**Table 4.** Summary of case–control studies on diabetes mellitus and liver cancer among Japanese

| Reference | Study period | Study subjects | | | | Magnitude of association |
|---|---|---|---|---|---|---|
| | | Sex | Age range | Number of cases | Number of controls | |
| Shibata *et al.* (34) | 1992–95 | Men | 40–69 years | 115 | 115 Community controls | ↑↑↑ |
| Matsuo (35) | 1995–2000 | Men | 40–75 years | 177 | 177 Community controls | ↑↑↑ |
| | | women | 40–75 years | 45 | 45 Community controls | ↑↑ |
| Kabutake *et al.* (36) | 1994–2006 | Men and women | Not specified | 96 | 65 (Alcoholic cirrhosis) | ↑↑↑ |
| Kuriki *et al.* (37) | 1989–2000 | Men | ≧18 years | 265 | 14 199 | ↑↑↑ |
| | | Women | ≧18 years | 75 | 33 569 | ↑↑↑ |
| Ohishi *et al.* (38) | 1970–2002 | Men and women | Not specified | 224 | 644 | ↑ |
| Taniguchi *et al.* (39) | Not described | Men and women | Not specified | 230 | 219 (HCV-associated CLD) | – |
| Horie *et al.* (40) | 2007–08 | Men | Not specified | 243 | 509 (Alcoholic cirrhosis) | ↑↑ |
| | | Women | Not specified | 22 | 89 (Alcoholic cirrhosis) | ↑↑↑ |

HCV, hepatitis C virus; CLD, chronic liver disease.

## DISCUSSION

Overall, 17 of the 24 RR estimates in the cohort studies and 9 of the 10 RR estimates in the case–control studies showed a weak to strong positive association between diabetes and liver cancer risk, indicating that the overall evidence in Japan strongly supports an increased risk of liver cancer among diabetic patients. The summary RR was estimated at 2.2, which is analogous to those previously reported in several meta-analyses, with a range of 1.6–3.6 (3–7). The overall association was almost similar regardless of study type (case–control or cohort studies) or sex (men, women or both) although three RR estimates from two early studies on diabetic patients (15,16) showed a summary RR of 4.6 (Table 5) that was significantly higher than that in subsequent studies on general populations (summary RR = 2.1) or CLD patients (summary RR = 1.9). Both studies (15,16) differed from the others in that they followed only diabetic patients and compared liver cancer mortality in such patients with that in the general population, adjusting only for age and observation period.

A major concern on the association between diabetes and liver cancer may be that diabetic subjects possibly include patients with hepatogenous diabetes as a complication of an advanced stage of CLD such as cirrhosis (41), thereby showing a higher liver cancer risk in appearance. Hepatogenous diabetes manifests clinically as liver function deteriorates, and it appears difficult to differentiate Type 2 diabetes from hepatogenous diabetes (41). This issue will be particularly problematic for studies on general populations or diabetic patients without clinical information on the status of subjects' liver disease and hepatitis virus markers. However, the majority of recent cohort studies on CLD patients with adjustment for the severity of CLD and hepatitis virus status (19,24,25,27,28,30–32) also found a positive association between diabetes and liver cancer risk.

As for the diagnosis of diabetes, self-reported histories were used in 6 (8,33–35,37,38) of the 27 studies evaluated, and the method of ascertaining diabetes was not clearly described in five studies (20,25,26,36,39). Virtually no studies took into account onset age, duration and treatment of diabetes, which appear difficult to verify but likely have influence on the disease course if diabetes truly causes a risk increase of liver cancer. Of note, some anti-diabetic drugs have been suspected to be protective (e.g. metformin (42)) or promotive (e.g. insulin and sulfonylurea (43)) in human carcinogenesis. These issues may have caused some underestimation or overestimation of true associations. Although Type 1 and Type 2 diabetes were not clearly distinguished in most studies, it seems reasonable to assume that most study subjects had Type 2 diabetes because Type 1 diabetes is rare in adults. Besides, diabetic patients may undergo more medical checkups than non-diabetic subjects, leading to increased detection of cancer and thus some overestimation of the positive association.

Additional methodological limitations should be considered. First, selection bias and information bias (e.g. recall bias on self-reported history of diabetes) might have distorted the results, especially in the hospital-based case–control studies (34–37,39,40). Second, potential confounders were not always considered in the 27 studies evaluated. Hepatitis status, alcohol drinking or obesity (or body mass index) was not controlled in 10 (8,15–17,21,22,33–35,37), 15 (15–18,20–23,25,27,29,34,36,39,40) or 20 (15–18,20–23,25–27,29–32,34–36,39,40) studies, respectively, although whether or not obesity should be controlled may be open to question due to the possible similarity in etiological mechanisms between diabetes and obesity, as discussed below. Moreover, only five studies (8,33,35,37,38) controlled for smoking that is now regarded as a risk factor (44–46). Finally, publication bias could not be ruled out although statistical tests for the presence of such a bias revealed insignificant results ($P = 0.09$ and 0.17 by the Begg's and Egger's tests, respectively; data not shown) (13,14).

| No. | Study | Reference | Sex | Design | RR (95% CI) |
|---|---|---|---|---|---|
| 1 | Tsukuma et al. (1987) | 15 | Men | Cohort | 9.50 (5.72-14.8) |
| 2 | Tsukuma et al. (1987) | 15 | Women | Cohort | 1.49 (0.04-8.32) |
| 3 | Sasaki et al. (1996) | 16 | Men and women | Cohort | 3.02 (2.37-3.80) |
| 4 | Kato et al. (1997) | 17 | Men and women | Cohort | 1.73 (0.42-7.15) |
| 5 | Kato et al. (1997) | 17 | Men and women | Cohort | 1.17 (0.78-1.75) |
| 6 | Tazawa et al. (2002) | 18 | Men and women | Cohort | 5.68 (1.80-18.2) |
| 7 | Ohata et al. (2003) | 19 | Men and women | Cohort | 1.58 (0.62-3.99) |
| 8 | Uetake et al. (2003) | 20 | Men | Cohort | 0.75 (0.22-2.51) |
| 9 | Khan et al. (2006) | 21 | Men and women | Cohort | 3.38 (0.30-38.7) |
| 10 | Muto et al. (2006) | 22 | Men and women | Cohort | 1.57 (1.00-2.45) |
| 11 | Torisu et al. (2007) | 23 | Men | Cohort | 21.7 (2.40-193.7) |
| 12 | Ohki et al. (2008) | 24 | Men and women | Cohort | 1.26 (0.92-1.71) |
| 13 | Tomiyama et al. (2008) | 25 | Men and women | Cohort | 4.54 (0.48-42.9) |
| 14 | Ikeda et al. (2009) | 26 | Men and women | Cohort | 3.89 (1.22-12.5) |
| 15 | Konishi et al. (2009) | 27 | Men and women | Cohort | 4.63 (1.68-12.8) |
| 16 | Kurosaki et al. (2010) | 28 | Men and women | Cohort | 0.75 (0.42-1.33) |
| 17 | Kuroda et al. (2011) | 29 | Men and women | Cohort | 0.91 (0.55-1.59) |
| 18 | Takahashi et al. (2011) | 30 | Men and women | Cohort | 19.5 (3.70-104.1) |
| 19 | Kawamura et al. (2012) | 31 | Men and women | Cohort | 3.21 (1.09-9.50) |
| 20 | Arase et al. (2013) | 32 | Men and women | Cohort | 1.73 (1.30-2.30) |
| 21 | Nakamura et al. (2013) | 33 | Men | Cohort | 2.18 (1.27-3.74) |
| 22 | Nakamura et al. (2013) | 33 | Women | Cohort | 0.65 (0.16-2.69) |
| 23 | Sasazuki et al. (2013) | 8 | Men | Cohort | 2.07 (1.70-2.53) |
| 24 | Sasazuki et al. (2013) | 8 | Women | Cohort | 1.71 (1.14-2.57) |
| 25 | Shibata et al. (1998) | 34 | Men | Case-control | 3.54 (1.63-7.67) |
| 26 | Matsuo et al. (2003) | 35 | Men | Case-control | 2.52 (1.27-5.02) |
| 27 | Matsuo et al. (2003) | 35 | Women | Case-control | 4.20 (0.81-21.8) |
| 28 | Kabutake et al. (2007) | 36 | Men and women | Case-control | 2.29 (1.20-4.37) |
| 29 | Kuriki et al. (2007) | 37 | Men | Case-control | 2.19 (1.56-3.07) |
| 30 | Kuriki et al. (2007) | 37 | Women | Case-control | 2.26 (1.05-4.88) |
| 31 | Ohishi et al. (2008) | 38 | Men and women | Case-control | 1.98 (0.63-6.27) |
| 32 | Taniguchi et al. (2009) | 39 | Men and women | Case-control | 1.35 (0.93-1.95) |
| 33 | Horie et al. (2011) | 40 | Men | Case-control | 1.71 (1.26-2.33) |
| 34 | Horie et al. (2011) | 40 | Women | Case-control | 13.8 (4.65-40.7) |
| | | | Summary RR | Cohort | 2.10 (1.60-2.76) |
| | | | | Case-control | 2.32 (1.73-3.12) |
| | | | | Total | 2.18 (1.78-2.69) |

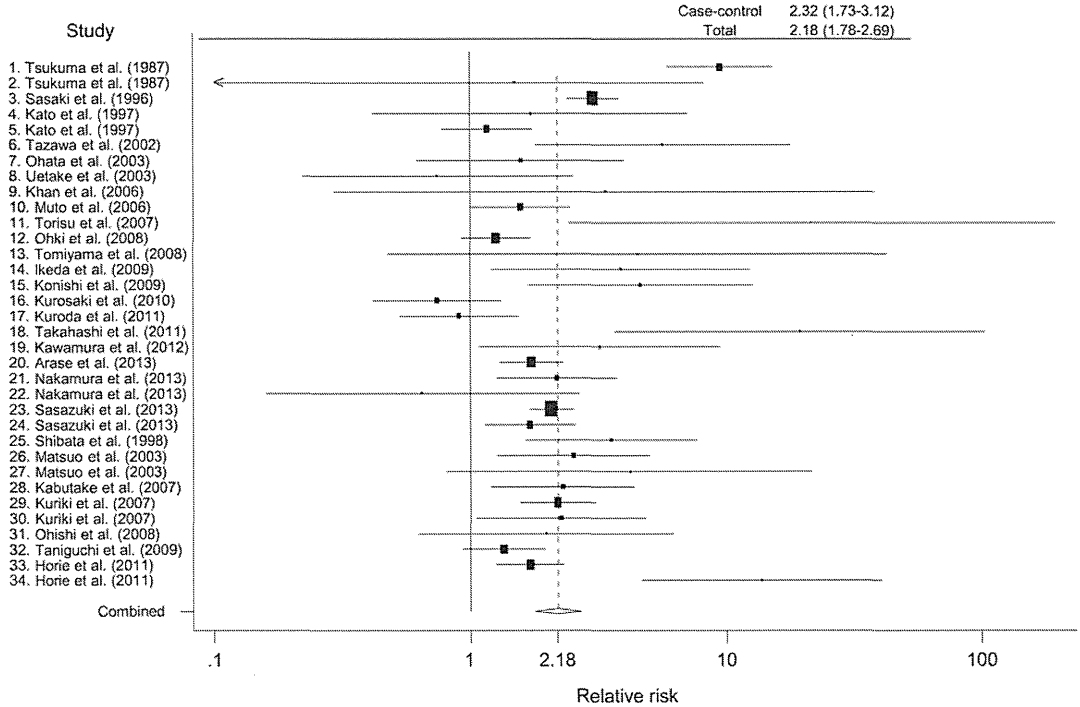


**Figure 1.** Forest plot of the relative risks (RRs) and their 95% confidence intervals of liver cancer for diabetes mellitus in cohort and case–control studies evaluated and the corresponding summary RR. For both the cohort studies and case–control studies as well as all studies combined, the individual RRs were turned out to be significantly heterogeneous ($P < 0.001$, 0.011 and $<0.001$, respectively), so a random effects model was used to estimate the summary RR.

In relation to the biological plausibility for the observed positive association between diabetes and liver cancer, several mechanisms have been proposed. First, Type 2 diabetes is characterized by insulin resistance and resulting hyperinsulinemia. Insulin can exert a potentially mitogenic effect by activating the insulin receptor and then triggering intracellular signaling cascades that have the potential to be both mitogenic and anti-apoptotic (e.g. phosphatidylinositol 3-kinase-AKT pathway) (47) and by interacting with the insulin-like growth factor-1 (IGF-1) receptor playing a pivotal role in cancer cell

**Table 5.** Summary relative risks (RR) and 95% confidence intervals (CI) of liver cancer for diabetes mellitus in subgroups by study type, sex, and study population among Japanese

| Subgroup | No. of RR estimates | Summary RR (95% CI) | *P* for difference between subgroups[a] |
|---|---|---|---|
| Study type | | | |
| Cohort | 24 | 2.10 (1.60–2.76) | 0.39 |
| Case–control | 10 | 2.32 (1.73–3.12) | |
| Sex | | | |
| Men | 9 | 2.68 (1.81–3.96) | 0.33 |
| Women | 6 | 2.56 (1.19–5.50) | |
| Both | 19 | 1.88 (1.44–2.45) | |
| Study population | | | |
| General population | 11 | 2.10 (1.82–2.42) | 0.01 |
| Diabetic patients | 3 | 4.56 (1.64–12.7) | |
| Patients with CLD | 20 | 1.90 (1.47–2.47) | |

CLD, chronic liver disease.
[a]Based on random effects meta-regression including covariates of study type (cohort or case–control), sex (men, women or both) and study population (general population, diabetic patients or CLD patients).

proliferation (48). Elevated insulin can also increase free IGF-1 (i.e. bio-active form of IGF-1) in blood via reducing the production of IGF-1 binding proteins 1 and 2 in the liver, thereby leading to tumor development (49). This is the most frequently proposed hypothesis, which also represents a possible mechanism underlying the association between obesity and liver cancer (49,50). If this mechanism mainly contributes to hepatocarcinogenesis, adjusting for obesity as a common complication of Type 2 diabetes might be overadjustment. Secondly, hyperglycemia among diabetic patients can increase oxidative stress in the cell due to an overload of glucose oxidation and other mechanisms leading to the production of reactive oxygen species (ROS) such as hydroxyl radical (51). ROS can bind DNA, can cause gene mutations and may induce cancer development. Although it is still unclear whether hyperglycemia is associated with the development of cancer via ROS production, it is noteworthy that long-term iron reduction therapy with phlebotomy and low-iron diet, which is believed to suppress the production of ROS including hydroxyl radical (52), has lowered the incidence of hepatocellular carcinoma in patients with chronic hepatitis C (53). Lastly, patients with Type 2 diabetes often have obesity leading to elevated levels of pro-inflammatory factors such as tumor necrosis factor-alpha and interleukin-6 and decreased levels of adiponectin with anti-inflammatory actions, and resulting chronic inflammation can promote hepatocarcinogenesis (50).

### Evaluation of Evidence on Diabetes and Liver Cancer Risk among Japanese

Based on the results from the epidemiological studies evaluated and the biological plausibility as described above, we conclude that diabetes mellitus probably increases the risk of liver cancer among the Japanese population. Preventing or treating diabetes may be recommended for the prevention of liver cancer, particularly in high risk individuals such as patients with CLD and hepatitis virus carriers.

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## Conflict of interest statement

None declared.

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## Appendix

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# Meat Consumption and Colorectal Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population

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**Objective:** The association between meat consumption and colorectal cancer remains inconsistent among Asians. The present study systematically evaluated and meta-analyzed epidemiologic studies on the association between consumption of total and specific meats and colorectal cancer risk among Japanese.

**Methods:** Original data were obtained from MEDLINE searched using PubMed or from searches of the *Ichushi* database, complemented with manual searches. The associations were evaluated based on the strength of evidence, the magnitude of association and biologic plausibility. A meta-analysis was performed according to total meat, red and processed meat as well as poultry and site-specific cancers.

**Results:** Six cohort studies and 13 case–control studies were identified. In cohort studies, most investigations found no association between total meat consumption and colon/rectal cancer, and several studies showed a weak-to-moderate positive association of red meat and processed meat consumption with colon/rectal cancer. The majority of case–control studies showed no association between total meat consumption and colon and rectal cancer; however, several ones reported a weak-to-strong positive association of red and processed consumption with colon and rectal cancer. In meta-analysis, the summary relative risks (95% confidence interval) for the highest versus lowest categories of red meat consumption were 1.16 (1.001–1.34) and 1.21 (1.03–1.43) for colorectal and colon cancer, respectively, and those for processed meat consumption were 1.17 (1.02–1.35) and 1.23 (1.03–1.47) for colorectal and colon cancer, respectively. Poultry consumption was associated with lower risk of rectal cancer; summary relative risk (95% confidence interval) was 0.80 (0.67–0.96).

**Conclusions:** High consumption of red meat and processed meat possibly increases risk of colorectal cancer or colon cancer among the Japanese population.

*Key words: systematic review – epidemiology – meat – colorectal cancer – Japanese*

## INTRODUCTION

Colorectal cancer was ranked third and second of all cancers in men and women, respectively, according to global cancer statistics in 2008 (1). This form of cancer has a significant impact on public health in economically developed countries (2), including Japan, where colorectal cancer remains among countries with the highest incidence rate worldwide (3). Accumulating evidence suggests that diet and nutrition play a role in the development of colorectal cancer (4,5). Of dietary factors associated with colorectal cancer, meat consumption has received a growing interest (6). A high consumption of meat and animal fat in Japan was once considered as a contributor to increased colorectal cancer incidence and mortality over the last three decades (1970–2000) (7). A link between meat consumption and colorectal cancer has been ascribed to high-fat content in meat, heterocyclic amines (HCAs) and/or polycyclic aromatic hydrocarbons (PAHs) formed during cooking of meat, *N*-nitroso compounds and heme iron (8).

Many epidemiological studies have investigated the association of consumption of meat and its components with colorectal cancer, however, data are not entirely consistent. To date, just over a dozen of systematic reviews and/or meta-analyses of consumption of meat or its components and colorectal cancer have been conducted since 2001. In 2007, the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) (9), concluded that there is convincing evidence that red meat consumption (based on a systematic review and meta-analysis of 16 cohort studies and 71 case–control studies) and processed meat consumption (based on pooled data of 14 cohort studies and 44 case–control studies) increase colorectal cancer risk. Earlier systematic reviews and meta-analyses have also consistently found a positive association between meat consumption, mainly red meat and processed meat and colorectal cancer (10–12). Following the review by WCRF/AICR (9), additional nine systematic reviews and/or meta-analyses were published on this issue, with five showing a positive association (6,13–17) and three reporting no association (18–20). Most current pooled data suggest that meat consumption may increase risk of colorectal cancer. However, such evidence has been obtained largely from studies conducted among Westerners, but evidence is limited among Asians including Japanese who consume much lower amount of meat compared with their western counterparts (21).

To assess the strength and consistency of the association between meat consumption and colorectal cancer risk among the Japanese population, we conducted a systematic and meta-analytic review of epidemiological studies on this issue in Japan. This is one in a series of articles that summarized epidemiologic evidence on the relation of lifestyles to cancers in Japan, including colorectal cancer (22–25).

## PATIENTS AND METHODS

Relevant epidemiological studies were identified by searching MEDLINE for the literature published through August 2013. A search of the *Ichushi* (*Japana Centra Revuo Medicina*) database was also conducted to identify the studies written in Japanese. These methods of literature identification were complemented by manual searches of references from pertinent articles where necessary. We employed the term 'meat', 'red meat', 'processed meat', 'poultry' combined with 'colorectal cancer',

**Table 1.** Summary of study design and the association between total meat consumption and colorectal cancer risk, cohort study

| Reference: author, publication year (reference number) | Study period | Study population | | | | | Magnitude of association[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Sex | No. of subjects | Age range (years) | Event | No. of incident cases or deaths | Colon | Rectum | Colorectum |
| Hirayama (1990) (30) | 1965–82 | Men and women | 265 118 | ≥40 | Death | 1115 | – | ↓ | n/a |
| Khan et al. (2004) (31) | 1984–2002 | Men | 1524 | ≥40 | Death | 15 | n/a | n/a | n/a |
| | | Women | 1634 | ≥40 | Death | 14 | n/a | n/a | n/a |
| Kojima et al. (2004) (32) | 1988–99 | Men | 45 181 | 40–79 | Death | 254 | n/a | n/a | n/a |
| | | Women | 62 643 | 40–79 | Death | 203 | n/a | n/a | n/a |
| Sato et al. (2006) (33) | 1990–2001 | Men and women | 41 835 | 40–64 | Incidence | 474 | – | – | – |
| Oba et al. (2006) (34) | 1992–2000 | Men | 13 894 | ≥35 | Incidence | 111 | ↑ | n/a | n/a |
| | | Women | 16 327 | ≥35 | Incidence | 102 | – | n/a | n/a |
| Takachi et al. (2011) (35) | 1995–2006 | Men | 38 462 | 40–79 | Incidence | 714 | ↑↑[b] | – | n/a |
| | | Women | 42 196 | 40–79 | Incidence | 431 | – | – | n/a |

n/a, not available.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see the text for a more detailed definition).
[b]Distal colon (when the magnitude of association differs between proximal and distal colon, the strongest association was reported).

'colon cancer', 'rectal cancer', 'case–control studies', 'cohort studies', 'Japan' and 'Japanese'. Articles written in either English or Japanese were reviewed. Only studies on Japanese populations living in Japan were included. Individual results were summarized in tables separately according to study design as cohort or case–control studies.

The studies were evaluated on the basis of the magnitude of association and the strength of evidence. First, relative risks (RR) or odds ratios (OR) in each epidemiologic study were grouped by the magnitude of association, considering statistical significance (SS) or no statistical significance (NS), into: strong (symbol ↑↑↑ or ↓↓↓), <0.5 or >2.0 (SS); moderate (symbol ↑↑ or ↓↓), either (i) <0.5 or >2.0 (NS), (ii) >1.5–2.0 (SS) or (iii) 0.5 to <0.67 (SS); weak (symbol ↑ or ↓), either (i) >1.5–2.0 (NS), (ii) 0.5 to <0.67 (NS) or (iii) 0.67–1.5 (SS); or no association (symbol −), 0.67–1.5 (NS). We chose 0.67 for the cutoff for decreased risk by dividing 1 by 1.5 (the cutoff for increased risk). After this stage, the strength of evidence was evaluated in a similar fashion to that used in the WHO/FAO Expert Consultation Report (26), where evidence was classified as 'convincing', 'probable', 'possible' and 'insufficient'. We assumed that biological plausibility based on evidence in experimental models, human studies and other pertinent data. Despite the use of this quantitative assessment rule, an arbitrary evaluation is inevitable when considerable variation exists in the magnitude of association between the findings of each study. The final judgment was made based on a consensus of the research group members, and it was therefore not necessarily objective. We assessed the evidence based on the aforementioned policy for total meat as well as according to meat groups (red meat, processed meat and poultry). In some studies with no results corresponding to these meat groups, we used culinary names for classification: red meat (beef, pork, liver or viscera) and processed meat (ham or sausage). If two or more results were presented within the same category of meat type (for instance, one for beef and another for port), we selected data showing the strongest association; however, if they showed an opposite direction of association, those data were not used for assessment.

In addition, we conducted a meta-analysis using random effects model (27) to estimate the summary RR and 95% confidence interval (CI) of subsite-specific cancers for the highest versus lowest category of meat consumption (total meat and meat types). We selected only the most recent study if there is overlapping period of data collection at the same setting, and excluded reports without showing 95% CI; and if 90% CI was reported, we converted it to 95% CI. We conducted statistical tests for heterogeneity, and quantified heterogeneity using the $I^2$ index (28); $I^2$ values range from 0–100%, with 0% indicating no heterogeneity and greater values expressing higher heterogeneity (29). We drew funnel plot to examine the possibility of publication bias. Additionally, we performed four types of sensitivity analysis by limiting studies that; (i) used validated dietary questionnaires, (ii) adjusted for anthropometrics or lifestyles, (iii) satisfied both of these conditions or (iv) measured incidence (rather than death). All statistical analyses were performed using Stata (version 13.0; StataCorp, College Station, TX, USA).

**Table 2.** Summary of the association[a] between meat consumption by type and colorectal cancer risk, cohort study

| Reference: author, publication year (reference number) | Sex | Cancer site | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Colon | | | Rectum | | | Colorectum | | |
| | | Red meat | Processed meat | Poultry | Red meat | Processed meat | Poultry | Red meat | Processed meat | Poultry |
| Hirayama (1990) (30) | Men | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| | Women | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Khan et al. (2004) (31) | Men | n/a | n/a | n/a | n/a | n/a | n/a | ↑↑[b] | ↓ | − |
| | Women | n/a | n/a | n/a | n/a | n/a | n/a | n/a | − | ↑ |
| Kojima et al. (2004) (32) | Men | − | − | ↑ | − | − | − | n/a | n/a | n/a |
| | Women | − | − | − | ↓↓ | ↑ | − | n/a | n/a | n/a |
| Sato et al. (2006) (33) | Men and women | − | − | ↑ | − | − | − | − | − | − |
| Oba et al. (2006) (34) | Men | − | ↑↑ | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| | Women | − | − | n/a | | | | n/a | n/a | n/a |
| Takachi et al. (2011) (35) | Men | − | − | − | − | − | − | n/a | n/a | n/a |
| | Women | ↑ | − | − | − | − | − | n/a | n/a | n/a |

[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; −, no association (see the text for a more detailed definition).
[b]Liver.

## RESULTS

A total of 6 cohort studies (30–35) and 13 case–control studies (36–48) were identified (Supplementary data, Tables S1 and S2, respectively). Of cohort studies, two reported data for men and women combined (30,33), and the remaining ones showed results separately for men and women. Among the case–control studies, nine gave findings for both sexes combined (36–38,40–42,44,45,48), two presented results for men and women separately (43,47), and the remainder investigated only men (39,46). The magnitude of association of consumption of total meat and specific types of meat with colorectal cancer is summarized in Tables 1 and 2, respectively, for cohort studies and in Tables 3 and 4, respectively, for case–control studies.

Of total six cohort studies, four showed relative risk for colon and rectum separately (30,32,33,35), but not combined; one reported results for colon cancer only (34), and the remaining study displayed data for both sites combined (31). Of four investigations reporting data for total meat consumption, two displayed a weak-to-moderate positive association with colon cancer (34,35) and one exhibited an inverse association with rectal cancer (30) (Table 1). The majority of studies observed no association between red meat with colorectal cancer, but a weak positive association with colon was noted in one report (35), and a moderate positive association with colorectal cancer was noticed in another (31) (Table 2). Regarding processed meat, two studies found a weak or moderate positive association with rectal (32) and colon cancer (34), whereas another found a weak inverse association with

**Table 3.** Summary of study design and the association between total meat consumption and colorectal cancer risk, case–control study

| Reference: author, publication year (reference number) | Study period | Study subjects | | | | Magnitude of association[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | Sex | Age range | No. of cases | No. of controls | Colon | Rectum | Colorectum |
| Kondo (1975) (36) | 1967–73 | Men and women | Not specified | 393 | 582 | n/a | n/a | n/a |
| Haenszel et al. (1980) (37) | NA | Men and women | Not specified | 588 | 1176 | n/a | n/a | – |
| Watanabe et al. (1984) (38) | 1977–83 | Men and women | Not specified | 203 (M: 110, F: 93) | 203 (M: 110, F: 93) | – | – | n/a |
| Tajima and Tominaga. (1985) (39) | 1981–83 | Men | 40–79 years | 52 | 111 | n/a | n/a | n/a |
| Kato et al. (1990) (40) | 1986–90 | Men and women | Not specified | 223 | 578 | – | ↓ | n/a |
| Hoshiyama et al. (1993) (41) | 1984–90 | Men and women | 40–69 years | 181 (M: 98, F: 83) | 653 (M: 343, F: 310) | ↓ | ↓ | n/a |
| Kotake et al. (1995) (42) | 1992–94 | Men and women | Not specified | 363 (M: 214, F: 149) | 363 (M: 214, F: 149) | n/a | n/a | n/a |
| Inoue et al. (1995) (43) | 1988–92 | Men | 24–86 years | 257 | 8621 | n/a | n/a | n/a |
| | | Women | 24–88 years | 175 | 23 161 | n/a | n/a | n/a |
| Nishi et al. (1997) (44) | 1987–90 | Men and women | Not specified | 330 | 660 | n/a | n/a | – |
| Ping et al. (1998) (45) | 1986–94 | Men and women | 40–84 years | 100 (M: 77, F: 23) | 265 (NA) | n/a | n/a | – |
| Murata et al. (1999) (46) | 1989–97 | Men | Not specified | 426 | 794 | [b] | [b] | n/a |
| Wakai et al. (2006) (47) | 2001–04 | Men | 20–79 years | 295 | 1475 | – | – | n/a |
| | | Women | 20–79 years | 212 | 1060 | – | ↓ | n/a |
| Kimura et al. (2007) (48) | 2000–03 | Men and women | 20–74 years | 782 | 793 | n/a | n/a | n/a |

M, men; F, women

[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see the text for a more detailed definition).

[b]Although the precise estimate for highest versus lowest intake category was not shown, a score assigned to eating frequency was significantly associated with increased risk.

**Table 4.** Summary of the association[a] between meat consumption by type and colorectal cancer risk, case–control study

| Reference: author, publication year (reference number) | Sex | Cancer site | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Colon | | | Rectum | | | Colorectum | | |
| | | Red meat | Processed meat | Poultry | Red meat | Processed meat | Poultry | Red meat | Processed meat | Poultry |
| Kondo (1975) (36) | Men and women | n/a | n/a | ↑ | ↓↓ | n/a | – | n/a | n/a | n/a |
| Haenszel et al. (1980) (37) | Men and women | n/a | n/a | n/a | n/a | n/a | n/a | – | n/a | n/a |
| Watanabe et al. (1984) (38) | Men and women | – | – | – | ↑ | ↓ | – | n/a | n/a | n/a |
| Tajima and Tominaga (1985) (39) | Men | ↑↑ | ↑↑↑ | ↑↑↑ | ↑↑ | – | ↑↑ | n/a | n/a | n/a |
| Kato et al. (1990) (40) | Men and women | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Hoshiyama et al. (1993) (41) | Men and women | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Kotake et al. (1995) (42) | Men and women | ↑ | n/a | – | ↑ | n/a | ↓ | n/a | n/a | n/a |
| Inoue et al. (1995) (43) | Men | Excluded[b] | ↑ | – | – | – | ↓ | n/a | n/a | n/a |
| | Women | – | – | – | – | ↑ | – | n/a | n/a | n/a |
| Nishi et al. (1997) (44) | Men and women | ↑↑[c] | ↑↑ | n/a | ↑↑↑[c] | ↑ | n/a | n/a | n/a | n/a |
| Ping et al. (1998) (45) | Men and women | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Murata et al. (1999) (46) | Men | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Wakai et al. (2006) (47) | Men | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| | Women | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Kimura et al. (2007) (48) | Men and women | – | – | ↓[d] | – | – | – | – | – | – |

[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; –, no association (see the text for a more detailed definition).
[b]Due to an opposite direction of association for each type of meat in this group.
[c]Animal viscera.
[d]Distal colon (when the magnitude of association differed between proximal and distal colon, the strongest association was reported).

colorectal cancer (31). Some studies found that poultry consumption was weakly, positively associated with colon (32,33) and cancer of both sites (31).

Most case–control studies (36,38–44,46–48) presented data for the colon and rectum separately; of these, one additionally gave results for colon and rectum cancers combined (48). Two studies reported only results for cancer of two sites combined (37,45). Of eight studies with data for total meat consumption, three found a weak inverse association with colon cancer (41) or rectal cancer (40,41,47), four reported no association (37,38,44,45), and one reported a positive association (46) (Table 3). As regards red meat, we did not include data of men in one study (43) in the assessment of colon cancer risk because the direction of association differed between beef and pork. Four studies found a weak to strong positive association of red meat consumption with cancer of the colon (39,42,44) or rectum (38,39,42,44), whereas one study displayed a moderate inverse association with rectal cancer (36) (Table 4). Similarly, there was a weak to strong positive association of processed meat consumption with colon cancer (39,43,44), whereas only one showed a weak inverse association with rectal cancer (38). As for poultry consumption, some studies reported a weak-to-strong positive association with colon cancer (36,39) and rectal cancer (39), whereas some others observed a weak inverse association with colon cancer (48) and rectal cancer (42,43).

A total of 14 studies (six cohort and eight case–control studies) reporting either total, red or processed meat were included in meta-analysis after excluding five studies: three without reporting 95% CI (36,37,39,45) and one conducted at the same hospital with an overlapping period of survey (40). We converted 90% CI to 95% CI in one study (30). Total meat consumption was not significantly associated with colorectal cancer ($RR_{combined}$: 1.06, 95% CI: 0.92–1.22), colon ($RR_{combined}$: 1.17, 95% CI: 0.99–1.39) or rectal cancer ($RR_{combined}$: 0.90, 95% CI: 0.71–1.14). Red meat and processed meat consumption was associated with an increased risk of colorectal and colon, but not rectal, cancer; pooled RR (95% CI) for red mead was 1.16 (1.001–1.34) and 1.21 (1.03–1.43) for colorectal and colon cancer, respectively (Fig. 1), and that for processed meat was 1.17 (95% CI: 1.02–1.35) and 1.23 (95% CI: 1.03–1.47) for colorectal cancer and colon cancer, respectively (Fig. 2). High poultry consumption was associated with a significantly lower risk of rectal cancer ($RR_{combined}$: 0.80, 95% CI: 0.67–0.96). There was no evidence of significant inter-study heterogeneity for the above associations. Funnel plot did not indicate publication bias. Sensitivity analyses among studies of good quality (use of a

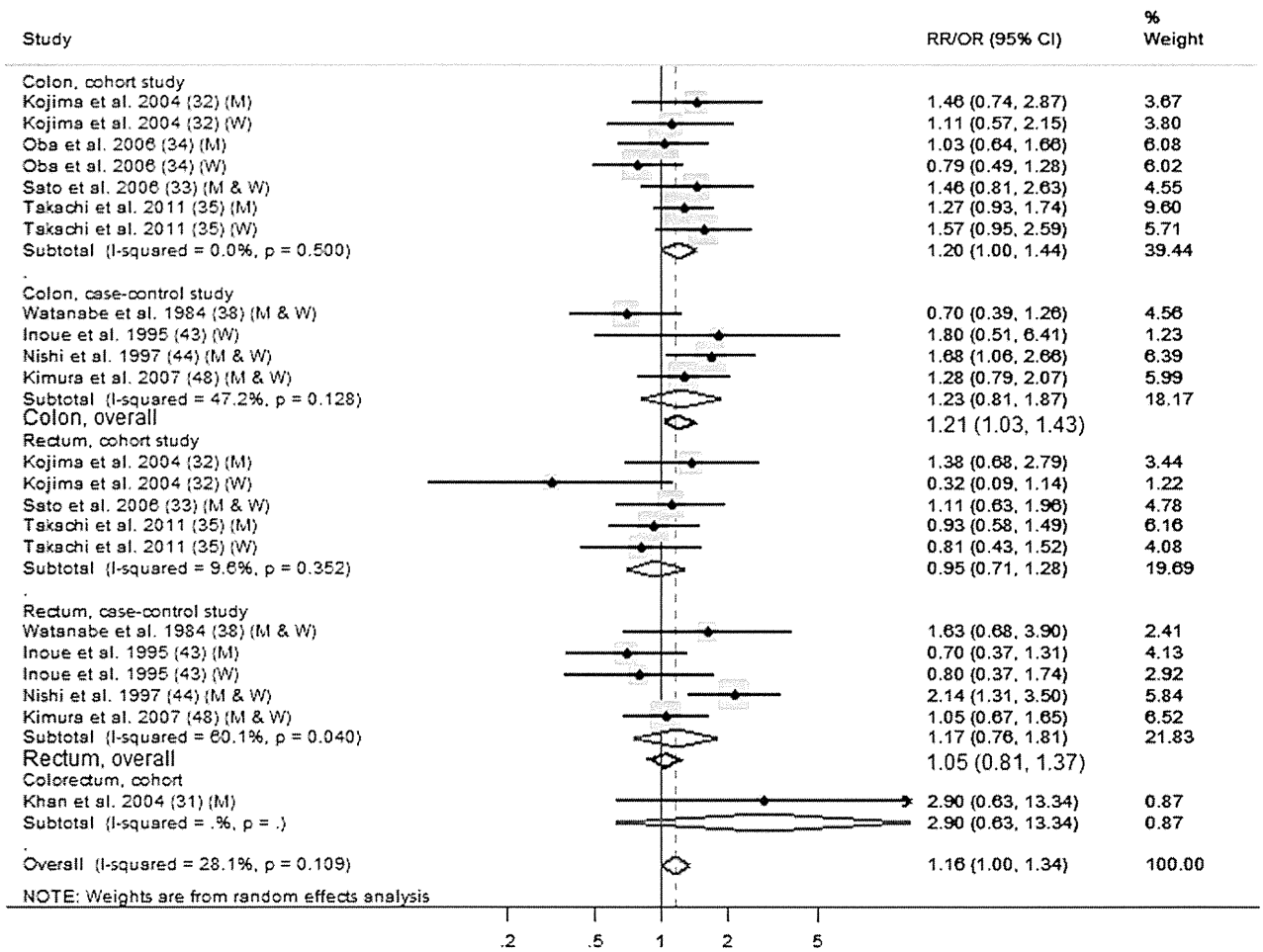


**Figure 1.** Red meat consumption and colorectal cancer in Japanese.

validated dietary questionnaire, adjustment for confounders or follow-up of incidence) showed similar results; pooled RR for red meat ranged from 1.10 to 1.13 and from 1.18 to 1.22 for colorectal cancer and colon cancer, respectively; that for processed meat ranged from 1.07 to 1.18 and from 1.18 to 1.24 for colorectal cancer and colon cancer, respectively.

## DISCUSSION

Several methodological aspects are worth mentioning in interpreting the present results. First, all studies reviewed herein used food frequency questionnaires (FFQ) to assess meat intake. Although FFQ is a practical instrument for nutritional epidemiological studies, it is prone to measurement error either chance or systematic bias. Most of the studies inquired only about consumption frequency, and most case–control studies did not report having utilized validated questionnaires and cohort studies adopted questionnaires with low-to-moderate validity. These issues may preclude evaluation of levels of meat consumption and comparison among studies regarding the magnitude of association. Second, there was a lack of uniform classification and/or categorization of meat consumed, i.e. the lowest and highest category of meat consumption, which may complicate data interpretation such as dose–response relationship. For example, the studies that reported only meat consumption did not clarify meat types (12,30,40,41,45,47), or red meat was defined as a combination of beef/pork and processed meat in a large case–control study (48). Third, almost all studies did not consider cooking methods for meat and its doneness levels; several studies reported that that fried, broiled and very well-done meat consumption was associated with increased colorectal cancer risk (49). Fourth, most of case–control studies did not control for important potential confounding factors for colorectal cancer including smoking, alcohol drinking, physical activity and vegetable/fruit consumption. Finally, case–control and cohort studies by their nature are susceptible to different forms of bias such as random error, misclassification and confounding (50). In particular, recall bias and selection bias are concerning issues in case–control studies (51).

Meat is a primary source of protein, rich in several minerals and vitamins, and a supplier of fat (52). There are several possible mechanisms to explain carcinogenic effects of meat.

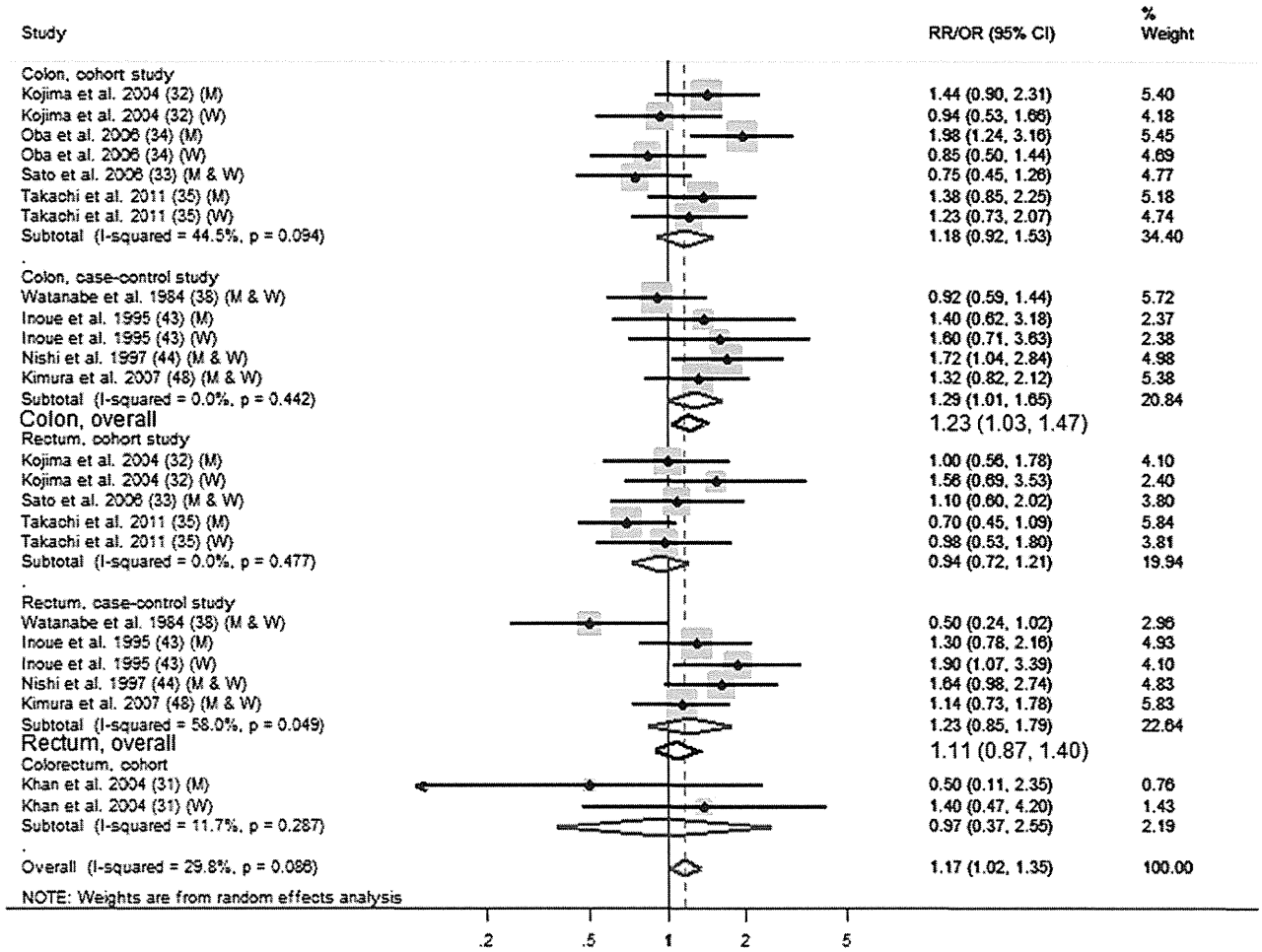


**Figure 2.** Processed meat consumption and colorectal cancer in Japanese.

First, heme iron in red meat has shown to increase endogenous *N*-nitroso compounds (NOCs) (53) known as multisite carcinogens (9,54). Heme iron can also induce DNA damage (55), which is involved in carcinogenesis (56), and catalyze the formation of cytotoxic and genotoxic aldehydes (15). Moreover, NOCs are produced when meat is processed, whereby increasing risk of cancer (57). Second, carcinogenic HCAs and PAHs are formed while cooking meat at a high temperature or on open flame (9). Third, a high consumption of total and saturated fats in meat has been suggested to increase colorectal cancer risk (57,58) by enhancing excretion of bile acids, the products of which have been shown to promote tumorigenesis (59,60).

HCAs, PAHs and NOCs are meat-derived mutagens, which can be activated by Phase I and Phase II xenobiotic metabolizing enzymes to exert their carcinogenic effects (61,62). For instance, some enzymes including cytochrome P450 (CYP)1A2, CYP1B1, sulfotransferases (SULTs) and *N*-acetyltransferases (NATs) are known to promote HCAs metabolism (63). Recently, two large case–control studies (64,65) showed a synergistic interaction between 2-amino-3, 8-dimethylimidazo {4,5-*f*}-quinoxaline (MeIQx), a meat-derived mutagen, and HCA-metabolizing enzymes (CYP1A2, CYP1B1, NATs) on risk of colorectal adenomas, a well-established precursor of colorectal cancer. In addition, HCA-metabolizing gene polymorphisms were shown to modify the association between red meat intake and the risk of colorectal adenomas (64). These data suggesting gene–diet interaction offer an additional support for the role of red and processed meat in colorectal carcinogenesis.

The present review showed no clear evidence to support a positive association between total meat consumption and colorectal cancer in Japanese. Consistent with this review, a previous meta-analysis of 6 cohort studies and 18 case–control studies (11) including three Japanese investigations in the present review (30,37,46) revealed no significant increase in risk of colorectal cancer for the highest versus lowest category of total meat consumption; pooled RR were 1.03 and 1.18 for cohort studies and case–control ones, respectively. Similarly, null association was observed in a meta-analysis of seven case–cohort studies in the UK (summary OR for the highest versus lowest category was 0.97) (19). Furthermore, a recent

individual-level meta-analysis of eight cohort studies in Asia reporting no association between total meat consumption and risk of cancer mortality (66); summary hazard ratio and 95% confidence interval (CI) in the highest level of consumption versus lowest level was 1.11 (0.94–1.30) in men and 0.90 (0.78–1.04) in women. The present review and previous ones (11,19) suggest that total meat intake may not increase risk of colorectal cancer.

We found positive associations of red meat and processed meat consumption with colorectal and colon cancer. Accruing meta-analyses consistently reported an elevated risk of colon cancer (6,11–14,16,17,20,49,67) or colonic adenomas (67) with higher consumption of red meat (6,11–13,17,20,49,67) and processed meat (11,12,14,17,67). For instance, a previous meta-analysis of nine cohort studies (12), pooled RR and 95% CI of colon cancer for the highest versus lowest category of red meat was 1.21 (1.05–1.40), which is similar to our data (1.21, 1.03–1.43). Concerning processed meat, an earlier pooled data of 15 cohort and case–control studies showed a 22% significantly higher risk of colon cancer in the highest category of consumption than in the lowest one (11), almost the same magnitude as did the present preview (23%). There is substantial evidence for a positive association between processed meat consumption and colorectal cancer (11,12,14,17). Of particular note, WCRF/AICR concludes that red and processed meats are convincing causes of colorectal cancer. We have no clear reason for the lack of an association between red/processed meat consumption and rectal cancer, but this could be ascribed to a difference in carcinogenic mechanisms between rectal and colon cancers (68). The evidence reviewed herein and accumulating data suggest that consumption of red and processed meat is associated with colon and colorectal cancer.

We found a decreased risk of rectal cancer associated with high poultry consumption. Similarly, a cohort study in Australia (69) reported a lower, albeit statistically non-significant, risk of rectal cancer in the group of highest poultry consumption; the RRs (95% CI) for the highest versus lowest category of poultry consumption was 0.7 (0.5–1.2). Cohort studies in the US (70) and Europe (71), however, showed no association with poultry, with RR (95% CI) being 0.93 (0.68–1.26) and 0.99 (0.71–1.37), respectively. It should be noted that most case–control studies in Japan (included in the present meta-analysis) did not adjust for potentially important confounding variables including alcohol use, smoking, physical activity and vegetable/fruit consumption. We repeated the meta-analysis only among prospective studies with adjustment for these variables and found that the association was attenuated; the pooled RR (95% CI) for the highest versus lowest poultry consumption was 0.86 (0.66–1.12). Further longitudinal studies are needed to clarify the role of poultry in colorectal cancer.

In summary, the present review and meta-analysis found a modest increased risk of colorectal cancer or colon cancer with a higher consumption of red meat and processed meat. Moderation in intake of these types of meat may protect colorectal cancer in Japanese.

## EVALUATION OF EVIDENCE ON FISH CONSUMPTION AND COLORECTAL CANCER IN JAPANESE

From these results and on the basis of assumed biological plausibility, we conclude that red meat and processed meat consumption possibly increases risk of colorectal (colon) cancer among Japanese population.

### Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

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### Conflict of interest statement

None declared.

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## APPENDIX

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# Burden of Total and Cause-Specific Mortality Related to Tobacco Smoking among Adults Aged ≥45 Years in Asia: A Pooled Analysis of 21 Cohorts

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## Abstract

*Background:* Tobacco smoking is a major risk factor for many diseases. We sought to quantify the burden of tobacco-smoking-related deaths in Asia, in parts of which men's smoking prevalence is among the world's highest.

*Methods and Findings:* We performed pooled analyses of data from 1,049,929 participants in 21 cohorts in Asia to quantify the risks of total and cause-specific mortality associated with tobacco smoking using adjusted hazard ratios and their 95% confidence intervals. We then estimated smoking-related deaths among adults aged ≥45 y in 2004 in Bangladesh, India, mainland China, Japan, Republic of Korea, Singapore, and Taiwan—accounting for ~71% of Asia's total population. An approximately 1.44-fold (95% CI = 1.37–1.51) and 1.48-fold (1.38–1.58) elevated risk of death from any cause was found in male and female ever-smokers, respectively. In 2004, active tobacco smoking accounted for approximately 15.8% (95% CI = 14.3%–17.2%) and 3.3% (2.6%–4.0%) of deaths, respectively, in men and women aged ≥45 y in the seven countries/regions combined, with a total number of estimated deaths of ~1,575,500 (95% CI = 1,398,000–1,744,700). Among men, approximately 11.4%, 30.5%, and 19.8% of deaths due to cardiovascular diseases, cancer, and respiratory diseases, respectively, were attributable to tobacco smoking. Corresponding proportions for East Asian women were 3.7%, 4.6%, and 1.7%, respectively. The strongest association with tobacco smoking was found for lung cancer: a 3- to 4-fold elevated risk, accounting for 60.5% and 16.7% of lung cancer deaths, respectively, in Asian men and East Asian women aged ≥45 y.

*Conclusions:* Tobacco smoking is associated with a substantially elevated risk of mortality, accounting for approximately 2 million deaths in adults aged ≥45 y throughout Asia in 2004. It is likely that smoking-related deaths in Asia will continue to rise over the next few decades if no effective smoking control programs are implemented.

*Please see later in the article for the Editors' Summary.*



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**Abbreviations:** CVD, cardiovascular disease; HR, hazard ratio; PAR, population attributable risk; RR, relative risk.

## Introduction

Tobacco smoking is a major risk factor for many diseases, including cardiovascular disease (CVD), respiratory disease, and cancers of the lung and multiple other sites [1,2]. In the US and many other Western countries, the epidemic of tobacco smoking started in men in the early 1900s and reached its peak in the 1960s; a similar epidemic occurred among women ~40 y later [3–5]. The main increase in tobacco-related deaths in these countries was not seen until the second half of the 20th century [3,6–8]. By the 1990s, tobacco smoking accounted for an estimated one-third of all deaths and >50% of cancer deaths in adult men [3,6–8]. With increasing awareness of smoking-associated risks and heightened anti-smoking campaigns, tobacco use has steadily declined in the US and many other developed countries over the past 20–30 y [3–5,9,10], resulting in a recent decrease in lung cancer and other smoking-related diseases in these countries [3,11].

In Asia, where ~60% of the world population lives, tobacco control programs are less well developed, particularly in low- and middle-income countries including China and India, the two most populous countries in the world. Inadequate public awareness of smoking risks, combined with aggressive marketing by tobacco companies, has resulted in a sharp increase in tobacco smoking among men in many Asian countries over the past few decades [3,11,12]. Smoking prevalence in women was traditionally very low but has increased in recent decades in some Asian countries [3,11,12]. More than 50% of men in many Asian countries are smokers [12,13], approximately twice the level in many Western countries. Despite a recent decline in smoking prevalence in several high-income Asian countries [11,13], tobacco use in most Asian countries remains very high. Indeed, Asia is now considered the largest tobacco producer and consumer in the world. More than half of the world's 1.1 billion smokers live in Asia [3,13]. Because many Asian countries are in the early stages of the tobacco epidemic, it is likely that the burden of diseases caused by tobacco smoking will continue to rise over the next few decades, and much longer if the tobacco epidemic remains unchecked.

The size of the effect of tobacco smoking on risk of death, typically measured using smoking-associated relative risks (RRs), varies across countries because of differences in characteristics of smokers, smoking behaviors, and tobacco products. Over the past 15 y, several studies have investigated associations between smoking and selected health outcomes in certain Asian populations and have estimated smoking-associated population attributable risk (PAR) [14–21]. Some studies estimated burden of disease due to smoking in a specific Asian country/region [14,16,17,19,20]. However, most of these estimates were derived from either a single cohort study or studies using a less-than-optimal research design. In this study, we first estimated RRs of overall and cause-specific mortality associated with tobacco smoking as well as smoking prevalence, using data from ~1 million participants recruited in 21 prospective cohort studies in seven countries/regions that account for ~71% of Asia's total population. We then used these estimates and mortality data from the World Health Organization [22] to quantify deaths attributable to tobacco smoking in these Asian populations.

## Methods

This study was approved by the ethics committees for all the participating studies and of the Fred Hutchinson Cancer Research Center.

This study utilized resources from a recent pooling project of prospective cohort studies conducted as part of the Asia Cohort Consortium that quantified the association between body mass index and risk of overall and cause-specific mortality in Asians [23]. Cohorts included in the current analysis were in Bangladesh, India, mainland China, Japan, Republic of Korea, Singapore, and Taiwan. A brief description of each of the participating cohort studies is provided in Text S1. All of the cohort studies collected baseline data on demographics, lifestyle factors, body mass index, and history of tobacco smoking, which included current smoking status, duration, and amount and types of tobacco products. Data on all-cause and cause-specific mortality were ascertained through linkage to death certificate data or active follow-up. Additional data were collected on other baseline variables, including education, marital status, alcohol consumption, physical activity, and previous diagnosis of selected diseases, including diabetes, hypertension, cancer, and CVDs. Individual-level data from all participating cohorts were collected and harmonized for statistical analysis.

The association between tobacco smoking and risk of death was examined using Cox proportional hazards regression models, employing a categorical representation of tobacco smoking as the predictor variable. Lifetime nonsmokers were used as the reference for estimating hazard ratios (HRs)—as measures of RR of death for the exposed versus the non-exposed population—and 95% confidence intervals associated with ever, former, and current smoking, as well as pack-years smoked, after adjusting for potential confounders including baseline age, education, urban/rural residence, body mass index, and marital status. All analyses were conducted separately for men and women because of large differences in smoking prevalence. Analyses were country-specific unless otherwise noted. To improve the stability of point estimates in the analyses of pack-years of smoking and for risk of death due to site-specific cancer, as well as types of CVD and respiratory diseases, cohorts were combined into broad ethnic groupings: South Asians (Indians and Bangladeshis) and East Asians (Chinese [including cohorts from mainland China, Singapore, and Taiwan], Japanese, and Koreans), and categorized further among East Asians into Chinese/Koreans and Japanese. No smoking-associated HR was estimated for Bangladesh separately because of the small sample size. The number of Koreans in this study was small, and, thus, they were combined with Chinese individuals in some analyses. Bidi smoking is common in India and Bangladesh; thus, information regarding bidi smoking was incorporated to construct smoking variables, including pack-years smoked (4 bidis = 1 cigarette based on approximately 0.25 and 1.0 g of tobacco per bidi and cigarette, respectively).

In the models, the effect of tobacco smoking on mortality was assumed to be cohort-specific. For each cohort, we assumed that the log-HR for tobacco smoking has a fixed-effect component that is common to all cohorts within each country and a random effect that is cohort-specific. Random effects for log-HRs were assumed to be normally distributed, with mean zero; that is, we assumed that $\hat{\beta}_{ij}$, the estimated log-HR for the $j$-th smoking level in the $i$-th cohort, has distribution $\hat{\beta}_{ij} \sim N\left(\beta_j, \hat{\sigma}_{ij}^2 + \tau_j^2\right)$, where $\hat{\sigma}_{ij}^2$ is the within-study variance of $\hat{\beta}_{ij}$ as estimated from the Cox regression model and $\tau_j^2$ is the between-cohort variance of $\hat{\beta}_{ij}$ [24,25]. Parameter $\beta_j$ and 95% CIs were estimated in the meta-analysis. Age at study entry and exit was used to define the time-to-event variable in the Cox models. Age at study exit was defined as age at date of death or end of follow-up, whichever occurred first. Cox

model estimation for each cohort was performed using the PHREG procedure in SAS version 9.2. Meta-analysis estimation was performed using the SAS MIXED procedure.

To estimate PAR, we used the following formula: $PAR = P(RR-1)/[P(RR-1)+1]$, where smoking prevalence and smoking-associated RR are denoted as P and RR (measured using HR in this analysis), respectively. PARs for overall mortality and major causes of death associated with tobacco smoking were estimated for each cohort and then combined using meta-analyses to derive summary PARs per country. To estimate PARs for East Asians (Chinese, Japanese, and Koreans), South Asians (Bangladeshis and Indians), or all seven countries/regions combined, we used the population size of each country/region as a weight to derive weighted HR and smoking prevalence values. To estimate the number of deaths attributable to tobacco smoking, we used World Health Organization age-specific death rates for 2004 for each country. Most of the cohort studies enrolled participants after the mid-1980s; therefore, smoking prevalence rates estimated in this study reflect smoking status in the 1990s (Table 1). Given the long latency of chronic diseases—typically 15 y and longer—it is reasonable to use smoking prevalence rates assessed in the 1990s to estimate number of deaths due to tobacco smoking in 2004.

The number of deaths from a particular disease attributable to tobacco smoking was calculated by multiplying the PAR for that disease by the total number of deaths in the population from that disease. Analyses also were performed to estimate the number of deaths from a particular disease due to smoking for age groups 45–59, 60–69, and ≥70 y using age-specific HRs and smoking prevalence and then summing these age-specific estimates to obtain the overall number of deaths due to smoking for that disease. This age-specific method yielded similar results to the one without age-specific estimates, and, thus, the latter method was used, as it provides a tighter 95% CI than the age-specific method.

## Results

A total of 1,223,092 participants were included in the 21 participating cohorts for this study. Because most studies were conducted among adults aged ≥45 y, participants ($n = 70,812$) who did not contribute person-years in the age group ≥45 y were excluded from this analysis. Also excluded (not mutually exclusively) were participants with prior history of cancer or CVD at baseline ($n = 47,585$), with missing data on tobacco smoking ($n = 38,898$) or vital status ($n = 451$), or with less than 1 y of observation after baseline survey ($n = 30,039$). After these exclusions, 1,049,929 participants (510,261 men; 539,668 women) remained (Table 1). Overall, the mean prevalence of tobacco smoking was 65.1% for men and 7.1% for women. Over a mean follow-up of 10.2 y through roughly the mid-2000s for most cohorts, a total of 123,975 deaths were identified in these cohorts.

Compared with never-smokers, a 1.44-fold higher risk (95% CI = 1.37–1.51) of deaths from all causes was observed among male ever-smokers in pooled analyses of all cohorts (Table 2). The estimated HRs related to smoking were slightly higher in Singapore, Republic of Korea, Japan, and Taiwan than in India and mainland China, although 95% CIs overlapped in some of these point estimates (heterogeneity test: $p<0.001$, $I^2 = 89$ [95% CI = 85–92]). Among women, ever smoking was associated with a 1.48-fold higher risk (95% CI = 1.38–1.58) of death from any cause. This risk also varied across study populations (heterogeneity test: $p<0.001$, $I^2 = 82$ [95% CI = 74–88]). The lowest elevation of risk was observed among Indian women, in which ever smoking was related to a 1.16-fold (95% CI = 0.98–1.36) elevated risk of deaths from all causes. Elevated risk of death was also seen among former smokers, although the risk was lower than among current smokers (Table S1).

Among men, elevated risk of death due to CVD, cancer, and respiratory diseases was statistically significantly associated with ever smoking in virtually all study populations (Table 3). Ever smoking was associated with a 1.35-fold elevated risk (95% CI = 1.26–1.45) of death due to CVD in the analysis that included all cohorts. The risk, however, varied considerably across populations, with the strongest association observed in Taiwan (HR = 1.69; 95% CI = 1.36–2.10) and the weakest association observed in mainland China (HR = 1.17; 95% CI = 1.11–1.25) (heterogeneity test: $p<0.001$, $I^2 = 77$ [95% CI = 66–85]). A 1.75-fold elevated risk (95% CI = 1.67–1.85) of death due to cancer in men was associated with ever smoking in the combined analysis of all cohorts. The association with cancer risk was, in general, quite consistent across study populations (heterogeneity test: $p = 0.76$). For death due to respiratory diseases in men, a 1.53-fold elevated risk (95% CI = 1.39–1.69) was associated with ever smoking in the combined analysis of all cohorts, and no statistically significant heterogeneity was identified ($p = 0.29$). Among East Asian women, positive associations were also observed between ever smoking and risk of major cause-specific deaths, with HRs ranging from 1.44 (95% CI = 1.23–1.69) for respiratory diseases to 1.59 for CVD (95% CI = 1.41–1.79) and cancer (95% CI = 1.45–1.75). Heterogeneity tests were statistically significant for cancer ($p<0.001$) and respiratory diseases ($p = 0.003$) but not for CVD ($p = 0.20$). Some of the country-specific risk estimates for East Asian women were not statistically significant because of low smoking prevalence among women in Asia. Among Indian women and all South Asian women combined, the association between ever smoking and risk of cause-specific deaths was weak and statistically nonsignificant.

To quantify risk associated with smoking status and pack-years of smoking, we combined cohorts by ethnic background to improve the stability of point estimates. For men (Table 4) and women (Table 5), risk of total mortality and cause-specific mortality was elevated with increased tobacco smoking among current smokers, measured by pack-years of smoking. Excess deaths were also observed among former smokers, compared with never-smokers, although the risk was lower than for current smokers for deaths due to any cause, CVD, and cancer. A substantially elevated risk of death from respiratory diseases was found among former smokers, particularly in Chinese/Koreans and Indians/Bangladeshis. This excess is probably caused by some smokers quitting smoking after they developed respiratory diseases. Risks associated with smoking status and pack-years of smoking were not estimated for South Asian women because of the small sample size.

Further analyses were performed to estimate smoking-associated HRs for selected cancers as well as for other common diseases (Table 6). Among men and women, the strongest association with tobacco smoking was lung-cancer mortality: a 3- to 4-fold elevated risk consistently across all populations. In East Asian men, ever smoking was also associated with elevated risk for cancers of the mouth/pharynx/larynx, esophagus, stomach, colorectum, liver, pancreas, and bladder, cancers that have been consistently related to smoking in previous studies. HR estimates for South Asians were statistically nonsignificant or unreliable for several cancers, probably because of small sample sizes. Because of the relatively small sample size of female ever-smokers in South Asia, results are presented for East Asian women only. As in men, risks were elevated for virtually all smoking-related cancers.

Among East Asian men and women, risks of death associated with smoking were elevated for coronary heart disease, stroke, and chronic obstructive pulmonary disease. Among South Asian men,

**Table 1.** Characteristics of participating cohorts in the Asia Cohort Consortium.

| Cohort | Number of Participants[a] | Study Entry | Mean Years of Follow-Up | Women (Percent) | Mean Age at Entry | Ever-Smokers (Percent) | | Number of Deaths | Cause of Death (Percent)[b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Men | Women | | Cancer | CVD | Respiratory Diseases | Other |
| **India** | | | | | | | | | | | | |
| Mumbai | 120,055 | 1991–1997 | 5.3 | 36.4 | 53.4 | 31.8 | 0.5 | 10,839 | 8.5 | 45.0 | 14.4 | 32.2 |
| Trivandrum | 103,942 | 1995–2002 | 7.8 | 59.6 | 52.7 | 60.1 | 1.8 | 9,406 | 10.6 | 36.6 | 12.8 | 40.0 |
| Bangladesh | 4,572 | 2000–2002 | 6.7 | 41.0 | 46.8 | 83.0 | 15.5 | 206 | 13.7 | 51.2 | 10.2 | 24.9 |
| **Mainland China** | | | | | | | | | | | | |
| CHEFS | 137,460 | 1990–1992 | 7.8 | 50.9 | 54.9 | 63.9 | 13.4 | 14,776 | 23.4 | 44.8 | 5.0 | 26.8 |
| SCS | 18,010 | 1986–1989 | 16.4 | 0.0 | 55.2 | 57.2 | NA | 4,902 | 39.6 | 33.9 | 10.7 | 15.9 |
| SMHS | 54,707 | 2001–2006 | 3.1 | 0.0 | 55.1 | 69.6 | NA | 596 | 53.1 | 25.7 | 5.4 | 15.7 |
| SWHS | 67,245 | 1996–2000 | 8.7 | 100.0 | 51.3 | NA | 2.7 | 1,921 | 48.2 | 23.5 | 2.6 | 25.7 |
| **Taiwan** | | | | | | | | | | | | |
| CBCSP | 22,961 | 1991–1992 | 15.4 | 50.1 | 47.2 | 56.4 | 1.0 | 2,400 | 38.1 | 19.5 | 5.9 | 36.4 |
| CVDFACTS | 4,170 | 1990–1993 | 15.0 | 55.8 | 50.7 | 54.9 | 1.3 | 711 | 27.5 | 26.1 | 10.7 | 35.7 |
| Singapore (SCHS) | 57,714 | 1993–1999 | 11.7 | 56.1 | 56.1 | 57.1 | 8.4 | 8,234 | 36.7 | 33.1 | 14.8 | 15.4 |
| **Japan** | | | | | | | | | | | | |
| 3 Pref Aichi | 29,316 | 1985 | 12.1 | 50.6 | 56.3 | 84.3 | 17.5 | 5,330 | 32.4 | 35.0 | 11.9 | 20.7 |
| Ibaraki | 91,847 | 1993–1994 | 11.6 | 66.3 | 58.5 | 77.8 | 5.6 | 9,545 | NA | NA | NA | NA |
| JACC | 74,465 | 1988–1990 | 12.9 | 56.4 | 57.0 | 79.1 | 6.6 | 10,099 | 38.6 | 29.1 | 11.4 | 20.9 |
| JPHC1 | 40,574 | 1990–1992 | 14.7 | 52.2 | 49.6 | 75.7 | 7.3 | 3,007 | 45.0 | 24.6 | 6.0 | 24.3 |
| JPHC2 | 52,838 | 1992–1995 | 11.7 | 52.9 | 54.1 | 75.7 | 7.6 | 4,708 | 44.6 | 24.1 | 8.7 | 22.6 |
| 3 Pref Miyagi | 18,951 | 1984 | 12.0 | 53.4 | 56.2 | 77.1 | 12.0 | 3,307 | 31.0 | 38.5 | 11.0 | 19.5 |
| Miyagi | 38,560 | 1990 | 12.9 | 45.2 | 51.5 | 81.5 | 11.1 | 2,932 | 54.9 | 25.9 | 6.3 | 12.9 |
| Ohsaki | 37,884 | 1995 | 10.5 | 47.0 | 59.5 | 81.1 | 11.0 | 5,093 | 37.4 | 30.7 | 12.9 | 19.0 |
| RERF | 47,532 | 1963–1993 | 22.0 | 59.2 | 51.6 | 86.2 | 15.5 | 24,128 | 27.4 | 37.2 | 13.3 | 22.2 |
| **Republic of Korea** | | | | | | | | | | | | |
| KMCC | 13,446 | 1993–2004 | 6.6 | 62.5 | 57.9 | 79.1 | 10.0 | 1,036 | 29.3 | 24.8 | 8.6 | 37.3 |
| Seoul | 13,680 | 1992–1993 | 14.7 | 0.0 | 49.2 | 77.3 | NA | 799 | 53.6 | 16.8 | 3.0 | 26.7 |
| **Total** | 1,049,929 | 1963–2006 | 10.2 | 51.4 | 54.3 | 65.1 | 7.1 | 123,975 | 29.8 | 35.0 | 10.8 | 24.3 |

[a]Including only participants eligible for the current analysis.
[b]Deaths from unknown causes are not included.
3 Pref, Three Prefecture Cohort Study; CBCSP, Community-Based Cancer Screening Project; CHEFS, China National Hypertension Survey Epidemiology Follow-Up Study; CVDFACTS, Cardiovascular Disease Risk Factor Two-Township Study; JACC, Japan Collaborative Cohort Study, JPHC, Japan Public Health Center-Based Prospective Study; KMCC, Korea Multi-Center Cancer Cohort; NA, not available; RERF, Radiation Effects Research Foundation; SCHS, Singapore Chinese Health Study; SCS, Shanghai Cohort Study; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.
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