Dietary exposure to acrylamide and cancer risk:

a summary of recent epidemiological evidence

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Outline

- Concerns about acrylamide
  - Animal studies, occupational studies, acrylamide in diet
- Epidemiological studies of dietary exposure
  - Characteristics of studies to date
  - Main results by cancer site
- Summary and discussion points

Concerns about acrylamide

- Acrylamide (AA) was classified by IARC as a probable human carcinogen in 1994 mainly on the basis of animal studies
- Exposure to humans thought at that time to be mainly from occupational exposure and smoking
- In 2002 presence of AA was discovered in carbohydrate-rich food cooked at high temperatures
- JECFA monograph summarising evidence in 2005, but more epidemiological data since then

Occupational studies

Sobel (1986)

- 371 male US AA workers, updated and extended by Swaen (2007) to now include 696 employees with longer follow-up
- More deaths than expected from pancreatic cancer (SMR 222), but not significant and not related to estimated AA exposure

- Collins (1994)
  - Mainly male workers from US and Dutch plants, updated by Marsh (2007); based on nearly 9000 workers
  - Potential overall excess risk of various cancers from earlier analysis now less strong
  - However non-significant raised SMRs (141 for pancreatic, 140 for rectal, 127 for renal cancer) when restricted to "exposed" workers

Epidemiological studies of diet

Study	Design	Dietary assessment	Cancer sites	Sample Size	References
Italian and Swiss hospital-based case-control studies 1991-2000	C-C	2 questions on fried/baked potatoes and estimated daily AA intake from FFQ	Oral Oesophageal Laryngeal Colorectal Breast Ovarian Prostate Renal	749/1772 395/1066 527/1297 2280/4675 2900/3122 1031/2411 1294/1451 767/1534	Pelucchi (IJC, 2003, 2004, 2006, 2007)
Swedish	C-C	FFQ used to estimate daily AA intake, plus specific foods	Colorectal Bladder Renal	591/538 263/538 133/538	Mucci (BJC, 2003)
Swedish	C-C	FFQ used to estimate daily AA intake, plus specific foods	Renal	379/353	Mucci (IJC, 2004)
Swedish Women's Lifestyle and Health Cohort	Cohort	FFQ used to estimate daily AA intake, plus specific foods	Breast	667 40k cohort	Mucci (JAMA, 2005)
Swedish Mammography Cohort	Cohort	FFQ used to estimate daily AA intake, plus specific foods	Colorectal	741 60k cohort	Mucci (IJC, 2006)

More recent studies

Study	Design	Dietary measure	Cancer sites	Sample size	References
Nurses' Mothers' Study	C-C	Childhood French fries from FFQ asked of mothers	Breast	582/1569	Michels (IJC, 2006)
Netherlands Cohort Study on Diet and Cancer	Case-cohort	FFQ used to estimate daily AA intake, plus specific foods	Endometrial Ovarian Breast Renal Bladder Prostate	221 195 1350 339 1210 2246 1.5 to 4k subcohort	Hogervorst (CEBP, 2007, AJ Clin Nutr 2008)
Danish Diet Cancer and Health Study	Case-cohort	Biomarkers AA	Breast	374/374	Olesen (IJC, 2008)

Breast cancer

Relative risk	Dietary measure	Design	Sample size	Reference
0.9 (0.8-1.1) >1/week vs 0	Consumption of fried/baked potatoes	Case-control	2569/2588	Pelucchi, 2003
1.19 (0.91-1.55) highest vs lowest quintile	AA intake estimated from FFQ	Cohort	667/43404	Mucci, 2005
1.27 (1.12-1.44) per additional serving/week	Pre-school 30-item FFQ obtained from mothers: French fries	Case-control	582/1569	Michels, 2006
1.06 (0.88-1.28) highest vs lowest quintile	AA intake estimated from FFQ	Case-control	2900/3122	Pelucchi, 2006
0.90 (0.73-1.13) highest vs lowest quintile	AA intake estimated from FFQ	Case-cohort	1350/1796	Hogervorst, 2007
1.5 (0.8-3.0) per 10-fold increase in adduct concentration	AA haemoglobin adduct levels	Nested case-control	374/374	Olesen, 2007

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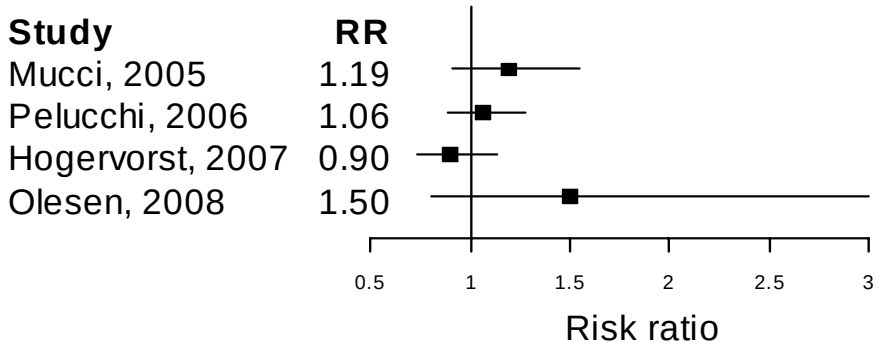
Breast cancer



Olesen observed an even stronger effect on risk for ER +ve breast cancer
After adjusting for smoking RR 2.7 (1.1-6.6)

Ovarian and endometrial cancer

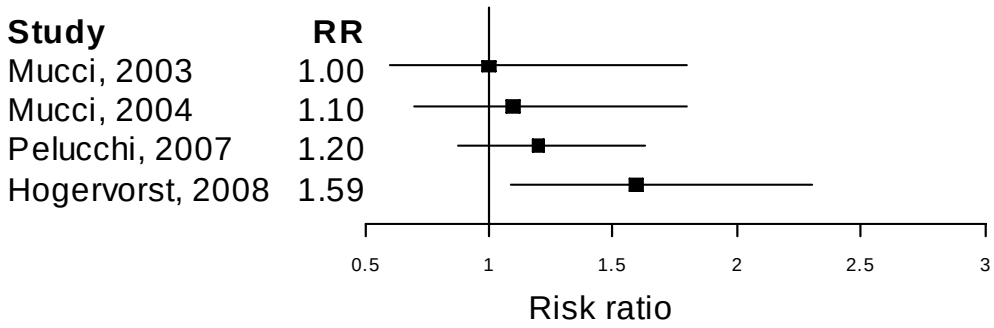
Relative risk	Dietary measure	Design	Sample size	Reference
Ovarian				
0.97(0.73-1.31) highest vs lowest quintile	AA intake estimated from FFQ	Case-control	1031/2411	Pelucchi, 2006
1.77 (1.11-2.82) highest vs lowest quintile	AA intake estimated from FFQ	Case-cohort	195/1778	Hogervorst, 2007
Endometrial				
1.17 (0.76-1.79) highest vs lowest quintile	AA intake estimated from FFQ	Case-cohort	221/1481	Hogervorst, 2007

Hogervorst observed stronger effect for endometrial cancer when restricting analysis to non-smokers: RR 1.99 (1.12-3.52) after adjustment for other covariates

Renal cancer

Relative risk	Dietary measure	Design	Sample size	Reference
1.0 (0.6-1.8) highest vs lowest quartile	AA intake estimated from FFQ	Case-control	133/538	Mucci, 2003
1.1 (0.7-1.8) highest vs lowest quartile	AA intake estimated from FFQ	Case-control	379/353	Mucci 2004
1.20 (0.88-1.63) highest vs lowest quartile	AA intake estimated from FFQ	Case-control	767/1534	Pelucchi 2007
1.59 (1.09-2.30) highest vs lowest quintile	AA intake estimated from FFQ	Case-cohort	339/4095	Hogervorst 2008

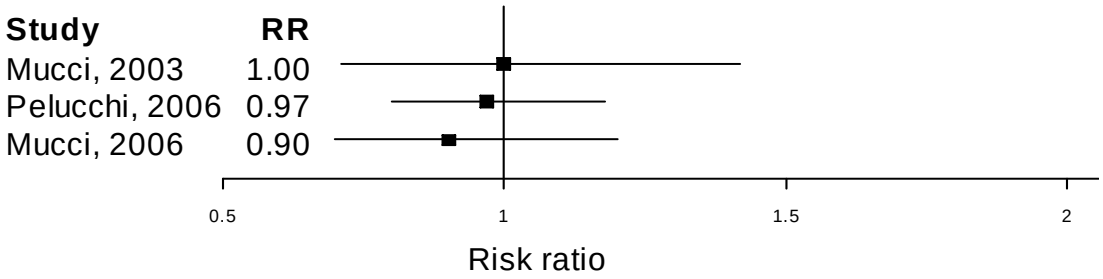
Renal cancer estimates



Colorectal cancer

Relative risk	Dietary measure	Design	Sample size	Reference
1.0 (0.71-1.42) highest vs lowest quartile	AA intake estimated from FFQ	Case-control	591/538	Mucci, 2003
0.97 (0.80-1.18) highest vs lowest quintile	AA intake estimated from FFQ	Case-control	2280/4675	Pelucchi, 2006
0.9 (0.7-1.2) highest vs lowest quintile	AA intake estimated from FFQ	Cohort	741/60k	Mucci, 2006

Colorectal cancer



Discussion points from studies

- How well is dietary intake of AA measured?
- Study design
  - Retrospective vs prospective studies
  - Could anything be gained by pooling data?
- Sample size and power
- Adjustment for confounders (especially smoking)

Measures of exposure: FFQ

- Apart from some early studies that only examined specific food items, all but one study (Olesen, 2008) estimate AA intake by applying estimates of average AA content of food items to FFQ responses on key foods
- Two potential sources of uncertainty and heterogeneity:
  - FFQ as measure of usual diet
  - Conversion of FFQ data into AA intake. (How much) has this improved over time?
- Additionally it is uncertain what is the most relevant exposure (total lifetime exposure, early exposure?)

Measures of exposure: biomarkers

- Several studies have used biomarkers (AA adduct levels in blood) to assess validity of estimates based on reported diet
- Olesen (2008) used these biomarkers (and glycidamide adduct levels) as measures of exposure in study of breast cancer
- Biomarkers provide a more direct measure, but
  - Inevitable small sample size
  - Only a measure of short-term exposure
  - Cannot distinguish between sources (e.g diet vs smoking)

Study design

- Two categories of design
  - Case-control studies where diet measured retrospectively
  - Cohort based studies (cohort, case-cohort, nested case-control) where diet measured prospectively
- Cohort studies avoid recall bias, but generally at expense of sample size
- Pooling data would increase sample size/power but studies are probably too heterogeneous

Sample size and power

- Some studies have – on the face of it – good sample sizes (>1000 cases and controls)
- However what effect size are we expecting to see?
- Few studies conducted to date can rule out ~ 20% increase in risk from high to low exposure
- It may be unlikely risk is greater than this (extrapolating from animal studies and based on epidemiological evidence to date), but this size of effect would represent an important public health issue

Adjustment for confounders

- Smoking is a major potential confounder since it is a risk factor for numerous cancers and also a major source of AA exposure. This is a particular issue when using biomarkers
- Some studies have stratified by smoking status and found differences in results. Some studies are too small for this or have incomplete smoking data
- Should future studies by matched/stratified for smoking status?
- What about other potential confounders?

Summary

- The epidemiological evidence to date probably rules out a very strong effect on risk of most cancers from dietary intake
- Nonetheless the evidence is certainly consistent with an important increase in risk in public health terms, for some cancers especially
- Need to come up with creative study designs, perhaps combining FFQ with biomarker data, so preserving advantages of sample size, and adjusting adequately for confounders
- It may take some time to accumulate sufficient evidence to rule AA out or in as a cancer risk factor