Red and processed meat intake and risk of colorectal adenomas: a systematic review and meta-analysis of epidemiological studies.

Dagfinn Aune[1], Doris S.M. Chan[1], Ana Rita Vieira[1], Deborah A. Navarro Rosenblatt[1], Rui Vieira[1], Darren C. Greenwood[2], Ellen Kampman[3], Teresa Norat[1].

Affiliations

[1] Department of Epidemiology and Biostatistics, Imperial College, London, United Kingdom

[2] Biostatistics Unit, Centre for Epidemiology and Biostatistics, University of Leeds, Leeds, United Kingdom

[3] Division of Human Nutrition, Wageningen University and Research Centre, Wageningen, The Netherlands

Correspondence and requests for reprints to: Mr. Dagfinn Aune, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St. Mary's Campus, Norfolk Place, Paddington, London W2 1PG, UK.

Telephone: +44 (0) 20 7594 8478

Fax: +44 (0) 20 7594 0768

E-mail: d.aune@imperial.ac.uk

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E-mail co-authors:

Doris S.M. Chan d.chan@imperial.ac.uk

Ana Rita Vieira a.vieira@imperial.ac.uk

Deborah A. Navarro Rosenblatt d.navarro-rosenblatt@imperial.ac.uk

Rui Vieira r.vieira@imperial.ac.uk

Darren C. Greenwood D.C.Greenwood@leeds.ac.uk

Ellen Kampman Ellen.Kampman@wur.nl

Teresa Norat t.norat@imperial.ac.uk

Abstract

Background: Current evidence indicates that red and processed meat intake increases the risk of colorectal cancer, however, the association with colorectal adenomas is unclear.

Objective: To conduct a systematic review and meta-analysis of epidemiological studies of red and processed meat intake and risk of colorectal adenomas.

Design: PubMed and several other databases were searched for relevant studies up to 31st of December 2011. Summary relative risks were estimated using a random effects model.

Results: Nineteen case-control studies and seven prospective studies were included in the analyses. The summary relative risk (RR) per 100 g/d of red meat was 1.29 (95% CI: 1.18, 1.41, I^2=0%, n=16) for all studies combined, 1.20 (95% CI: 1.06-1.36, I^2=0%, n=6) for prospective studies and 1.38 (95% CI: 1.18-1.62, I^2=18%, n=10) for case-control studies. The summary RR per 50 g/d of processed meat intake was 1.29 (95% CI: 1.09, 1.51, I^2=26%, n=10) for all studies combined, 1.45 (95% CI: 1.10-1.90, I^2=0%, n=2) for prospective studies and 1.22 (95% CI: 0.99-1.51, I^2=35%, n=8) for case-control studies. There was evidence of a nonlinear association between red meat ($p_{nonlinearity}<0.001$) and processed meat ($p_{nonlinearity}=0.01$) intake and colorectal adenoma risk.

Conclusion: These results indicate an elevated risk of colorectal adenomas with intake of red and processed meat, but further prospective studies are warranted.

Key words: Red meat, processed meat, diet, colorectal adenomas, polyps, meta-analysis, the Continuous Update Project.

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Introduction

Colorectal cancer is the third most common cancer worldwide with 1.2 million new cases diagnosed in 2008 (1). Colorectal cancer is thought to develop through the adenoma-carcinoma sequence, with a stepwise progression leading to dysplastic changes in the epithelium of the colon and rectum (2). The histologic type, size and number of adenomas determine the risk of developing colorectal cancer (3). Screening for colorectal adenomas and removal of such adenomas by colonoscopy is an important strategy to reduce colorectal cancer risk (4). Although lifestyle factors are considered to be of major importance in colorectal cancer etiology (5-9), less is known about how such factors are related to risk of colorectal adenomas. Studying risk factors for colorectal adenomas could enhance our understanding of the early stages of colorectal carcinogenesis.

Red and processed meat intake were judged to be convincing risk factors for colorectal cancer in the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report "Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective" from 2007 and we recently confirmed a positive association between red and processed meat intake and colorectal cancer in an updated meta-analysis of the evidence from prospective studies up to 2011 (9). However, the WCRF/AICR report did not find a significant association between red or processed meat intake and colorectal adenomas, but the number of studies assessed was modest (a total of 5 prospective studies, 4 case-control studies) (5). A number of additional case-control (10-16) and prospective studies (17-22) have since been published on the subject. We update the evidence as accumulated up to December 2011 and explore whether the associations reported differed by study design and other study characteristics. We further investigated if the association between red and processed meat intake differs for small and large adenomas.

Methods

Search strategy

We updated the systematic literature review published in 2007 (5) by searching the PubMed database from its inception up to December 2011 for studies of red and processed meat intake and colorectal adenoma risk. Several reviewers at Wageningen University carried out the literature search and extracted data up to end of December 2005 during the systematic literature review for the WCRF/AICR report (http://www.dietandcancerreport.org/cancer_resource_center/downloads/SLR/Colorectal_polyps_SLR.pdf). Initially several databases were used for the searches, including PubMed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, Latin American and Caribbean Center on Health Sciences Information, Cochrane library, Cumulative Index to Nursing and Allied Health Literature, the Allied and Complementary Medicine Database, National Research Register, and In Process Medline. However, as all the relevant studies were identified through PubMed a change was made to the protocol and only PubMed was used for the updated searches. A predefined protocol was used for the review (http://www.dietandcancerreport.org/cup/report_overview/index.php), and includes details of the search terms used. The search from January 2006 and up to end of December 2011 was conducted by one of the authors (DSMC). Data was extracted by three authors (DSMC, DANR and ARV). We also reviewed the reference lists of the relevant articles and a previously published systematic reviews for additional studies (23;24). We followed standard criteria for conducting and reporting meta-analyses (25).

Study selection

Studies were eligible for inclusion if they were prospective or case-control studies and presented estimates of the relative risk (such as hazard ratio, risk ratio or odds ratio) with the 95% confidence intervals. For the dose-response analysis, a quantitative measure of intake had to be provided. When we identified duplicate publications we selected the publication with the largest number of cases. In a few cases several papers were published from the same study, but reported on different meat items or subgroups in the different papers and in this case several papers from the same study were included, but each publication was only included once in each analysis. Fifty-seven potentially relevant full text publications (10-22;26-69) were identified. We excluded eight duplicate publications (21;31;46;49-53). Additional publications that did not report on red or processed meat intake (54;55;57-65), or reported only on serrated polyps (66), or a combined adenoma and cancer outcome (neoplasia) (48) or adenoma recurrence (67-69) were also excluded. For the dose-response analysis we further excluded three publications because there were only two categories of exposure (14;37) or intake was not quantified (32). We used data from a previous publication from the Nurses' Health study (34) in the dose-response analysis because the most recent publication only provided a high vs. low comparison (18). For the subgroup analysis by adenoma size we used data from the publication by Gunter et al (30) in the analysis of red meat because such results were not available in the original publication (26). Authors of 6 papers (10;12;14;26;29;33) were contacted for clarification of the definition of red meat and sufficient detail was provided by 3 of these (10;29;33).

Data extraction

The following data were extracted from each study: The first author's last name, publication year, country where the study was conducted, the study name, study design,

adenoma size when available, follow-up period, sample size, gender, age, number of cases, dietary assessment method (type, number of food items and whether it had been validated), meat exposure, quantity of intake, relative risks (RRs) and 95% CIs and variables adjusted for in the analysis.

Statistical methods

We used random effects models to calculate summary RRs and 95% CIs associated with red and processed meat intake (70). The natural logarithm of the RR from each study was weighted by the inverse of its variance and pooled across studies. A two-tailed $p<0.05$ was considered statistically significant. For studies that reported results stratified by gender (32;33), adenoma size (38) or other subgroups (10;28) we calculated a combined estimate of the association by using a fixed effects model before including the study in the overall analysis.

We used the method described by Greenland and Longnecker (71) to compute study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs across categories of red and processed meat intake. The method requires that the distribution of cases and person-years or non-cases and the RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of cases or person-years in studies that did not report these. The reported median or mean level of red and processed meat intake in each category of intake was assigned to the corresponding relative risk for each study. For studies that reported intake by ranges we estimated the midpoint in each category by calculating the average of the lower and upper bound. When the highest or lowest category was open-ended it was assumed that the open-ended interval length had the same length as the adjacent interval. When studies reported the intake in servings and times

per day or week, we converted the intakes to grams of intake per day using standard units of 120 g for red meat and 50 g for processed meat (72). Results are presented per 100 g per day for red meat and 50 g per day for processed meat. A potential nonlinear dose-response relationship was examined using fractional polynomial models (73). We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity (73).

Statistical heterogeneity among studies was assessed by I^2 which is the amount of total variation that is explained by between-study variation and the Q test (74). We conducted subgroup and meta-regression analyses by study characteristics to investigate potential sources of heterogeneity. Small study bias, such as publication bias, was assessed with funnel plots, Egger's test (75) and with Begg' test (76) and the results were considered to indicate potential small study bias when $p<0.10$. We used the trim and fill method to assess the potential influence of small study bias on the results (77). We also excluded small studies with <100 cases from the analyses to assess whether they explained the small study bias. We conducted sensitivity analyses excluding one study at a time to explore whether the results were robust to the influence of single studies. Results from these sensitivity analyses are presented excluding the two studies with the most positive and negative influence on the summary estimate.

Stata version 10.1 software (StataCorp, College Station, TX, USA) was used for the statistical analyses.

Results

Nineteen case-control studies (24 publications) (10-16;26-30;35-45;56) and seven cohort studies (9 publications) (17-20;22;32;33) were included in the analyses of red and processed meat intake and colorectal adenomas (Table 1 and 2). Ten studies were from Europe, twelve from the US, three from Asia and one from Australia. A summary of the study characteristics of the included studies is provided in Table 1 and 2.

Red meat

Eleven case-control studies (10-16;26-28;56) and seven cohort studies (17-20;22;32;33) investigated red meat intake and colorectal adenomas and included 21493 cases among 234451 participants. Some studies included processed red meat in the red meat variable (Table 1 and Table 2). The summary RR for high vs. low intake was 1.22 (95% CI: 1.11-1.34), with moderate heterogeneity, I^2=46% and $p_{heterogeneity}$=0.02 (Supplementary Figure 1a). In the dose-response analysis the summary RR was 1.29 (95% CI: 1.18-1.41, I^2=0%, $p_{heterogeneity}$=0.51) per 100 g/d (Figure 1a). The summary RR for prospective studies was 1.20 (95% CI: 1.06-1.36, I^2=0%, $p_{heterogeneity}$=0.97) and it was 1.38 (95% CI: 1.18-1.62, I^2=18%, $p_{heterogeneity}$=0.28) for case-control studies (Figure 1a), but there was no evidence of heterogeneity by study design, $p_{heterogeneity}$=0.17 (Table 3). In sensitivity analyses excluding the studies with the most influence on the summary estimate the summary RR ranged from 1.22 (95% CI: 1.11-1.35) when the study by Fu et al (16) was excluded to 1.31 (95% CI: 1.19-1.45) when the study by Ferrucci et al (22) was excluded. There was no indication of small study effects with Egger's test, p=0.56, or with Begg's test, p=0.34. The association

between red meat intake and colorectal adenoma risk appeared to be nonlinear, $p_{nonlinearity}<0.001$, with the steepest increase in risk at the lower levels of intake (Figure 1b). Further restricting the analysis to the studies that reported on fresh red meat and colorectal adenoma risk (10;13;15-17;20;22;28;33;45;56) did not materially alter the results, the summary RR was 1.35 (1.19-1.53, $I^2=0\%$, $p_{heterogeneity}=0.48$) for all studies combined, 1.20 (95% CI: 1.00-1.44, $I^2=0\%$, $p_{heterogeneity}=0.94$) for cohort studies and 1.50 (95% CI: 1.26-1.78, $I^2=1\%$, $p_{heterogeneity}=0.42$) for case-control studies.

Processed meat

Nine case-control studies (11;12;16;26;35;37-39;78) and two cohort studies (17;22) were included in the analysis of processed meat and colorectal adenoma risk and included 5891 cases among 41107 participants. The summary RR for high vs. low intake was 1.29 (95% CI: 1.15, 1.45), with no heterogeneity, $I^2=18\%$, $p_{heterogeneity}=0.27$ (Figure Supplementary Figure 1b). The summary RR for a 50 g/d increase in the intake was 1.29 (95% CI: 1.09, 1.51), with low heterogeneity, $I^2=26\%$, $p_{heterogeneity}=0.21$ (Figure 2a). The summary RR was 1.45 (95% CI: 1.10-1.90, $I^2=0\%$, $p_{heterogeneity}=0.41$) for prospective studies and 1.22 (95% CI: 0.99-1.51, $I^2=35\%$, $p_{heterogeneity}=0.15$) for case-control studies, with no evidence of heterogeneity by study design, $p_{heterogeneity}=0.44$. In sensitivity analyses excluding the studies with the most influence on the summary estimate the summary RR ranged from 1.23 (95% CI: 1.02, 1.49) when the study by Fu et al (16) was excluded to 1.37 (95% CI: 1.20, 1.57) when the study by Benito et al (35) was excluded. There was no indication of small study effects with Egger's test, p=0.25, or with Begg's test, p=0.37. The association between processed meat intake and colorectal adenoma risk appeared to be nonlinear, $p_{nonlinearity}=0.01$, with a slight flattening of the curve at higher levels of intake (Figure 2b).

Subgroup, sensitivity and meta-regression analyses

In subgroup analyses of red meat intake and colorectal adenoma, there were positive associations across all strata and heterogeneity between subgroups was only indicated between studies that adjusted or not for dairy or calcium intake ($p_{heterogeneity}$=0.07), with a slightly weaker, but still significant association with such adjustment (Table 3). When we further restricted the subgroup analyses to prospective studies the results for red meat persisted in all strata of subgroups with adjustment for different confounding factors (Supplementary Table 1 and 2). In the analyses of processed meat and colorectal adenomas there was significant heterogeneity in subgroups defined by geographic location, $p_{heterogeneity}$=0.04, number of cases, $p_{heterogeneity}$=0.04 and adjustment for energy intake, $p_{heterogeneity}$=0.03 (Table 3). The association was restricted to American studies, and was more pronounced in studies with a large number of cases and in studies that adjusted for energy intake. Exclusion of one study (37) that reported unadjusted results from the high vs. low analysis of processed meat intake and colorectal adenoma did not change the conclusions, summary RR=1.27 (95% CI: 1.14, 1.41, I^2=11%, $p_{heterogeneity}$=0.34) (the study was not included in the dose-response analysis). We also conducted nonlinear dose-response analyses stratified by study design (Supplementary Figure 2a and 2b), but the conclusions were similar, with a weaker effect for red meat in prospective studies and a stronger effect of processed meat in prospective studies compared with case-control studies.

Because adenomas often develop without symptoms it is possible that some of the included studies may have included prevalent adenoma cases if no colonoscopy was conducted at baseline. For this reason we conducted an additional sensitivity analysis among the four prospective studies of red meat with both a baseline and follow-up colonoscopy

which included only incident adenoma cases (17;20;22;34). The summary RR for was 1.18 (95% CI: 1.01-1.37, I^2=0%, $p_{heterogeneity}$=0.95), similar to the overall analysis.

For the case-control studies we restricted the analysis to the two studies that reported that diet was assessed before colonoscopy (before the participants knew their case-control status) (11;16) and the summary RR was 1.69 (95% CI: 1.34, 2.12).

High vs. low intake of beef (summary RR=1.40 (95% CI: 1.18, 1.67, I^2=19%, $p_{heterogeneity}$=0.28) (16;26;29;41-44;79), hamburgers (summary RR=1.23, 95% CI: 1.06, 1.43, I^2=0%, $p_{heterogeneity}$=0.67) (16;17;44;45) and pork (summary RR=1.55, 95% CI: 1.05, 2.30, I^2=37%, $p_{heterogeneity}$=0.20) (16;44;79), but not bacon (summary RR=1.12, 95% CI: 0.99, 1.27, I^2=0%, $p_{heterogeneity}$=0.58) (16;39;45), was also associated with significantly increased risk of colorectal adenomas (Table 3).

High vs. low red meat intake was associated with an increased risk of large adenomas (≥1 cm diameter), summary RR=1.57 (95% CI: 1.12, 2.19, I^2=7%) (17;19;30;31), but not with small sized adenomas (<1 cm), summary RR=0.97 (95% CI: 0.66, 1.42, I^2=0%) (17;19), although there was no heterogeneity between subgroups, $p_{heterogeneity}$=0.13. The association was similar for advanced, summary RR=1.38 (95% CI: 1.04, 1.84, I^2=0.31) and nonadvanced adenomas, summary RR=1.31 (95% CI: 1.10, 1.57, I^2=0.31) (10;16). Because one of the criteria for advanced adenomas is a large adenoma size and because of the limited number of studies in the analyses by adenoma size and stage we conducted an additional analysis where we combined studies that reported results for large and advanced adenomas and studies that reported on small and non-advanced adenomas. The summary RRs were 1.47 (95% CI: 1.18, 1.81) for advanced or large adenomas (10;16;17;19;30;31) and 1.24 (95% CI: 1.05, 1.46) for nonadvanced or small adenomas (10;16;17;19), but there was no heterogeneity between

subgroups, $p_{heterogeneity}$=0.26. Similar analyses were not possible for processed meat because of a lack of studies.

Discussion

In this meta-analysis we found an increased risk of colorectal adenomas with higher intake of red and processed meat intake and the positive associations appeared to be consistent across strata in subgroup analyses. Although there was no heterogeneity by study design, the results for red meat appeared to be stronger in case-control studies than in cohort studies, while for processed meat the opposite was observed.

The findings of this meta-analysis are consistent with the previously reported increased risks of colorectal cancer associated with red and processed meat intake (5;9) and provide further support for an association between red and processed meat intake and colorectal carcinogenesis. Two previous meta-analyses did not find a significant association between intake of red and processed meat and colorectal adenomas, but were limited by a low number of studies included in the analyses (5;23). However, with a total of 26 studies accumulated up to 2011 we found significant associations between both red and processed meat and subtypes, such as beef, pork and hamburger and increased risk of colorectal adenomas. A few additional studies did not find an association between meat intake and colorectal adenoma recurrence (67;69;80), but it is possible that risk factors differ for incidence and recurrence of adenomas.

Our meta-analysis may have several limitations that deserve comment. High intake of red and processed meat is oftentimes associated with other risk factors such as low intake of fiber, lower physical activity, higher prevalence of obesity, smoking and high alcohol intake (22). Many of the studies adjusted for these confounders and in several subgroup analyses we

found that the results persisted across subgroups with adjustment for these and other potential confounders. In addition, there was little evidence that the results differed whether or not confounding factors had been adjusted for or not. However, we cannot exclude the possibility that residual confounding could partly explain the results. Small study effects, such as publication bias can be a problem in meta-analyses of published literature, but we found no evidence of small study effects in this analysis. Since we included case-control studies there is a possibility that recall bias and selection bias partly could explain the results in such studies. However, when we restricted the results to the two studies that assessed diet before colonoscopy was conducted (before the subjects knew their case-control status) the results persisted. When we restricted the analysis to prospective studies the results also persisted, although the results were somewhat weaker for red meat. Because adenomas often develop without symptoms a potential limitation is that some of the studies may have included prevalent adenoma cases if a colonoscopy had not been conducted at baseline (in cohort studies) or previously (in case-control studies). None of the case-control studies conducted analyses restricted to subjects with a previous colonoscopy. In addition, although most of the case-control studies asked about diet at least ≥1 year before the adenomas were detected it is still possible that the adenomas may already have existed at the time point they were asked to recall their diet for. However, when we restricted the analysis to the four cohort studies with both a baseline and a follow-up colonoscopy, which included only incident adenoma cases, the results were similar to the overall results for cohort studies for red meat.

Due to the limited number of studies reporting results for subsites within the colorectum we did not have adequate power to clarify whether the risk differed between colon or rectum or proximal and distal colon. Although we found that the results for red meat did not differ by geographic location or study size, there was heterogeneity between these subgroups in the analysis of processed meat. The association between processed meat and

colorectal adenomas was observed only in the American studies and not in the European studies, but it is not clear what the reason for this is. It might be due to differences in the consumption patterns, additives used for processing or a chance finding because there were only three European studies in the analysis. The association between processed meat and adenomas was stronger in the larger studies than in the smaller studies. In addition, we cannot exclude the possibility that low numbers of observations at the low or high ends of the range of intakes partly could contribute to the nonlinear observations that we observed.

Measurement error in the dietary assessment is another limitation of our results. None of the studies included in our analysis made any corrections for measurement error.

Several mechanisms might explain an increased risk of colorectal adenoma with high red and processed meat intakes. Heterocyclic amines and polycyclic aromatic hydrocarbons, meat mutagens that are formed during frying and barbecuing of meats, have been shown to be gastrointestinal carcinogens in experimental animal studies (81). These compounds can form DNA adducts and induce genetic alterations characteristic of colorectal tumors (82). The heme-iron content of meats may contribute to colorectal neoplasia by inducing oxidative DNA damage (83) and by increasing endogenous formation of N-nitroso compounds (84) which are known to be powerful multisite carcinogens (85). Red meat intake was positively associated with risk of large adenomas, but not small adenomas, although there were few studies in these analyses. However, when we grouped large and advanced adenomas and small and non-advanced adenomas together the association was significant for both types, but was somewhat stronger for the large and advanced adenomas. Large or advanced adenomas convey a greater colorectal cancer risk than small or non-advanced adenomas (3), suggesting that red meat intake might play a role in the progression to malignancy. However, we cannot exclude the possibility that persons with a high intake of red and processed meat are less likely to undergo screening and that this could have contributed to this finding. The summary

estimate per 100 g/d for red meat and colorectal adenomas among cohort studies, RR=1.20 (95% CI: 1.06, 1.36, n=6) is similar to that of a recent meta-analysis (24) and is also similar to the summary estimate that we previously reported for colorectal cancer, RR=1.17 (95% CI: 1.05, 1.31), although for processed meat the results for adenomas are stronger, summary RR=1.45 (1.10, 1.90, n=2) for colorectal adenomas vs. 1.18 (95% CI: 1.10, 1.28, n=9) for colorectal cancer, however, there were only 2 cohort studies in the analysis of colorectal adenomas, thus this difference might have been due to chance (9).

Strengths of this meta-analysis include the comprehensive search strategy, dose-response, subgroup, and sensitivity analyses. With the large number of studies and study participants we had adequate statistical power to detect significant associations in the main analyses.

In conclusion, we found a positive association between red and processed meat intake and risk of colorectal adenomas. Our results provide further support that red and processed meat intake is implicated in colorectal carcinogenesis, however, further prospective studies are warranted.

Conflict of interest: The authors have declared no conflicts of interest.

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risk. The systematic literature review team at the Wageningen University conducted the search, data selection and data extraction up to December 2005. DSMC did the updated literature search and study selection. DSMC, DANR and ARV did the updated data extraction. DA conducted the statistical analyses and wrote the first draft of the original manuscript. DCG was expert statistical advisor and contributed towards the statistical analyses. All authors contributed to the revision of the manuscript. DA had primary responsibility for final content. EK was PI of the SLR at Wageningen University and TN is the PI of the Continuous Update Project. All authors had full access to all of the data in the study. The authors declare that there are no conflicts of interest.

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Table 1: Case-control studies of red and processed meat intake and colorectal adenoma risk

Author, publication year, country	Study period	Number of cases and controls, age	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Macquart-Moulin G et al, 1987, France	1980-1985	252 colorectal adenoma cases 238 hospital controls Age 15-≥80 years	FFQ, 158 food items	Charcuterie	≥42.9 vs. <10 g/d	1.17 (0.71, 1.92)	Age, sex, weight, calories
Kune G et al, 1991, Australia	NR	49 colorectal adenoma cases (>1 cm diameter) 727 population controls Mean age 68/65 years	Diet history, >300 food items	Beef, men only, large polyps Pork, large polyps	>360 vs. ≤360 g/wk >15/>27 vs. ≤15/≤27 g/wk	2.42 (1.02, 5.76) 0.69 (0.35, 1.36)	Age, sex
Sandler RS et al, 1993, USA	1988-1990	236 colorectal adenoma cases 409 colonoscopy controls Age ≥30 years	Validated FFQ, >100 food items	Beef Beef	≥2.3 vs. <0.5/wk ≥2.6 vs. <0.6/wk	1.59 (0.72, 3.50) 2.07 (0.82, 5.19)	Age, alcohol intake, BMI, calories
Benito E et al, 1993, Spain	1987-1990	101 colorectal adenoma cases 144 population controls Age ≤80 years	FFQ, 99 food items	Processed meat	≥26 vs. <4/mo	0.56 (0.29, 1.08)	Age, sex, physical activity in longest held job, rural residence
Probst-Hensch NM et al, 1997, USA	1991-1993	488 left-sided colorectal adenoma cases 488 sigmoidoscopy controls Age 50-74 years	Validated FFQ, 126 food items	Beef, pork, lamb - main dish Beef, pork, lamb as mixed dish Hamburger Bacon	>1/wk vs. <1/mo >1/wk vs. <1/mo >1/wk vs. <1/mo >1/wk vs. <1/mo	1.7 (1.1, 2.5) 1.5 (1.0, 2.4) 1.1 (0.7, 1.7) 1.4 (0.9, 2.2)	Age, calories, smoking
Haile, RW et al, 1997, USA	1991-1993	488 left-sided colorectal adenoma cases 488 sigmoidoscopy controls Age 50-74 years	Validated FFQ, 126 food items	Red meat Beef Processed meat	1083 vs. 78.5 g/wk 930 vs. 42.5 g/wk 175 vs. 0 g/wk	1.62 (1.00, 2.63) 1.83 (1.12, 2.99) 1.48 (0.92, 2.39)	Age, sex, BMI, calories, physical activity, ethnicity
Lubin F et	NR	196 colorectal adenoma cases	FFQ, 180	Beef	>43 vs. <15 g/d	1.6 (0.9, 2.7)	Age, sex, country of origin,

al, 1997, Israel		196 colonoscopy controls Age 21-75 years	food items				duration of follow-up, energy intake, physical activity
Sinha, R et al, 1999, USA	1994-1996	146 colorectal adenoma cases 228 colonoscopy controls Age 18-74 years	Validated FFQ, 100 food items	Red meat (incl. processed meat) Red meat Red meat, left-sided adenomas Red meat, colon adenomas	Per 10 g/d Quintile 5 vs. 1 Per 10 g/d Per 10 g/d	1.11 (1.03, 1.19) 2.28 (1.01, 5.16) 1.09 (1.00, 1.22) 1.10 (1.00, 1.22)	Age, sex, total calories, reason for screening, physical activity, pack-years of cigarette smoking, NSAID use
Breuer-Katschinski BB, 2001, Germany	1993-1995	182 colorectal adenoma cases 178 colonoscopy controls 182 population controls Mean age 63.8/ 63.4/64.2 years	Validated FFQ	Beef, colonoscopy controls Beef, large polyps Beef, small polyps Beef, population controls Beef, large polyps Beef, small polyps	Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1	3.10 (1.46, 6.43) 1.36 (0.45, 4.13) 4.24 (1.24, 12.7) 1.29 (0.47, 3.54) 2.05 (0.74, 5.65) 2.08 (0.80, 5.44)	Age, sex, energy, relative weight, social class
Senesse P et al, 2002, France	1985-1990	154/208 small/large colorectal adenoma cases 427 colonoscopy controls Age 30-79 years	Validated FFQ, 190 food items	Delicatessen, small adenomas Delicatessen, large adenomas	64.2/37.7 vs. 0/0 g/d m/w 64.2/37.7 vs. 0/0 g/d m/w	0.9 (0.5, 1.7) 1.5 (0.9, 2.6)	Age, sex, energy intake, BMI, alcohol, tobacco
Erhardt, JG, 2002, Germany	1995-1997	207 colorectal adenoma cases 224 colonoscopy controls Age 39-73 years	Validated dietary history, 300 foods	Ham, sausage, adenomas	>15g/day	1.87 (1.12, 3.11)	Univariate
Voskuil	1995-1998	57/62	Validated	Red meat (beef, veal, pork,	7 vs ≤4/wk	4.1 (0.7,	Age, sex, energy, total meat

DW, 2002, Netherlands		Sporadic/HNPCC family colorectal adenoma cases 148 colonoscopy controls Age <75 years	FFQ, 178 food items	lamb, game, organs), sporadic cases Red meat, HNPCC cases	7 vs ≤4/wk	23.0) 0.4 (0.1, 2.2)	
Tiemersma EW et al, 2004, Netherlands	1997-2000	431 colorectal adenoma cases 433 colonoscopy controls Age 18-75 years	Validated FFQ, 178 food items	Beef patties	≥1.4 vs. <0.16	1.0 (0.7, 1.4)	Age, sex, indication of endoscopy
Chiu BCH et al, 2004, USA	1994-1996	146 colorectal adenoma cases 146 colonoscopy controls Age 18-74 years	Validated FFQ, 100 food items	Beef roasts Beef steaks Hamburgers/Cheeseburgers Pork chops, ham steaks	≥0.57 vs. <0.11 serv/wk ≥1.00 vs. <0.23 serv/wk ≥0.57 vs. <0.11 serv/wk ≥0.57 vs. <0.11 serv/wk	0.6 (0.2, 1.4) 1.9 (1.0, 3.6) 1.6 (0.8, 3.0) 2.3 (1.1, 5.0)	Age, sex, total energy intake, pack-years of smoking, physical activity, NSAIDS
Gunter MJ et al, 2005, USA	1991-1993	261 left-sided colorectal adenoma cases 304 sigmoidoscopy controls Age 50-74 years	FFQ	Red meat, large (>1 cm) adenomas	28.2-127.3 vs. 0-1.8 g/d	0.85 (0.38, 1.90)	Age, sex, energy, center, fruit and vegetable intake, smoking status, BMI
Wark PA et al, 2006, Netherlands	1997-2000	81 K-ras$^+$ & 453 K-ras$^-$ colorectal adenoma cases 709 colonoscopy controls Age 18-75 years	Validated FFQ, 178 food items	Red meat, K-ras$^+$ Red meat, K-ras$^-$	>70.5 vs. ≤38.2 g/d >70.5 vs. ≤38.2 g/d	1.70 (0.94-3.09) 1.00 (0.73-1.39)	Age, sex, total energy
Ward MH et al, 2007, USA	1994-1996	146 colorectal adenoma cases 228 colonoscopy controls Age 18-74 years	Validated FFQ, 100 food items	Total processed meat Bacon Breakfast sausage Hot dogs, other sausages Ham steak, pork chops Ham, bologna, salami, lunchmeats	≥24.0 vs. <3.7 g/d ≥1.85 vs. 0 g/d ≥4.2 vs. 0 g/d ≥6.7 vs. 0 g/d ≥6.3 vs. 0 g/d ≥8.0 vs. 0 g/d	2.0 (1.0, 4.0) 1.2 (0.7, 2.2) 1.6 (0.8, 3.2) 1.9 (1.0, 3.7) 2.2 (1.3, 3.7) 1.2 (0.7, 2.3)	Age, sex, total calories, pack-years of smoking

				Liverwurst	>0 vs. 0 g/d	1.9 (0.8, 4.2)	
Sæbø M et al, 2008, Norway	NR	197/194 high/low-risk colorectal adenoma cases 201 healthy screening controls Mean age 67.3 yrs	FFQ	Red meat (fresh), high-risk adenomas Red meat, low-risk adenomas	>45.0 vs. ≤22.5 g/d >45.0 vs. ≤22.5 g/d	1.05 (0.57, 1.92) 1.47 (0.75, 2.85)	Age, sex, smoking
Ferrucci LM et al, 2009, USA	2000-2002	158 female colorectal adenoma cases 649 colonoscopy controls Mean age 60.2/57.2 years	Validated DHQ, 124 food items	Red meat (beef, cheeseburgers, hamburgers, bacon, cold cuts, ham, hot dogs, liver, pork, sausages, veal, venison, red meat from mixed dishes) Processed meat	111.1 vs. 34.2 g/1000 kcal/d Per 10 g/1000 kcal/d 15.7 vs. 1.5 g/1000 kcal/d Per 10 g/1000 kcal/d	2.02 (1.06, 3.83) 1.07 (0.95, 1.21) 1.05 (0.59-1.85) 0.98 (0.78-1.23)	Age, education, race, smoking status, physical activity, BMI, study center, current HRT use, FH – CRA/ CRC, regular NSAID use, alcohol, fiber, dietary calcium, calcium from supplements, total calories
Ramadas A et al, 2009, Malaysia	2005	59 colorectal adenoma cases 59 colonoscopy controls Age ≥30 years	FFQ	Red meat	≥3 vs. <3/wk	2.51 (1.00-6.28)	Age, sex, ethnicity, physical activity, height, BMI, waist circumference, energy intake, drinking, smoking
Northwood EL et al, 2010, UK	NR	317 colorectal adenoma cases 296 screening controls Age 50-69 yrs	Validated FFQ	Red meat (beef, pork, lamb, burgers)	>19 vs. 6 serv/mo	0.85 (0.53-1.30)	Age, sex, smoking
Wang H et al, 2011, USA	1995-2007	914 colorectal adenoma cases 1185 population controls Mean age 66/67 years	Validated FFQ, >200 food items	Total red meat Processed meat	>89 vs. <42 g/d >27 vs. <11 g/d	1.11 (0.83-1.48) 1.23 (0.94-1.61)	Age, sex, ethnicity, energy intake, recreational physical activity, BMI, pack-years

							of smoking, aspirin use, years of schooling, calcium, non-starch polysaccharides from vegetables
Burnett, Hartman AN et al, 2011, USA	2004-2007	519 colorectal adenoma cases 227 colorectal adenoma and hyperplastic polyp cases 772 controls Age 20-74 years	FFQ,	Red meat (beef, veal, lamb, mutton, pork, venison), colorectal adenoma Red meat, proximal colorectal adenoma Red meat, distal colorectal adenoma Red meat, both types of polyps	>3/wk vs. 0/wk >3/wk vs. 0/wk >3/wk vs. 0/wk >3/wk vs. 0/wk	1.19 (0.80, 1.78) 1.10 (0.62, 1.94) 1.49 (0.87, 2.56) 1.31 (0.73, 2.35)	Age, gender, race, education, BMI, alcohol intake, NSAIDs use, hormone therapy use
Fu Z et al, 2011, USA	2003-2010	1881 colorectal adenoma cases 2503 total polyp cases (includes hyperplastic polyps) 3764 controls Age 40-75 years	Validated FFQ,	Red meat, all polyps Red meat, colorectal adenoma Red meat, nonadvanced Red meat, advanced Processed meat, all polyps Processed meat, CRA Fast food hamburgers Non-fast food hamburgers Beef patties, steaks Pork chops Short ribs, spareribs Bacon Sausage Hot dogs, frankfurters	≥51.4 vs. ≤9.5 g/d ≥51.4 vs. ≤9.5 g/d ≥51.4 vs. ≤9.5 g/d ≥51.4 vs. ≤9.5 g/d >22.5 vs. 0 g/d >22.5 vs. 0 g/d Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1	1.4 (1.2, 1.6) 1.4 (1.2, 1.6) 1.3 (1.1, 1.6) 1.5 (1.1, 2.1) 1.3 (1.1, 1.5) 1.3 (1.1, 1.5) 1.2 (1.0, 1.4) 1.2 (1.0, 1.5) 1.3 (1.1, 1.5) 1.4 (1.2, 1.6) 1.1 (0.9, 1.5) 1.1 (1.0, 1.3) 1.3 (1.1, 1.5) 1.2 (1.0, 1.4)	Age, sex, race, study sites, education, indications for colonoscopy, smoking, alcohol, BMI, physical activity, NSAIDs use, total energy, recruitment before or after colonoscopy

BMI= body mass index, CRA = colorectal adenoma, CRC = colorectal cancer, d=day, FFQ=food frequency questionnaire, FH = family history, g=gram, HRT=hormone replacement therapy, mo=month, m/w=men/women, NSAID = non-steroidal anti-inflammatory drugs, serv=serving, wk=week,

Table 2: Prospective studies of red and processed meat intake and colorectal adenoma risk

Author, publication year, country	Follow-up period	Study size, gender, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Giovannucci E et al, 1992, USA	1986-1988	7284 men, age 40-75 years: 170 distal colon/ rectum adenoma cases	Validated FFQ, 131 food items	Red meat	>110 vs. <24 g/d	1.23 (0.70, 2.14)	Age, energy
Kahn HS et al, 1998, USA	1982-1992	72868 men and 81356 women, age 40-64 years: 7504/ 5111 colon polyps	FFQ, 28 food items	Red meat, men Red meat, women	10^{th} vs. 1^{st} decile 10^{th} vs. 1^{st} decile	0.97 (0.85, 1.12) 1.25 (1.06, 1.48)	Age, education, race, BMI, exercise, smoking, alcohol, coffee, aspirin use, multivitamin use, FH – CRC, diet change, women: parity, ERT, menopausal status
Nagata C et al, 2001, Japan	1992 - 1995	12788 men and 15852 women, age 35+ years: 181/98 colorectal adenoma cases	FFQ, 169 food items	Red meat (fresh), men Red meat (fresh), women	Tertile 3 vs. 1 Tertile 3 vs. 1	1.18 (0.81, 1.72) 0.83 (0.47, 1.43)	Age, total energy, years of smoking, alcohol
Chan AT et al, 2005, USA	1989-90 – 1998	Nested case-control study: 527 female colorectal adenoma cases 527 matched controls Mean age 57 yrs	Validated FFQ, 131 food items	Red meat (incl. processed meat)	1+/d vs. 1 serv/wk	1.57 (0.93, 2.65)	Age, fasting status, date of blood draw, time of blood draw, previous endoscopy, time period of endoscopy, time period of prior endoscopy symptoms, BMI, pack-yrs of smoking, physical activity, calcium, folate, alcohol multivitamins, aspirin, menopausal status, postmenopausal hormone use, age at menarche, age at last menstrual period

Wu K et al, 2006, USA	1986-2002	14032 men, mean age ~63 years: 581 distal colon adenomas	Validated FFQ, 131 food items	Total red meat (incl. processed meat) Total red meat, small adenomas Total red meat, large adenomas Hamburger Beef, lamb, pork as main dish Processed meats	7.2 vs. 1.1 serv/wk 7.2 vs. 1.1 serv/wk 7.2 vs. 1.1 serv/wk 2.5 vs. 0.16 serv/wk 3.3 vs. 0.33 serv/wk 4.5 vs. 0.16 serv/wk	1.18 (0.87, 1.62) 0.96 (0.54, 1.72) 1.95 (0.97, 3.91) 1.24 (0.91, 1.70) 1.26 (0.92, 1.74) 1.52 (1.12, 2.08)	Age, FH – CRC, reason of endoscopy, negative endoscopy before 1986, physical activity, smoking status, race, aspirin, total energy intake, calcium, folate
Cho E, 2007, USA	1984-2002	39246 women, age 38-63 years: 2408 distal colorectal adenoma cases	Validated FFQ, 130 food items	Red meat	Quintile 5 vs. 1	1.36 (1.15, 1.60)	Age, pack-years of smoking, BMI, physical activity, FH – CC, history of endoscopic screening, year of endoscopy, aspirin use, menopausal status and postmenopausal hormone use, energy intake, alcohol, folate, total fiber, calcium
Rohrmann S et al, 2009, Germany	1994-98 – 2007	4215 men and women, age 35-65 years: 516 colorectal adenoma cases	Validated FFQ, 146 food items	Red and processed meat, colorectal adenomas Red and processed meat, colon adenomas Red and processed meat, proximal colon adenomas Red and processed meat, distal colon adenomas Red and processed meat, rectal adenomas Red and processed meat, small adenomas Red and processed meat, large adenomas	Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1	1.33 (0.95, 1.85) 1.53 (1.01, 2.30) 1.63 (0.87, 3.05) 1.50 (0.87, 2.59) 0.85 (0.42, 1.74) 0.97 (0.58, 1.62) 1.98 (1.09, 3.58)	Age, sex, energy, alcohol, milk and milk products, fiber, BMI, FH – CRC, physical activity, NSAIDs, smoking status, pack-years of smoking, education

Tantamango YM et al, 2011, USA	1976-2002-2005	**2818 men and women: 441 colorectal polyp cases** **Mean age 73.4/71.2 years**	FFQ, 55 food items	**Red meat (beef, pork)** **Beef**	**≥1/wk vs. never** **≥1/wk vs. never**	**1.08 (0.84, 1.41)** **1.09 (0.84, 1.41)**	**Age, sex, BMI**
Ferrucci LM et al, 2012, USA	1993/2001 - 2006	**17072 men and women, age 55-74 years: 1008 distal colorectal adenoma cases**	FFQ, 137 food items	**Red meat (beef, pork, lamb), distal colorectal adenoma** **Red meat, distal colon adenoma** **Red meat, rectal adenoma** **Processed meat, distal colorectal adenoma** **Processed meat, distal colon adenoma** **Processed meat, rectal adenoma**	**60.1 vs. 13.5 g/1000 kcal/d** **60.1 vs. 13.5 g/1000 kcal/d** **60.1 vs. 13.5 g/1000 kcal/d** **15.5 vs. 1.5 g/1000 kcal/d** **15.5 vs. 1.5 g/1000 kcal/d** **15.5 vs. 1.5 g/1000 kcal/d**	**1.22 (0.98, 1.52)** **1.22 (0.95, 1.56)** **1.33 (0.87, 2.04)** **1.23 (0.99, 1.54)** **1.24 (0.99, 1.59)** **1.08 (0.71, 1.65)**	**Age, study centre, gender, ethnicity, education, FH – CRC, BMI, NSAIDs use, physical activity, smoking status, alcohol intake, dietary calcium, supplemental calcium, dietary fibre, total energy intake**

BMI=Body Mass Index, CC=colon cancer, CRC=colorectal cancer, d=day, ERT=estrogen replacement therapy, FFQ=food frequency questionnaire, FH=Family history, g=grams, mo= month, NR = Not reported, NSAID=non-steroidal anti-inflammatory drugs, serv = servings, wk=week,

Table 3: Subgroup analyses of red and processed meat intake and colorectal adenomas, dose-response

	Red meat, per 100 g/d					**Processed meat, per 50 g/d**				
	n	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]	*n*	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]
All studies	16	1.29 (1.18-1.41)	0	0.51		10	1.29 (1.09, 1.52)	0	25.7	0.21
Prospective studies	6	1.20 (1.06-1.36)	0	0.97	0.17	2	1.45 (1.10, 1.90)	0	0.41	0.44
Case-control studies	10	1.38 (1.18-1.62)	17.6	0.28		8	1.22 (0.99, 1.51)	35.2	0.15	
Type of controls										
Colonoscopy-based	9	1.45 (1.23-1.70)	7.2	0.38	0.34	5	1.39 (1.16, 1.66)	0	0.58	0.60
Population-based	1	1.12 (0.82-1.53)				2	0.92 (0.39, 2.16)	81.2	0.02	
Hospital-based	0					1	1.10 (0.68, 1.76)			
Location in colorectum										
Colon	2	1.58 (1.03-2.45)	19.3	0.27	0.32	0				0.53
Proximal colon	2	1.25 (0.87-1.80)	0	0.49		0				
Distal colon	3	1.22 (1.03-1.44)	0	0.56		2	1.47 (1.10, 1.97)	0	0.45	
Rectum	2	1.07 (0.74-1.53)	15.1	0.28		1	1.10 (0.55, 2.16)			
Distal colon and rectum	6	1.23 (1.08-1.40)	0	0.98		2	1.38 (1.00, 1.91)	0	0.49	

Geographic location											
Europe		5	1.31 (1.07-1.61)	0	0.98	0.71	3	0.95 (0.65, 1.40)	49.3	0.14	0.04
America		10	1.29 (1.13-1.48)	33.1	0.14		7	1.45 (1.24, 1.69)	0	0.87	
Asia		1	1.11 (0.64-1.91)				0				
Number of cases											
Cases <250		3	2.05 (1.18-3.57)	0	0.38	0.23	3	0.92 (0.53, 1.62)	55.6	0.11	0.045
Cases 250-<500		6	1.30 (1.03-1.63)	0	0.94		3	1.20 (0.91, 1.58)	0	0.57	
Cases ≥500		7	1.26 (1.11-1.43)	31.0	0.19		4	1.47 (1.24, 1.73)	0	0.85	
Adjustment for confounders											
Alcohol	Yes	6	1.31 (1.13-1.52)	27.1	0.23	0.64	4	1.35 (1.14-1.60)	0	0.49	0.84
	No	10	1.25 (1.08-1.45)	0	0.62		6	1.25 (0.92-1.69)	47.6	0.09	
Smoking	Yes	10	1.32 (1.15-1.51)	30.4	0.17	0.49	7	1.39 (1.20-1.61)	0	0.78	0.10
	No	6	1.21 (1.00-1.46)	0	0.98		3	1.00 (0.56-1.79)	62.0	0.07	
Body mass index, weight	Yes	9	1.29 (1.17-1.44)	0	0.44	0.98	7	1.34 (1.15-1.55)	0	0.73	0.72
	No	7	1.27 (1.04-1.56)	4.3	0.39		3	1.14 (0.60-2.17)	75.9	0.02	
Physical activity	Yes	9	1.31 (1.15-1.49)	36.5	0.13	0.62	7	1.30 (1.04-1.64)	44.4	0.10	0.52
	No	7	1.21 (0.96-1.52)	0	0.97		3	1.19 (0.91-1.55)	0	0.75	
NSAID, aspirin use	Yes	8	1.30 (1.11-1.53)	47.2	0.07	0.84	5	1.43 (1.22-1.69)	0	0.70	0.13
	No	8	1.26 (1.06-1.50)	0	1.00		5	1.11 (0.81-1.52)	40.3	0.15	
Fiber	Yes	4	1.21 (1.04-1.39)	0	0.89	0.35	3	1.28 (0.99-1.66)	0	0.66	0.93
	No	12	1.34 (1.18-1.52)	10.4	0.34		7	1.27 (1.01-1.61)	46.5	0.08	
Dairy, calcium	Yes	6	1.19 (1.06-1.34)	0	0.97	0.07	4	1.38 (1.11-1.71)	0	0.60	0.59

	No	10	1.43 (1.23-1.66)	5.5	0.39		6	1.21 (0.92-1.58)	50.0	0.08	
Energy intake	Yes	11	1.30 (1.15-1.46)	22.3	0.23	0.74	9	1.37 (1.20-1.57)	0	0.80	0.03
	No	5	1.23 (0.97-1.55)	0	0.88		1	0.58 (0.31-1.05)			
Meat subtypes[3]											
Beef		8	1.40 (1.18-1.67)	18.8	0.28						
Hamburger		4	1.23 (1.06-1.43)	0	0.67						
Pork		2	1.55 (1.05-2.30)	37.3	0.20						
Bacon							3	1.12 (0.99-1.27)	0	0.58	

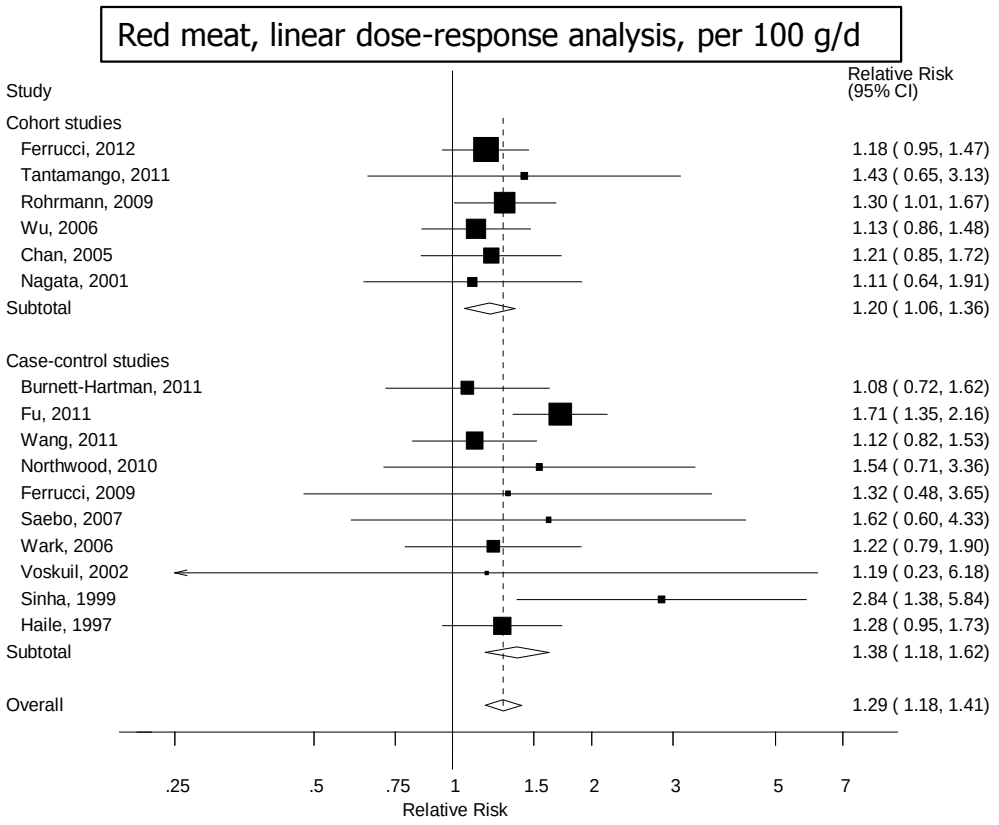
n denotes the number of studies. [1] P for heterogeneity within each subgroup, [2] P for heterogeneity between subgroups with meta-regression analysis, [3]Summary estimates are for high vs. low comparison for meat subtypes

Figure legends

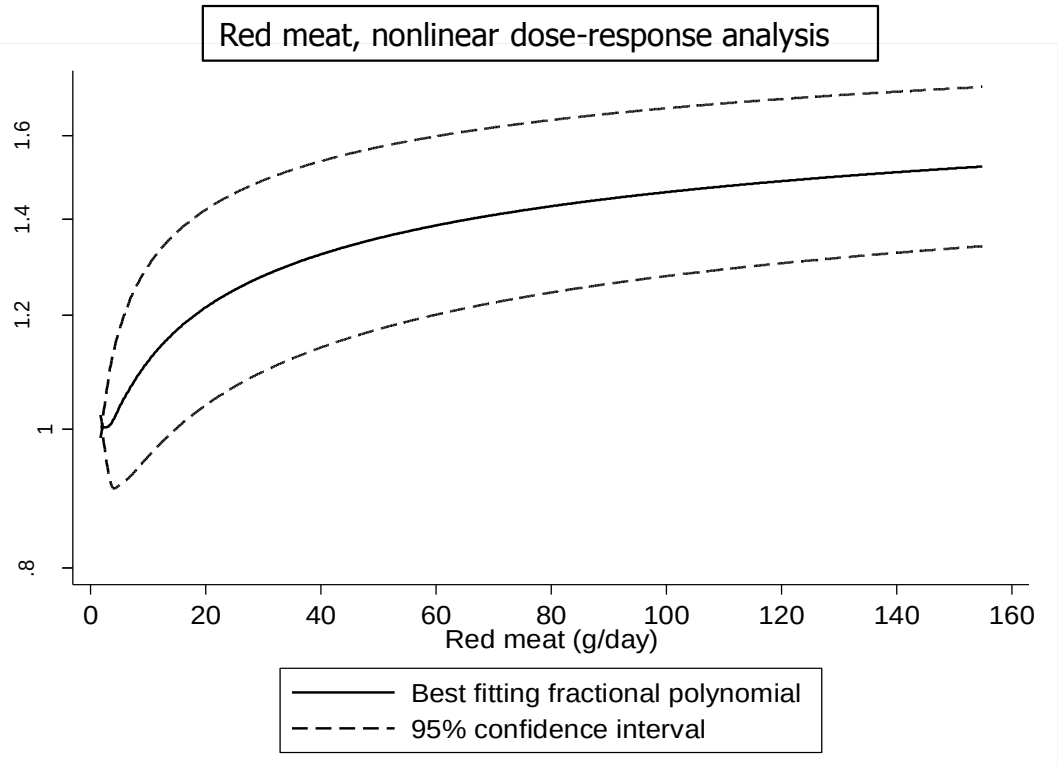
Figure 1. Red meat and colorectal adenomas

Figure 2. Processed meat and colorectal adenomas

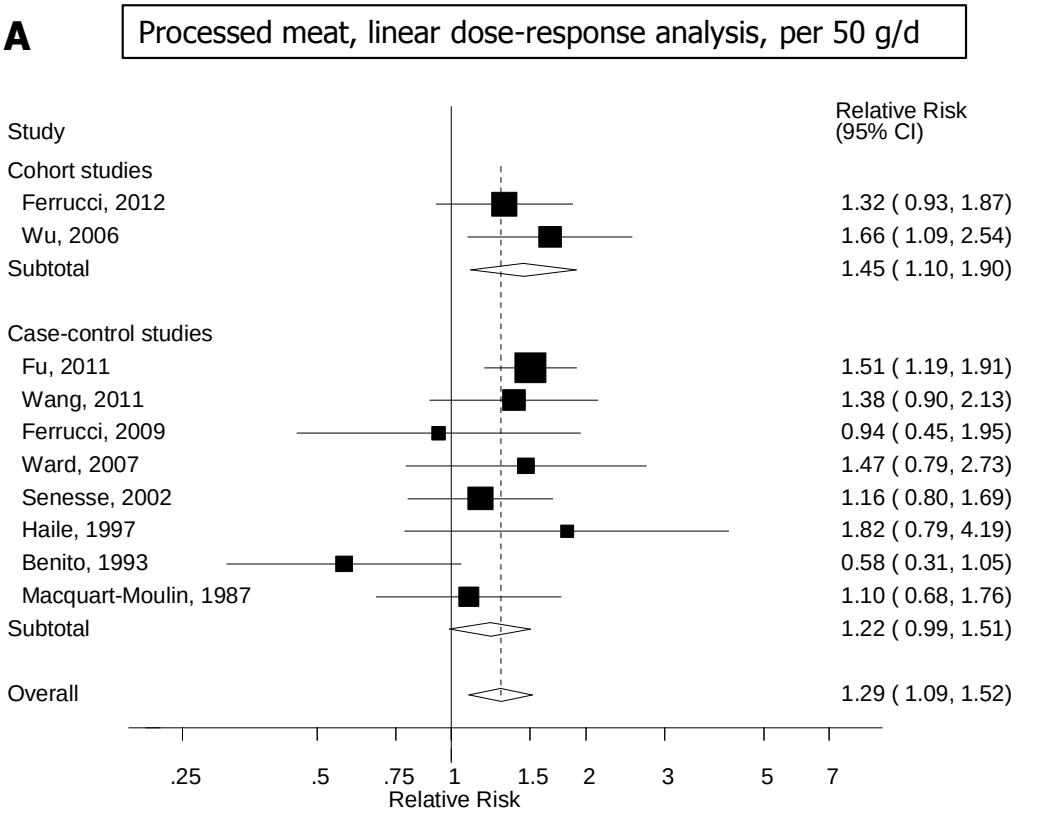
A


Red meat, linear dose-response analysis, per 100 g/d
Study
Relative Risk (95% CI)
Cohort studies
Ferrucci, 2012 1.18 (0.95, 1.47)
Tantamango, 2011 1.43 (0.65, 3.13)
Rohrmann, 2009 1.30 (1.01, 1.67)
Wu, 2006 1.13 (0.86, 1.48)
Chan, 2005 1.21 (0.85, 1.72)
Nagata, 2001 1.11 (0.64, 1.91)
Subtotal 1.20 (1.06, 1.36)
Case-control studies
Burnett-Hartman, 2011 1.08 (0.72, 1.62)
Fu, 2011 1.71 (1.35, 2.16)
Wang, 2011 1.12 (0.82, 1.53)
Northwood, 2010 1.54 (0.71, 3.36)
Ferrucci, 2009 1.32 (0.48, 3.65)
Saebo, 2007 1.62 (0.60, 4.33)
Wark, 2006 1.22 (0.79, 1.90)
Voskuil, 2002 1.19 (0.23, 6.18)
Sinha, 1999 2.84 (1.38, 5.84)
Haile, 1997 1.28 (0.95, 1.73)
Subtotal 1.38 (1.18, 1.62)
Overall 1.29 (1.18, 1.41)
.25 .5 .75 1 1.5 2 3 5 7
Relative Risk

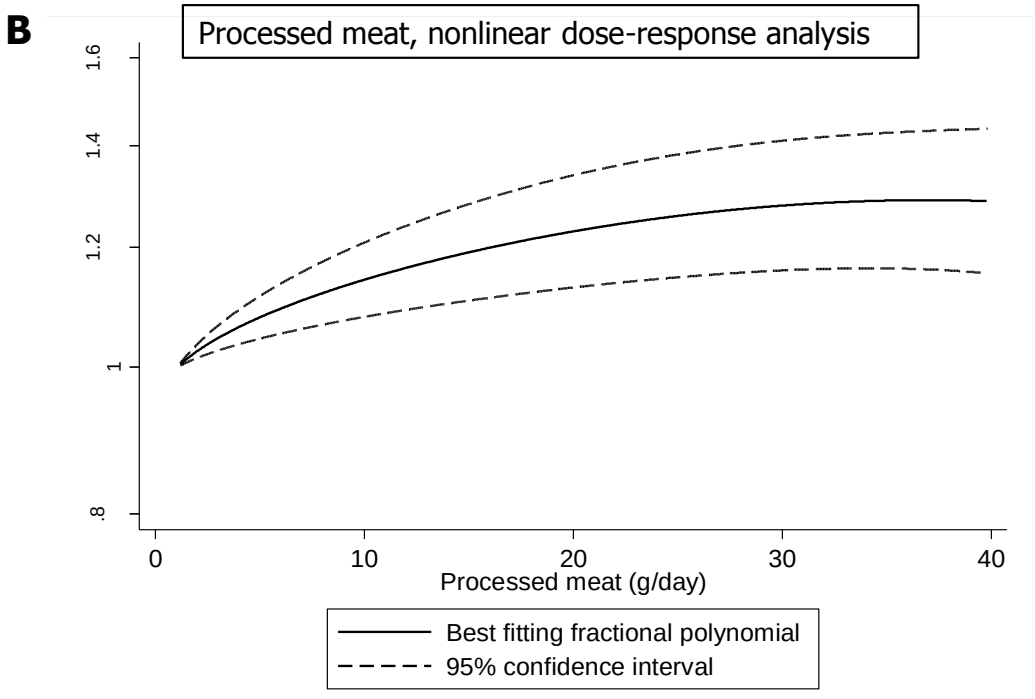
B


Red meat, nonlinear dose-response analysis
.8 1 1.2 1.4 1.6
0 20 40 60 80 100 120 140 160
Red meat (g/day)
Best fitting fractional polynomial
95% confidence interval

A


Processed meat, linear dose-response analysis, per 50 g/d
Study
Relative Risk (95% CI)
Cohort studies
Ferrucci, 2012
1.32 (0.93, 1.87)
Wu, 2006
1.66 (1.09, 2.54)
Subtotal
1.45 (1.10, 1.90)
Case-control studies
Fu, 2011
1.51 (1.19, 1.91)
Wang, 2011
1.38 (0.90, 2.13)
Ferrucci, 2009
0.94 (0.45, 1.95)
Ward, 2007
1.47 (0.79, 2.73)
Senesse, 2002
1.16 (0.80, 1.69)
Haile, 1997
1.82 (0.79, 4.19)
Benito, 1993
0.58 (0.31, 1.05)
Macquart-Moulin, 1987
1.10 (0.68, 1.76)
Subtotal
1.22 (0.99, 1.51)
Overall
1.29 (1.09, 1.52)
.25
.5
.75
1
1.5
2
3
5
7
Relative Risk

B


Processed meat, nonlinear dose-response analysis
.8
1
1.2
1.4
1.6
0
10
20
30
40
Processed meat (g/day)
Best fitting fractional polynomial
95% confidence interval

Supplementary Table 1: Subgroup analyses of red meat intake and colorectal adenomas overall and stratified by study design, dose-response

		Red meat, per 100 g/d, all studies					**Red meat, per 100 g/d, case-control studies**					**Red meat, per 100 g/d, cohorts**				
		n	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]	*N*	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]	*n*	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]
Geographic location																
Europe		5	1.31 (1.07-1.61)	0	0.98	0.71	4	1.33 (0.94-1.88)	0	0.93	0.90	1	1.30 (1.01-1.67)			0.51
America		10	1.29 (1.13-1.48)	33.1	0.14		6	1.39 (1.10-1.75)	51.9	0.07		4	1.18 (1.01-1.37)	0	0.95	
Asia		1	1.11 (0.64-1.91)				0					1	1.11 (0.64, 1.91)			
Number of cases																
Cases <250		3	2.05 (1.18-3.57)	0	0.38	0.23	3	2.05 (1.18-3.57)	0	0.38	0.29					1.00
Cases 250-<500		6	1.30 (1.03-1.63)	0	0.94		3	1.33 (1.02-1.74)	0	0.84		2	1.20 (0.77-1.88)	0	0.60	
Cases ≥500		7	1.26 (1.11-1.43)	31.0	0.19		4	1.30 (1.01-1.67)	54.8	0.09		4	1.20 (1.06-1.37)	0	0.89	
Adjustment for confounding factors																
Alcohol	Yes	6	1.31 (1.13-1.52)	27.1	0.23	0.64	3	1.41 (1.00-2.00)	47.0	0.15	0.73	3	1.23 (1.06-1.42)	0	0.85	0.66
	No	10	1.25 (1.08-1.45)	0	0.62		7	1.30 (1.09-1.55)	0	0.44		3	1.15 (0.91-1.45)	0	0.84	
Smoking	Yes	10	1.32 (1.15-1.51)	30.4	0.17	0.49	6	1.54 (1.19-2.00)	34.9	0.17	0.21	4	1.20 (1.06-1.37)	0	0.89	1.00
	No	6	1.21 (1.00-1.46)	0	0.98		4	1.21 (0.98-1.49)	0	0.93		2	1.20 (0.77-1.88)	0	0.60	
Body mass index, weight	Yes	9	1.29 (1.17-1.44)	0	0.44	0.98	5	1.32 (1.08-1.62)	39.1	0.16	0.43	4	1.23 (1.07-1.43)	0	0.93	0.55
	No	7	1.27 (1.04-1.56)	4.3	0.39		5	1.53 (1.12-2.10)	0	0.42		2	1.12 (0.88-1.43)	0	0.95	
Physical activity	Yes	9	1.31 (1.15-1.49)	36.5	0.13	0.62	5	1.47 (1.13-1.90)	53.4	0.07	0.41	4	1.20 (1.06-1.37)	0	0.89	1.00
	No	7	1.21 (0.96-1.52)	0	0.97		5	1.21 (0.93-1.58)	0	0.91		2	1.20 (0.77-1.88)	0	0.60	

NSAID, aspirin use	Yes	8	1.30 (1.11-1.53)	47.2	0.07	0.84	5	1.43 (1.06-1.94)	59.9	0.04	0.71	3	1.20 (1.04-1.38)	0	0.74	0.97
	No	8	1.26 (1.06-1.50)	0	1.00		5	1.30 (1.04-1.63)	0	0.98		3	1.21 (0.92-1.59)	0	0.87	
Fiber	Yes	4	1.21 (1.04-1.39)	0	0.89	0.35	2	1.13 (0.84-1.53)	0	0.76	0.30	2	1.23 (1.04-1.45)	0	0.57	0.71
	No	12	1.34 (1.18-1.52)	10.4	0.34		8	1.45 (1.21-1.73)	18.5	0.28		4	1.17 (0.96-1.42)	0	0.94	
Dairy, calcium	Yes	6	1.19 (1.06-1.34)	0	0.97	0.07	2	1.13 (0.84-1.53)	0	0.76	0.30	4	1.20 (1.06-1.37)	0	0.89	1.00
	No	10	1.43 (1.23-1.66)	5.5	0.39		8	1.45 (1.21-1.73)	18.5	0.28		2	1.20 (0.77-1.88)	0	0.60	
Energy intake	Yes	11	1.30 (1.15-1.46)	22.3	0.23	0.74	7	1.41 (1.16-1.73)	34.4	0.17	0.58	4	1.19 (1.04-1.37)	0	0.87	0.82
	No	5	1.23 (0.97-1.55)	0	0.88		3	1.21 (0.86-1.70)	0	0.60		2	1.25 (0.91-1.72)	0	0.71	

n denotes the number of studies. [1] P for heterogeneity within each subgroup, [2] P for heterogeneity between subgroups with meta-regression analysis

Supplementary table 2: Subgroup analyses of processed meat intake and colorectal adenomas overall and stratified by study design, dose-response

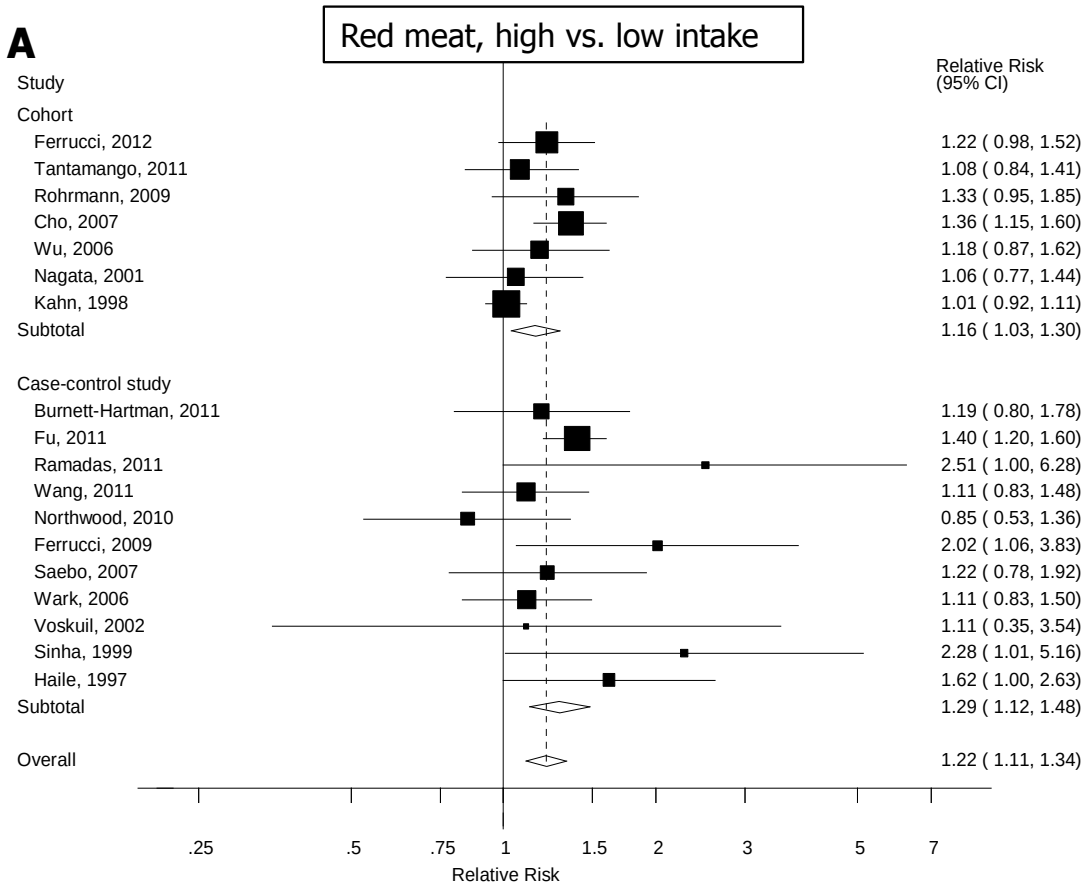
	Processed meat, per 50 g/d					**Processed meat, case-control studies**					**Processed meat, cohort studies**				
	n	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]	*n*	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]	*n*	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]
Geographic location															

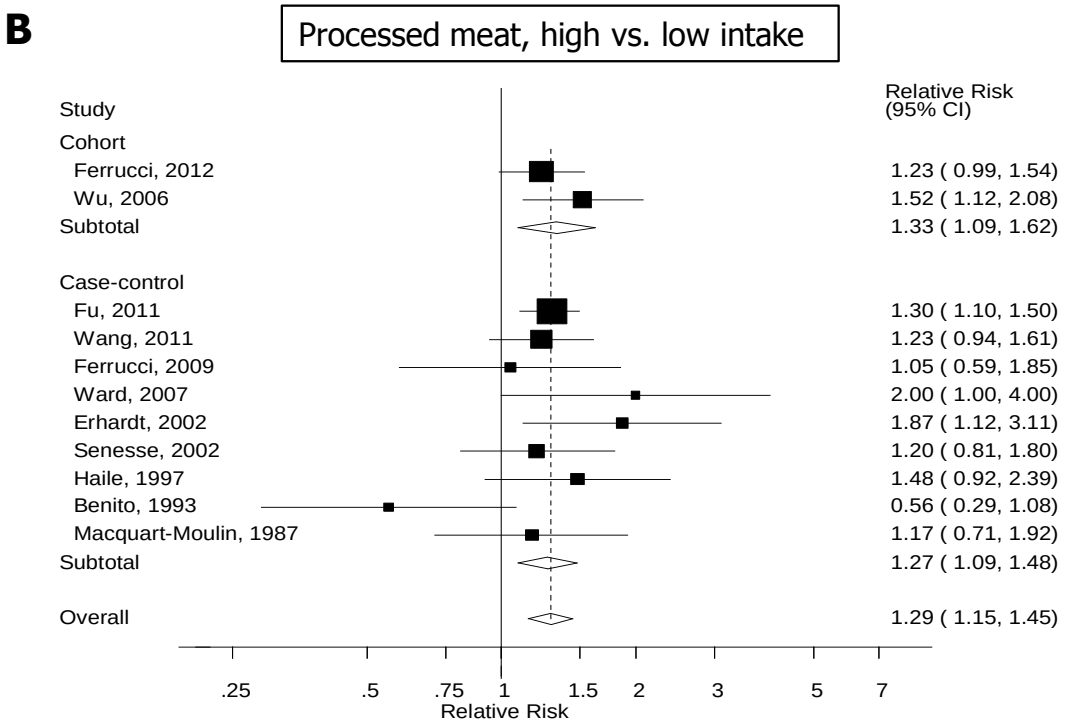
Europe		3	0.95 (0.65, 1.40)	49.5	0.15	0.04	3	0.95 (0.65-1.40)	49.5	0.15	0.07	0				NC
America		7	1.45 (1.24, 1.69)	0	0.87		5	1.45 (1.20-1.74)	0	0.78		2	1.45 (1.10, 1.90)	0	0.41	
Asia		0					0					0				
Number of cases																
Cases <250		3	0.92 (0.53, 1.62)	55.6	0.11	0.045	3	0.92 (0.53-1.62)	55.6	0.11	0.07	0				NC
Cases 250-<500		3	1.20 (0.91, 1.58)	0	0.57		3	1.20 (0.91-1.58)	0	0.57		0				
Cases ≥500		4	1.47 (1.24, 1.73)	0	0.85		2	1.48 (1.20-1.82)	0	0.73		2	1.45 (1.10, 1.90)	0	0.41	
Adjustment for confounding factors																
Alcohol	Yes	4	1.35 (1.14, 1.60)	0	0.49	0.84	3	1.33 (1.06-1.67)	15.8	0.31	0.67	1	1.32 (0.93-1.87)			NC
	No	6	1.25 (0.92, 1.69)	47.6	0.09		5	1.16 (0.82-1.64)				1	1.66 (1.09-2.54)			
Smoking	Yes	7	1.39 (1.20, 1.61)	0	0.78	0.10	5	1.37 (1.15-1.62)	0	0.66	0.18	2	1.45 (1.10, 1.90)	0		NC
	No	3	1.00 (0.56, 1.79)	62.0	0.07		3	1.00 (0.56-1.79)	62.0	0.07		0				
Body mass index, weight	Yes	7	1.34 (1.15, 1.55)	0	0.73	0.72	6	1.34 (1.14-1.58)	0	0.61	0.22	1	1.32 (0.93-1.87)			NC
	No	3	1.14 (0.60, 2.17)	75.9	0.02		2	0.92 (0.37-2.30)	77.8	0.03		1	1.66 (1.09-2.54)			
Physical activity	Yes	7	1.30 (1.04, 1.64)	44.4	0.10	0.52	5	1.19 (0.83-1.70)	59.3	0.04	0.97	2	1.45 (1.10, 1.90)	0		NC
	No	3	1.19 (0.91, 1.55)	0	0.75		3	1.19 (0.91-1.55)	0	0.75		0				
NSAID, aspirin use	Yes	5	1.43 (1.22, 1.69)	0	0.70	0.13	3	1.43 (1.17-1.74)	0	0.48	0.21	2	1.45 (1.10, 1.90)	0		NC
	No	5	1.11 (0.81, 1.52)	40.3	0.15		5	1.11 (0.81-1.52)	40.3	0.15		0				
Fiber	Yes	3	1.28 (0.99, 1.66)	0	0.66	0.93	2	1.25 (0.86-1.81)	0	0.37	1.00	1	1.32 (0.93-1.87)			NC
	No	7	1.27 (1.01, 1.61)	46.5	0.08		6	1.21 (0.92-1.58)	50.0	0.08		1	1.66 (1.09-2.54)			
Dairy, calcium	Yes	4	1.38 (1.11, 1.71)	0	0.60	0.59	2	1.25 (0.86-1.81)	0	0.37	1.00	2	1.45 (1.10, 1.90)	0		NC
	No	6	1.21 (0.92, 1.58)	50.0	0.08		6	1.21 (0.92-1.58)	50.0	0.08		0				

Energy intake	Yes	9	1.37 (1.20, 1.57)	0	0.80	0.03	7	1.35 (1.15-1.58)	0	0.72	0.04	2	1.45 (1.10, 1.90)	0		NC
	No	1	0.58 (0.31, 1.05)				1	0.58 (0.31-1.05)				0				

n denotes the number of studies. [1] P for heterogeneity within each subgroup, [2] P for heterogeneity between subgroups with meta-regression analysis, NC = not calculable

Supplementary Figure 1. Red and processed meat intake and colorectal adenomas, high vs. low intake





Supplementary Figure 2. Red and processed meat intake and colorectal adenomas, nonlinear analysis stratified by study design