Diet-wide analyses for risk of colorectal cancer: prospective study of 12,250 incident cases among 543,000 women in the UK

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Diet and colorectal cancer

2017	DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing	Physical activity[1,2]	Processed meat[3] Alcoholic drinks[4] Body fatness[5] Adult attained height[6]
	Probable	Wholegrains Foods containing dietary fibre[7] Dairy products[8] Calcium supplements[9]	Red meat[10]
LIMITED EVIDENCE	Limited – suggestive	Foods containing vitamin C[11] Fish Vitamin D[12] Multivitamin supplements[13]	Low intakes of non-starchy vegetables[14] Low intakes of fruits[14] Foods containing haem iron[15]
	Limited – no conclusion	Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine; beta-carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern	
STRONG EVIDENCE	Substantial effect on risk unlikely		

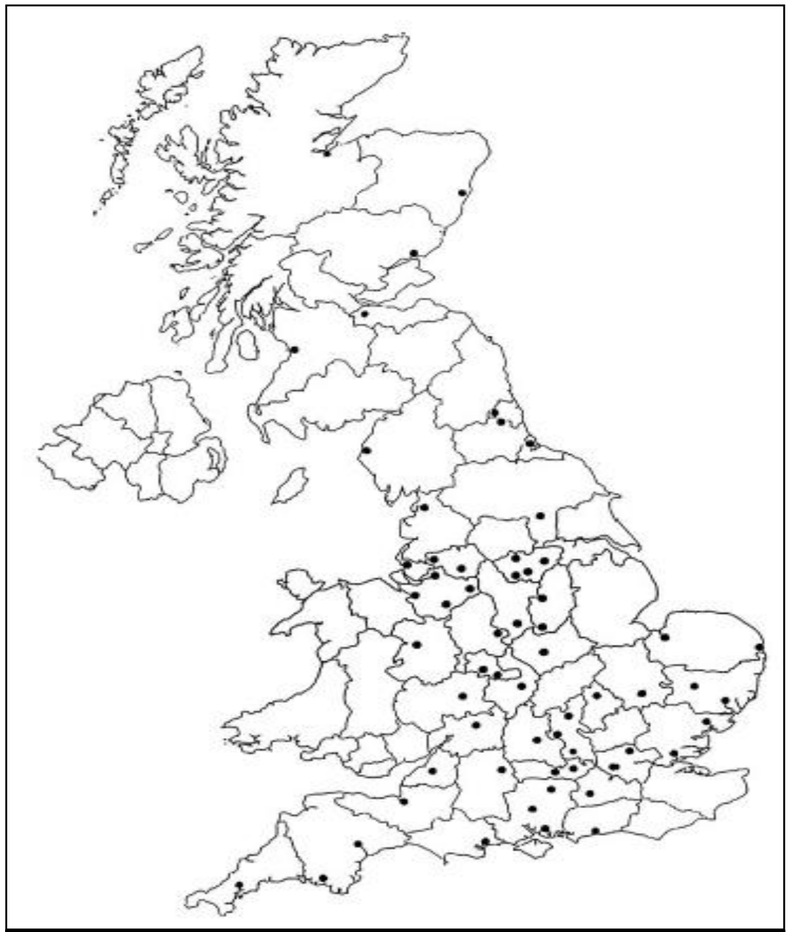
- Uncertainty remains regarding the role of diet in the aetiology of colorectal cancer
- **Aims**: Conduct a diet-wide association study of colorectal cancer risk, together with a targeted genetic analysis

World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Expert Report 2018. From dietandcancerreport.org

Study cohort: The Million Women Study

- Cohort of 1.32 million women
- Recruited through breast cancer screening centres in 1996-2001
- Age at recruitment 50-64 years
- Ongoing follow-up

Outcome: colorectal cancer (ICD-10 C18-C20) over 16.6 years of follow-up (N=12,251)



Location of the Breast Screening Centres recruiting into the Million Women Study

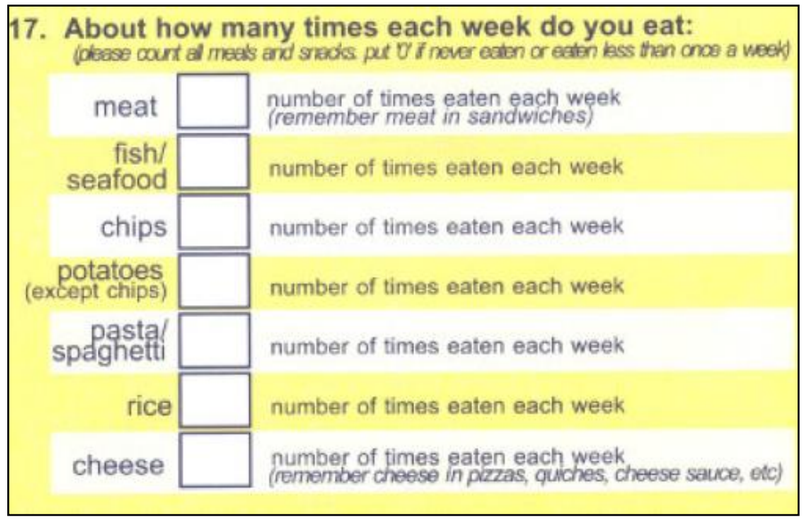
Green et al. 2019

Dietary data in the Million Women Study

- Assessed in 2000-2004 using 130-item short food frequency questionnaire

- 7% of participants completed one or more Oxford WebQ (24 hour recall) ~10 years later
  - Used to estimate calibrated intakes

97 dietary factors available in both surveys and selected for analysis



17. About how many times each week do you eat:
(please count all meals and snacks. put '0' if never eaten or eaten less than once a week)

meat		number of times eaten each week *(remember meat in sandwiches)*
fish/ seafood		number of times eaten each week
chips		number of times eaten each week
potatoes (except chips)		number of times eaten each week
pasta/ spaghetti		number of times eaten each week
rice		number of times eaten each week
cheese		number of times eaten each week *(remember cheese in pizzas, quiches, cheese sauce, etc)*

Oxford WebQ

Did you eat any meat or poultry yesterday? ○ No ◉ Yes | Show Help |

Think about curry, stirfry, sandwiches, pie fillings, sausages/burgers, liver, pâté or mince.

Meat	Amount	None	½	1	2	3	4	5+
Sausage	Each	○	○	○	○	○	○	○
Beef (e.g. roast, steak, mince, curry, burger)	Serving	○	○	○	○	○	○	○
Pork (e.g roast, chops, sweet and sour)	Serving	○	○	○	○	○	○	○
Lamb or mutton (e.g. roast, chops, stew, burger)	Serving	○	○	○	○	○	○	○
Chicken or turkey in breadcrumbs or deep fried (e.g. nuggets, KFC)	Serving	○	○	○	○	○	○	○
Chicken or turkey (e.g. roast, drumsticks, curry)	Serving	○	○	○	○	○	○	○
Bacon	Rasher	○	○	○	○	○	○	○
Ham, Parma ham, salami, pastrami, cured meats	Slice	○	○	○	○	○	○	○
Liver or liver pâté	Serving	○	○	○	○	○	○	○
Other (e.g. duck, goose, kidney)	Serving	○	○	○	○	○	○	○

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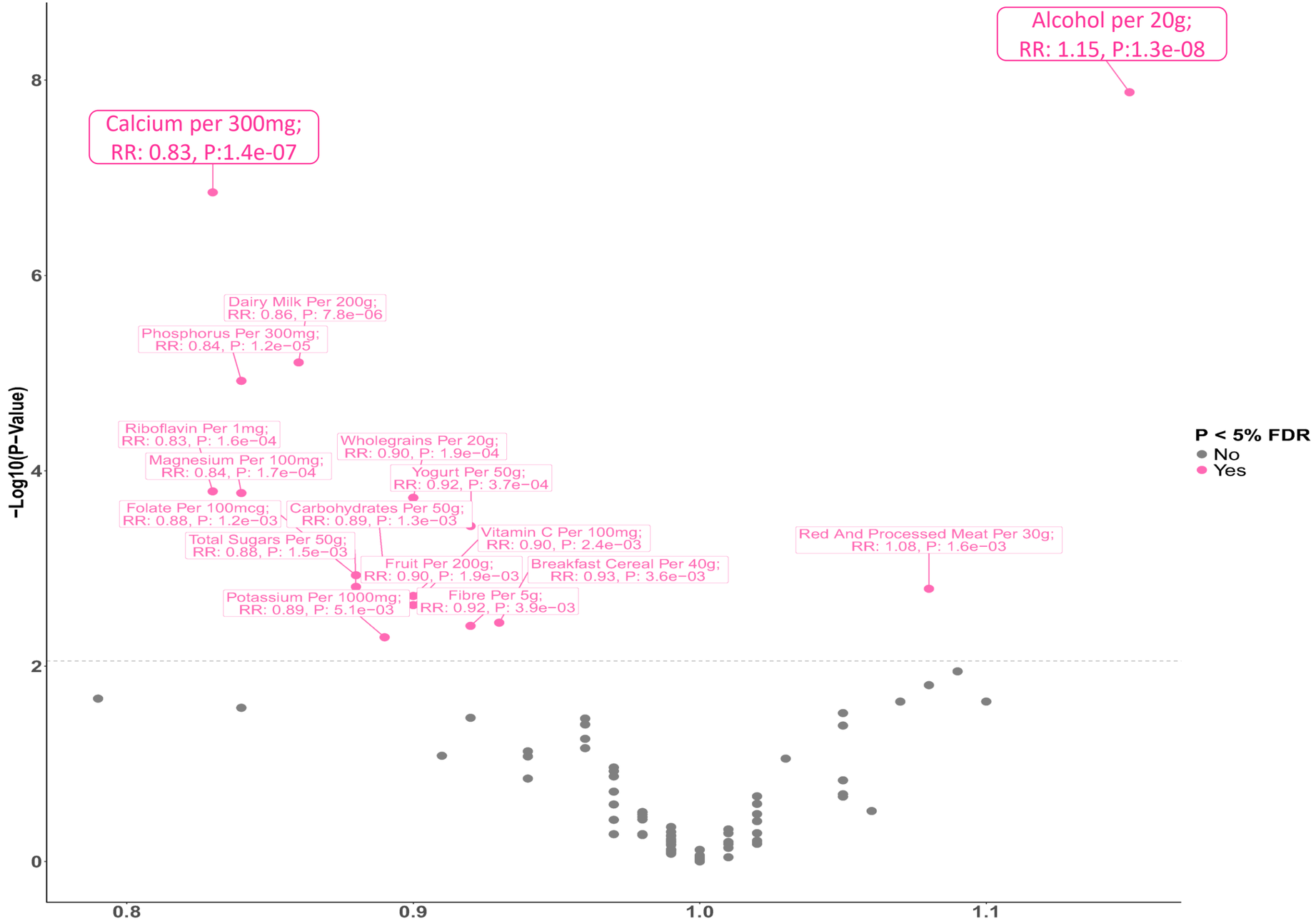
Statistical analysis

Analytical sample: **542,778 women**

Cox proportional hazards regression:

- 97 foods/nutrients (log-linear trends in risk across baseline categories)
- Covariates: age, lifestyle, socio-demographic factors, disease history, personal, health, total energy
- Further adjusted for foods/nutrients robust to correction for multiple testing

Volcano plot for associations of 97 dietary risk factors with risk of colorectal cancer



Associations of FDR-significant dietary factors with risk of colorectal cancer, further adjusted for calcium, dairy milk, fruit, wholegrains

Food or nutrient from diet only	Trend Increment	RR (95% CI) Main model	RR (95% CI) + Calcium added	RR (95% CI) + Dairy milk added	RR (95% CI) + Fruit added	RR (95% CI) + Wholegrains added
Alcohol	20 g/day	1.15 (1.09,1.20)	1.12 (1.07,1.18)	1.13 (1.07,1.18)	1.12 (1.07,1.17)	1.14 (1.09,1.20)
Calcium	300 mg/day	0.83 (0.77,0.89)	-	0.86 (0.79,0.95)	0.88 (0.81,0.97)	0.84 (0.78,0.90)
Dairy milk	200 g/day	0.86 (0.81,0.92)	0.94 (0.86,1.02)	-	0.86 (0.80,0.92)	0.87 (0.82,0.93)
Phosphorus	300 mg/day	0.84 (0.78,0.91)	0.95 (0.85,1.05)	0.89 (0.82,0.98)	0.92 (0.84,1.01)	0.88 (0.81,0.95)
Riboflavin	1 mg/day	0.83 (0.75,0.91)	0.96 (0.85,1.09)	0.91 (0.81,1.03)	0.95 (0.84,1.07)	0.86 (0.78,0.95)
Magnesium	100 mg/day	0.84 (0.77,0.92)	0.83 (0.83,1.01)	0.88 (0.80,0.97)	0.93 (0.84,1.04)	0.80 (0.99,4.69)
Wholegrains	20 g/day	0.90 (0.85,0.95)	0.91 (0.86,0.96)	0.90 (0.85,0.96)	0.92 (0.87,0.98)	-
Yogurt	50 g/day	0.92 (0.88,0.96)	0.96 (0.91,1.00)	0.92 (0.88,0.96)	0.93 (0.89,0.98)	0.93 (0.89,0.97)
Folate	100 µg/day	0.88 (0.82,0.95)	0.92 (0.86,1.00)	0.91 (0.84,0.98)	0.94 (0.87,1.02)	0.90 (0.83,0.97)
Carbohydrates	50 g/day	0.89 (0.83,0.96)	0.92 (0.86,0.98)	0.91 (0.85,0.97)	0.93 (0.87,1.00)	0.91 (0.85,0.98)
Total sugars	50 g/day	0.88 (0.81,0.95)	0.92 (0.85,1.00)	0.90 (0.83,0.98)	0.94 (0.86,1.03)	0.88 (0.82,0.96)
Red/proc meat	30 g/day	1.08 (1.03,1.12)	1.06 (1.01,1.11)	1.07 (1.03,1.12)	1.06 (1.02,1.11)	1.06 (1.02,1.11)
Fruit	200 g/day	0.90 (0.85,0.96)	0.92 (0.86,0.98)	0.90 (0.84,0.96)	-	0.92 (0.86,0.98)
Vitamin C	100 mg/day	0.90 (0.83,0.96)	0.91 (0.84,0.97)	0.88 (0.82,0.95)	0.92 (0.85,1.01)	0.91 (0.84,0.98)
Breakfast cereal	40 g/day	0.93 (0.89,0.98)	0.95 (0.90,1.00)	0.95 (0.91,1.00)	0.96 (0.91,1.01)	0.95 (0.91,1.00)
Fibre	5 g/day	0.92 (0.86,0.97)	0.93 (0.87,0.98)	0.92 (0.86,0.97)	0.96 (0.89,1.03)	0.97 (0.90,1.04)
Potassium	1000 mg/day	0.89 (0.82,0.97)	0.96 (0.88,1.05)	0.94 (0.86,1.02)	1.01 (0.91,1.11)	0.91 (0.84,0.99)

Calcium intake was independently associated with risk of colorectal cancer

Mendelian randomisation analysis of genetically predicted milk intake per 200 g/day with colorectal cancer risk

Cancer site	Relative risk, 95% CIs
Colorectal cancer	0.60, 0.46-0.74
Colon cancer	0.60, 0.43-0.77
Rectal cancer	0.49, 0.31-0.67

Summary statistics for the associations of the LCT variant (rs4988235) with colorectal cancer were obtained from a GWAS of 99,152 participants (52,865 colorectal cancer cases and 46,287 controls) from the ColoRectal Transdisciplinary Study, the Colon Cancer Family Registry, and the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)

We assigned each additional genetically predicted milk intake increasing allele an increment of 17.1 g/d of dairy milk

Limitations and conclusions

Limitations

- The range of re-measured intakes across baseline groups was small for some foods
- Generalisability (older-aged predominantly white women)
- Residual confounding

Conclusions

- This large prospective analysis provides robust evidence for the protective role of dairy milk and dairy products in colorectal cancer incidence, which is likely to be driven largely if not wholly by calcium.
- More research is needed to understand the potential health impacts of increasing calcium intake in some populations

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