIA          | Beth Israel Deacooness Medical Center | 8             |
| Moschovi et al. | 2010  | Acute leukemia    | Greece              | Caucasian | Plasma       | 4.3/5.2                  | 9/9                    | Prospective case-control | Other        | Linco Research           | 7             |
| Aref et al.    | 2013  | Acute leukemia    | Egypt               | African   | Serum        | 42.8/49.1                | 80/20                  | Case-control | Elisa        | R&D Systems               | 5             |
| Miyoshi et al. | 2003  | Breast cancer     | Japan               | Asian     | Serum        | 54.0/52.8                | 102/100                | Case-control | Elisa        | NR                        | 7             |
| Mantzoros et al. | 2004 | Breast cancer     | Greece              | Caucasian | Serum        | NR                       | 174/167                | Case-control | RIA          | Beth Israel Deacooness Medical Center | 8             |
| Chen et al.    | 2006  | Breast cancer     | Taiwan              | Asian     | Serum        | 49.9/49.9                | 100/100                | Case-control | RIA          | Linco Research           | 7             |
| Korner et al.  | 2007  | Breast cancer     | Greece              | Caucasian | Serum        | 62.5/55.6                | 74/76                  | Case-control | RIA          | ALPCO Diagnostics          | 7             |
| Yamaji et al.  | 2010  | Colorectal adenoma| Japan               | Asian     | Plasma       | NR                       | 778/735                | Case-control | Elisa        | AdipoGen                 | 7             |
| Al Awadhi et al. | 2012 | Breast cancer     | Kuwait              | Asian     | Plasma       | 50.3/50.7                | 144/77                 | Case-control | RIA          | Linco Research           | 7             |
| Stocks et al.  | 2008  | Colorectal adenoma| Japan               | Asian     | Plasma       | 65.6/648                | 778/735                | Case-control | Elisa        | Sekisui Medical           | 6             |
| Danese et al.  | 2013  | Colorectal adenoma| Italy               | Caucasian | Serum        | 63.0/59.5                | 40/40                  | Case-control | Elisa        | Medigraphit              | 7             |
| Wei et al.     | 2005  | Colorectal cancer | USA                 | Caucasian | Plasma       | 66.6/66.5                | 179/356                | Nested case-control | RIA          | Linco Research           | 8             |
| Guadagni et al. | 2009 | Colorectal cancer | Italy               | Caucasian | Serum        | 63.0/59.0                | 90/30                  | Case-control | Ria           | BioVendor Laboratory Medicine | 8             |
| Kumon et al.   | 2009  | Colorectal cancer | Poland              | Caucasian | Serum        | 58.6/60.1                | 36/25                  | Case-control | Elisa        | R&D Systems               | 7             |
| Eraslan et al. | 2009  | Colorectal cancer | Turkey              | Asian     | Plasma       | 57.0/59.0                | 23/50                  | Case-control | Elisa        | RayBio                   | 8             |
| Nakajima et al. | 2010 | Colorectal cancer | Japan               | Asian     | Plasma       | 63.7/63.5                | 115/115                | Case-control | Elisa        | Sekisui Medical           | 6             |
| Otake et al.   | 2010  | Colorectal cancer | Japan               | Asian     | Plasma       | 66.7/67.9                | 91/25                  | Case-control | Elisa        | Sekisui Medical           | 6             |
| Kemik et al.   | 2010  | Colorectal cancer | Turkey              | Asian     | Serum        | 43.5/40.4                | 126/38                 | Case-control | RIA          | Linco Research           | 7             |
| Gonullu et al. | 2010  | Colorectal cancer | Turkey              | Asian     | Serum        | 56.6/51.0                | 36/37                  | Case-control | Elisa        | BioSource                | 8             |
| Catalan et al. | 2011  | Colorectal cancer | Spain               | Caucasian | Plasma       | 66.0/44.0                | 11/18                  | Case-control | Elisa        | R&D Systems               | 8             |
| Study (et al.) | Year | Tumor Type          | Country | Ethnicity | Tumor Material | Test | Biomarker | Case-control | Laboratory |  |  |  |
|---------------|------|---------------------|---------|-----------|----------------|------|-----------|--------------|------------|---|---|---|
| Chen et al.   | 2012 | Colorectal cancer   | China   | Asian     | Plasma         | 61.9/58.3 | 165/102   | Case-control | Elisa      |  |  |  |
| Touvier et al.| 2012 | Colorectal cancer   | France  | Caucasian | Plasma         | 51.8/52.1 | 50/100    | Nested case-control | Elisa | R&D Systems | 9 |
| Aleksandrova et al. | 2012 | Colorectal cancer | Germany | Caucasian | Serum          | 58.3/58.3 | 1206/1206 | Case-control | Elisa | ALPCO Diagnostics | 9 |
| Song et al.   | 2013 | Colorectal cancer   | USA     | Caucasian | Plasma         | 61.9/61.9 | 616/1205 | Case-control | Elisa | ALPCO Diagnostics | 9 |
| Cust et al.   | 2007 | Endometrical carcinoma | UK     | Caucasian | Plasma         | 56.9/56.9 | 284/548   | Nested case-control | Elisa | R&D Systems | 8 |
| Soliman et al.| 2006 | Endometrical carcinoma | USA | Caucasian | Serum          | 66.6/61.2 | 117/238   | Case-control | Elisa | R&D Systems | 5 |
| Ashizawa et al.| 2010 | Endometrical carcinoma | Japan  | Asian     | Serum          | 59.9/57.5 | 146/150   | Case-control | RIA | Linco Research | 8 |
| Dossus et al. | 2013 | Endometrical carcinoma | Greece | Caucasian | Serum          | 57.7/57.7 | 233/446   | Case-control | Elisa | R&D Systems | 8 |
| Friedenreich et al. | 2012 | Endometrical carcinoma | USA | Caucasian | Serum          | 59/59    | 514/962   | Case-control | Elisa | ALPCO Diagnostics | 9 |
| Luhn et al.   | 2013 | Endometrical carcinoma | USA | Caucasian | Serum          | NR       | 167/327   | Nested case-control | RIA | Linco Research | 8 |
| Erdogan et al.| 2013 | Endometrical carcinoma | Turkey  | Asian     | Serum          | 56.6/49.7 | 60/70     | Case-control | Elisa | eBioscience | 6 |
| Ma et al.     | 2013 | Endometrical carcinoma | China   | Asian     | Serum          | 53.2/53.3 | 206/310   | Case-control | Elisa | Beinder MedSystems | 9 |
| Dallal et al. | 2013 | Endometrical carcinoma | USA     | Caucasian | Serum          | 67.4/67.5 | 62/124    | Nested case-control | Elisa | Millipore | 8 |
| Mihu et al.   | 2013 | Endometrical carcinoma | Romania | Caucasian | Serum          | 60.2/58.5 | 44/44     | Case-control | Elisa | R&D Systems | 6 |
| Obbuchi et al.| 2014 | Endometrical carcinoma | Japan   | Asian     | Serum          | 61.2/58.1 | 43/62     | Case-control | Elisa | Daichi Co. Ltd. | 8 |
| Diao et al.   | 2009 | Esophageal cancer    | China   | Asian     | Plasma         | 58.0/49.0 | 43/33     | Case-control | Elisa | Adlitteram Diagnostic Laboratories. Inc. | 6 |
| Nakajima et al.| 2010 | Esophageal cancer    | Japan   | Asian     | Blood          | 63.6/63.6 | 117/117   | Case-control | Elisa | Otsuka Pharmaceutical | 6 |
| Yildirim et al.| 2009 | Esophageal cancer    | Turkey  | Asian     | Serum          | 64/61    | 62/30     | Case-control | Elisa | Avibion | 6 |
| Ishikawa et al.| 2005 | Gastric cancer       | Japan   | Asian     | Plasma         | 64.2/59.3 | 75/52     | Case-control | Elisa | Otsuka Pharmaceutical | 6 |
| Nakajima et al.| 2009 | Gastric cancer       | Japan   | Asian     | Blood          | 61.0/60.8 | 156/156   | Case-control | Elisa | Otsuka Pharmaceutical | 8 |
| Seker et al.  | 2010 | Gastric cancer       | Turkey  | Asian     | Plasma         | 60.0/38.6 | 40/43     | Case-control | Elisa | Linco Research | 5 |
| Duikowska et al. | 2014 | Gastroesophageal cancer | Poland | Caucasian | Serum          | 60.0/58.0 | 85/60     | Case-control | Elisa | R&D Systems | 7 |
| Kotani et al. | 2009 | Hepatocellular carcinoma | Japan  | Asian     | Serum          | 63.5/62.7 | 59/334    | Nested case-control | Elisa | Daichi Co. Ltd. | 8 |
| Liu et al.    | 2009 | Hepatocellular carcinoma | Taiwan| Asian     | Serum          | 50.7/53.8 | 120/116   | Case-control | Elisa | B-Bridge International Inc. | 5 |
| Sumie et al.  | 2011 | Hepatocellular carcinoma | Japan  | Asian     | Serum          | 67.4/61.2 | 97/97     | Case-control | Elisa | EikenChemical Co. Ltd. | 7 |
| Sadik et al.  | 2012 | Hepatocellular carcinoma | Egypt  | African   | Serum          | 58.9/55.7 | 69/121    | Case-control | Elisa | Assaypro | 7 |
| Chen et al.   | 2012 | Hepatocellular carcinoma | Taiwan| Asian     | Serum          | 52.4/52.2 | 65/165    | Case-control | RIA | Linco Research | 6 |
| Khattab et al.| 2012 | Hepatocellular carcinoma | Egypt  | African   | Plasma         | 43.9/42.9 | 147/320   | Case-control | Other | Linco Research | 5 |
| Chen et al.   | 2014 | Hepatocellular carcinoma | Taiwan| Chinese   | Plasma         | NR        | 185/373   | Nested case-control | Elisa | B-Bridge International Inc. | 8 |
| Petridou et al.| 2010 | Hodgkin lymphoma    | Greece  | Caucasian | Serum          | 11.5/11.2 | 75/75     | Case-control | RIA | Linco Research | 7 |
| Jamieson et al.| 2004 | Lung cancer         | UK      | Caucasian | Serum          | 64.0/65.0 | 20/13     | Case-control | RIA | Linco Research | 7 |
| Karapanagiotou et al. | 2008 | Lung cancer        | Greece  | Caucasian | Serum          | 64.2/55.5 | 101/51    | Case-control | Elisa | BioVendor | 6 |
| Petridou et al.| 2007 | Lung cancer         | Greece  | Caucasian | Serum          | NR        | 85/170    | Case-control | RIA | Beth Israel Deaconess Medical Center | 8 |
| Gulen et al.  | 2012 | Lung cancer         | Turkey  | Asian     | Serum          | 65.6/63.5 | 63/25     | Case-control | Elisa | BioVendor | 7 |
| Kerendii et al.| 2013 | Lung cancer         | Greece  | Caucasian | Serum          | 62.9/NR   | 80/40     | Case-control | Elisa | Linco Research | 7 |
| Antoniadis et al. | 2011 | Melanoma            | Greece/ Canada | Caucasian | Serum          | 52.7/53.3 | 55/165    | Case-control | RIA | Beth Israel Deaconess Medical Center | 8 |
| Dalamaga et al. | 2009 | Multiple myeloma    | Greece/ Canada | Caucasian | Serum          | NR        | 73/73     | Case-control | Elisa | Avibion | 8 |
The remaining 254 studies were included for full-text reading, of which 151 studies were removed for one of the following reasons: (i) reviews, comments or letters (n = 37); (ii) shared population (n = 13); (iii) no report of adiponectin levels and/or SDs for both patients and controls or there was not enough information to calculate them (n = 25); (iv) not case-control study (n = 76). 4 additional studies were included from checking the references list. Finally, 107 studies met the inclusion criteria and were used for further analysis [12, 13, 15, 16, 20-112]. The flow diagram of this selection process was showed in Figure 1.

### Study characteristics

Among the 107 studies, a total of 25,675 controls and 19,319 cases were enrolled until August, 2015. Geographic regions were various, among which 46 studies from Asia, 39 studies from Europe, 19 studies from America, and 3 studies from Africa. 16 types of malignancies were investigated in this meta-analysis, with digestive system cancers accounting for the largest percentage (43 studies); other types included: prostate cancer (20 studies), breast cancer (13 studies), endometrial carcinoma (11 studies), lung cancer (5 studies), renal cancer (3 studies), acute leukemia (3 studies), non-Hodgkin’s lymphoma (3 studies), Hodgkin’s lymphoma (1 study), multiple myeloma (2 studies), etc.

| Study Characteristics | Description |
|-----------------------|-------------|
| Study inclusion       | 107 studies |
| Study type            | Case-control studies |
| Study population      | Various geographies |
| Study malignancies    | 16 types |
| Malignancies           | Digestive system cancers, prostate cancer, breast cancer, endometrial carcinoma, lung cancer, renal cancer, acute leukemia, non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, multiple myeloma |

### Abbreviations

- NR: not reported
- Elisa: enzyme-linked immunosorbent assay
- RIA: radioimmunoassay

### Table: Study characteristics

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The following table shows the characteristics of the studies included in this meta-analysis.

| Study Authors           | Year of Publication | Study Type | Study Population | Study Malignancy   | Study Region | Study Characteristics | Study Controls | Study Cases |
|-------------------------|---------------------|------------|------------------|--------------------|--------------|-----------------------|----------------|-------------|
| Hofmann et al.          | 2012                | Multiple myeloma | USA | Caucasian | Plasma | 174/348 | Case-control | Elisa | R&D Systems | 7 |
| Parmak et al.           | 2006                | Non-Hodgkin's lymphoma | Turkey | Asian | Serum | 63.2/58.5 | 28/17 | Case-control | Elisa | Otsuka Co. Ltd | 5 |
| Petridou et al.         | 2009                | Non-Hodgkin's lymphoma | Greece | Caucasian | Serum | 37/8.8/l | 121/121 | Case-control | RIA | NR | 7 |
| Conroy et al.           | 2013                | Non-Hodgkin's lymphoma | USA | Caucasian | Plasma | 70.0/70.0 | 272/541 | Nested case-control | Elisa | R&D Systems | 7 |
| Chang et al.            | 2007                | Pancreatic cancer | Taiwan/ China | Asian | Serum | 64.6/49.5 | 72/290 | Case-control | Elisa | R&D Systems | 8 |
| Dalamagia et al.        | 2009                | Pancreatic cancer | Greece | Caucasian | Serum | 69.0/70.1 | 81/81 | Case-control | RIA | Linco Research | 7 |
| Solomon et al.          | 2008                | Pancreatic cancer | USA | Caucasian | Serum | 58.0/58.0 | 311/510 | Case-control | Elisa | Millipore | 8 |
| Krechler et al.         | 2011                | Pancreatic cancer | Czech Republic | Caucasian | Plasma | 51.9/64.5 | 64/64 | Case-control | RIA | DRG Inc. | 8 |
| Grote et al.            | 2012                | Pancreatic cancer | Germany | Caucasian | Serum | 58.0/60.0 | 452/452 | Nested case-control | Other | R&D Systems | 8 |
| Hao et al.              | 2013                | Pancreatic cancer | USA | Caucasian | Plasma | NR | 468/1080 | Nested case-control | Elisa | ALPCO Diagnostics | 8 |
| Goitkas et al.          | 2005                | Prostate cancer | Turkey | Asian | Plasma | 65.8/62.2 | 30/36 | Case-control | RIA | Linco Research | 8 |
| Goitkas et al.          | 2005                | Prostate cancer | Turkey | Asian | Plasma | 65.8/65.0 | 30/41 | Case-control | RIA | Linco Research | 8 |
| Baillargeon et al.      | 2006                | Prostate cancer | USA | Caucasian | Serum | 63.5/63.2 | 125/125 | Nested case-control | Other | LumineX | 7 |
| Michalakis et al.       | 2007                | Prostate cancer | Greece | Caucasian | Serum | 74.0/64.0 | 75/150 | Case-control | RIA | Linco Research | 5 |
| Michalakis et al.       | 2007                | Prostate cancer | Greece | Caucasian | Serum | 74.0/70.0 | 75/75 | Case-control | RIA | Linco Research | 5 |
| Housa et al.            | 2008                | Prostate cancer | Czech Republic | Caucasian | Serum | 63.6/70.5 | 43/25 | Case-control | RIA | Linco Research | 5 |
| Grosman et al.          | 2010                | Prostate cancer | Argentina | Caucasian | Serum | NR | 25/25 | Case-control | RIA | Linco Research | 7 |
| Li et al.               | 2010                | Prostate cancer | USA | Caucasian | Plasma | 59.0/58.6 | 620/599 | Nested case-control | Elisa | Linco Research | 7 |
| Dhillon et al.          | 2011                | Prostate cancer | USA | Caucasian | Plasma | 57.9/57.5 | 1286/1267 | Nested case-control | RIA | Linco Research | 8 |
| Lopez Fontana et al.    | 2011                | Prostate cancer | Argentina | Caucasian | Serum | 63.8/64.9 | 35/35 | Case-control | Elisa | Linco Research | 6 |
| Al Khaldi et al.        | 2011                | Prostate cancer | Kuwait | Asian | Plasma | 59.0/60.0 | 14/68 | Case-control | Elisa | Linco Research | 7 |
| Touvier et al.          | 2013                | Prostate cancer | France | Caucasian | Plasma | 54.9/51.5 | 156/1024 | Nested case-control | Elisa | R&D Systems | 9 |
| Tewari et al.           | 2013                | Prostate cancer | India | Asian | Blood | 65.6/65.7 | 95/95 | Case-control | Other | NR | 5 |
| Spyridopoulos et al.    | 2012                | Renal cancer | Greece | Caucasian | Serum | 61.5/60.7 | 60/236 | Case-control | RIA | Beth Israel Deaconess Medical Center | 8 |
| Liao et al.             | 2013                | Renal cancer | Finland/ USA | Caucasian | Serum | 57/57 | 273/273 | Nested case-control | Elisa | Millipore | 9 |
| Liao et al.             | 2013                | Renal cancer | Canada/ USA | Caucasian | Serum | NR | 768/917 | Case-control | Elisa | Millipore | 9 |
| Mitsiades et al.        | 2011                | Thyroid cancer | USA | Caucasian | Serum | 51.2/55.4 | 175/107 | Case-control | RIA | Beth Israel Deaconess Medical Center | 5 |
| Guo et al.              | 2013                | Tongue cancer | China | Asian | Serum | 57.2/52.7 | 59/50 | Case-control | Elisa | Adipobiotech | 8 |

Abbreviations: NR, not reported; Elisa, enzyme-linked immunosorbent assay; RIA, radioimmunoassay.
Figure 2: Forest plot of studies in circulating total adiponectin and cancer risk. The combined SMD and 95% CIs were calculated through a random-effect model.
Table 2: Subgroup analysis of the relationships between circulating adiponectin levels and study characteristics.

| Characteristics                        | Number of studies | Number (Case/control) | SMD  | 95% CI       | Heterogeneity (I²) |
|----------------------------------------|-------------------|-----------------------|------|--------------|--------------------|
| **Ethnicity**                          |                   |                       |      |              |                    |
| Caucasian                              | 58                | 14178/19758           | -0.269 | -0.400 to -0.138 | 96.8%              |
| Asian                                  | 46                | 4845/5456             | -0.555 | -0.812 to -0.298 | 97.1%              |
| African                                | 3                 | 296/461               | 1.821  | -2.201 to 5.843  | 99.6%              |
| **Cancer Types**                       |                   |                       |      |              |                    |
| Acute leukemia                         | 3                 | 290/230               | -2.236 | -4.418 to -0.054 | 97.3%              |
| Multiple myeloma                       | 2                 | 247/421               | -0.621 | -0.966 to -0.276 | 69.7%              |
| Breast cancer                          | 20                | 4545/5292             | -0.334 | -0.543 to -0.126 | 95.5%              |
| Colorectal cancers                     | 23                | 4749/5591             | -0.496 | -0.653 to -0.339 | 91.3%              |
| Endometrial cancer                     | 11                | 1876/3281             | -0.594 | -0.825 to -0.363 | 92.8%              |
| Prostate cancer                        | 13                | 2609/3565             | -0.892 | -1.345 to -0.438 | 97.9%              |
| Thyroid cancer                         | 1                 | 175/107               | -0.358 | -0.601 to -0.116 | 91.8%              |
| Tongue cancer                          | 1                 | 59/50                 | -1.172 | -1.580 to -0.764 | NA                 |
| Hepatocellular cancer                  | 7                 | 742/1526              | 1.385  | 0.240 to 2.530  | 99.2%              |
| Gastroesophageal cancer                | 7                 | 578/491               | -0.278 | -0.553 to -0.004 | 78.1%              |
| Hodgkin lymphoma                       | 1                 | 75/75                 | 0.28   | -0.041 to 0.602  | NA                 |
| Non-Hodgkin lymphoma                   | 3                 | 421/679               | 0.316  | -0.048 to 0.68  | 79.7%              |
| Lung cancer                            | 5                 | 349/299               | -0.085 | -0.58 to 0.409  | 87.1%              |
| Melanoma                               | 1                 | 55/165                | -0.112 | -0.418 to 0.193 | NA                 |
| Pancreatic cancer                      | 6                 | 1448/2477             | 0.037  | -1.207 to 1.281 | 99.6%              |
| Renal cancer                           | 3                 | 1101/1426             | 0.021  | -0.246 to 0.288 | 86.6%              |
| **Study Design**                       |                   |                       |      |              |                    |
| Case-control study                     | 86                | 11965/14210           | -0.346 | -0.505 to -0.188 | 97.2%              |
| Nested case-control study              | 21                | 7354/11465            | -0.290 | -0.553 to -0.026 | 98.5%              |
| **Blood samples**                      |                   |                       |      |              |                    |
| Serum                                  | 65                | 9171/11101            | -0.335 | -0.483 to -0.186 | 95.8%              |
| Plasma                                 | 37                | 8303/12010            | -0.238 | -0.497 to 0.022 | 98.6%              |
| NR                                     | 5                 | 1845/2564             | -1.072 | -1.775 to -0.369 | 98.8%              |
| **Assay methods**                      |                   |                       |      |              |                    |
| RIA                                    | 29                | 6190/7587            | -0.316 | -0.459 to -0.172 | 93.0%              |
| Elisa                                  | 71                | 12179/16968           | -0.266 | -0.426 to -0.106 | 97.4%              |
| Others                                 | 7                 | 950/1120              | -1.305 | -3.113 to 0.502 | 99.5%              |
| **Study size**                         |                   |                       |      |              |                    |
| ≥100 patients                          | 48                | 16057/21437           | -0.135 | -0.299 to 0.030 | 98.3%              |
| <100 patients                          | 59                | 3262/4238            | -0.549 | -0.825 to -0.273 | 96.5%              |
| **Study quality**                      |                   |                       |      |              |                    |
| ≥6                                     | 96                | 16352/22425           | -0.334 | -0.465 to -0.203 | 97.3%              |
| <6                                     | 11                | 2967/3250             | -0.267 | -0.700 to 0.165 | 98.2%              |
| **Patients’ age (mean)**               |                   |                       |      |              |                    |
| ≥60                                    | 44*               | 4770/6414*            | -0.489 | -0.689 to -0.288 | 95.6%              |
| <60                                    | 47*               | 9782/12935*           | -0.194 | -0.383 to -0.004 | 97.7%              |

Abbreviations: NA, not assessable. *There are 91 studies with 14,552 cases and 19,349 controls reported the mean age of cancer patients.
Table 3: The pooled SMDs and 95% CIs of the included studies through sensitivity analysis.

| Study omitted               | Estimate         | 95% CI           |
|-----------------------------|------------------|------------------|
| Miyoshi et al. (2003)       | -0.33362126      | -0.46549249 to -.20175007 |
| Jamieson et al. (2004)      | -0.32790136      | -0.45929646 to -.19650623 |
| Mantzoros et al. (2004)     | -0.3366529       | -0.46877834 to -.20452745 |
| Goktas et al. (2005)        | -0.31018904      | -0.44067159 to -.1797065 |
| Goktas et al. (2005)        | -0.31467217      | -0.4453963 to -.18394804 |
| Wei et al. (2005)           | -0.33543056      | -0.46779135 to -.20306975 |
| Otake et al. (2005)         | -0.32370359      | -0.4541788 to -.19248928 |
| Ishikawa et al. (2005)      | -0.33179379      | -0.4634814 to -.20010617 |
| Petridou et al. (2006)      | -0.33611172      | -0.4683494 to -.20387407 |
| Baillargeon et al. (2006)   | -0.33559188      | -0.46757615 to -.2036076 |
| Chen et al. (2006)          | -0.32800215      | -0.45950019 to -.1965041 |
| Pamuk et al. (2006)         | -0.34167045      | -0.47312284 to -.21021806 |
| Soliman et al. (2006)       | -0.32821506      | -0.45972851 to -.19670163 |
| Cust et al. (2007)          | -0.33429027      | -0.46701819 to -.20156233 |
| Korner et al. (2007)        | -0.33221245      | -0.4639549 to -.20046999 |
| Kang et al. (2007)          | -0.33505732      | -0.46672907 to -.20338558 |
| Tworoger et al. (2007)      | -0.33802846      | -0.47386777 to -.20218913 |
| Tworoger et al. (2007)      | -0.3405844       | -0.47277904 to -.20838977 |
| Chang et al. (2007)         | -0.35825887      | -0.48626736 to -.2302504 |
| Michalakis et al. (2007)    | -0.32968622      | -0.46133375 to -.19803868 |
| Michalakis et al. (2007)    | -0.33015183      | -0.46179458 to -.19850905 |
| Hou et al. (2007)           | -0.33114624      | -0.46280947 to -.19948301 |
| Petridou et al. (2007)      | -0.33918613      | -0.47100937 to -.20736288 |
| Fukumoto et al. (2008)      | -0.33727011      | -0.47093907 to -.20360115 |
| Solomon et al. (2008)       | -0.3375347       | -0.47031215 to -.20475723 |
| Housa et al. (2008)         | -0.33494586      | -0.46656513 to -.2033266 |
| Karapanagiotou et al. (2008)| -0.337192        | -0.46895465 to -.20542936 |
| Stocks et al. (2008)        | -0.33803195      | -0.47080877 to -.20525511 |
| Dalamaga et al. (2009)      | -0.34321341      | -0.47464448 to -.21178232 |
| Dalamaga et al. (2009)      | -0.32902971      | -0.46060005 to -.19745934 |
| Petridou et al. (2009)      | -0.34161058      | -0.47322133 to -.2099998 |
| Kotani et al. (2009)        | -0.33791459      | -0.46976718 to -.20606196 |
| Study                  | Value 1     | Value 2               |
|------------------------|------------|-----------------------|
| Guadagni et al. (2009) | -0.31941918 | -.45032975 to -.18850861 |
| Kumor et al. (2009)    | -0.32856214 | -.46004361 to -.1970806 |
| Erarslan et al. (2009) | -0.33168712 | -.46326634 to -.20010787 |
| Kumor et al. (2009)    | -0.3339898  | -.4655939 to -.2023856  |
| Erarslan et al. (2009) | -0.33251002 | -.46413583 to -.20088424 |
| Cust et al. (2009)     | -0.33854863 | -.47171903 to -.20537826 |
| Nakajima et al. (2009) | -0.33416247 | -.4662253 to -.20209965 |
| Diao et al. (2009)     | -0.33897933 | -.47058302 to -.2073756 |
| Yildirim et al. (2009) | -0.3268407  | -.45826575 to -.19541568 |
| Li et al. (2009)       | -0.34737712 | -.47806501 to -.21668923 |
| Moschovi et al. (2010) | -0.31926209 | -.45011383 to -.18841037 |
| Hancke et al. (2010)   | -0.33801222 | -.46974581 to -.20627865 |
| Seker et al. (2010)    | -0.34004903 | -.47163537 to -.2084627 |
| Nakajima et al. (2010) | -0.33507797 | -.46703228 to -.20312366 |
| Petridou et al. (2010) | -0.33972663 | -.47141987 to -.20803338 |
| Grosman et al. (2010)  | -0.32690996 | -.45831883 to -.19550107 |
| Li et al. (2010)       | -0.3373847  | -.47090244 to -.20386696 |
| Nakajima et al. (2010) | -0.3372006  | -.46912611 to -.2052751 |
| Otake et al. (2010)    | -0.3304036  | -.46196187 to -.19884537 |
| Kemik et al (2010)     | -0.3278496  | -.45933568 to -.19636351 |
| Gonullu et al. (2010)  | -0.3353405  | -.46698609 to -.20369488 |
| Nakajima et al. (2010) | -0.33436027 | -.46614832 to -.20257224 |
| Ashizawa et al. (2010) | -0.33154425 | -.4634259 to -.19966258 |
| Shahar et al. (2010)   | -0.3222657  | -.4640207 to -.20043245 |
| Otake et al. (2010)    | -0.3297922  | -.46132797 to -.19825645 |
| Yamaji et al. (2010)   | -0.33636427 | -.47040036 to -.20232819 |
| Antoniadis et al. (2011)| -0.3360277 | -.46786067 to -.2041948 |
| Dhillon et al. (2011)  | -0.33877328 | -.47420669 to -.2033987 |
| Al Khaldi et al. (2011) | -0.3581396 | -.48865175 to -.22762746 |
| Sumie et al. (2011)    | -0.33623996 | -.46812296 to -.20435697 |
| Catalan et al. (2011)  | -0.3270525  | -.4584052 to -.19569978 |
| Dalamaga et al. (2011) | -0.33432293 | -.46621501 to -.20243084 |
| Al Khaldi et al. (2011) | -0.34966454 | -.48045498 to -.21887414 |
| Study                        | LogRR | 95% CI               |
|-----------------------------|-------|----------------------|
| Krechler et al. (2011)      | -0.33685401 | -.46860847 to -.20509957 |
| Mitsiades et al. (2011)     | -0.33370164 | -.46567562 to -.20172767 |
| Lopez Fontana et al. (2011) | -0.3409504  | -.47248313 to -.20941767 |
| Spyridopoulos et al. (2012) | -0.33505121 | -.46693206 to -.20317033 |
| Hofmann et al. (2012)       | -0.33265379 | -.46483427 to -.2004733 |
| Gulen et al. (2012)         | -0.33108562 | -.46266881 to -.1995024 |
| Sadik et al. (2012)         | -0.35871589 | -.48782459 to -.2296071 |
| Chen et al. (2012)          | -0.32368076 | -.45458078 to -.1927807 |
| Gulcelik et al. (2012)      | -0.32346013 | -.45471603 to -.19220424 |
| Aleksandrova et al. (2012)  | -0.33816311 | -.47353563 to -.2079059 |
| Friedenreich et al. (2012)  | -0.33428073 | -.46782497 to -.20073651 |
| Touvier et al. (2012)       | -0.3405067  | -.47251758 to -.20849583 |
| Gulcelik et al. (2012)      | -0.31726849 | -.44793424 to -.18660273 |
| Al Awadh et al. (2012)      | -0.34153    | -.47313255 to -.2099274 |
| Grote et al. (2012)         | 0.33630246  | -.46936187 to -.20324306 |
| Chen et al. (2012)          | -0.34161338 | -.47320184 to -.2100249 |
| Khattab et al. (2012)       | -0.38207525 | -.50227177 to -.2618787 |
| Dossus et al. (2013)        | -0.33401754 | -.46652448 to -.20151059 |
| Bao et al. (2013)           | -0.30136451 | -.41626969 to -.18645933 |
| Guo et al. (2013)           | -0.3258861  | -.45724642 to -.1945257 |
| Touvier et al. (2013)       | -0.3433828  | -.46610662 to -.2025699 |
| Liao et al. (2013)          | -0.33713764 | -.46957946 to -.20469585 |
| Liao et al. (2013)          | -0.3403554  | -.47350773 to -.20720309 |
| Conroy et al. (2013)        | -0.33808553 | -.47072488 to -.2054462 |
| Touvier et al. (2013)       | -0.3296572  | -.46145904 to -.19785538 |
| Kerendi et al. (2013)       | -0.3439351  | -.4753255 to -.21254471 |
| Danese et al. (2013)        | -0.34142008 | -.47294763 to -.20989256 |
| Song et al. (2013)          | -0.33765575 | -.47181916 to -.20349233 |
| Luhn et al. (2013)          | -0.33139816 | -.46341154 to -.19938481 |
| Ma et al. (2013)            | -0.32076678 | -.45034227 to -.1911912 |
| Dallal et al. (2013)        | -0.33651593 | -.4683443 to -.20468754 |
| Alokail et al. (2013)       | -0.30377382 | -.43343174 to -.17411587 |
| Ollberding et al. (2013)    | -0.33671638 | -.47059336 to -.20283943 |
melanoma (1 study), thyroid cancer (1 study), and tongue cancer (1 study). Circulating samples included serum (65 studies) and plasma (37 studies), while 5 studies did not mention the exact one. Most researches provided the mean concentrations of circulating adiponectin levels and the SDs of them. SDs from 11 studies were calculated based on the sample size and P values. 96 studies had NOS scores greater than 6 along with 11 studies had scores of 5. The main characteristics of eligible articles were listed in Table 1.

| Study ID          | SMD (95% CI)            | % Weight |
|-------------------|-------------------------|----------|
| Gross et al. (2013) | -0.33571425, -0.46818775 to -0.20324075 |
| Aref et al. (2013)  | -0.31502652, -0.4457356 to -0.18431742  |
| Tewari et al. (2013) | -0.28841972, -0.41580069 to -0.16103874  |
| Erdogan et al. (2013) | -0.33102214, -0.46268752 to -0.19935676  |
| Mihu et al. (2013)  | -0.3298324, -0.46139839 to -0.1982664    |
| Chen et al. (2014)  | -0.33950841, -0.47162384 to -0.20739301  |
| Ohbuchi et al. (2014) | -0.32285877, -0.46454135 to -0.20117618  |
| Minatoya et al. (2014) | -0.32982665, -0.46143582 to -0.19821748  |
| Diakowska et al. (2014) | -0.33376125, -0.46553349 to -0.20198898  |
| Combined          | -0.33375105, -0.46467104 to -0.20283107  |

Figure 3: Forest plot of studies in circulating high molecular weight adiponectin and cancer risk. The combined SMD and 95% CIs were calculated through a random-effect model.
Circulating adiponectin levels and carcinogenesis

Data from 107 studies were analyzed in a random-effect model to compare circulating adiponectin levels in people with different cancers and controls. Results showed that circulating adiponectin levels in cancer cases were significantly lower than in the controls with a pooled SMD of -0.334 μg/ml (95% CI, -0.465 to -0.203, \( P = 0.000 \)). Statistically significant amount of heterogeneity was observed across these studies (\( I^2 = 97.6\% \), \( P < 0.0001 \)), so subgroup analysis was carried out next. These results were presented in Figure 2.

HMW-adiponectin is the dominant form of adiponectin in plasma and correlates with cardiovascular disease, insulin resistance, and obesity [7, 113, 114]. But few studies have evaluated the relationship between circulating HMW-adiponectin levels and cancer risk. We analyzed data from 8 studies in a random-effect model to compare circulating HMW-adiponectin levels in people with different cancers [33, 56, 58, 72, 83, 94, 107, 108]. Results showed that circulating HMW-adiponectin levels in cancer cases were significantly lower than in the controls with a pooled SMD of -0.502 μg/ml (95% CI, -0.957 to -0.047, \( P = 0.000 \)), which is consistent with the results derived from total adiponectin levels. Statistically significant amount of heterogeneity was observed across these studies (\( I^2 = 97.0\% \), \( P < 0.0001 \)). These results were presented in Figure 3.

Subgroup analysis and meta-regression

Stratified subgroup analysis was performed to evaluate the potential sources of heterogeneity including ethnicity, cancer type, study design, blood sample, assay method, study size, study quality and mean age of cancer patients (Table 2). Lower levels of circulating adiponectin were observed in both Asian (SMD -0.555, 95% CI, -0.812 to -0.298) and Caucasian people (SMD -0.269, 95% CI, -0.400 to -0.138). Similar results were also presented in people with breast (SMD -0.334, 95% CI, -0.543 to -0.126), colorectal (SMD -0.496, 95% CI, -0.653 to -0.339), endometrial (SMD -0.594, 95% CI, -0.825 to -0.363), prostate (SMD -0.892, 95% CI, -1.345 to -0.438), thyroid (SMD -0.358, 95% CI, -0.601 to -0.116), tongue (SMD -1.172, 95% CI, -1.580 to -0.764), gastroesophageal (SMD -0.278, 95% CI, -0.553 to -0.004) cancer, multiple

Figure 4: Funnel plot of lower adiponectin expression and cancer risk. Circles indicate included studies.
myeloma (SMD -0.621, 95% CI, -0.966 to -0.276), and acute leukemia (SMD -0.594, 95% CI, -0.825 to -0.363). Notably, circulating adiponectin levels were higher in the patients with hepatocellular cancer than in controls among 7 studies included (SMD 1.385, 95% CI, 0.240 to 2.530).

Additionally, adiponectin was significantly lower in patients who used serum as test samples (SMD -0.335, 95% CI, -0.483 to -0.186), and in 37 studies who used plasma as testing samples, 26 studies showed the inverse relation of adiponectin to cancer risk. Assay method (radioimmunoassay or enzyme-linked immunosorbent assay) did not affect the results that circulating adiponectin was lower in cancer patients with pooled SMD of -0.316 and -0.266. Study size (more or less than 100 patients) did not change the result of estimated SMD either (SMD -0.135, 95% CI, -0.299 to -0.030; SMD -0.549, 95% CI, -0.825 to -0.273, respectively). Besides, no matter the mean age of cancer patients is older or younger than 60 years, decreased adiponectin levels were still exist in cancer patients (SMD -0.489, 95% CI, -0.689 to -0.288; SMD -0.194, 95% CI, -0.383 to -0.004, respectively).

Next we performed meta-regression to evaluate the effect of the above factors on the estimate of SMD. In meta-regression, none of the examined factors, such as ethnicity, cancer type, study design, blood sample, assay method, study size, study quality and mean age of cancer patients was proved to be significant contributing factors.

Sensitivity analysis

Sensitivity analysis was performed by excluding one study at a time and calculating the pooled SMDs for the remaining studies. It was found that the combined SMDs were similar to one another and statistically significant. None of the studies influence the pooled results substantially in this analysis (Table 3).

Publication bias

Publication bias was assessed by funnel plot and Egger’s regression test. Funnel plot shapes demonstrated a marginally asymmetrical distribution (Figure 4), accordingly we performed further analysis with Egger’s test. The tested result (Figure 5) showed no evidence of publication bias ($P = 0.123$).

DISCUSSION

By integrating 107 studies, our meta-analysis revealed that lower circulating adiponectin levels were associated with higher risk of cancers. Despite the existence of heterogeneity, the disparity of adiponectin levels between malignant individuals and controls reveals the potential ability of adiponectin to serve as a biomarker for early detection of cancers.

Aberrant adiponectin secretion is associated with tumor progression, metastasis and overall prognosis. Two previous meta-analysis indicated that lower adiponectin levels were associated with higher risk of breast cancer, colorectal cancer and colorectal adenoma [115, 116]. By synthesizing 107 studies involving 19,319 cases with different malignancies, the present meta-analysis estimate the inverse association between circulating adiponectin levels and cancer risk. Moreover, through subgroup analysis, we identified that this inverse relation of adiponectin to cancer risk might be more meaningful in
breast, colon, endometrial, prostate, and gastroesophageal cancers. Besides, adiponectin levels tend to decrease as tumor stage increases in gastric cancer [62]. Kang et al. also indicate that breast cancer patients with less than the median adiponectin levels are easy to develop lymph node metastasis [82]. Low adiponectin level is the independent predictor of unfavorable prognosis in colorectal cancer [117]. These findings demonstrate that adiponectin is not only associated with cancer risk, but also correlated with tumor progression. Additionally, in our included 107 studies, 8 studies evaluated the relationship between circulating levels of adiponectin subtypes and cancer risk. The changing trend of total adiponectin was almost same with the three adiponectin subtypes in cancer patients, especially with HMW-adiponectin, that it is inversely associated with cancer risk.

Circulating adiponectin levels are affected by various factors, including inflammatory, dietary, hormonal, genetic, and medicine. One of possible explanations for decreased adiponectin levels in malignancies is the sustained inflammatory status of cancer patients leads to the increased proinflammatory cytokines such as TNF-α and IL-6, which are all reported to suppress adiponectin transcription and translation in adipocyte cell line [118, 119]. Besides, in obesity-related cancers, adiponectin may control its own production through a negative feedback loop during the development of obesity [120]. Moreover, dietary with lower intake of fiber and magnesium can also reduce circulating adiponectin levels [121].

However, elevated adiponectin levels are also reported in hepatocellular carcinoma. Since adiponectin is mainly degraded in the liver and adiponectin levels are elevated in advanced disease including cirrhosis and virus-related cancer [61, 122]. One possible explanation for increased adiponectin level in hepatocellular carcinoma might be due to deteriorated hepatic metabolism resulted from repeated necroinflammation and regeneration. Besides, conflicting results also exist in clinical studies of pancreatic cancer that both higher and lower adiponectin levels are reported to be associated with cancer risk [45, 50]. After reviewing the pancreatic cancer studies with higher levels of adiponectin, we found that almost half of them were accompanied with jaundice [45]. Since cholestasis would lead to the chronic liver deterioration, it is possible that increased adiponectin levels might be due to the reduced degradation.

The peripheral functions of adiponectin are mainly mediated through AdipoR1 and AdipoR2. The expression levels of AdipoRs vary between malignant tissues and their peritumoral normal counterparts. The upregulation of AdipoR1 and AdipoR2 are reported in gastric carcinoma [123], whereas decreased in prostate cancer tissues compared with the nonmalignant tissues [36]. Increased expression of AdipoRs may be the response of reduced circulating as well as local adiponectin levels and reduced expression suggests that the sensitivity of AdipoRs to adiponectin is decreased in tumor tissues. Yabushita et al. indicate that poor expression of AdipoR1 is associated with tumor invasion and lymph node metastasis, as well as poor prognosis in endometrial cancer patients [124]. A study of non-small cell lung cancer also indicates that patients with higher expression of AdipoR1 have longer overall survival and AdipoR2 expression is inversely correlated with tumor size [125]. Those findings further illustrate the protective role of adiponectin as well as AdipoRs and shed light on exploiting them for cancer therapy. Recently, AdipoRs agonist called 355ADP is identified and might represent a new strategy to replace low adiponectin level in cancer [126].

Despite the inverse correlation between adiponectin and various cancers, the underlying mechanisms of adiponectin in potential cancer suppression are still need to elucidate. Adiponectin decreases low density lipoprotein (LDL) receptor expression in breast cancer cells through promoting autophagic flux and inhibits LDL-cholesterol-induced tumor cell proliferation [127]. Adiponectin induces the phosphorylation of p53, a tumor suppressor, which renders cell cycle arrest and apoptosis in cancer cell lines [128]. Adiponectin also inhibits leptin-induced metastasis by downregulating JAK/STAT3 pathway, displaying an inverse correlation with cancer development [129]. In contrast, adiponectin promotes the angiogenesis in human chondrosarcoma by increasing vascular endothelial growth factor-A expression [130]. It is also reported to exert anti-apoptotic effects on pancreatic cancer cells through activation of AMPK/Sirtuin-1 signaling pathway [131]. Taken together, adiponectin might play a complicated role in carcinogenesis and progression of cancers.

Our study has some limitations that need to be addressed when interpreting the results. The significant heterogeneity was observed among the studies thus the conclusion should be more conservative. Although stratified analysis was conducted, none of the factors including ethnicity, cancer type, study design, blood sample, assay method, study size, study quality, and mean age of cancer patients were confirmed to contributing factors. Some possible reasons may partially explain this heterogeneity. Adiponectin levels are changed along with the tumor development. The tumor type, size, histological grade, and lymph node metastasis are the possible contributors caused heterogeneity. It is difficult for us to acquire the detailed information from the included studies. Besides, the subjects were from different regions and the lifestyle combined with diet was varied, which might influence the level of adiponectin. Since adiponectin is mainly secreted from adipose tissue, variables such as age, hormone receptor expression, menopausal status and BMI could contribute to the secretion and those factors were not fully deliberated for the complexity of tumor environment.
CONCLUSIONS

In summary, the present study shows significant difference in circulating adiponectin levels between patients with malignancies and controls. Low circulating adiponectin level is associated with increased cancer risk, which suggests that adiponectin may serve as a potential biomarker for early detection of cancers considering its abundance in blood. Thorough understanding the roles of adiponectin and its receptors in the progression of cancers is helpful to cancer screening and promote individualized treatment.

MATERIALS AND METHODS

Search strategy

Based on the standard guidelines, a systematic search of English literature from Cochrane library, Wiley online library, PubMed was conducted to retrieve eligible studies until August 8, 2015. Searching terms included Medical Subject Heading (Mesh) and free text words “adiponectin”, “ADPN”, “Acrp 30”, “AdipoQ”, “GBP 28” or “apM1” in combination with “neoplasm”, “cancer”, “carcinoma”, “malignancy” or “tumor”. Furthermore, we manually searched references of relevant studies to add potential research to this meta-analysis.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (i) full text case-control studies published in peer-reviewed journals evaluating the relationship between circulating adiponectin concentration and carcinogenesis; (ii) all cases were diagnosed as cancer by pathological biopsy or other medical methods with blood sample obtained before any therapies and all the controls were people without any cancers. (iii) circulating adiponectin level and standard deviation (SD) of it were provided or there were enough information to estimate them. Reviews, letters or animal experiments were excluded and articles without key information to carry on further analysis were also beyond consideration. Meanwhile, if replicated patient cohort was published in different studies, only the most recent or complete one was chosen. Since all the studies included were acquired from literature, ethics committee approval was not needed.

Data extraction

Based on the checklist of MOOSE (Meta-analysis Of Observational Studies in Epidemiology) [132], two reviewers (Tai W and Peng Y) extracted the following data independently from eligible studies: the last name of first author, year of publication, geographic region, ethnicity, tumor type, study design, sample type, adiponectin assay method, number of patients and controls, assay source, mean ± SD of adiponectin concentration. Disagreement was resolved by discussion until the two reviewers reached a consensus.

Quality assessment of included studies

Two reviewers (Tai W and Peng Y) independently assessed the quality of each included study according to the Newcastle-Ottawa Quality Assessment Scale (NOS) [133] ranges from 0 to 9 stars. Studies with more than 6 stars were considered as high-quality studies. Any disagreement was resolved by discussion and reevaluation.

Statistical analysis

We acquired the mean ± SD of circulating adiponectin levels from cases and controls through three ways. The most accurate method was extracted them from the original research directly. However, a few studies presented the results as median values or standard error. In that case, we regarded median value as mean value considering the large sample size and calculated the SD value by using standard error and population number. If necessary, we contacted the author for detailed information. Standard mean differences (SMDs) and the corresponding 95% confidence intervals (CIs) of circulating adiponectin were calculated for all the eligible studies. Cochran’s Q-test was performed to test the heterogeneity of included studies and $P < 0.05$ was considered statistically significant. Higgins I-squared statistic was applied to offer evidence of heterogeneity with $I^2 > 50\%$ suggesting significant heterogeneity. The pooled SMD and 95\% CI was calculated using a fixed-effects model if the heterogeneity was not significant, otherwise a random-effect model was employed and subgroup analyses and meta-regression were adopted to detect the potential cause of heterogeneity.

Sensitivity analysis was executed to detect the robustness of the results. Publication bias was evaluated by use of funnel plot and Egger’s linear regression test. The Stata 13.0 software (Stata Corporation, College Station, TX, USA) was used to perform all the statistical analysis. All $P$ values were two-sided.

CONFLICTS OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial conflict with any materials discussed in the paper. All authors declare that there is no conflict of interest regarding the publication of this work.
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