SYSTEMATIC REVIEW AND META-ANALYSIS

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Association of Red Meat Intake and Colorectal Cancer among East-Asians: A Systematic Review and Meta-analysis of Observational Studies Performed between 2011-2021

Hoi Shan Cheung, Lok Yee Lu, Wang Leong So, Ho Wai Wong, Sei Hei Wong, Chloe Miu Mak

Division of Chemical Pathology, Department of Pathology, Hong Kong Children's Hospital, Hong Kong SAR, China

Address for correspondence:
Dr **Chloe M Mak**, PhD, MD, FRCPA, FHKAM
Chemical Pathology Laboratory, Department of Pathology, Hong Kong Children's Hospital, Hong Kong SAR, China
makm@ha.org.hk

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ABSTRACT

Background & Aims: Colorectal cancer has the third highest incidence and second highest mortality among all cancers worldwide. Although numerous studies investigating the associations between high red meat intake and risk of colorectal cancer have been published, the association between the intake of red meat and the risk of colorectal cancer in Asians remains unclear. We performed a systematic review and meta-analysis of cohort and case-control studies to estimate the association between red meat intake and colorectal cancer incidence rate between 2011-2021.
Method: We searched PubMed database from 1 Jan 2011 to 21 July 2021. Prospective cohort studies and nested case-control studies that reported results on the association between red meat consumption and colorectal cancer were included in the meta-analysis. The outcome of interest was the association between the intake of red meat and the risk of colorectal cancer. We performed a meta-analysis to calculate the odds ratios (OR) with 95% confidence intervals (CI).
Results: A total of 5 studies enrolling 48,158 participants were included. The results showed no significant association between red meat intake and colorectal cancer risks (OR=1.38; 95%CI: 0.98-1.93). The aspect of the corresponding funnel plot suggested the presence of significant publication bias. Egger's test confirmed the significant asymmetry of the funnel plot (t = 9.3024, p = 0.0026).
Conclusions: Contrary to many other meta-analyses, our study showed that intake of red meat was not associated with increased risk of colorectal cancer in East-Asians from China, Japan and South Korea. However, due to the limited number of included papers and the lack of confounders adjustments, our results warrant cautious interpretations.

Key words: red meat – colorectal cancer – Asians.

Abbreviations: BMI: body mass index; CI: confidence interval; OR: odds ratio; RR: relative risk.

INTRODUCTION

As per GLOBOCAN 2020, colorectal cancer had the third highest incidence and second highest mortality among all cancers [1]. There is a dire need to identify underlying risk factors for colorectal cancer. In 2015, World Health Organization classified red meat as Group 2A carcinogens [2], thereby indicating that a positive association was observed between the exposure to the agent and cancer, yet other possible explanations including chance, bias or confounding factors cannot be ruled out by now. Various mechanisms for such phenomena have been proposed. It showed that the heme content of red meat causes the endogenous formation of carcinogenic intestinal N-nitroso compounds [3]. It was also suggested that high cooking temperature induces a potential mutagenic effect of heterocyclic amines contained in red meat [4].

A number of studies was conducted over the past decades regarding the associated cancer risk, yet yielded inconsistent results [5]. Concerns were therefore raised as we aimed to evaluate their association. There has been a paucity of recent systematic review and meta-analysis on the relationship between red meat intake and risk of colorectal cancer. Moreover, despite the incidence and mortality number of colorectal cancer in Asia accounting for over half of the total cases [1], Asian-based systematic review and meta-analysis on such topic had been rare, with the studies predominantly based in Europe and

North America [6-8]. Given the research gap, we performed a systematic review and meta-analysis of cohort and case-control studies to estimate the association between red meat intake and colorectal cancer incidence rate in the last 10 years.

METHODS

Search Strategy

We conducted electronic searches of PubMed database for study papers published from 1 January 2011 to 21 July 2021. With reference to a meta-analysis of red and processed meat and colorectal cancer incidence [9], we adopted a standard search strategy implemented by World Cancer Research Fund. Detailed search strategy is attached in Supplementary file, Appendix 1. Reference lists of the relevant articles and reviews were also consulted to identify additional relevant studies.

Selection Criteria

Peer-reviewed case control, prospective cohort studies and nested case-control studies that reported results for the association between red meat intake and colorectal cancer were included in the meta-analysis. Included studies were also required to report relative risk (RR) estimates [e.g., rate ratios, hazard ratios, odds ratios (OR)], and 95% confidence intervals (CI) for intake categories of red meat and colorectal cancer. If data sets were duplicated or overlapped, only the most recent or complete studies were included. Studies included were only confined to those involving humans in the Asian population. All studies showing the association between colorectal cancer and red meat in the last 10 years were included. There was no language restriction for the published studies. All studies meeting the above criteria were obtained, but only studies that represented independent (non-overlapping) study populations or included extended follow-ups from prior analyses were included in the meta-analysis.

We excluded cross-sectional and ecological studies. Ecological studies focused on the aggregation of data at the level of population, thus may not be able to reflect the individual level reliably. Studies which adopted dichotomous classification, which classified subjects into red meat eater or non-eater only, but not quantifying the level of exposure, were excluded from the analysis. We also excluded studies in which data were incomplete or unable to be combined. Studies in which the full texts could not be obtained were excluded. We also excluded data of processed red meat, as processed meat was classified as Group 1 carcinogenic in 2015 by World Health Organization [10]. Processing of meat could be a factor causing cancer, which we would like to exclude. Studies which did not specify red or processed meat consumption and only showed white meat and total meat were excluded.

Data Extraction

For eligible studies, three reviewers independently abstracted the following items: study characteristics (year of publication, country, primary endpoint, and assessment method of red meat intake); population characteristics (sample size, age); description of dietary assessment (type of red meat); and data on outcomes of interest (OR for cancer incidence, and variables that entered into the multivariate model as potential confounders [family history of colorectal cancer and body mass index (BMI)]. Table I is a summary of the characteristics of the included study papers.

Statistical Analysis

All statistical analysis was performed using Review Manager (version 5.4, Cochrane, London, UK). Random-effects models were used to calculate the summary odds ratio and 95%CI. Heterogeneity among studies was detected using I2 statistics (I2< 50% was considered low heterogeneity and I2 > 50% was considered to indicate substantial heterogeneity [11]). Publication bias was assessed using funnel plots.

RESULTS

The search strategy generated 69,362 records, of which 288 were considered of potential value, and full text was retrieved for detailed review (Fig. 1). There were 207 studies excluded from the studies due to various reasons (Fig. 1). Among them, 74 studies had no original data/reviews, 53 studies did not report on the associations of interest, 15 articles were non peer-reviewed articles/commentary, 48 articles were meta-analyses/ migrant studies/case reports and 17 articles had duplicate data. An additional 76 articles were excluded as they were not related to Asia. Therefore, a total of 5 articles (3 case-control studies

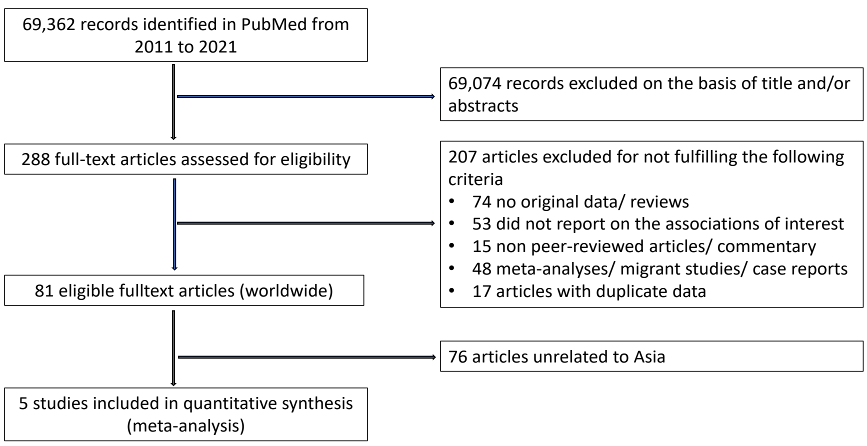

Fig. 1. Flow diagram of literature search on red meat and colorectal cancer

Table I. Summary of characteristics of the included study papers.

No	Author, year (ref)	Geographic location	Follow up period	No of patients (cases; control)	Age	Gender	BMI (kg/m^2)	Family history of CRC	Primary endpoint	Description of red meat	Method of dietary assessment
1	Takachi, 2011 [17]	Japan	758,116 person-years	1145; 79513	45-74	Male & female	≥25	Not shown	Colon cancer sub-sites (proximal & distal)	3 beef dishes (steak, grilled beef, and stewed beef), 6 pork dishes (stir-fried pork, deep-fried pork, stewed pork in Western style, stewed pork in Japanese style, pork in soup, and pork liver). 4 processed meat products (ham, sausage or Weiner sausage, bacon, and luncheon meat), and chicken liver.	Food Frequency Questionnaire
2	Chun, 2015 [21]	Seoul, Korea	No follow-up	150; 116	20-79	Male & female	< 18.5 – ≥ 30	Not shown	Hospitalized and newly diagnosed with colorectal cancer during the recent three months	7 food items but not shown clearly	Food frequency questionnaire developed and validated by the Korea Centers for Disease Control and Prevention.
3	Wada, 2017 [19]	Japan	306 months	858; 29473	≥35	Male & female	21.9 – 22.7	Not shown	Earliest occurrence of one of the following events: a diagnosis of colorectal cancer, emigration from the study area, death, or the end of the study period.	Beef and pork. Food items for red meat products included beef steak, pork steak, pork cutlet, grilled meat, grilled offal, and liver.	baseline survey and a self-administered questionnaire including an FFQ
4	Shen, 2019 [22]	China	No follow-up	100; 100	46.7-73.7	Male & female	19.6 – 26.6	Approximately 25% of individuals diagnosed with CRC have a family history of the disease, but 75% of CRC cases are not hereditary	Not stated	Not stated	Food frequency questionnaire
5	Budhathoki, 2020 [20]	Takayama, Japan	No follow-up	302; 403	40-79	Male & female	Cases (Mean; SD): 23.8; 3.4 Control: 23.6; 3.4	Adjusted but not shown	Not stated	Stroganoff (beef); Beef Milanese; Beef (roasted); Beef (pan-fried); Beef (grilled in a frying pan without oil or fat); Beef (Churrasco, grelha); Beef (Churrasco, espeto); Pork (pan-fried); Pork (Churrasco, grelha).	Detailed questionnaire

Table II. Odds ratios of colorectal cancer for the highest versus lowest groups of red meat intake

Study	High red meat intake		Low red meat intake		Weight (%)	Odds Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Budhathoki	91	191	63	164	19.1	1.46 [0.95, 2.23]
Chun	59	90	37	88	14.6	2.62 [1.43, 4.81]
Takachi	369	16131	407	16131	26.0	0.90 [0.78, 1.04]
Shen	62	103	35	94	15.3	2.55 [1.43, 4.53]
Wada	194	7582	203	7584	24.9	0.95 [0.78, 1.17]
Total	775	24,097	745	24,061	100.0	1.38 [0.98, 1.93]

Heterogeneity: Tau2=0.11; Chi2=24.95, df=4 (p<0.0001); I2=84%. Test for overall effect: Z = 1.84 (p = 0.07)

and 2 cohort studies), including 1,520 subjects with colorectal cancer and 46,638 controls were included in this meta-analysis (Table I). The selected studies were from China (n=1), Japan (n=3) and South Korea (n=1). The methods of assessments of exposure were all based on Food Frequency Questionnaire (FFQ) [12-18]. The Newcastle-Ottawa Scale was used to assess the validity of the 5 included studies (Tables III and IV).

In the meta-analysis, 5 studies were included, and the OR was 1.38 (95%CI: 0.98–1.93) with low heterogeneity (p=0.07, I2=84%) (Table III). The results showed no statistically significant association between red meat intake and incidence rate of colorectal cancer (Fig. 2A). Funnel plot analysis (Fig. 2B) indicated publication bias. Egger's test (Fig. 2B) showed significant asymmetry of the funnel plot (t=9.3024, p=0.0026).

DISCUSSION

Our statistical analysis found no significant association between red meat intake and incidence rate of colorectal cancer. Three out of five of our included papers showed no statistically significant association between red meat intake and incidence rate of colorectal cancer, including those conducted by Takachi et al. (2011) [17], Wada et al. (2017) [19] and Budhathoki et al. (2020) [20]. On the other hand, Chun et al. (2015) [21] and Shen et al. (2019) [22] showed statistically significant positive association between red meat and colorectal cancer. Nonetheless, Chun et al. (2015) [21] and Shen et al. (2019) [22] both recruited only a small sample size (178 and 197 subjects respectively). In contrast, the other three papers that showed insignificant associations involved larger sample sizes: 355 in the study conducted by Budhathoki et al. (2020) [20], 32,262 in Takachi et al. (2011) [17] and 15,166 in Wada et al. (2017) [10]. Therefore, the overall odds ratio with 95%CI did not show a significant association.

Comparing our study to the studies showing significant association between red meat intake, it should be noted that those studies were mainly targeting Western populations. For instance, a systematic review by Vieira et al. [23] which included 111 unique cohort studies reinforced the evidence that a high intake of red meat can increase the risk of colorectal cancer [the risk increase of colorectal cancer was 12% for each 100 g/day increase of red and processed meat intake (RR=1.12)] [23]. Another systematic review and meta-analysis by Magalhães et al. [24] also suggested that the consumption of red meat positively associates with the incidence of colorectal cancer [combined RR=1.29, 95%CI: 1.13–1.48, I^2=31.7%)]. Thus, it is known that in Western studies, red meat intake is associated directly with the risk of colorectal cancer.

While most Western studies showed positive association between red meat intake and risk of colorectal cancer, Asian studies, on the other hand, yielded inconsistent results for the association between red meat and colorectal cancer. A meta-analysis on meat intake and cause-specific mortality generated a similar conclusion as our meta-analysis [25]. The paper followed eight Asian prospective cohort studies consisting of 112,310 men and 184,411 women. Their pooled analysis found no association between intake of total meat (including red meat) and risks of cancer mortality. A systematic review focusing on diet and colorectal cancer risk in Asia found that most studies showed a positive association between red meat and the risk of colorectal cancer [5]. However, the results of their included studies showed a range of differences, for example Takachi et al. (2011) [17] only showed positive association among women and Ramadas et al. [26] (2009) showed that red meat intake increases the risk of colorectal

Table III. Newcastle-Ottawa scale (case control study)

Study	Selection				Comparability	Exposure		
	Case definition	Represenati-veness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate
Chun, 2015 [21]	-	-	*	*	*	-	*	-
Shen, 2019 [22]	*	-	-	*	-	*	*	-
Budhathoki, 2020 [20]	*	*	-	*	*	-	*	-

Rating criteria based on the assessment scale attached in Supplementary file, Appendix 3.

Table IV. Newcastle-Ottawa scale (cohort study)

Study	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Statistical analysis design features	Assessment of Outcome	Follow-up long enough	Adequacy of follow up of cohorts
Takachi, 2011 [17]	*	*	**	*	*	*	**	*
Wada, 2017 [19]	*	*	**	-	*	*	**	*

Rating criteria based on the assessment scale attached in Supplementary file, Appendix 4.

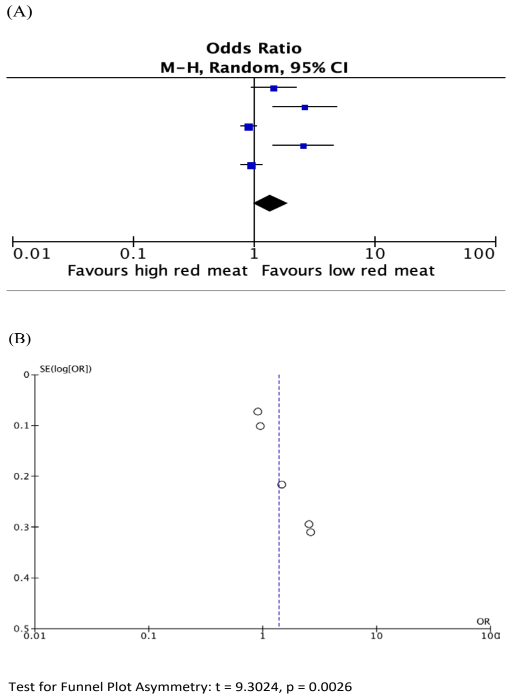

Fig. 2. (A) Forest plot and (B) Funnel plot of red meat consumption and colorectal cancer risk.

adenoma but not the risk of colorectal carcinoma. Therefore, the conclusion of a positive association between red meat and colorectal cancer is invalid.

Moreover, a meta-analysis focusing on Japanese studies showed that meat consumption was associated with an increased risk of colorectal and colon cancer, but no association was found for rectal cancer [27]. Also, the meta-analysis only included Japanese studies but not other Asian studies, therefore, it may have a conclusion different from our meta-analysis.

Our study, focusing on Asian countries, resembled the aforementioned Asian studies, showed no statistically significant association between red meat intake and incidence rate of colorectal cancer. There may be several factors contributing to the non-significant association, also taking into account that all of our studies are based in East-Asia.

First of all, fish intake was believed to be a protective factor in developing cancer [28, 29]. Fish and seafood consumption in East-Asian countries like Korea and Japan are much higher than Western countries, and the meat consumption of East-Asian countries is lower than the Western countries, indicating the dietary habits of East-Asians and Westerners are different, although the difference is being narrowed [25]. The mechanism of fish intake and the prevention of cancer could be explained by the inhibition of eicosanoid biosynthesis, and thus reducing the conversion of arachidonic acid to prostaglandin. This could delay the disease‘s progression [28, 29].

Moreover, higher intake of fruits and vegetables was believed to be associated with a lower risk of developing cancers [30, 31]. Traditional East-Asian dishes include many different types of vegetables, such as cabbage, broccoli, cauliflower, etc., which were believed to be a protective factor against different types of chronic diseases [32].

The cooking method difference may also contribute to our findings. Cooking with East-Asian style involves various techniques, including steaming and frying. Grilling is uncommon. However, many Western dishes are prepared quickly, using grilling and frying procedures. Usually no complicated processes are involved, unlike East-Asian diet [33]. Grilling involves high temperature cooking. Experiments showed that meat cooked with high temperature could form carcinogenic chemicals such as heterocyclic amines and other potent mutagens/carcinogens, due to the Maillard reaction [34]. Difference in East-Asians and European or North American cooking methods may also account for the different association of red meat and colorectal cancer between East-Asians and Westerners.

The major strength of the present study is its target of Asian population, which was rarely addressed before on red meat consumption and colorectal cancer incidence. Five out of the 81 study papers identified were Asian studies, indicating the necessity and importance of conducting further research on Asians. Another strength of our analysis is our comprehensive search strategy; the analyzed data was the most updated and the large number of analyzed subjects (1,520) and controls (46,638).

Presence of publication bias is indicated from the results of Egger's test. Research with positive results is more likely to be published. These results might not represent the complete picture of evidence. Moreover, size of effect differs according to study size [35]. Potential distortion may be caused by the drastically larger sample size from larger studies. Larger studies in our research (Takachi et al. [17], and Wada et al. [19]) showed no significant association, leading to the result of "no significant association" of this meta-analysis.

Our study has several potential limitations as well. Due to the limited number of previous studies, we were only able to identify and analyze five papers. All five papers were from East Asia (1 from China, 3 from Japan and 1 from South Korea), therefore other regions of Asia are not duly addressed. Two of the five papers had a dominant number of cases compared to the remaining, which implied that the results were significantly influenced by the two papers. Also, we did not address confounders in the study, thereby failing to obviate the possibility of a third variable in the supposed cause-and-effect relationship. There was a heterogeneity in the definition of high and low intake of red meat across different studies. Possible confounders included the following: age, gender, total energy intake, fruits and vegetable intake, meat preparation method, cooking procedures, BMI, habits of smoking and consuming alcohol, physical activity and education level. Moreover, we only identified the general association between red meat intake and colorectal cancer, but not its relations in different age group, gender, total energy intake and other possible factors. Finally, the definition of red meat varied between studies, therefore leading to heterogeneity that contributes to inconsistent results.

Contrary to two meta-analyses from Western populations [23, 24], our study shows that intake of red meat is not associated with increased risk of colorectal cancer in East-Asians from China, Japan and South Korea. However, clinicians should interpret our results with caution due to two major reasons. First, we did not account for confounders. Second, the population does not represent all Asians. Further studies are required to ensure the association between red meat intake and colorectal cancer in Asians, perhaps taking genetic variations into account.

CONCLUSIONS

No statistically significant association was found between the intake of red meat and the risk of colorectal cancer in East-Asian population, contrary to the significant association found in western populations by other meta-analyses. However, due to the limited number of included papers, the significant publication bias and the lack of confounders adjustments, our results warrant cautious interpretations.

Conflicts of interest: None to declare.

Authors' contributions: W.L.S. conceived the meta-analysis and developed its design with H.S.C., S.H.W., H.W.W. and L.Y.L.. S.H.W., H.S.C. and H.W.W. performed the systematic literature search. L.Y.L. and W.L.S. extracted the data and performed the statistical analyses. H.S.C., S.H.W. and H.W.W. contributed to data interpretation. All authors revised the manuscript and approved the final version.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-4778

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