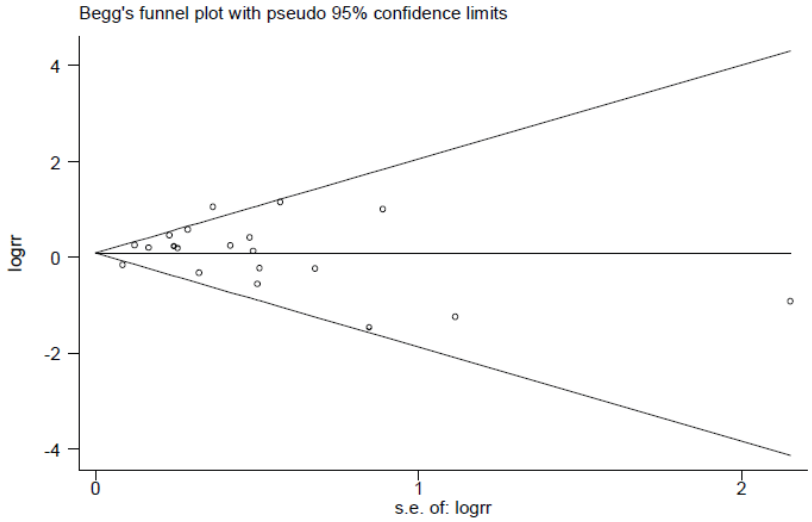
APPENDIX B – Funnel Plots for studies related to different Cancer sites included in the meta-analysis (assessment of publication bias)

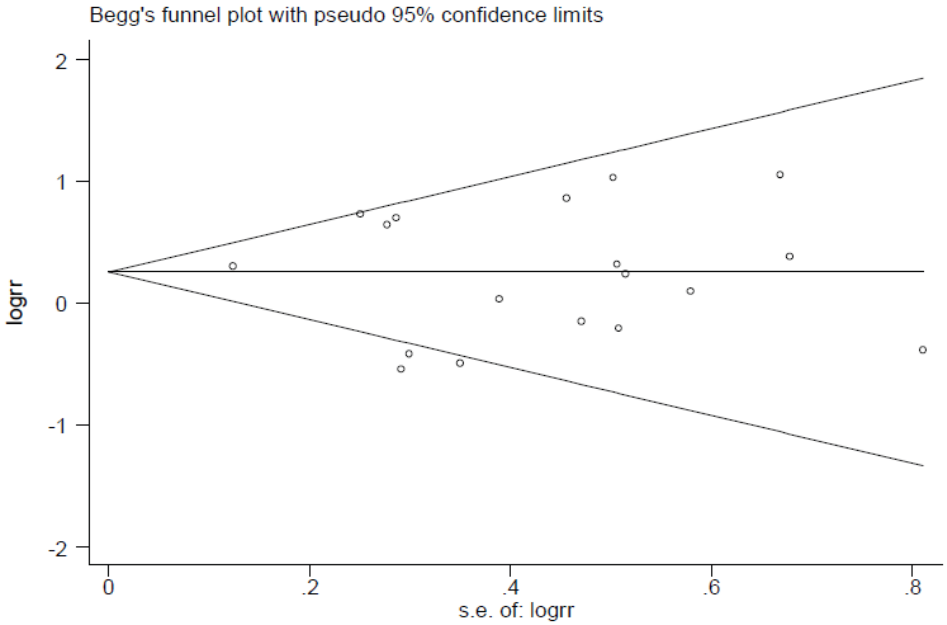
Studies of Bladder Cancer



[Begg's funnel plot of log relative risks according to their standard errors.]

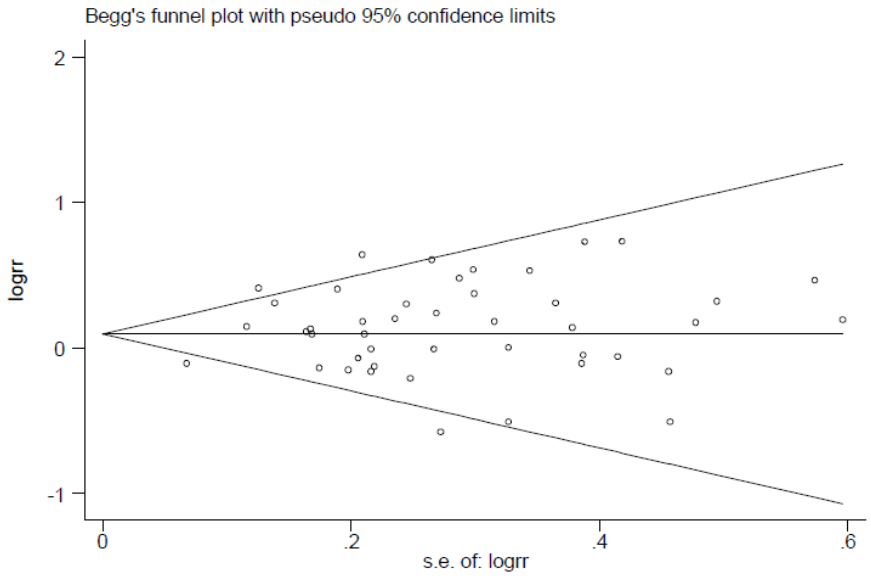
The funnel plot for the visual assessment of publication bias is shown above. This plot shows slightly more data points from small studies below the horizontal line. The horizontal line indicates the summary risk estimate of log RR, while the slopping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. The funnel plot appears slightly asymmetric but there was no evidence of bias using Egger method (p for bias = 0.47) or Begg's test (p = 0.27). The gradual inclusion of studies with lower precision did not increase the effect size of the estimate, thereby supporting that there is no evidence of a small study effect.

Brain and Central Nervous System Cancer



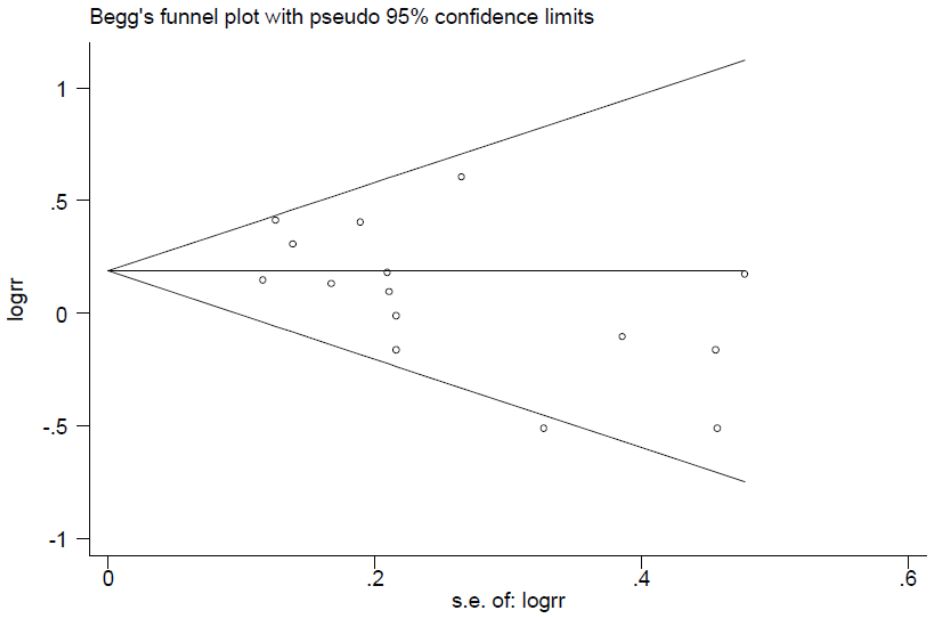
The funnel plot for the visual assessment of publication bias is shown above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. Because this visual inspection is subjective, a funnel plot should be seen as a generic means of examining small study effects rather than being a diagnostic tool for specific bias. The funnel plot did not appear asymmetric, indicating that there was no evidence of publication bias in favor of small studies with positive findings. The p-value of Begg's and Egger test were $p = 0.62$ and $p = 0.76$, respectively, suggesting a low probability of publication bias. We additionally evaluated whether the gradual inclusion of studies with lower precision increases the summary risk estimate, but there was no evidence of a small-study effect.

Colorectal Cancer



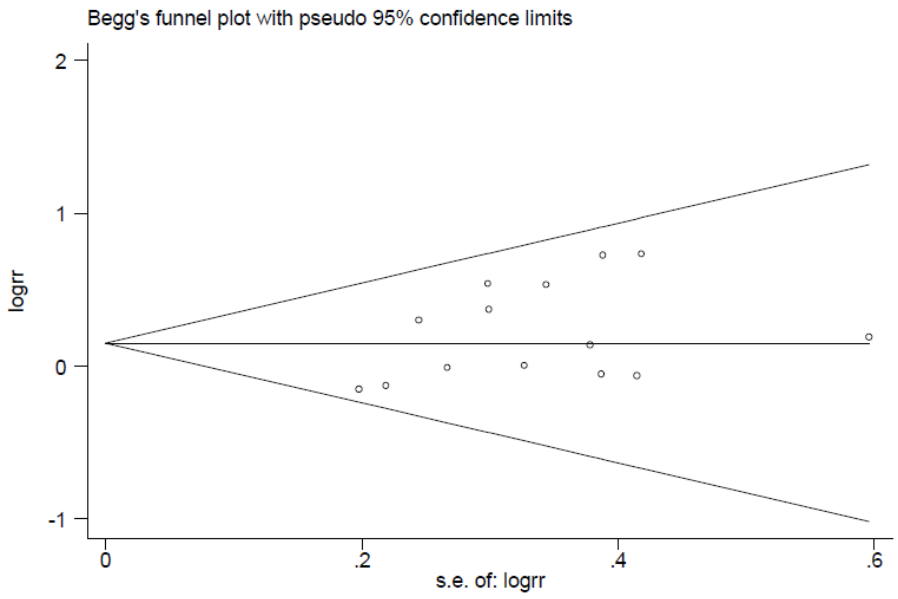
The funnel plot for the visual assessment of publication bias is given above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. No indication of publication bias was found, as investigated by visual inspection of the funnel plots and non-significant Begg's ($p = 0.91$) and Egger ($p = 0.18$) tests.

Colon Cancer



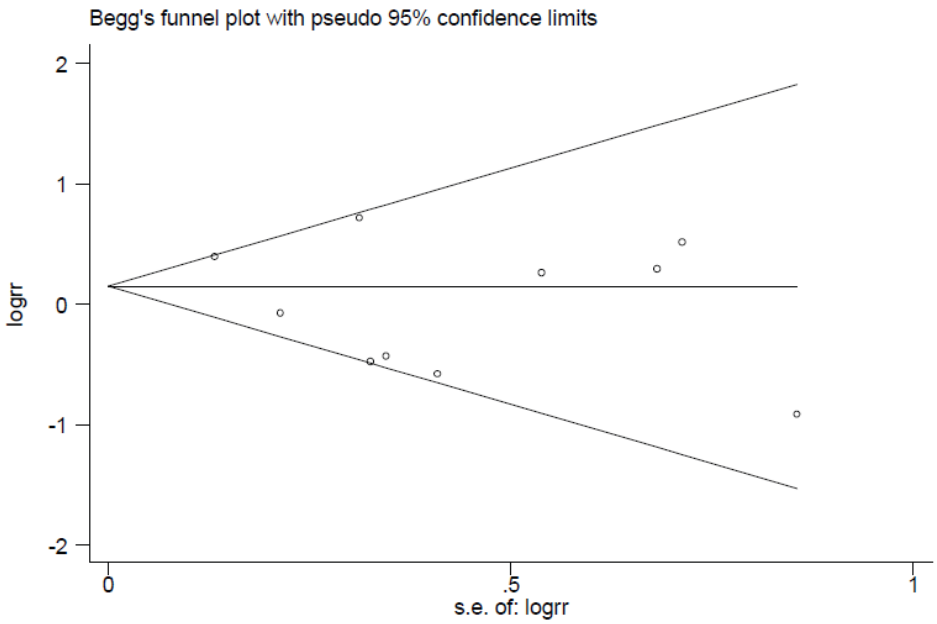
Publication bias (the association of publication probability with the statistical significance of study results) or the possibility that unpublished data would contradict the results of published studies is always a potential source of bias in meta-analyses. We checked the extent of publication bias using Begg's funnel plots and Egger tests. The funnel plot for the visual assessment of publication bias is shown above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. Because this visual inspection is subjective, funnel plots should be seen as a generic means of examining small study effect rather than a diagnostic tool for specific bias. The funnel plot showed little asymmetrical distribution, namely slightly more data points from small studies below the horizontal line. Begg's test failed to detect ($p = 0.08$) but Egger's test showed marginally significant publication bias ($p = 0.05$). There is a possibility that this asymmetry could be due to publication bias, or heterogeneity between studies. However, the gradual inclusion of studies with lower precision did not increase the summary risk estimate, suggesting that the likelihood of important selection or publication bias in our results is small.

Rectal Cancer



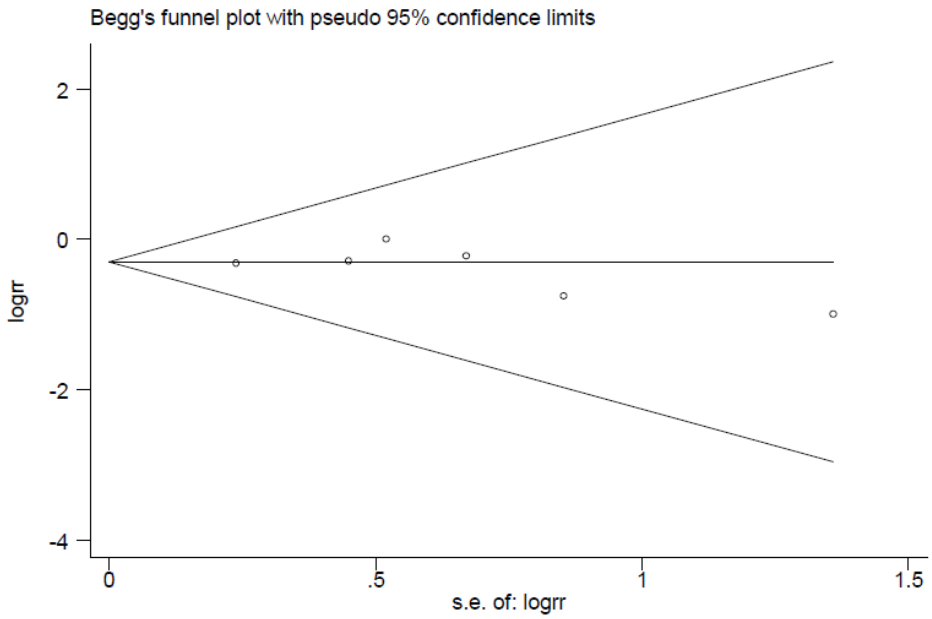
The funnel plot for the visual assessment of publication bias is given above. The horizontal line indicates the summary risk estimate of log RR while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. The funnel plot is slightly asymmetric, suggesting a low to moderate probability of publication bias. The p-value of Begg's and Egger tests were p = 0.10 and p = 0.07, respectively, indicating a possible minor publication bias. Evaluation of cumulative random-effects revealed that the gradual inclusion of studies with lower precision increased the summary risk estimate from 0.86 to 1.16. Considering all of the above, there may be a likelihood of a small-study effect in the results of rectal cancer mortality risk.

Esophageal Cancer



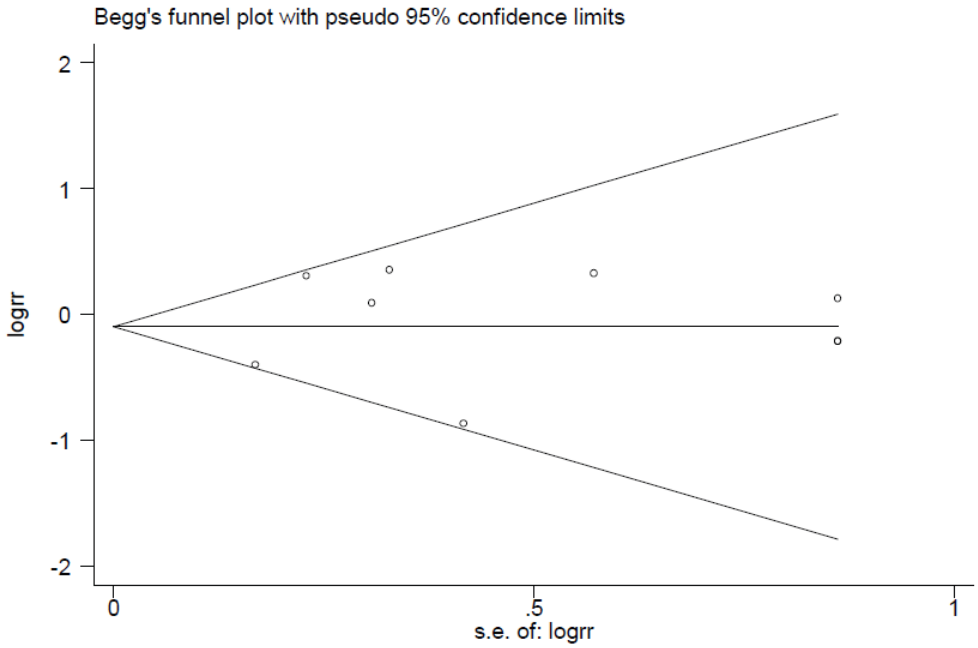
The funnel plot for the visual assessment of publication bias is shown above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. There was no indication of publication bias ($p = 0.72$ for the Begg test; $p = 0.23$ for the Egger test), although the funnel plot appeared slightly asymmetric. Also, there was no outlier study detected in the Galbraith plot. We additionally evaluated whether the gradual inclusion of studies with lower precision increases the summary risk estimate, but there was no evidence of a small-study effect.

Laryngeal Cancer



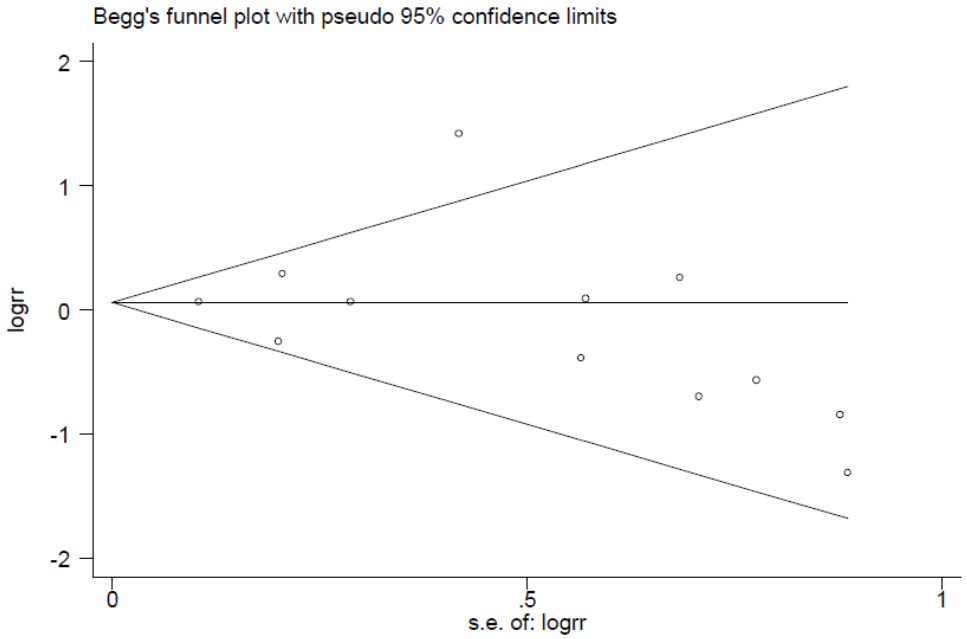
The funnel plot for the visual assessment of publication bias is given above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. The number of studies for laryngeal cancer was too few to detect publication bias using symmetry of funnel plots. At the same time, there was no indication of publication bias in favor of small studies with positive findings ($p = 0.70$ for the Begg's test; $p = 0.47$ for the Egger test).

Oral and Pharyngeal Cancer



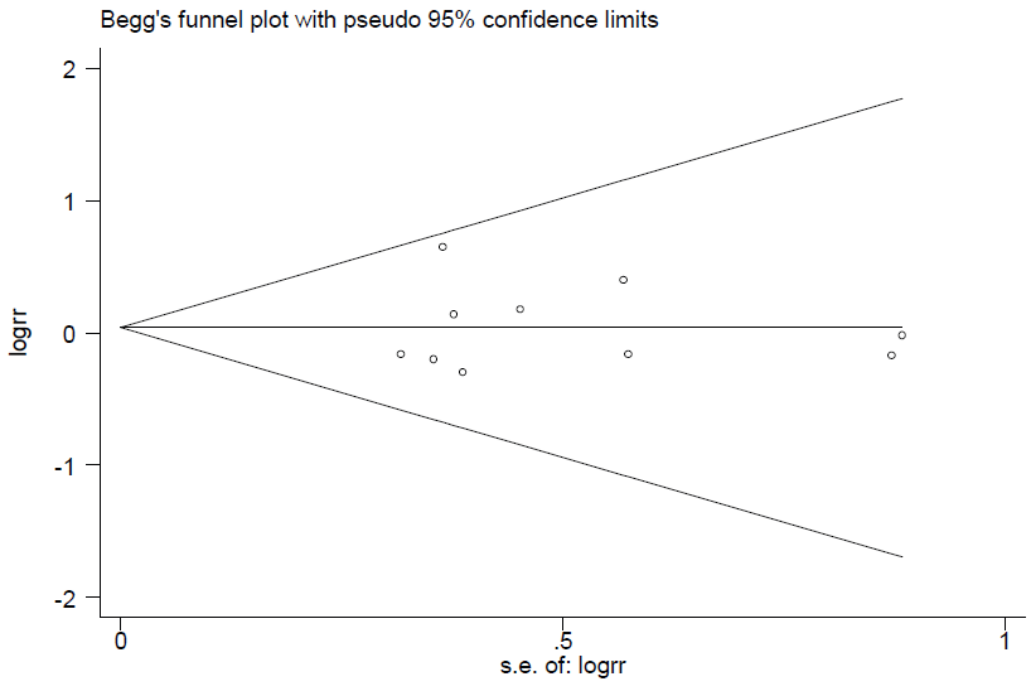
The funnel plot showed skewing distribution with more data points from small studies above the horizontal line. An asymmetric funnel plot may indicate a possible publication bias. However, the p-values of Begg's and Egger's test were p = 0.53 and p = 0.68, respectively, suggesting a low probability of publication bias. In reality, it is hard to conclude that there is some publication bias because these tests are of little use if the number of studies is small or with little variance in study size.

Kidney Cancer



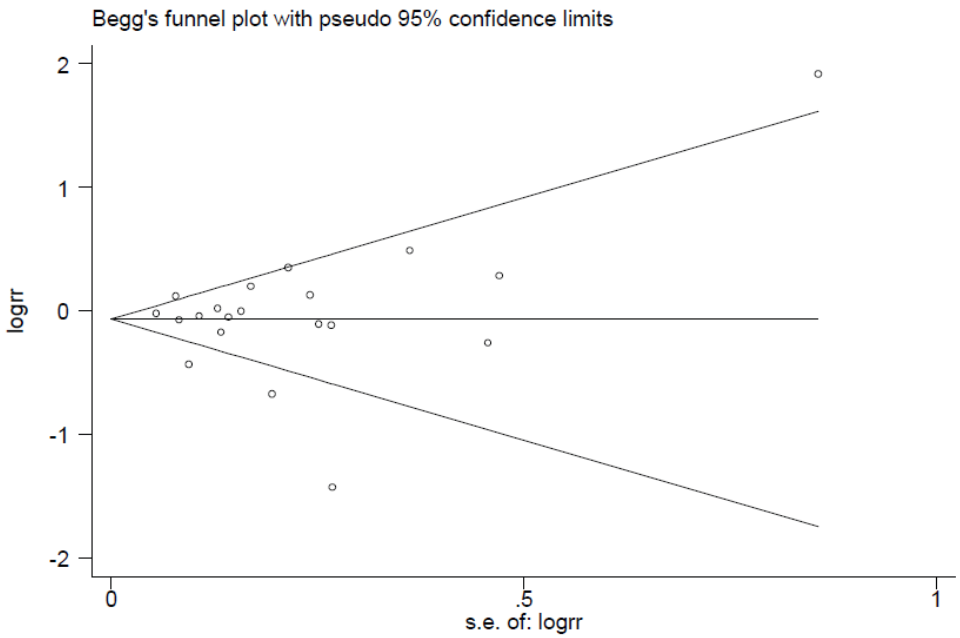
The funnel plot for the visual assessment of publication bias is shown above. This plot showed skewed distribution with more data points from small studies below the horizontal line. However, the p-value of Begg's and Egger's tests were p = 0.15 and p = 0.53, respectively, suggesting a low probability of publication bias. In addition, we evaluated whether the gradual inclusion of studies with lower precision increases the summary risk estimate, but there was no evidence of a small-study effect.

Liver and Gallbladder Cancer



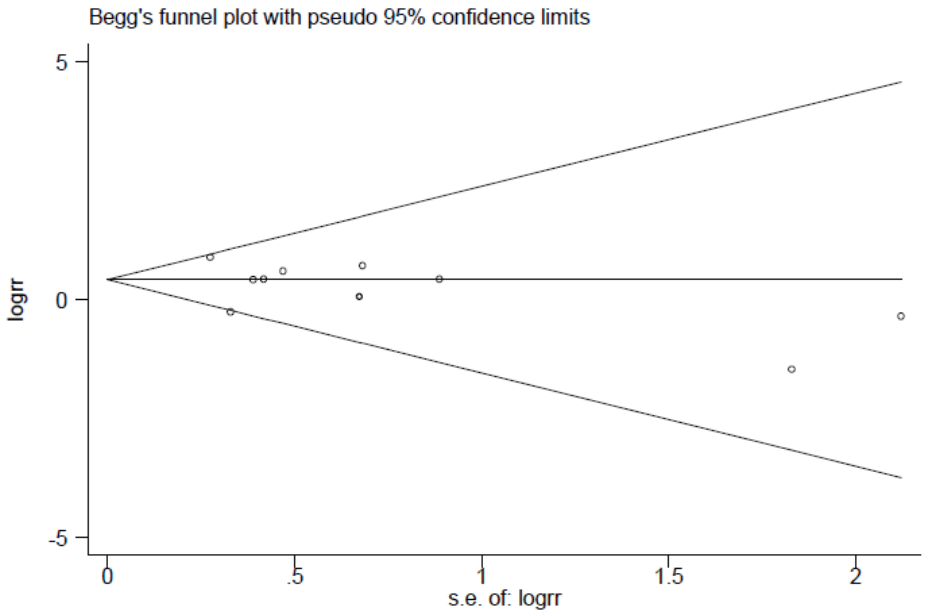
The funnel plot for the visual assessment of publication bias is shown above. The horizontal line indicates the summary risk estimate of log RR while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. This plot showed slightly skewed distribution with more data points from small studies below the horizontal line. The p-value of Begg's and Egger's tests were $p = 0.92$ and $p = 0.09$, respectively, suggesting a low probability of publication bias. However, there were not enough studies to detect publication bias. We additionally evaluated whether the gradual inclusion of studies with lower precision increased the summary risk estimate, but there was no evidence of a small-study effect.

Lung Cancer



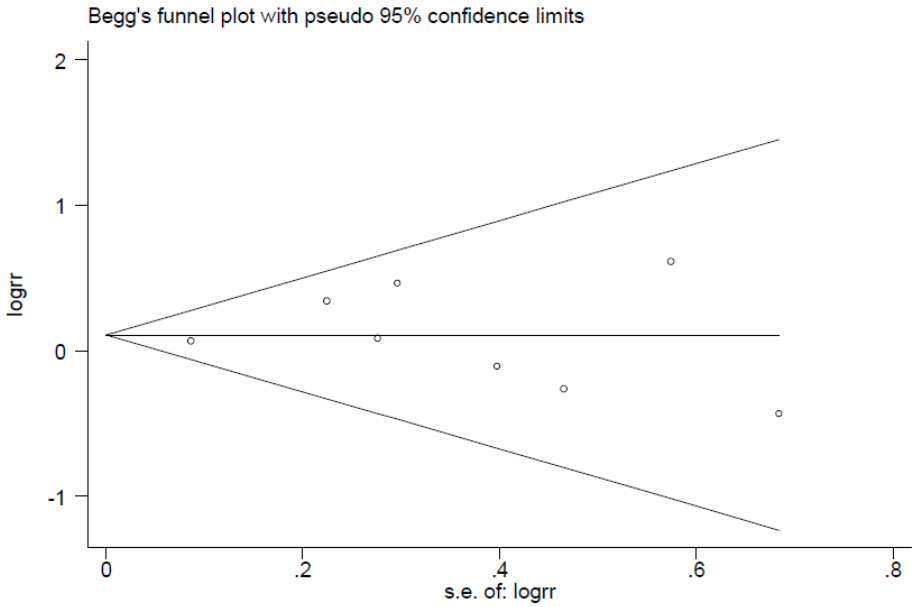
The funnel plot showed an asymmetric distribution, indicating that there was a likelihood of publication bias in favor of small studies with positive findings. However, neither of Begg's nor Egger's test detected significant evidence ($p = 0.99$ and $p = 0.95$, respectively). Additional investigation for the effect of less precise studies found that lower precision increased the summary risk estimate. Taken all together, there was moderate probability of publication bias or small-study effect.

Hodgkin's Lymphoma



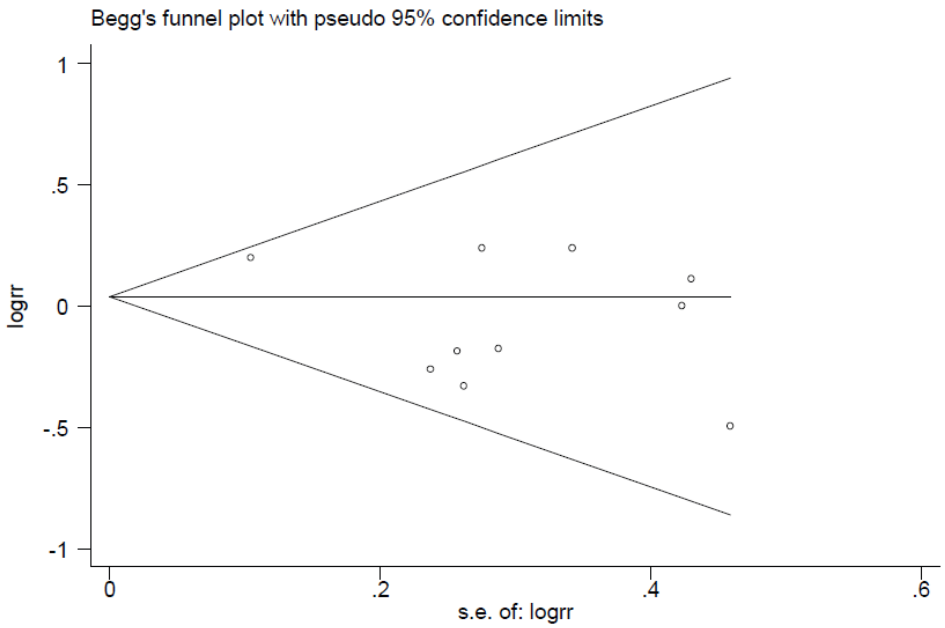
The number of incidence and mortality studies of good or adequate quality was not enough to determine publication bias. All studies on Hodgkin's lymphoma, regardless of study quality, did not show any evidence of publication bias. The p-values of Begg's and Egger's test were $p = 0.47$ and $p = 0.36$, respectively, suggesting a low probability of publication bias. Begg's funnel plot for mortality studies showed an asymmetrical distribution with more data points below the horizontal line from small studies. However, we still need to be cautious in the interpretation because these tests are of little use if the number of studies is small or with little variance in study size.

Non-Hodgkin's Lymphoma



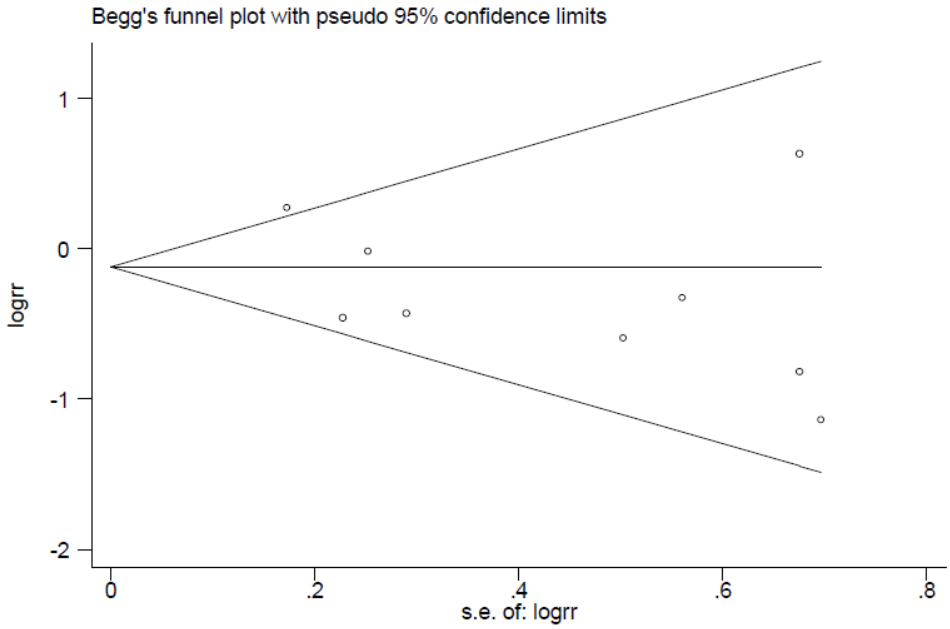
The funnel plot for the visual assessment of publication bias is given above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. The plot seems to be slightly asymmetric, although there was not enough number of studies to detect meaningful publication bias. The Egger's test provided no evidence for publication bias for the analysis of the risk of leukemia ($p = 0.93$) and neither did Begg's test ($p = 0.10$), both indicating that there was no evidence of publication bias in favor of small studies with positive findings. We additionally evaluated whether the gradual inclusion of studies with lower precision increases the summary risk estimate, but there was no evidence of a small-study effect.

Leukemia



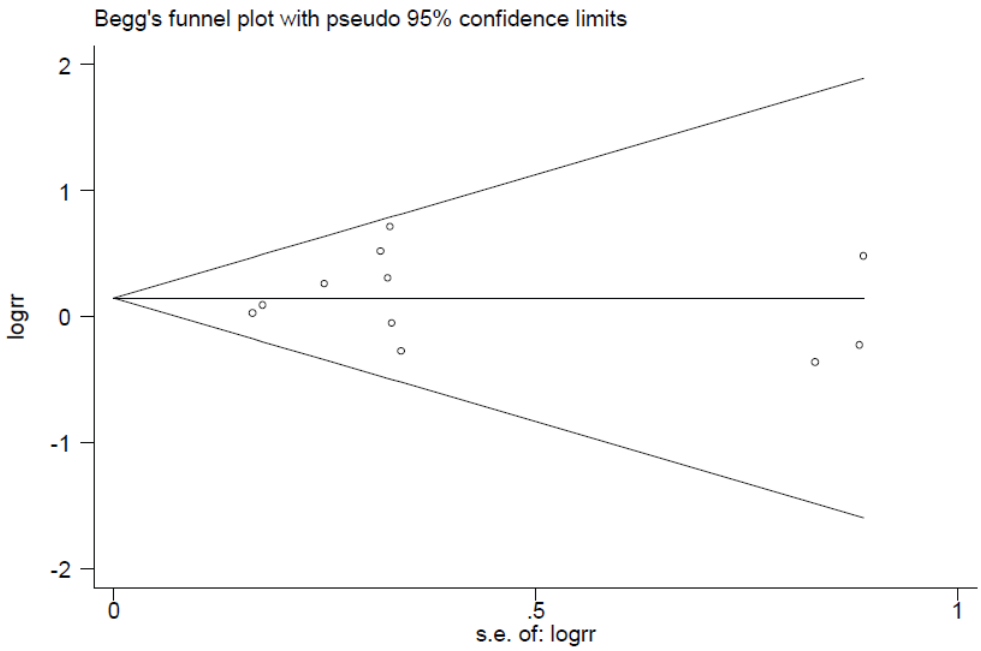
The funnel plot for the visual assessment of publication bias is given above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. This plot seems to be slightly asymmetric, although there were too few studies to detect meaningful publication bias. The Egger's test provided no evidence for publication bias for the analysis of the risk of leukemia ($p = 0.93$); neither did Begg's test ($p = 0.10$), both indicating that there was no evidence of publication bias in favor of small studies with positive findings. We additionally evaluated whether the gradual inclusion of studies with lower precision increases the summary risk estimate, but there was no evidence of a small-study effect.

Lymphatic and Hematopoietic Cancer



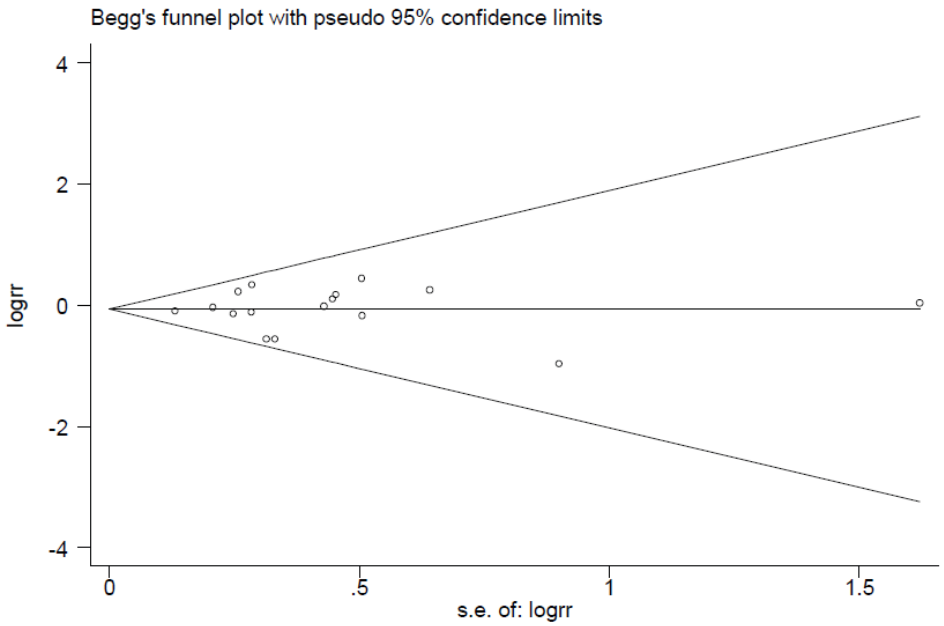
There is only one incidence study, so it was not possible to examine publication bias for incidence studies. The funnel plot for the visual assessment of publication bias among mortality studies is shown below. Begg's funnel plot showed slight skewing of less precise studies to one side of the pooled estimate but it was not significant (p = 0.60). Egger's test did not provide any evidence for publication bias either (p for bias = 0.18).

Multiple Myeloma



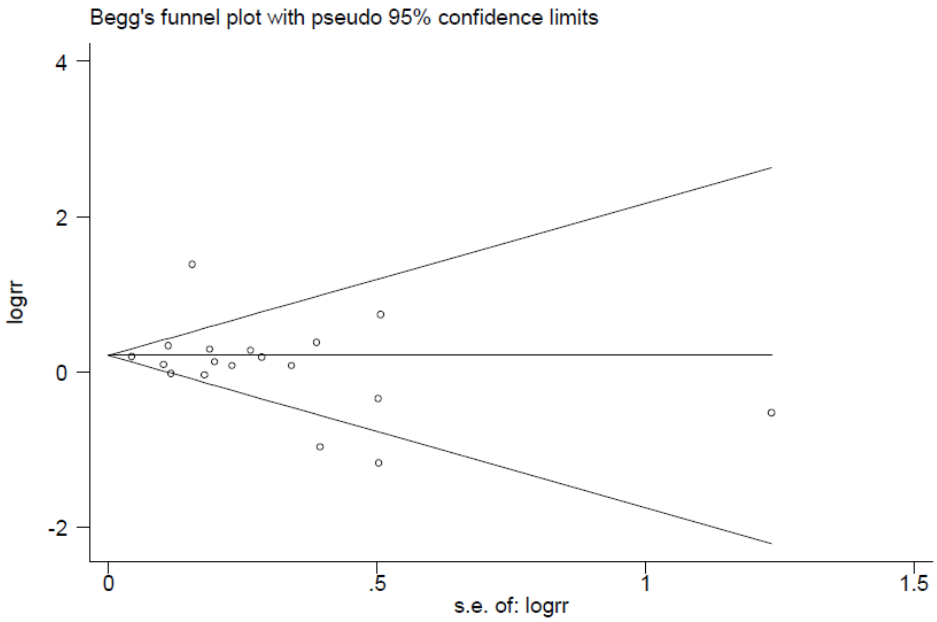
The funnel plot for the visual assessment of publication bias for all studies reporting multiple myeloma risk is given above. The funnel plot did not appear asymmetric, indicating that there was no evidence of publication bias in favor of small studies with positive findings. The p values for Begg's and Egger's tests were $p = 0.92$ and $p = 0.56$, respectively, suggesting a low probability of publication bias.

Pancreatic Cancer



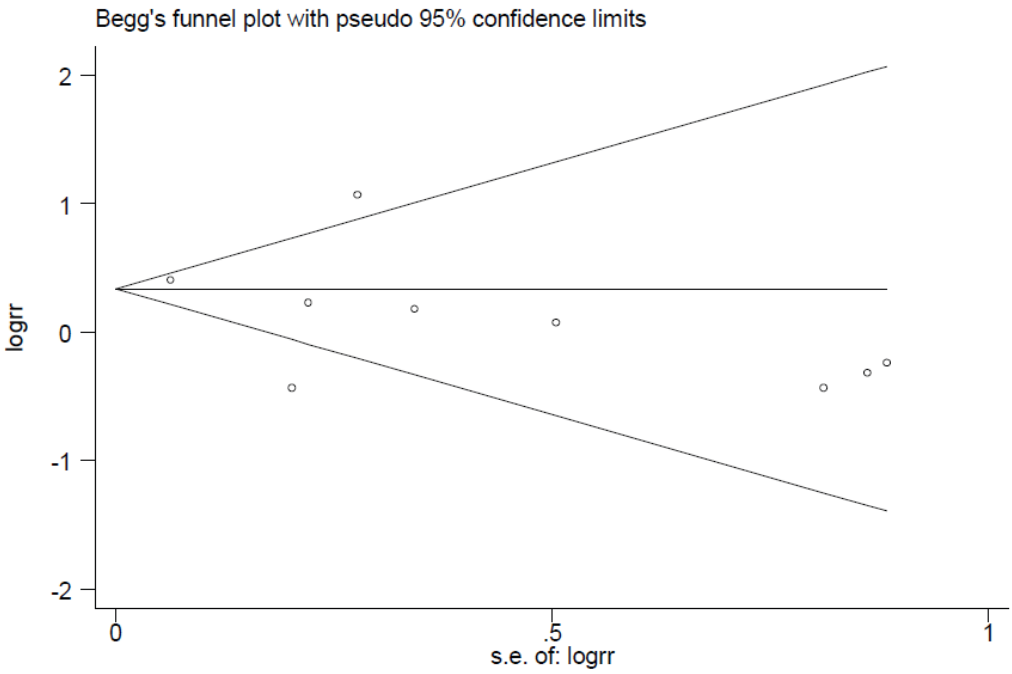
The funnel plot for the visual assessment of publication bias is given above. This plot shows a skewed distribution to one side of the pooled estimate but there was no evidence of publication bias in the Begg's test ($p = 0.78$) or the Egger test ($p = 0.90$). We additionally evaluated whether the gradual inclusion of studies with lower precision increases the summary risk estimate but there was no evidence of a small-study effect. Taken all together, the likelihood of important selection or publication bias in our results for pancreatic cancer risk is small.

Prostate Cancer



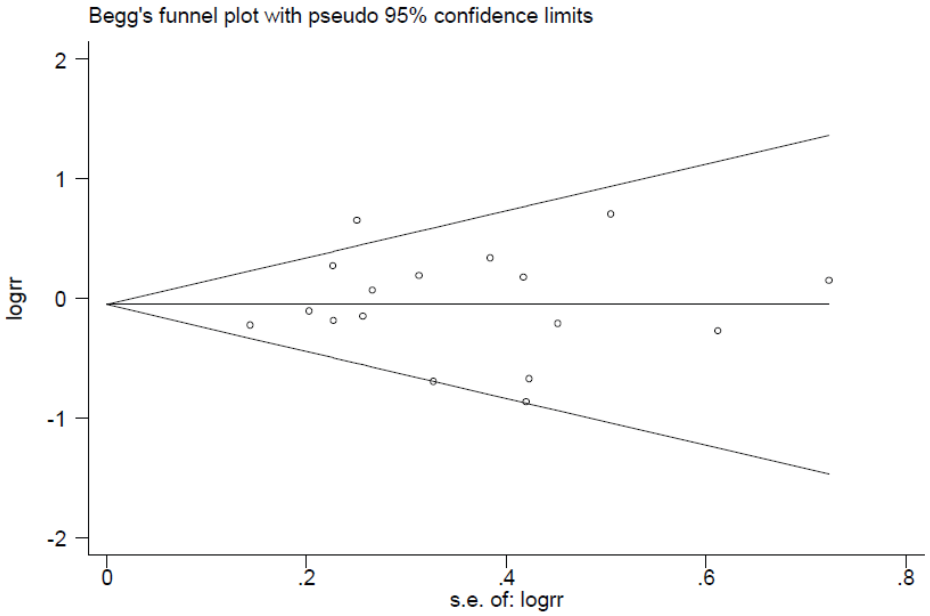
The funnel plot for the visual assessment of publication bias is given above. The horizontal line indicates the summary risk estimate of log RR while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. The funnel plot appeared slightly asymmetric, possibly indicating that there was minor evidence of publication bias in favor of small studies with positive findings. The p-value of Begg's and Egger's tests were $p = 0.62$ and $p = 0.65$, respectively, suggesting a low probability of publication bias. We additionally evaluated whether the gradual inclusion of studies with lower precision increases the summary risk estimate, but there was no evidence of a small-study effect.

Skin Melanoma



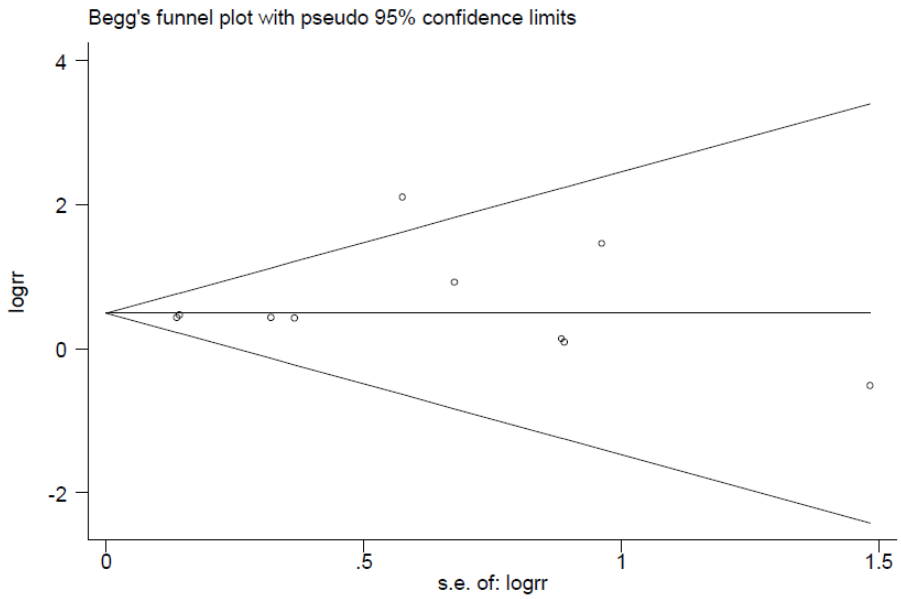
The funnel plot for the visual assessment of publication bias is shown above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. The funnel plot showed a clearly asymmetric distribution with more data points from small studies below the horizontal line. It may indicate evidence of publication bias in favor of small studies with positive findings, however, neither Begg's nor Egger's tests supported the existence of publication bias ($p = 0.29$ and $p = 0.34$, respectively). Given that these tests are of little use if the number of studies is small or with little variance in study size, it is hard to draw a conclusion. Additional investigation of individual study influence on the pooled risk estimate showed that the gradual inclusion of studies with lower precision increases the summary risk estimate, suggesting a small study effect. Taken all together, there is a likelihood of potential selection or publication bias in our result of skin melanoma.

Stomach Cancer



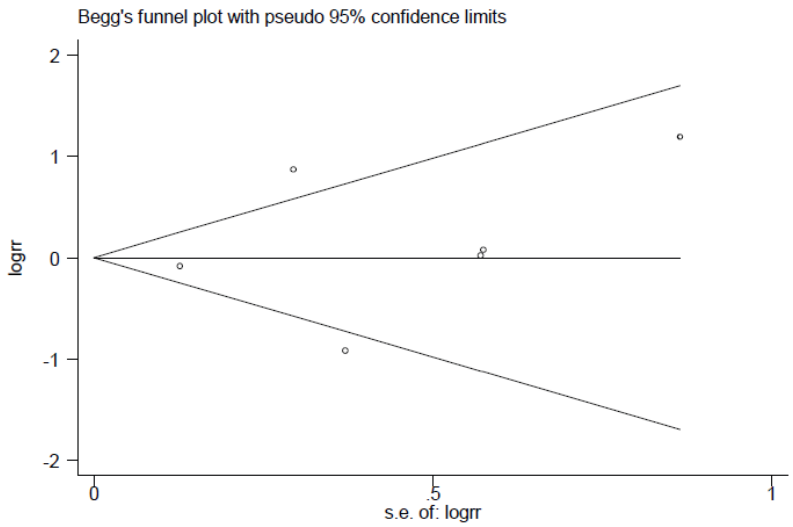
The funnel plot for the visual assessment of publication bias is given above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. The funnel plot did not appear asymmetric, indicating that there was no evidence of publication bias in favor of small studies with positive findings. The p-value of Begg's and Egger's tests were $p = 0.93$ and $p = 0.88$, respectively, suggesting a low probability of publication bias.

Testicular Cancer



The funnel plot for the visual assessment of publication bias is shown above. The horizontal line indicates the summary risk estimate of log RR, while the sloping lines indicate the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. The funnel plot did not appear asymmetric, although there were not enough studies to detect publication bias. Neither the Egger test ($p = 0.92$) nor Begg's test ($p = 0.88$) provided evidence of bias. Bates et al. (1995) was identified as an outlier in the Galbraith plot, as shown by the point outside the expected 95% confidence interval lines.

Urinary Cancer



Incidence studies could not be examined for publication bias because only one study was available. Mortality studies did not show any significant publication bias ($p > 0.66$ for both Begg's and Egger test). Begg's funnel plot for mortality studies showed no evidence of skewing of less precise studies to one side of the pooled estimate. However, there was no sufficient evidence to make a reasonable judgement because these tests are of little use if the number of studies is small or when there is little variability in study size.