

Nutritional Epidemiology: Weighing the Evidence



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Causal Inference in Food and Disease



The fundamental causal question, “*Is there evidence that dietary intake of a food or food group has an independent effect on disease risk?*” is complex, involving:

- **biological mechanisms**
- **genetic variation in metabolizing enzymes**
- **geographic and cultural variation in food consumption**
- **food definitions and compositions**
- **intake measurements and analytic metrics**
- **outcome classifications and disease induction**
- **statistical testing**
- **bias, confounding and residual confounding**
- **colinearity with other food items, lifestyle and behavioral characteristics**
- **differential reporting of findings in the peer-reviewed literature**

Weighing the scientific evidence

The Erosion of Causal Inference

Douglas L. Weed, D Alexander, P Boffetta



The practice of causal inference--wherein investigators make claims about causal relationships between exposures and diseases—is inconsistent in the peer-reviewed literature and across governing bodies.

Examine examples of questionable (i.e., not consistent with good methodological practice) practices in causal inference.

- **Lack of transparent and systematic methods**
- **Causal claims from meta-analysis alone**
- **Calculation of causal attribution (attributable risk) without a causal claim**
- **Causal claims in the absence of human health epidemiology**
- **Causal claims in the absence of statistically significant elevated risks.**
- **Causal claims based on cherry picked findings**
- **Confusing causality with public health recommendations or other forms of action.**
- **Overgeneralization: causal claims for an exposure and groups of diseases (e.g. all lymphohematopoietic cancers) or for a general category of exposure (e.g. pesticides).**

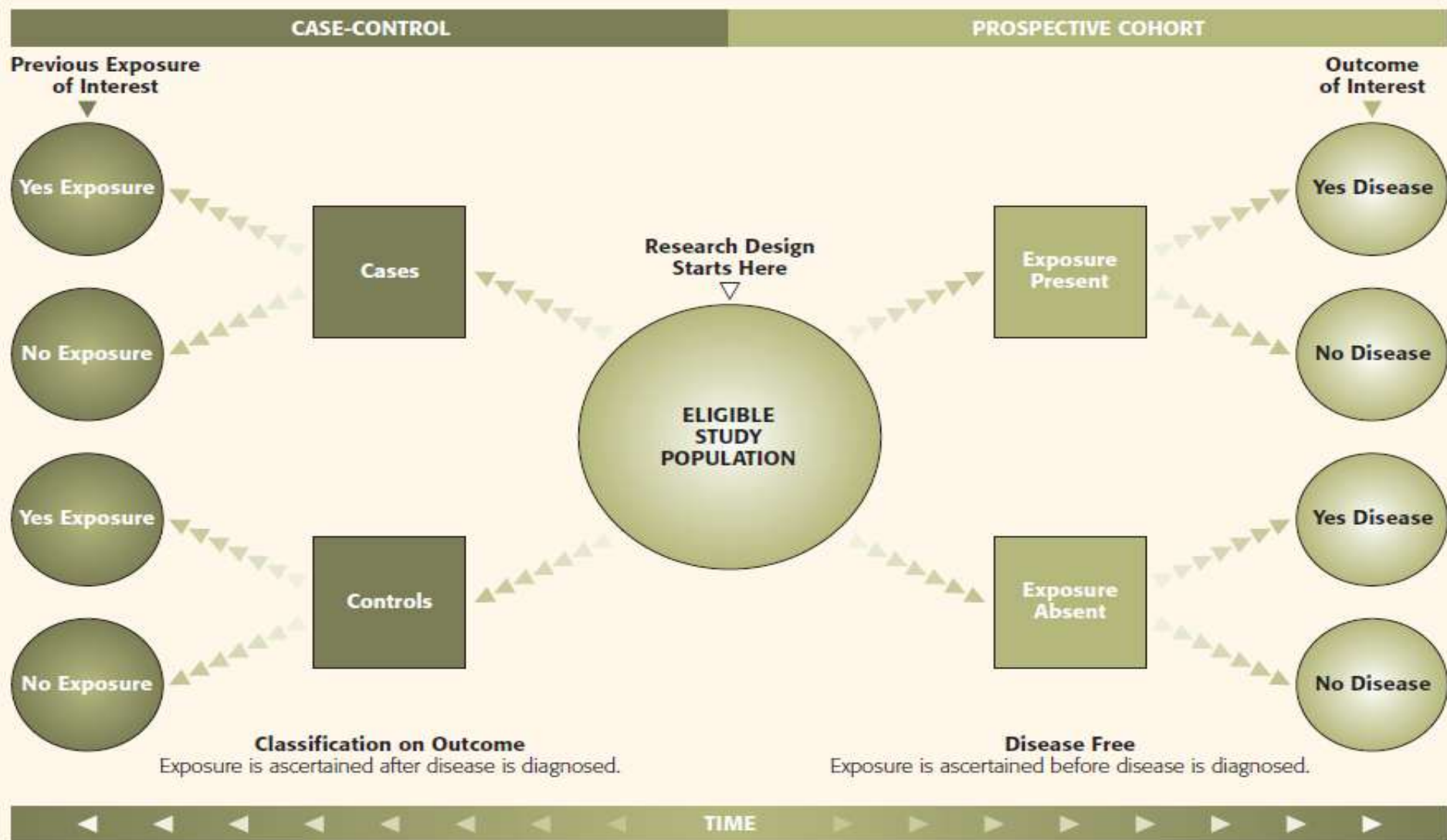
Epidemiology



“THE STUDY OF THE DISTRIBUTION AND DETERMINANTS OF HEALTH-RELATED STATES OR EVENTS IN SPECIFIED POPULATIONS, AND THE APPLICATION OF THIS STUDY TO CONTROL OF HEALTH PROBLEMS” [LAST, DICTIONARY OF EPIDEMIOLOGY]

NUTRITIONAL EPIDEMIOLOGY IS THE STUDY OF THE DIETARY FACTORS THAT INFLUENCE DISEASE FREQUENCY AND DISTRIBUTION IN HUMAN POPULATIONS

EPIDEMIOLOGIC STUDY DESIGNS



Odds of exposure among those with disease (cases) is compared with the odds of exposure among those without disease (controls)

Rate of disease among exposed group is compared with the rate of disease among the non-exposed group.

Assessing Food Intake



METHOD	ADVANTAGES	DISADVANTAGES
Food Frequency Questionnaire (FFQ)	<ul style="list-style-type: none">■ Identifies usual food intake patterns■ Low respondent burden, self-administered■ Relatively inexpensive■ May not be as sensitive to recent dietary changes■ Relatively efficient in ascertaining information from a large study population■ Generally effective at ranking individuals by frequency of intake	<ul style="list-style-type: none">■ Possible inaccuracies in:<ul style="list-style-type: none">□ Respondent memory of food consumption (differential recall)□ Estimation of portion size□ Estimation of specific food constituents within a mixture

- Dietary recall
- Food diary / Food record
- Biochemical indicators

Meta-Analysis: Weighing the Evidence....Literally!

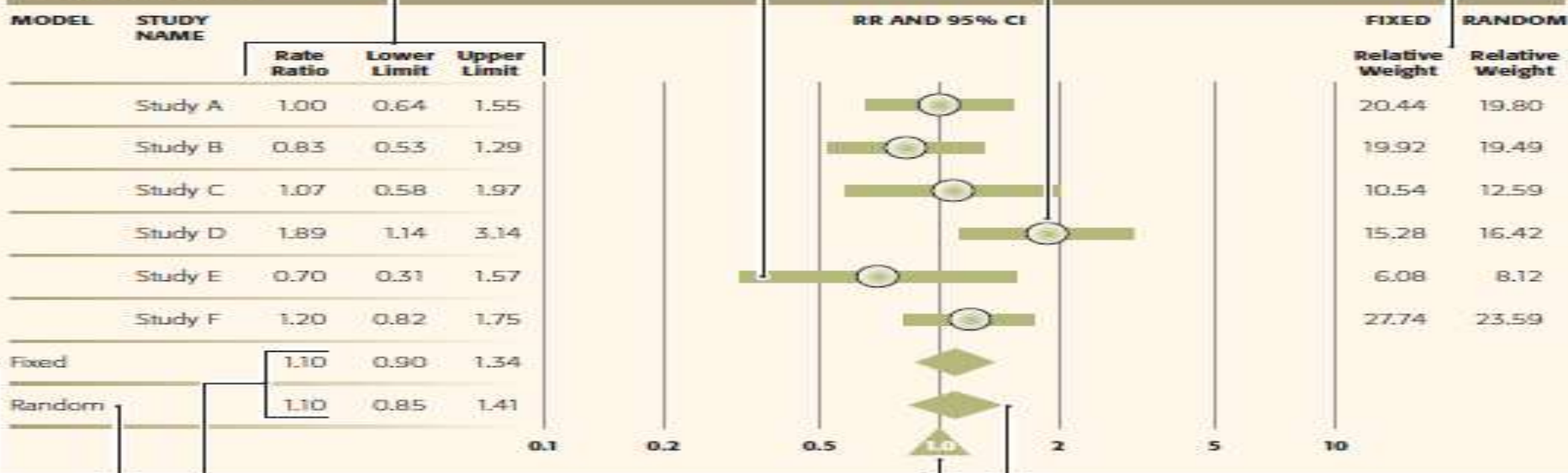
Statistical data (RRs and CIs) that are entered into the meta-analysis from each study

Horizontal bars represent the range of the confidence interval (CI).

The relative weights represent how much statistical weight or influence that each study has on the summary association. Large studies with low standard error contribute more weight than small studies with high variability.

Circles represent the point estimates (RRs and ORs from each study).

FOREST PLOT OF A META-ANALYSIS



Summary associations (SRRE) for all studies included in the meta-analysis model

1.0 is the null value.

Incorporates within- and between-study variability

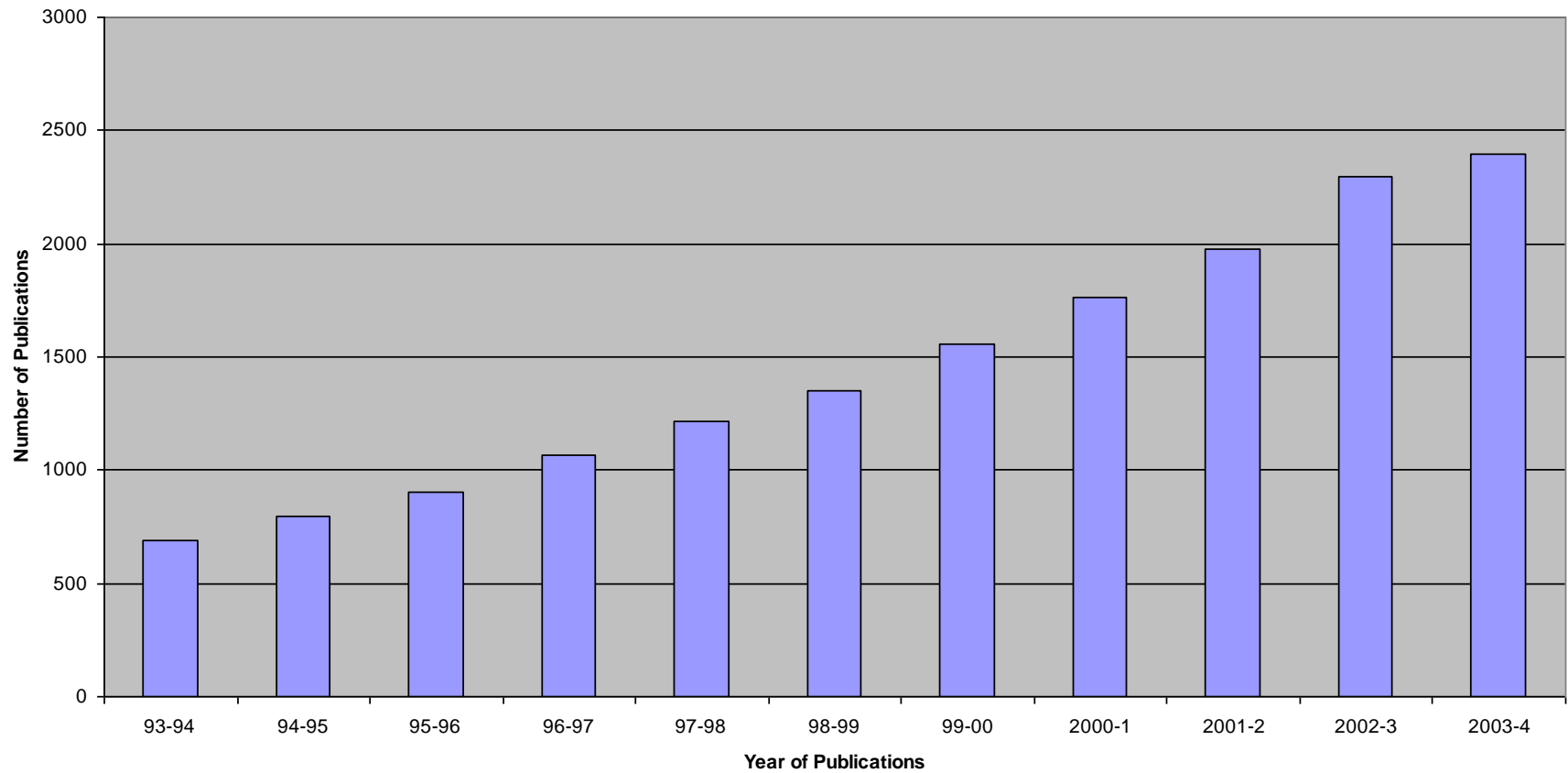
Incorporates within-study variability

Diamonds represent the summary relative risk estimate (SRRE). The horizontal tips of the diamonds represent the lower and upper bounds of the confidence interval.

Meta-Analysis Publications by Year in PubMed



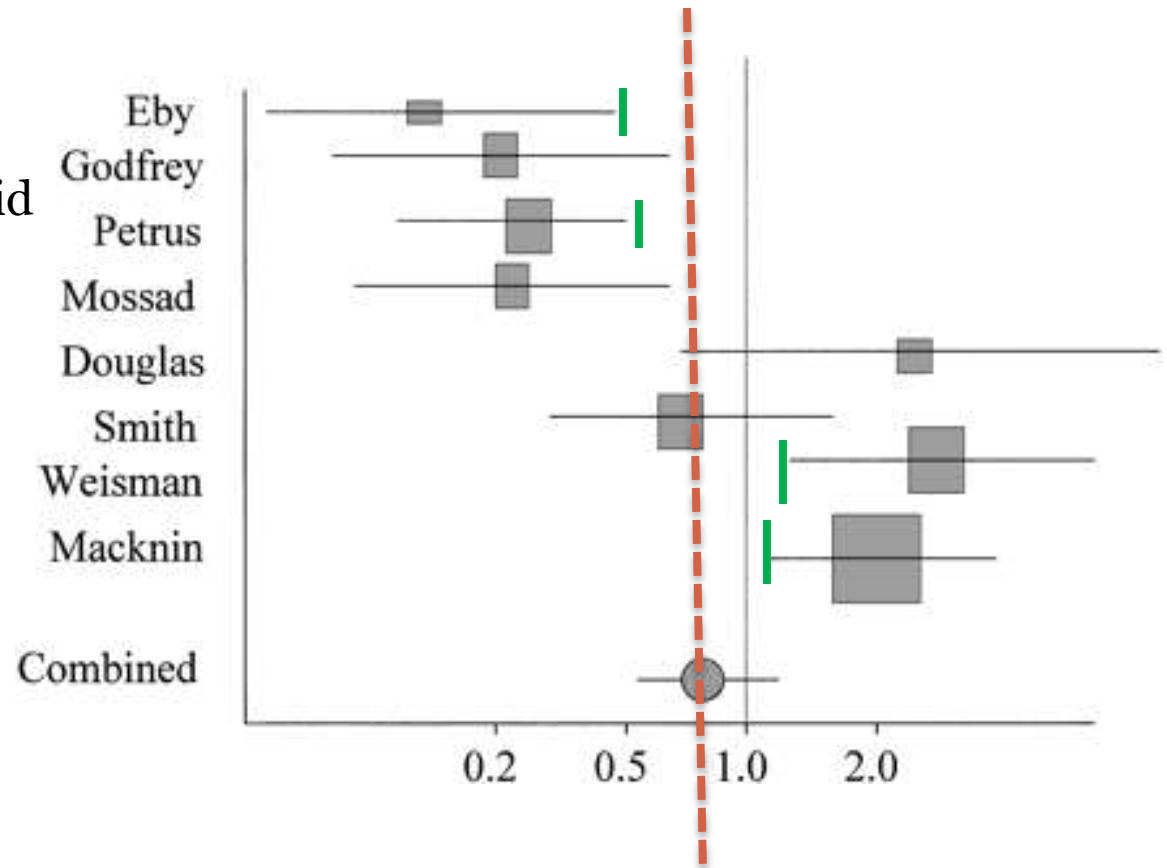
publications



Heterogeneity in Diet Studies



- reflects unexplained variation between study results
- a model that has significant heterogeneity may not be a valid quantitative summarization
- study design, measurement techniques, patterns of associations by gender or race, etc.



Combining “like” data across studies



Two 'average' men having an 'average' meal.

Publication bias



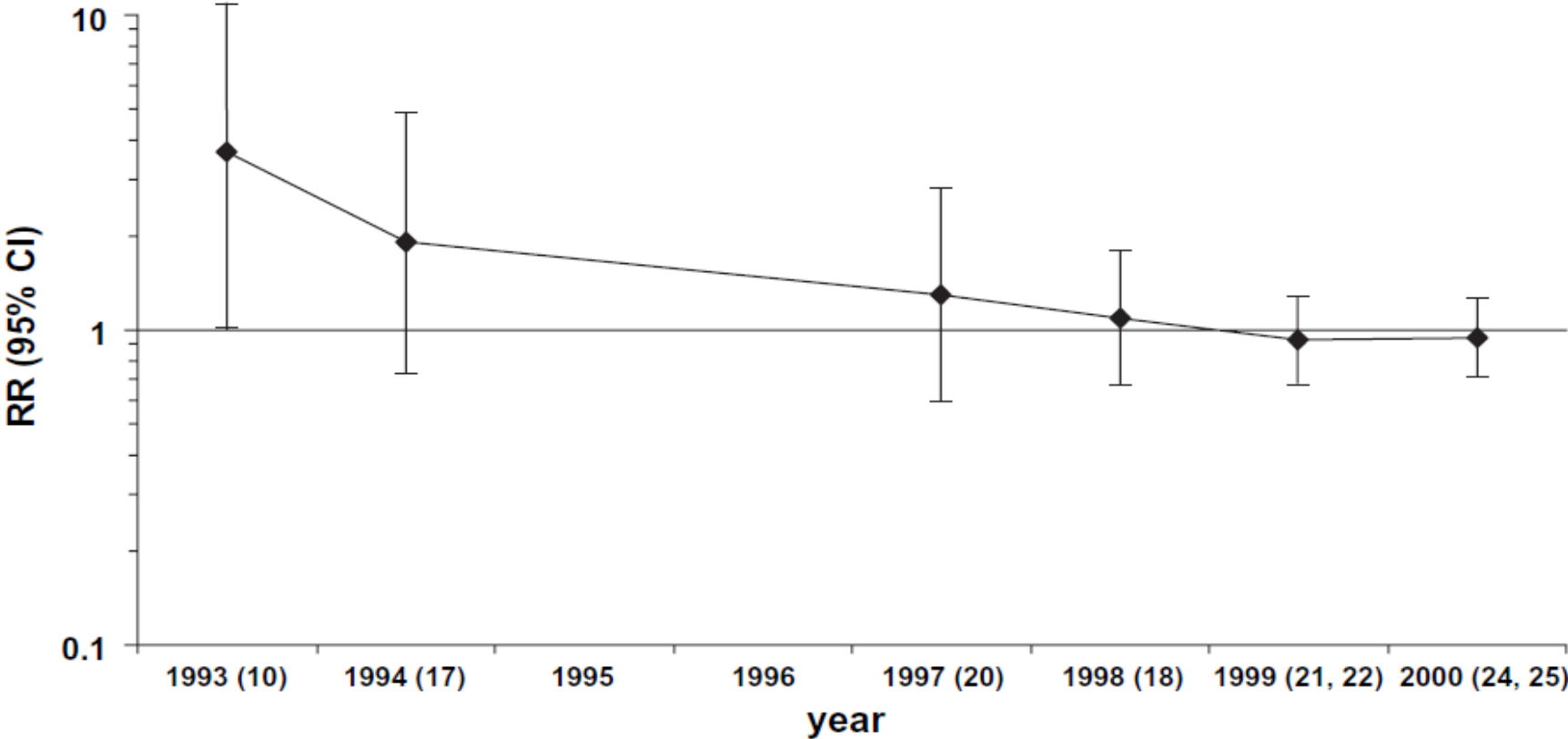
- Greater likelihood that studies with positive results will be published
- Assumption that studies that are published are more likely to report statistically significant findings
 - More likely to be cited by others
 - More likely to be picked up by the media
- Bias against null or negative findings
- Overestimation of effects sizes
 - Type I error rates in the published literature

Publication Bias



	All studies (n=520)	Clinical trials (n=130)
Positive > negative	2.32 (1.47 to 3.66)	3.13 (1.76 to 5.58)
Time to publication	4.8 vs 8.0 m	4.7 vs 8.0 m

Bandwagon Effect

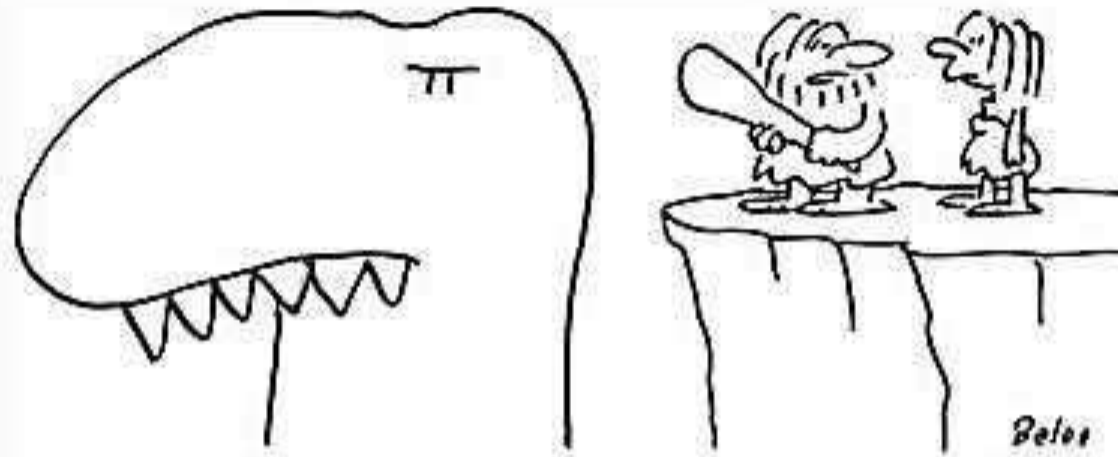


Once Upon a Time in Australia....



- Society for Epidemiologic Research annual conference
- Poster session: dietary factors and colorectal cancer
- Used a 150 item food frequency questionnaire
- Data for red meat intake non-existent

Red Meat Consumption and Cancer



"Didn't I read somewhere that too much red meat isn't good for you?"

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Health and Behavior

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Diet study reaffirms red meat as a culprit in colon cancer

By Liz Szabo, USA TODAY

CHICAGO — Three studies published in Wednesday's *Journal of the American Medical Association* shed new light on the role of diet and cancer.



You may think twice before taking a bite out of a juicy steak, new study confirms link to colon cancer and red meat consumption.

AP

In one article, scientists who studied the eating patterns of nearly 149,000 American adults over two decades found that those who ate the most red and processed meat over a 10-year period had a 30% higher risk of colon cancer and 40% greater risk of rectal cancer compared with those who consumed the least, says Marjorie McCullough, senior epidemiologist at the American Cancer Society and an author of the study.

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Source: [Blackwell Publishing](#)

More on: [Colon Cancer](#), [Breast Cancer](#), [Cancer](#), [Brain Tumor](#), [Lung Cancer](#), [Ovarian Cancer](#)

Eating Red Meat Will Not Increase Colorectal Cancer Risk, Study Suggests

Science Daily — Recent studies published in the journal *Cancer Science* have disproved the common myth that consumption of red meat increases colorectal cancer risk.

Published by the world's largest society publisher Wiley-Blackwell, the study also found that consumption of fish and fish products was similarly inversely related to the risk.

High intake of red meat has traditionally always been associated with increased risk of colorectal cancer, especially in Western countries. There has recently been heightened interest in examining the role n-3 polyunsaturated fatty acids (PUFA) plays in enabling colorectal cancer prevention further, as existing epidemiological findings are limited and inconsistent.



Steak on the grill. (Credit: [iStockphoto/Ken MacDougall](#))

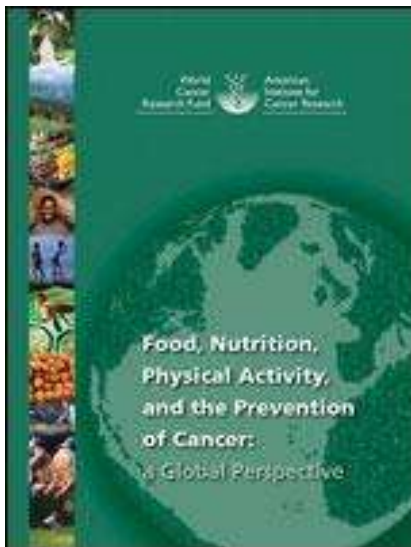
Red Meat Intake and Colorectal Cancer

World
Cancer
Research Fund



American
Institute for
Cancer Research

**Food, Nutrition, Physical Activity,
and the Prevention of Cancer:**
a Global Perspective - *Online*



www.dietandcancerreport.org

Released Nov 1, 2007
in Washington, DC and
several other locations
around the world

517 page report along with
CD-ROM of 20 systematic
literature reviews

“Red meat is a
convincing cause of
colorectal cancer.”

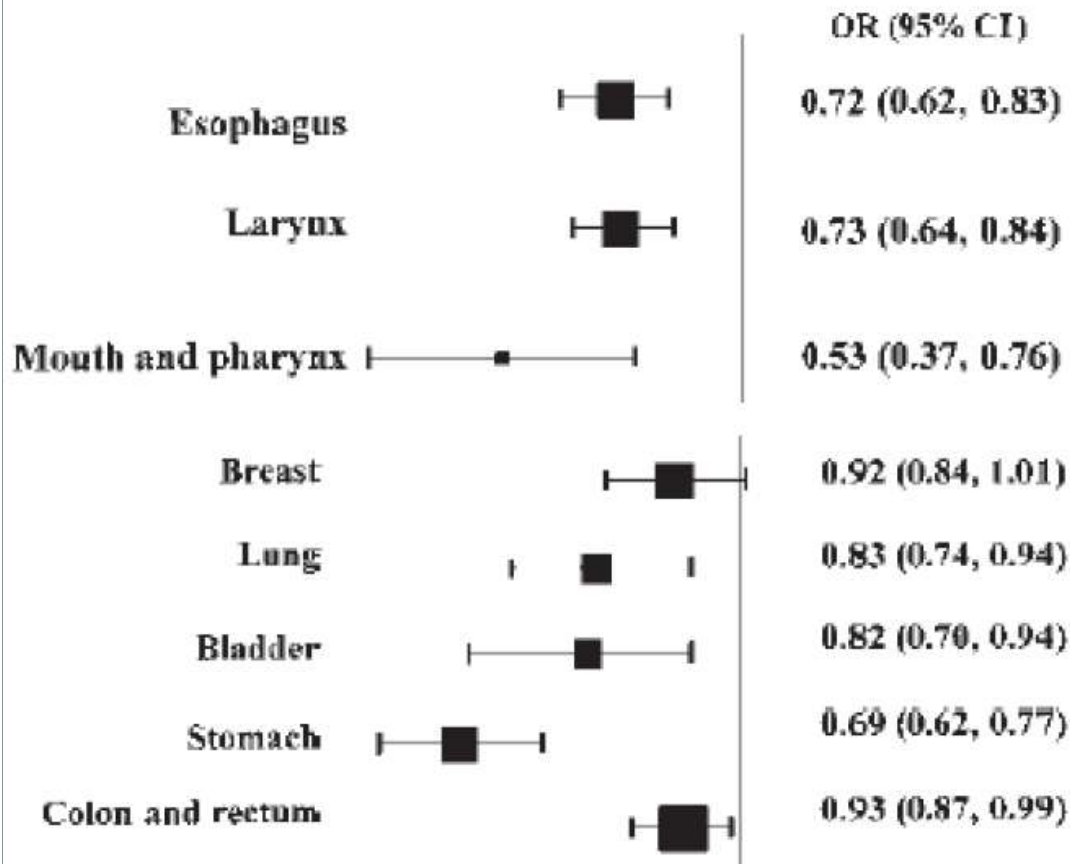
Red Meat and Cancer



- “casts doubt on the rationale to classify ‘convincing’ to the evidence linking high meat intake to colorectal cancer risk in the current report. This also raises questions about the evaluation process and about the robustness of the classification system”

(Boyle P, Boffetta P, Autier P. Diet, nutrition and cancer: public, media and scientific confusion. *Annals of Oncology* 19: 1665–1667, 2008)

Meta-Analysis of Case-Control Studies of Fruit and Vegetable Intake and Cancer



**Decreased
Risk
of
Several
Cancers**

High Fruit and Vegetable Intake and Cancer Risk: Weight of Evidence Over Time

1997

2007

Evidence

Vegetables

Fruits

Evidence

Vegetables

Fruits

Convincing

Oral, oesophagus,
lung, stomach,
colon, rectum

Oral, oesophagus,
lung, stomach

Convincing

-

-

Probable

Larynx, pancreas,
breast, bladder

Larynx, pancreas,
breast, bladder

Probable

Mouth, larynx,
esophagus, stomach

Mouth, larynx,
esophagus, lung,
stomach

Possible

Liver, cervix, ovary,
endometrium,
prostate, kidney,
thyroid

Cervix, ovary,
endometrium, thyroid

Possible

Lung, colorectum,
ovary, endometrium

Pancreas, liver,
colorectum

Fruits and Vegetables and Cancer Risk



Cancer site	Current evidence for association with fruit and vegetables	Comments
<i>Gastrointestinal tract</i>		
Oral cavity, pharynx, oesophagus	Consistent inverse association	Not clear if causal – might be due to residual confounding by other factors such as tobacco and alcohol
Stomach	Generally little or no association	—
Colorectum	Inconsistent, weak, inverse association	Could be due to protective effect of dietary fibre
Lung	Inconsistent, weak, inverse association	Could be due to residual confounding by smoking
Breast	Little or no association	—
Prostate	Little or no association	—

Fruit & Vegetable Intake: Correlation with Lifestyle Factors



Fruit and vegetable intake	Men		Women	
	Current smokers (%)	Alcohol intake 15 g per day (%)	Current smokers (%)	Alcohol intake 15 g per day (%)
<i>Fruit</i>				
Lowest fifth	21.8	38.3	26.6	17.2
Highest fifth	4.1	16.7	7.8	5.3
<i>Vegetables</i>				
Lowest fifth	16.9	32.1	20.6	12.6
Highest fifth	6.2	22.7	10.3	9.4

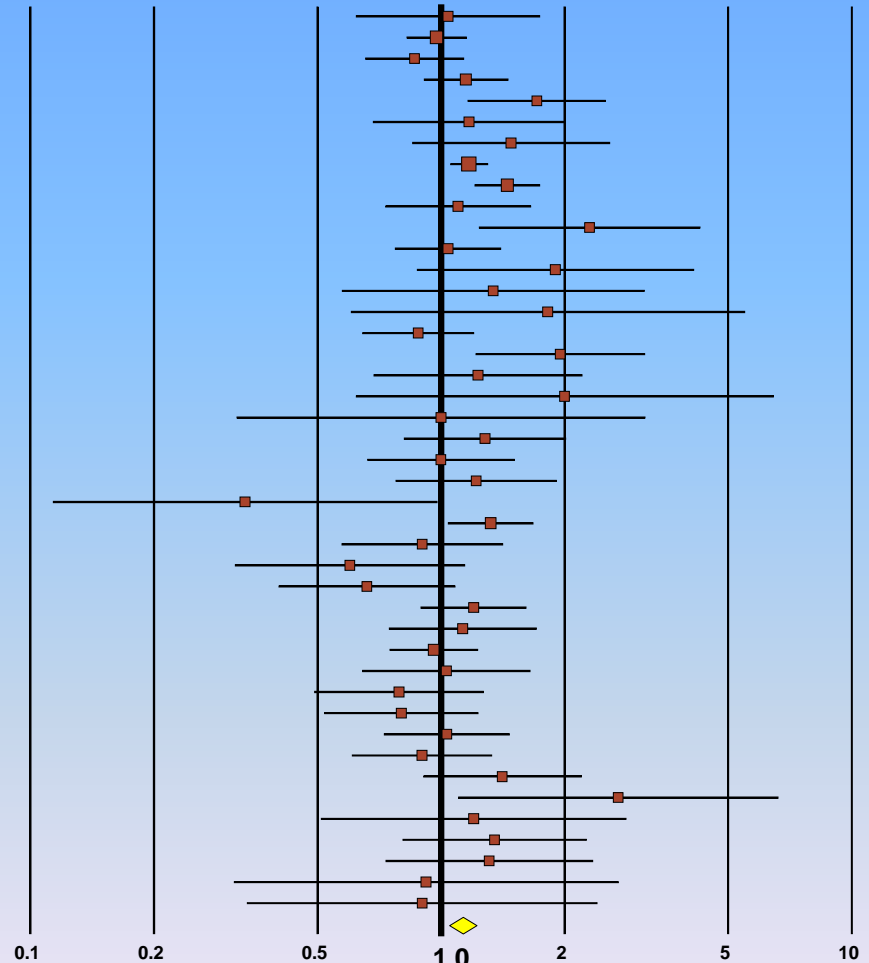
Meta-Analysis of Prospective Studies of Red Meat Intake and CRC

Author & Year

Cohort

RR and 95% CI

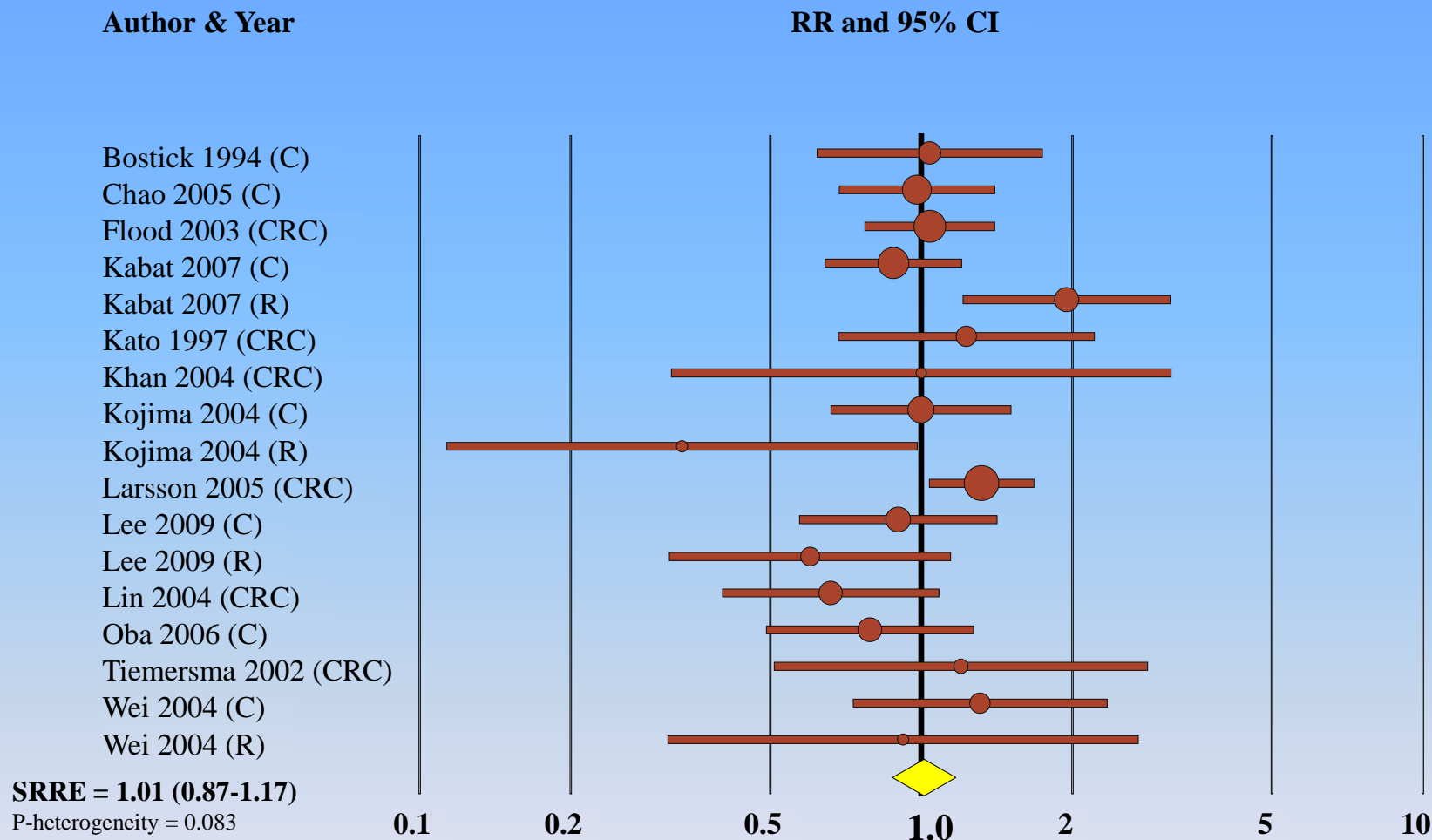
Bostick 1994 (C)	Iowa Women's Health Study
Brink 2005 (C)	Netherlands Cohort Study
Brink 2005 (R)	Netherlands Cohort Study
Chao 2005 (C)	Cancer Prevention Study II
Chao 2005 (R)	Cancer Prevention Study II
Chen 1998 (CRC)	Physicians Health Study
Chen 2003 (C)	China Cohort Study
Cross 2007 (C)	NIH-AARP Cohort Study
Cross 2007 (R)	NIH-AARP Cohort Study
English 2004 (C)	Melbourne Collaborative Cohort Study
English 2004 (R)	Melbourne Collaborative Cohort Study
Flood 2003 (CRC)	Breast Cancer Detection Demonstration Project
Hsing 1998 (CRC)	Lutheran Brotherhood Cohort
Jarvinen 2001 (C)	Mobile Clinic Health Examination Survey
Jarvinen 2001 (R)	Mobile Clinic Health Examination Survey
Kabat 2007 (C)	Canadian National Breast Screening Survey
Kabat 2007 (R)	Canadian National Breast Screening Survey
Kato 1997 (CRC)	New York, Florida Cohort Study
Khan 2004 (CRC) (M)	Japan Cohort Study
Khan 2004 (CRC) (W)	Japan Cohort Study
Kojima 2004 (C) (M)	Japan Collaborative Cohort Study
Kojima 2004 (C) (W)	Japan Collaborative Cohort Study
Kojima 2004 (R) (M)	Japan Collaborative Cohort Study
Kojima 2004 (R) (W)	Japan Collaborative Cohort Study
Larsson 2005 (CRC)	Swedish Mammography Cohort
Lee 2009 (C)	Shanghai Women's Health Study
Lee 2009 (R)	Shanghai Women's Health Study
Lin 2004 (CRC)	Women's Health Study
Norat 2005 (C)	EPIC Cohort
Norat 2005 (R)	EPIC Cohort
Nothlings 2009 (CRC)	Multiethnic Cohort Study
Oba 2006 (C) (M)	Japan Cohort Study
Oba 2006 (C) (W)	Japan Cohort Study
Pietinen 1999 (CRC)	Alpha-Tocopherol, Beta-Carotene Cancer Prev Study
Sato 2006 (C)	Miyagi Cohort Study
Sato 2006 (R)	Miyagi Cohort Study
Singh 1998 (C)	Adventist Health Study
Tiemersma 2002 (CRC) (M)	Prospective Netherlands Study
Tiemersma 2002 (CRC) (W)	Prospective Netherlands Study
Wei 2004 (C) (M)	Health Professionals Follow-up Study
Wei 2004 (C) (W)	Nurses Health Study
Wei 2004 (R) (W)	Nurses Health Study
Wei 2004 (R) (M)	Health Professionals Follow-up Study



SRRE = 1.12 (1.04-1.21)

P-heterogeneity = 0.014

Meta-Analysis of Prospective Studies of Red Meat and Colorectal Cancer Among Women



Meta-Analysis of Prospective Studies of Red Meat and Colorectal Cancer Among Men

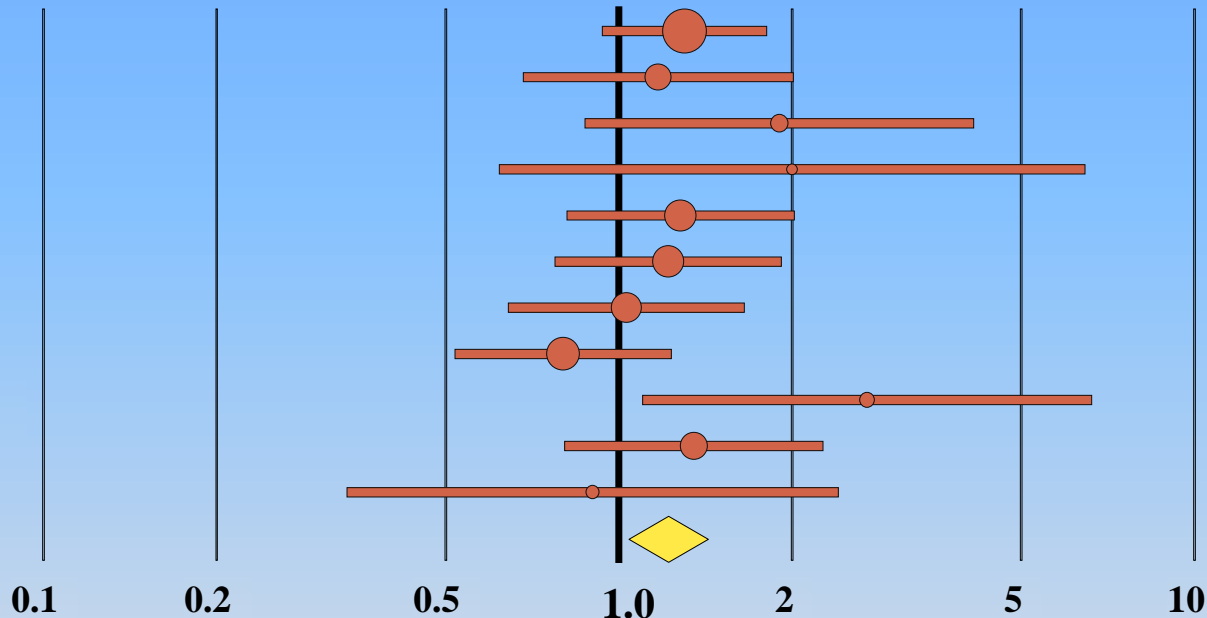
Author & Year

RR and 95% CI

Chao 2005 (C)
 Chen 1998 (CRC)
 Hsing 1998 (CRC)
 Khan 2004 (CRC)
 Kojima 2004 (C)
 Kojima 2004 (R)
 Oba 2006 (C)
 Pietinen 1999 (CRC)
 Tiemersma 2002 (CRC)
 Wei 2004 (C)
 Wei 2004 (R)

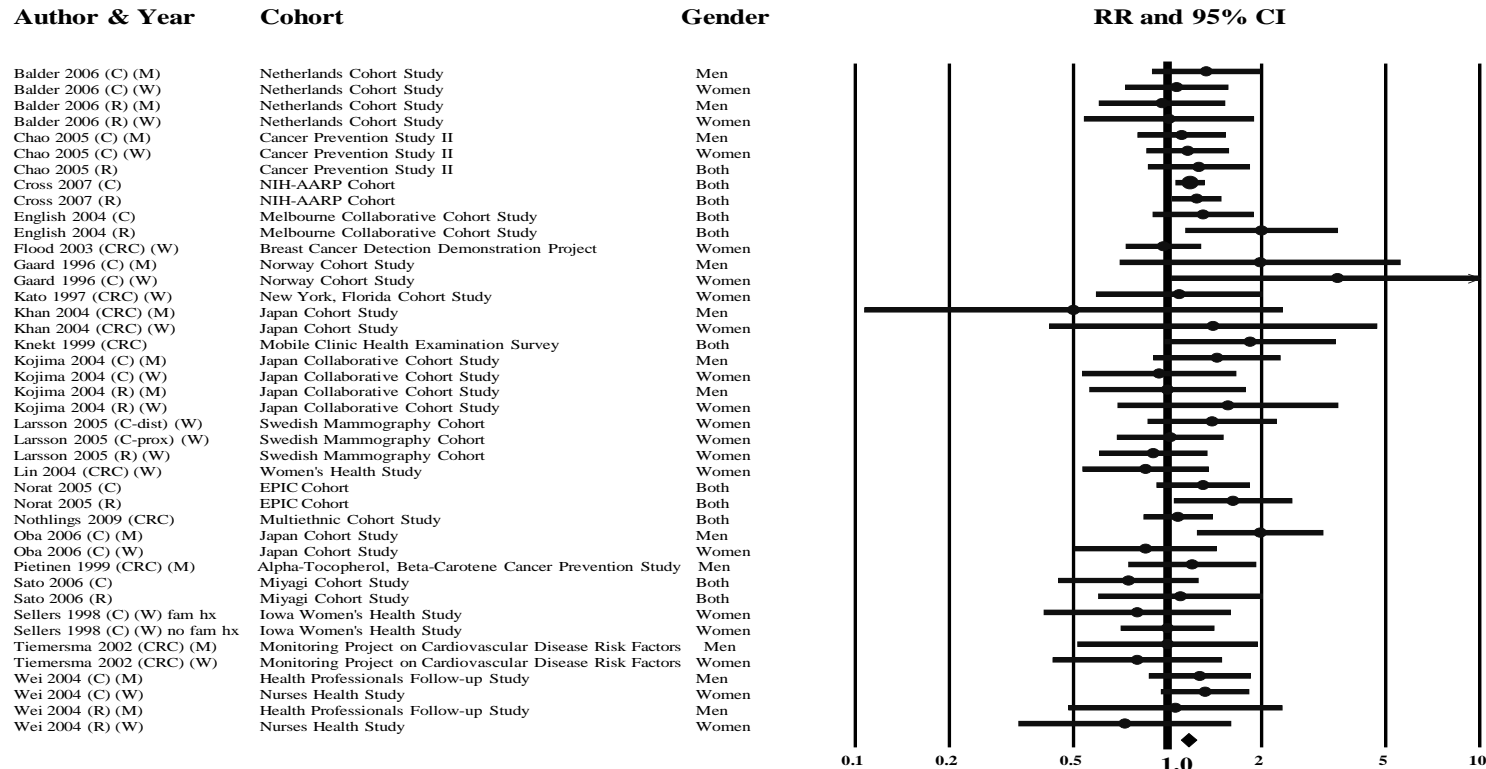
SRRE = 1.21 (1.04-1.42)

P-heterogeneity = 0.472



CRC: colorectal; C: colon; R: rectal

Meta-analysis of Prospective Studies On Processed Meat and Risk of Colorectal Cancer (CRC)*



Summary RR Estimate = 1.16 (95% CI: 1.10-1.23)

*Analysis based on high vs. low intake comparisons
 CRC: colorectal; C: colon; R: rectal

Cumulative Meta-Analysis of Studies on Processed Meat Intake and Colorectal Cancer since 1990*

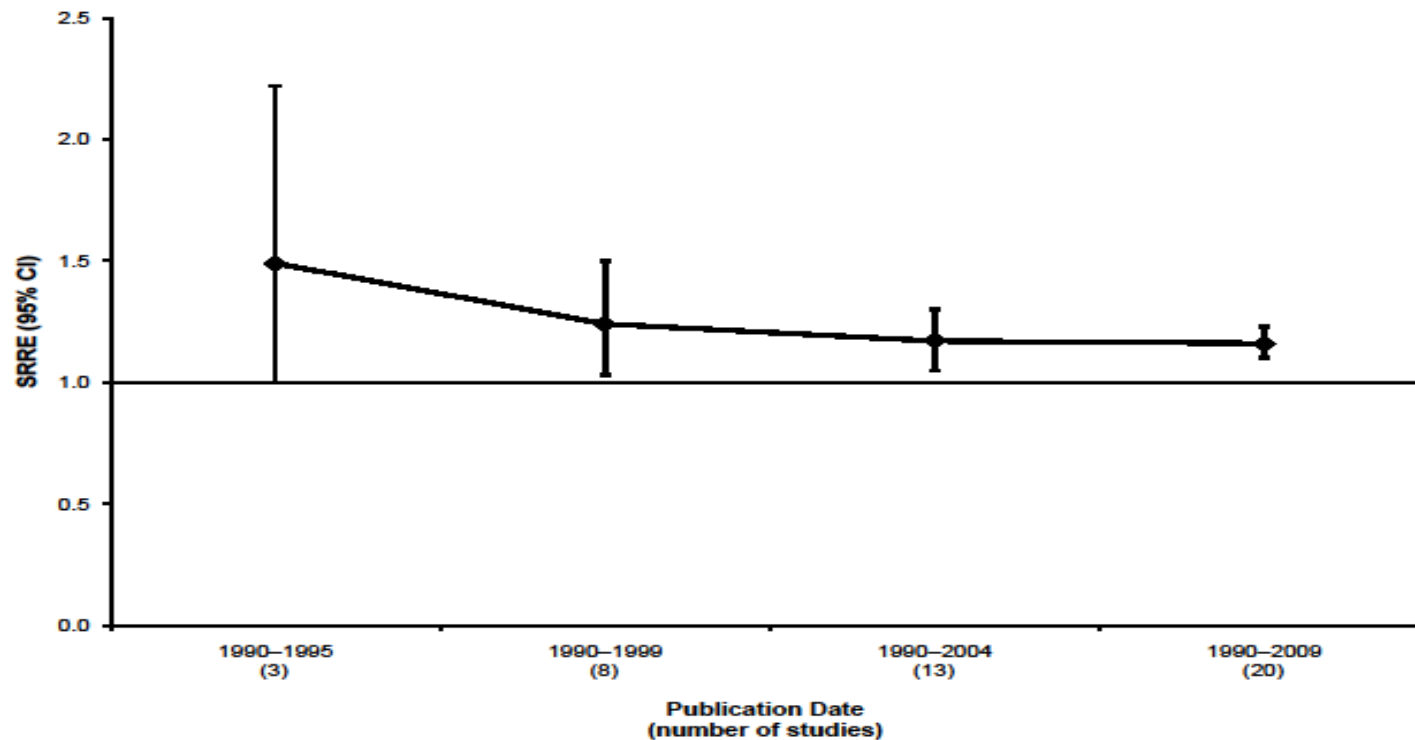


Figure 3. Cumulative meta-analysis of prospective studies of processed meat intake and colorectal cancer.

*Alexander DD et al. Processed meat and colorectal cancer: A quantitative review of prospective epidemiologic studies. *Eur J Cancer Prev* 2010 Sep; 19(5):328-341.

Recently Published Pooled Analysis of Meat Intake and Colorectal Cancer



- Pooled data from 7 European cohorts
- 579 cases of colorectal cancer
- Food Diaries
- “This study of prospectively measured food diary data and risk of colorectal cancer shows little evidence that moderate intakes of red meat...are related to the risk of colorectal cancers.”

Food intake (g/day)	Median intake within category (g/day)	No. of cases/ no. of controls	OR (95% CI) for colorectal cancer*	No. of cases/ no. of controls	Colon cancer	No. of cases/ no. of controls	Rectal cancer
Red meat							
<5	0	156/427	1.00 (reference)	104/269	1.00 (reference)	52/158	1.00 (reference)
5- < 25	16.6	124/462	0.84 (0.62-1.14)	77/302	0.73 (0.50-1.08)	47/160	1.11 (0.66-1.89)
25- < 50	36.7	157/599	0.82 (0.61-1.11)	98/414	0.70 (0.49-1.01)	59/185	1.20 (0.71-2.02)
≥50	68.4	142/508	0.91 (0.66-1.24)	101/331	0.92 (0.62-1.35)	41/177	0.87 (0.50-1.52)
<i>P_{trend}**</i>			<i>P</i> = 0.89		<i>P</i> = 0.72		<i>P</i> = 0.78
OR per 50 g/day increase			1.01 (0.84-1.22)		1.04 (0.83-1.31)		0.96 (0.70-1.31)

Methodological Challenges



- Definitions of analytical variables: Universal definitions of red meat are not available as scientific variables, and consumption patterns differ by geography and culture. For example, in three different studies, red meat was defined as:
 - “beef, pork, or lamb as a main dish”
 - “beef, pork, ham, liver, smoked meats, frankfurters, sausage, fried bacon, fried hamburger”
 - “red meat” [undefined]

Methodological Variation



- Dietary instruments
 - 33-item FFQ
 - 169-item FFQ
- Cut-points of exposure categories
 - > 80 g/day vs. < 10 g/day
 - > 203 g/day vs. < 80 g/day
- Types of exposure metrics
 - > 2 servings/month vs. < 2 servings/month
 - 3-4 servings/week vs. almost never
 - 4th quartile of intake vs. 1st quartile of intake

Red Meat Correlated with Other Factors



Parameter	Men Q1	Men Q5	Women Q1	Women Q5
Cross et al. 2007				
Red meat intake (g/1000 kcal)	12.0	67.0	7.8	54.7
BMI (kg/m ²)	26.1	28.4	25.4	28.2
Smoking: Never smoked (%)	34.3	25.8	46.6	41.5
Smoking: Current smoker (%)	6.7	17.5	9.7	22.7
Education, higher (%)	51.8	38.5	38.2	23.3
Physical activity (5+ times/wk) (%)	29.4	16.0	23.9	11.3
Energy intake (kcal/day)	1,911	2,127	1,528	1,639
Fruit intake (serv./1000 kcal)	2.2	1.1	2.6	1.4
Vegetable intake (serv./1000 kcal)	2.3	1.9	2.9	2.3

Red Meat Correlated with Other Factors



Parameter	Q1	Q5
Song et al. 2004		
Red meat intake (servings/day)	0.13	1.42
BMI (kg/m ²)	24.7	27.0
Smoking: Current smoker (%)	7.97	18.8
Physical activity (4+ times/wk) (%)	18.2	5.74
Multivitamin use (%)	34.0	25.1
Hypertension history (%)	22.2	28.2
Diabetes family history (%)	24.1	26.9
Energy intake (kcal/day)	1,458	2,127
Total fat intake (g/day)	48.4	66.1
Saturated fat intake (g/day)	16.0	23.0
Cholesterol intake (mg/day)	186	259
Fiber intake (g/day)	22.7	16.2

Conclusions



The available epidemiologic data are not sufficient to support an independent and unequivocal positive association between red meat intake and cancer.

- Summary associations weak in magnitude
- Heterogeneity across studies
- Inconsistent patterns of associations across sub-group analyses
- Likely influence of confounding by lifestyle characteristics and other dietary factors

Thank You

Today's Random Medical News

from the New England
Journal of
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Gobbledygook



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