# The Associations of Soy Intakes with Non-communicable Diseases: A Scoping Review of Meta-Analyses

Yip, C.S.C., Yip, Y.C, Chan, W.

Cynthia Sau Chun Yip (Correspondence)

Chu Hai College of Higher Education,

Email: ycynthia@connect.hku.hk

# Appendix A1: Excluded studies

Afshin et al. (1): exclusion of studies focused on soy, soy milk, or soybean oil.

Anderson et al. (2): not meta-analysis

Ding et al. (3): not meta-analysis

Dong and Qin (4): included studies of Urinary genistein, Plasma genistein

Fritz et al. (5): no meta-analysis

Goodman et al. (6): no meta-analysis

He and Chen (7): no-meta-analysis

Ishimi et al.(8): included studies of ingesting soy isoflavones

Issac(9): inappropriate methods for statistical combination of results, confusing risk with mortalities, low AMSTAR 2 score 5.5/16

Jian(10): no meta-analysis

Messina(11) not a systematic review

Nagata et al.(12): no meta-analysis

Otun et al.(13): outcome biomarker: thyroid hormone levels

Tang et al.(14): soy milk, and tofu

Trock et al.(15): study estimated soy protein based on urinary Isoflavone levels

Wu and Liu(16): included dietary intake of total isoflavones

Yang et al.(17): Duplicate

You et al.(18): dietary isoflavones

Zhao et al.(19): Isoflavone-rich food

Appendix A2: Selecting the best meta-analysis studies for the significant associations of total soy intakes with non-communicable diseases: high vs. low intakes

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Incidence | Case/cohort (n) | Included study publication years | RR (95% CI) | Heterogeneity,I2 %, p  | Sources | AMSTAR score Max.=16 | Conclusion | Selected best study |
| Cancer  | 8 | 2002-2014 | Nonsignificant |  | Namazi et al.(20) | 14.5 | Negative | Nachvak et al.(21) included 10 studies, missing one study from (20) which included only 4 studies |
|  | 14 |  | 0.90 (0.81,1.00) |  | Nachvak et al.(21) | 14.5 |  |  |
| Stroke | 14 | 2002-2015 | 0.82 (0.68, 0.99) | 78.8, <0.001 | Yan et al.(22) | 12.5 | Negative | Yan et al.(22) included all studies in Lou et al.(23) |
|  | 5 | 2006-2009 | 0.54 (0.34, 0.87) | 79.5, 0.001 | Lou et al.(23) | 13 |  |
|  | 4 | 2005-2014 | Nonsignificant |  | Lou et al.(23) | 13 |  |
| CHD | 16 | 2001-2014 | 0.83 (0.72, 0.95) | 64.6, <0.001 | Yan et al.(22) | 12.5 | Negative | Yan et al.(22) included all studies in Lou et al.(23) |
|  | 5 | 2001-2013 | 0.66 (0.56, 0.77) | 0.0, 0.421 | Lou et al.(23) | 13 |  |
|  | 6 | 2001-2014 | Nonsignificant |  | Lou et al.(23) | 13 |  |
| Cancer |  |  |  |  |  |  |  |  |
| Gastrointestinal | 34 | 1988-2013 | 0.93 (0.87,0.99) | NR, 0.01 | Tse and Eslick (24) | 9.5 | Negative | Tse and Eslick (24) |
|  | 14 | 2005-2015 | 0.86 (0.77, 0.96) | 44.3, 0.038 | Lu et al.(25) | 12.5 |  |  |
| Gastric | 8 | 2005-2015 | 0.85 (0.72, 0.99) | 52, 0.52 | Lu et al.(25) | 12.5 | Negative | Lu et al.(25) |
|  | 7 |  | 0.78 (0.62, 0.98) | 47.5, 0.013 | Weng and Yuan (26) | 9.5 |  |  |
|  | 12 | 1991-2006 | 0.58 (0.52, 0.65) |  | Tong et al.(27) | 8.5 |  |  |
|  | 4 | 2002-2009 | 0.56 (0.49, 0.71) | 0, 0.609 | Woo et al.(28) | 6.5 |  |  |
| Colorectal  | 7 | 2007-2009 | Nonsignificant |  | Lu et al.(25) | 12.5 | Negative | Yu et al.(29) included more up-to-date studies, all studies in (30), missing one study in Lu et al.(25) |
|  | 20 | 1993-2009 | Nonsignificant |  | Yan et al.(30) | 9 |  |
|  | 3† | 2003-2005 | Nonsignificant |  | Woo et al.(28) | 6.5 |  |
|  | 26 | 1993-2015 | 0.79 (0.69–0.89) | 46.2, 0.006 | Yu et al.(29) | 11 |  |  |
| Endocrine-related gynaecological | 7 | 1997-2008 | 0.61 (0.53, 0.72) | 12.1, NR | Myung et al.(31) |  | Negative |  |
| Endometrial  | 3 | 1997-2003 | 0.70 (0.57, 0.86) | 34.6, | Myung et al.(31) | 11.5 | Negative | Zhang et al.(32) |
|  | 10 | 1996-2014 | 0.81 (0.72, 0.91) | 20, 0.26 | Zhang et al.(32) | 13.5 |  |  |
| Breast  | 9 | 1990-2005 | 0.75 (0.59, 0.95) | NR | Qin et al.(33) | 7.5 | Negative | Zhong and Zhang (34) |
|  | 3† | NR | 0.61 (0.38, 0.99) | 65.1, 0.057 | Woo et al.(28) | 6.5 |  |  |
|  | 13 | 1992-2012 | 0.72 (0.48, 0.97) | 91.4, 0.000 | Chen et al.(35) | 15 |  |  |
|  | 11 | 1997-2010 | 0.64 (0.49, 0.80) | 66.5, 0.001 | Chen et al.(35) | 15 |  |  |
|  | 28 | 1991-2010 | 0.86 (0.78, 0.96) | 45, 0.12 | Zhong and Zhang (34) | 10 |  |  |
|  | 8 | 2005-2013 | 0.83 (0.69,.0.99) | 15.5, 0.07 | Nachvak et al.(21) | 14.5 |  |  |
| Prostate  | 5 | 2000-2007 | 0.69 (0.57, 0.84) | NR, 0.544 | Hwang et al.(36) | 11.5 | Negative  | Yan and Spitznagel (37) |
|  | 14 | 1988-2008 | 0.74 (0.63, 0.89) | NR | Yan and Spitznagel(37) | 11.5 |  |
|  | 8 | 1998-2004 | 0.70 (0.59–0.83) | NR | Yan and Spitznagel(38) | 6 |  |
| n number of component estimate. †: number of included studies, might include higher number of number of component estimate in the analysis. NR: not reported. |

Appendix A3: Selecting the best meta-analysis studies for the significant associations of unfermented, and fermented soy intakes with non-communicable of diseases: high vs. low intakes

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Incidences | Product types | Case/cohort (n) | Included study publication years | RR (95% CI) | Heterogeneity,I2 %, p  | Sources | AMSTAR score Max.=16 | Conclusion | Selected best study |
| Lung cancer | Unfermented | 4† | 1999-2009 | Negative | 0, 0.767 | (39) | 13.5 | Negative | (39) |
|  |  | 6† | NR | Nonsignificant |  | (40) | 13.5 |  |  |
| Gastric cancer | Unfermented soy | 23 | 1992-2009 | 0.64 (0.54, 0.77) | 64.27, 0.001 | Kim et al.(41) | 10.5 | Negative | Kim et al.(41), Weng and Yuan (26) rejected for small sample size, Wu et al.(42) rejected for low AMSTAR score and outdated |
|  |  | 4 | NR | 0.63 (0.50, 0.79) | 0.0, 0.001 | Weng and Yuan(26) | 9.5 |  |
|  |  | 11 |  | 0.72 (0.63, 0.82) | NR | Wu et al.(42) | 3 |  |
|  | Fermented soy | 29 | 1988-2009 | 1.22 (1.02, 1.44) | 71.48, 0.001 | Kim et al.(41) | 10.5 | Positive | Kim et al.(41) |
|  |  | 4 | 2002-2015 | Nonsignificant | 0.0, | Weng and Yuan(26) | 9.5 |  |  |
|  |  | 17 | 1970-1998 | 0.90 (0.86, 0.94) | NR | Wu et al.(42) | 3 |  |  |
| Colorectal cancer | Unfermented soy  | 3† | NR | 0.85 (0.73, 0.99) | 41.0, 008 | Zhu et al.(43) | 11 | Inconclusive |  |
|  |  | 3† |  | Nonsignificant |  | Woo et al.(28) | 6.5 |  |  |
| Prostate cancer | Unfermented soy | 11 | 1989-2008 | 0.65 (0.52, 0.83) | 60.3, 0.005 | Applegate et al.(44) | 12 | Negative  | Applegate et al.(44) |
|  |  | 8 | 1989-2004 | 0.75 (0.62, 0.89) | NR, 0.413 | Hwang et al.(36) | 11.5 |  |  |
|  |  | 8 | 1998-2008 | 0.70 (0.56, 0.88) | NR | Yan and Spitznagel(37) | 11.5 |  |  |
|  | Fermented soy | 8 | 1989-2008 | Nonsignificant |  | Applegate et al.(44) | 12 | Nonsignificant |  |
|  |  | 5 | NR | Nonsignificant |  | Hwang et al.(36) | 11.5 |  |  |
|  |  | 6 | 1988-2007 | Nonsignificant | NR | Yan and Spitznagel(37) | 11.5 |  |  |
| n number of component estimate. †: number of included studies, might include higher number of number of component estimate in the analysis. NR: not reported. |

## References

1. Afshin A, Micha R, Khatibzadeh S *et al.* (2014) Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis–. *The American journal of clinical nutrition* 100, 278-288.

2. Anderson JW, Smith BM Washnock CS (1999) Cardiovascular and renal benefits of dry bean and soybean intake. *The American journal of clinical nutrition* 70, 464S-474S.

3. Ding M, Pan A, Manson JE *et al.* (2016) Consumption of soy foods and isoflavones and risk of type 2 diabetes: a pooled analysis of three US cohorts. *European journal of clinical nutrition* 70, 1381-1387.

4. Dong JY & Qin LQ (2011) Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. *Breast cancer research and treatment* 125, 315-323.

5. Fritz H, Seely D, Flower G *et al.* (2013) Soy, red clover, and isoflavones and breast cancer: a systematic review. *PloS one* 8, e81968.

6. Goodman MT, Wilkens LR, Hankin JH *et al.* (1997) Association of soy and fiber consumption with the risk of endometrial cancer. *American journal of epidemiology* 146, 294-306.

7. He F-J & Chen J-Q (2013) Consumption of soybean, soy foods, soy isoflavones and breast cancer incidence: Differences between Chinese women and women in Western countries and possible mechanisms. *Food Science and Human Wellness* 2, 146-161.

8. Ishimi Y, Taku K Yamauchi J (2010) Systematic review and verification of preventive effects of soy constituents on lifestyle-related diseases: effects of ingesting soy isoflavones on bone turnover markers in menopausal women and blood pressure in adult humans: systematic review and meta-analysis of randomized controlled trials (Part III). *Soy Protein Research, Japan* 13, 1-15.

9. Issac A (2020) Association Between Intake of Soy and Its Constituents and its Relation to Various Health Conditions: A Systematic Review and Meta-Analysis.

10. Jian L (2009) Soy, isoflavones, and prostate cancer. *Molecular Nutrition & Food Research* 53, 217-226.

11. Messina M (2016) Impact of Soy Foods on the Development of Breast Cancer and the Prognosis of Breast Cancer Patients. *Forschende Komplementarmedizin (2006)* 23, 75-80.

12. Nagata C, Mizoue T, Tanaka K *et al.* (2014) Soy intake and breast cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Japanese journal of clinical oncology* 44, 282-295.

13. Otun J, Sahebkar A, Östlundh L *et al.* (2019) systematic Review and Meta-analysis on the Effect of Soy on thyroid Function. *Scientific reports* 9, 1-9.

14. Tang J, Wan Y, Zhao M *et al.* (2020) Legume and soy intake and risk of type 2 diabetes: A systematic review and meta-analysis of prospective cohort studies. *The American journal of clinical nutrition* 111, 677-688.

15. Trock BJ, Hilakivi-Clarke L Clarke R (2006) Meta-analysis of soy intake and breast cancer risk. *Journal of the National Cancer Institute* 98, 459-471.

16. Wu SH & Liu Z (2013) Soy food consumption and lung cancer risk: a meta-analysis using a common measure across studies. *Nutrition and cancer* 65, 625-632.

17. Yang G, Shu XO, Chow WH *et al.* (2012) Soy food intake and risk of lung cancer: evidence from the Shanghai Women's Health Study and a meta-analysis. *American journal of epidemiology* 176, 846-855.

18. You J, Sun Y, Bo Y *et al.* (2018) The association between dietary isoflavones intake and gastric cancer risk: a meta-analysis of epidemiological studies. *BMC Public Health* 18, 1-7.

19. Zhao T-T, Jin F, Li J-G *et al.* (2019) Dietary isoflavones or isoflavone-rich food intake and breast cancer risk: A meta-analysis of prospective cohort studies. *Clinical nutrition* 38, 136-145.

20. Namazi N, Saneei P, Larijani B *et al.* (2018) Soy products consumption and the risk of all-cause, cardiovascular and cancer mortality: a systematic review and meta-analysis of cohort studies. *Food & function*.

21. Nachvak SM, Moradi S, Anjom-Shoae J *et al.* (2019) Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose–Response Meta-Analysis of Prospective Cohort Studies. *Journal of the Academy of Nutrition and Dietetics* 119, 1483-1500. e1417.

22. Yan Z, Zhang X, Li C *et al.* (2017) Association between consumption of soy and risk of cardiovascular disease: A meta-analysis of observational studies. *European journal of preventive cardiology* 24, 735-747.

23. Lou D, Li Y, Yan G *et al.* (2016) Soy Consumption with Risk of Coronary Heart Disease and Stroke: A Meta-Analysis of Observational Studies. *Neuroepidemiology* 46, 242-252.

24. Tse G & Eslick GD (2016) Soy and isoflavone consumption and risk of gastrointestinal cancer: a systematic review and meta-analysis. *European journal of nutrition* 55, 63-73.

25. Lu D, Pan C, Ye C *et al.* (2017) Meta-analysis of Soy Consumption and Gastrointestinal Cancer Risk. *Scientific reports* 7, 4048.

26. Weng KG & Yuan YL (2017) Soy food intake and risk of gastric cancer: A dose-response meta-analysis of prospective studies. *Medicine* 96, e7802.

27. Tong X, Li W Qin LQ (2010) [Meta-analysis of the relationship between soybean product consumption and gastric cancer]. *Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]* 44, 215-220.

28. Woo HD, Park S, Oh K *et al.* (2014) Diet and cancer risk in the Korean population: a meta-analysis. *Asian Pac J Cancer Prev* 15, 8509-8519.

29. Yu Y, Jing X, Li H *et al.* (2016) Soy isoflavone consumption and colorectal cancer risk: a systematic review and meta-analysis. *Scientific reports* 6, 25939.

30. Yan L, Spitznagel EL Bosland MC (2010) Soy consumption and colorectal cancer risk in humans: a meta-analysis. *Cancer Epidemiology and Prevention Biomarkers* 19, 148-158.

31. Myung SK, Ju W, Choi HJ *et al.* (2009) Soy intake and risk of endocrine-related gynaecological cancer: a meta-analysis. *BJOG : an international journal of obstetrics and gynaecology* 116, 1697-1705.

32. Zhang GQ, Chen JL, Liu Q *et al.* (2015) Soy Intake Is Associated With Lower Endometrial Cancer Risk: A Systematic Review and Meta-Analysis of Observational Studies. *Medicine* 94, e2281.

33. Qin LQ, Xu JY, Wang PY *et al.* (2006) Soyfood intake in the prevention of breast cancer risk in women: a meta-analysis of observational epidemiological studies. *Journal of nutritional science and vitaminology* 52, 428-436.

34. Zhong X & Zhang C (2012) Soy food intake and breast cancer risk: a meta-analysis.

35. Chen M, Rao Y, Zheng Y *et al.* (2014) Association between soy isoflavone intake and breast cancer risk for pre- and post-menopausal women: a meta-analysis of epidemiological studies. *PloS one* 9, e89288.

36. Hwang YW, Kim SY, Jee SH *et al.* (2009) Soy food consumption and risk of prostate cancer: a meta-analysis of observational studies. *Nutrition and cancer* 61, 598-606.

37. Yan L & Spitznagel EL (2009) Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis. *The American journal of clinical nutrition* 89, 1155-1163.

38. Yan L & Spitznagel EL (2005) Meta-analysis of soy food and risk of prostate cancer in men. *International journal of cancer* 117, 667-669.

39. Yang WS, Va P, Wong MY *et al.* (2011) Soy intake is associated with lower lung cancer risk: results from a meta-analysis of epidemiologic studies. *The American journal of clinical nutrition* 94, 1575-1583.

40. Li W, Ruan W, Peng Y *et al.* (2018) Soy and the risk of type 2 diabetes mellitus: A systematic review and meta-analysis of observational studies. *Diabetes research and clinical practice* 137, 190-199.

41. Kim J, Kang M, Lee JS *et al.* (2011) Fermented and non-fermented soy food consumption and gastric cancer in Japanese and Korean populations: a meta-analysis of observational studies. *Cancer Sci* 102, 231-244.

42. Wu AH, Yang D Pike MC (2000) A meta-analysis of soyfoods and risk of stomach cancer: the problem of potential confounders. *Cancer Epidemiol Biomarkers Prev* 9, 1051-1058.

43. Zhu B, Sun Y, Qi L *et al.* (2015) Dietary legume consumption reduces risk of colorectal cancer: evidence from a meta-analysis of cohort studies. *Scientific reports* 5, 8797.

44. Applegate CC, Rowles JL, Ranard KM *et al.* (2018) Soy Consumption and the Risk of Prostate Cancer: An Updated Systematic Review and Meta-Analysis. *Nutrients* 10, 40.