

Meat intake and the recurrence of colorectal adenomas

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A large multicenter randomized controlled trial was re-assessed to check whether meat intake and a reduction in its consumption are associated with recurrence of adenomatous polyps of the large bowel, which are precursors of most colorectal malignancies. All subjects ($n = 1905$; 958 interventions and 947 controls) had one or more histologically confirmed colorectal adenomas removed during a colonoscopy within 6 months before randomization. The subjects were followed-up for approximately 4 years after randomization and a colonoscopy for detecting adenomas was conducted at the 1st and 4th year after randomization. Dietary variables were assessed at baseline (T0) and in conjunction with annual visits at the end of the 1st (T1), 2nd (T2), 3rd (T3) and 4th (T4) years. Odds ratios using logistic regression models for meat variables were estimated based on the average intake at T0, T1, T2, T3 and T4 (prior to the T4 colonoscopy) as well as change (T0–T4) in intake. In the intervention group, the total reduction in median intake of red meat from T0 to T4 was observed by the end of 1st year itself (30 and 31% for men and women, respectively). The analysis provide no evidence to suggest that lower intake or reduction in total and in red meat consumption during a period of 4 years reduces the

risk of adenoma recurrence (including multiple or advanced adenoma), whereas the data suggest that high intake of fish is associated with lower risk of adenoma recurrence. *European Journal of Cancer Prevention* 13:159–164 © 2004 Lippincott Williams & Wilkins.

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Introduction

Epidemiological studies suggest that a high intake of meat, especially red meat (defined as beef, pork or lamb), or varying meat-cooking methods such as frying and how well-done are associated with increased risk for colorectal cancers (Willett *et al.*, 1990; de-Verdier *et al.*, 1991; Goldbohm *et al.*, 1994; Gaard *et al.*, 1996) and colorectal adenomas (Giovannucci *et al.*, 1994; Sinha *et al.*, 1999) although several studies indicate that various types of meat did not modify cancer risk appreciably (Kampman *et al.*, 1999; Voskuil *et al.*, 2002; Flood *et al.*, 2003). However, little is known about the role of meat intake and the recurrence of adenomas. This paper examines whether meat intake and a reduction in its consumption are associated with recurrence of colorectal adenomas in the Polyp Prevention Trial (PPT), a large multicentre, randomized, intervention trial. As adenomas are generally thought to be precursor lesions for colorectal cancers (Hill *et al.*, 1978), their recurrence has been used as surrogate end point for invasive cancers in the PPT and similar trials.

Materials and methods

The PPT recruitment was undertaken at eight clinical centres in the US during 1991–1994 (Schatzkin *et al.*, 2000). All the subjects were between 35 and 89 years and had one or more histologically confirmed colorectal adenomas removed during a colonoscopy within 6 months before randomization. Eligible subjects had no history of colorectal cancer, surgical resection of adenomas, bowel resection, polyposis syndrome or inflammatory bowel disease and weighed not more than 150% of the recommended level. They had also not taken any lipid-lowering drugs or had any medical conditions or dietary restrictions or practices that would substantially limit compliance with the protocol. Details of the study design, eligibility criteria, randomization procedures, dietary intervention and end-point assessment have been described elsewhere (Lanza *et al.*, 1996; Schatzkin *et al.*, 1996). Of the total randomized subjects, 1905 (91.6%) completed the study. The institutional review boards of the National Cancer Institute and each participating centre

approved the study. All subjects provided written informed consent.

The subjects were followed-up for approximately 4 years after randomization. Colonoscopy was carried out at the 1st and 4th year after randomization. The 1st year colonoscopy was performed at least 180 days but less than 2 years after randomization. The primary end point was the recurrence of adenomas during the interval from the 1st year to the 4th year colonoscopy. Secondary end points were advanced and multiple adenomas. Advanced adenomas were defined as those that had either a maximum diameter of at least 1 cm or at least 25% villous elements or evidence of high-grade dysplasia (including carcinoma). Two or more recurrent adenomas were defined as 'multiple'.

A validated self-administered food frequency questionnaire, a modified version of the Block Health Habits and History questionnaire (Block *et al.*, 1986; Mares-Perlman *et al.*, 1993) was administered at baseline (T0) and in conjunction with annual visits at the end of the 1st, 2nd, 3rd and 4th years to obtain dietary information from the past year. The annual visits at the end of the 1st, 2nd, 3rd and 4th years are denoted as T1, T2, T3 and T4, respectively. Frequencies and serving sizes of consumption at each visit were collected.

Total meat (g/day) is the sum of items such as hamburger, beef, beef stew, pork, liver, sausage, hot dogs, lunchmeat, lean lunchmeat, bacon, fried chicken, chicken/turkey, fried fish, tuna, shellfish, other fish and other sea food. Only 24% of total beef stew intake was considered as meat. Items such as hamburger, beef, beef stew, pork, liver, sausage, hot dogs and bacon were counted towards the red meat intake (g/day) whereas white meat (g/day) was considered to come from fried chicken, chicken/turkey, fried fish, tuna, shellfish, other fish and other seafood. White meat was then further split up into poultry (fried chicken and chicken/turkey) and fish (fried fish, tuna, shellfish, other seafood and other fish). The intake of red meat intake cooked at high temperature (g/day) was estimated from items such as bacon, hamburger, beef and pork and intake from processed meat (g/day) was derived from bacon, sausage, lunchmeat and ham.

Data analysis

As there was no difference in the recurrence pattern between the intervention and the control groups (Schatzkin *et al.*, 2000), both were combined for the present analysis. The amount of total meat intake (g/day) and its subtypes (g/day) from the frequencies and portion sizes of consumption at each visit were estimated. Then the meat intake was averaged at T0, T1, T2, T3 and T4

(prior to the T4 colonoscopy). Further change (T0–T4) in meat consumption during the interval from baseline to the 4th year was calculated by subtracting the corresponding meat intake at T0 and T4.

Odds ratios (OR) and 95% confidence intervals (CI) were calculated using a logistic regression model (Hosmer and Lemeshow, 1989) based on the meat intake averaged over T0, T1, T2, T3 and T4 (prior to the T4 colonoscopy). We examined meat (estimated OR and CI) both as continuous and categorical (quintile) variables. We also estimated ORs and CI based on the change (T0–T4) in meat intake; these models also included the baseline (T0) meat intake. The risk estimates for all meat variables in the above two types of analyses were represented as an effect of 10 g/day increase in consumption. We checked the linear relationship by adding a quadratic term to the regression model, which however, was not statistically significant. All analyses were adjusted for age, gender and group (intervention/control). Non-steroidal anti-inflammatory drug (NSAID) use was tested as a potential confounder as an association between NSAIDs and colorectal adenoma in the PPT trial had been published elsewhere (Tangrea *et al.*, 2003).

We looked at addition effects, which are the risks associated with adding the amount of each specific type of meat while keeping the consumption of meat from other sources constant (Kipnis *et al.*, 1993; Kulldorff *et al.*, 2000). Sequentially nested models were used in the regression analyses. In model 1, total meat is the only meat variable included. In model 2, total meat is divided into red meat and white meat and both were included simultaneously. In model 3, white meat is further split into poultry and fish and once again there was a simultaneous inclusion of both these variables as well as red meat. In model 4, only high-temperature red meat and in model 5, only processed meat was included.

Results

Of the 1905 subjects (958 interventions and 947 controls) who completed the study, at least one adenomatous polyp recurred in 754 subjects. Of these 754, 125 had advanced and 320 had multiple adenomas.

Median intake of meat and its subtypes at T0 were essentially the same for the intervention and control groups in both men and women (Tables 1 and 2). In the intervention group, the overall reduction in median intake from T0 to T4 of all meat was achieved by the end of the first year (T1) and then remained steady in later years for both men and women. In this group, the median intake of total meat (g/day) from T0 to T4 declined by 14% among men and 20% among women. Over the same period, the median intake in the control

Table 1 Median intake of meat (10th, 90th percentile): summary items: females

Summary items (g/day)	Control					Intervention				
	T0 (n=349)	T1 (n=336)	T2 (n=323)	T3 (n=314)	T4 (n=319)	T0 (n=328)	T1 (n=310)	T2 (n=300)	T3 (n=292)	T4 (n=307)
All meat	116 (61,196)	111 (68,167)	115 (64,175)	107 (63,164)	112 (60,172)	120 (63,181)	97 (49,152)	95 (52,150)	99 (56,152)	96 (55,158)
Red meat	55 (18,122)	52 (17,103)	53 (20,111)	54 (20,108)	54 (19,105)	59 (22,114)	39 (11,86)	39 (12,86)	42 (13,87)	41 (15,85)
White meat	50 (20,109)	53 (20,102)	53 (20,93)	47 (20,94)	50 (17,103)	52 (18,108)	51 (20,92)	50 (20,92)	52 (20,93)	52 (19,93)
Fish	14 (3,46)	15 (3,48)	14 (3,38)	14 (3,38)	13 (3,38)	18 (4,47)	16 (3,38)	16 (3,36)	14 (3,37)	16 (3,42)
Poultry	31 (11,75)	31 (11,72)	31 (11,72)	27 (11,72)	27 (7,75)	28 (9,75)	27 (7,72)	27 (7,72)	31 (7,72)	27 (7,72)
High temp. red meat	34 (7,85)	31 (9,74)	32 (7,82)	35 (8,77)	32 (6,74)	38 (11,82)	22 (4,58)	21 (4,57)	24 (4,61)	24 (4,61)
Processed-meat	11 (1,37)	10 (0,3,35)	10 (0,5,36)	11 (0,8,30)	12 (0,36)	11 (1,37)	8 (0,32)	8 (0,33)	8 (0,28)	9 (0,29)

Table 2 Median intake of meat (10th, 90th percentile): summary items: males

Summary items (g/day)	Control					Intervention				
	T0 (n=349)	T1 (n=336)	T2 (n=323)	T3 (n=314)	T4 (n=319)	T0 (n=328)	T1 (n=310)	T2 (n=300)	T3 (n=292)	T4 (n=307)
All meat	145 (84,237)	135 (82,210)	138 (79,208)	134 (79,203)	136 (86,216)	144 (83,221)	123 (67,192)	127 (74,190)	125 (73,190)	126 (71,194)
Red meat	86 (35,168)	79 (30,145)	83 (32,147)	80 (32,144)	83 (35,157)	81 (31,154)	58 (19,121)	60 (21,118)	56 (19,118)	57 (20,116)
White meat	52 (22,104)	48 (20,97)	50 (22,97)	47 (19,93)	49 (20,93)	54 (22,111)	57 (22,112)	58 (25,111)	60 (22,115)	60 (23,113)
Fish	18 (5,48)	16 (4,43)	17 (5,41)	15 (4,36)	15 (3,39)	18 (4,50)	18 (5,46)	18 (4,49)	17 (4,45)	18 (4,46)
Poultry	28 (8,72)	27 (7,72)	27 (8,72)	27 (7,72)	28 (7,72)	28 (10,75)	31 (11,75)	41 (11,75)	41 (11,75)	41 (11,75)
High temp. red meat	54 (17,117)	49 (17,103)	50 (16,100)	49 (17,101)	54 (17,107)	49 (15,109)	30 (7,75)	32 (6,82)	28 (6,81)	29 (7,72)
Processed	20 (3,60)	19 (3,52)	19 (4,58)	19 (2,55)	20 (4,55)	21 (1,37)	16 (1,37)	16 (1,37)	16 (1,37)	16 (1,37)

group declined by 6 and 3% among men and women, respectively (Tables 1 and 2).

In the intervention group, the total reduction in median intake of red meat from T0 to T4 was also observed by the end of the first year (30 and 31% for men and women, respectively) and then remained steady in the subsequent years. Median red meat intake in the control group declined from T0 to T4 by only 3 and 2%, respectively for men and women (Tables 1 and 2). The highest percentage reduction in meat intake from T0 to T4 was observed for red meat cooked at high temperature in the intervention group (41 and 37% in men and women, respectively) and the overall reduction was seen by the end of the first year itself. In the control group, the corresponding reduction in red meat cooked at high temperature was almost negligible. The percentage reduction in processed meat intake was almost nil in the control group, 24% in the intervention group. The participants in the intervention group consumed more white meat, than controls (Tables 1 and 2).

There were no significant associations of total meat or red meat intake with adenoma recurrence (Table 3). Results were similar when total and red meat were analysed as continuous variables (data not shown). When the first quintile was compared with the second, third, fourth, and fifth quintiles, the ORs for fish were 0.72 (CI 0.53–0.97), 0.70 (CI 0.52–0.95), 0.83 (CI 0.62–1.13) and 0.86 (CI 0.63–1.17), respectively (Table 3).

No association between total meat or red meat intake and the recurrence of advanced and multiple adenomas was observed in either the continuous (data not shown) or categorical (Table 4) analyses. In the categorical analyses for recurrence of multiple adenomas, when first quintile was compared with the second, third, fourth, and fifth quintiles, the ORs for fish were 0.54 (CI 0.36–0.81), 0.58 (CI 0.38–0.87), 0.79 (CI 0.53–1.17) and 0.64 (CI 0.42–0.98), respectively. In the continuous variable analyses of multiple adenomas, the OR for poultry intake (per 10 g/day) was 0.96 (CI 0.90–1.03); for fish, the OR (per 10 g/day) was 0.95 (CI 0.87–1.04).

We observed no significant associations between recurrent adenoma risk (including multiple or advanced adenoma), and meat intake when we included change in meat intake (T0–T4) and T0 in the model (data not shown).

Discussion

We found that the development of recurrent adenomas was not associated with total or red meat intake and its reduction in consumption during a 4-year period. There was also no association between multiple or advanced recurrent adenoma risk and increased intake of total and red meat.

Previous studies specifically linked the increased risk of colorectal cancer with high intake of meat, especially red

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) (adjusted for age, sex and group) by quintiles in daily consumption of meat variables (T0 + T1 + T2 + T3 + T4)/4 before colonoscopy (Outcome: Any adenoma recurrence versus no recurrence)

Variables (g/day)	Q1	Q2	Q3	Q4	Q5
Model 1					
All meat					
Range	13.5–96.4	96.5–116.6	116.7–136.6	136.7–164.1	164.2–279.7
OR (CI)	1.0	0.84 (0.62–1.13)	1.01 (0.75–1.36)	0.82 (0.60–1.10)	0.86 (0.63–1.18)
Model 2					
Red meat					
Range	0–38.0	38.1–57.8	57.9–76.1	76.1–101.2	101.3–201.2
OR (CI)	1.0	1.12 (0.83–1.51)	0.90 (0.66–1.22)	0.84 (0.61–1.15)	0.98 (0.71–1.35)
White meat					
Range	0–35.3	35.3–47.8	47.8–61.5	61.6–78.3	78.3–201.1
OR (CI)	1.0	0.87 (0.64–1.17)	0.91 (0.68–1.23)	0.93 (0.69–1.25)	0.88 (0.65–1.19)
Model 3					
Red meat					
OR (CI)	1.0	1.15 (0.85–1.56)	0.92 (0.68–1.25)	0.87 (0.64–1.19)	1.00 (0.72–1.38)
Fish					
Range	0–9.5	9.6–15.1	15.1–21.0	21.0–30.4	30.4–138.4
OR (CI)	1.0	0.72 (0.53–0.97)*	0.70 (0.52–0.95)*	0.83 (0.62–1.13)	0.86 (0.63–1.17)
Poultry					
Range	0–19.6	19.7–29.2	29.3–39.8	39.9–51.9	51.9–203.3
OR (CI)	1.0	0.93 (0.69–1.26)	0.83 (0.61–1.12)	0.92 (0.68–1.25)	0.98 (0.72–1.33)
Model 4					
High temp. meat					
Range	0–20.9	21.0–33.7	33.8–47.5	47.6–65.5	65.6–167.7
OR (CI)	1.0	0.79 (0.58–1.06)	0.98 (0.73–1.32)	0.92 (0.68–1.24)	0.92 (0.68–1.25)
Model 5					
Processed meat					
Range	0–6.4	6.5–13.3	13.4–20.6	20.7–33.3	33.4–167.7
OR (CI)	1.0	0.79 (0.58–1.06)	0.98 (0.73–1.32)	0.92 (0.68–1.24)	0.92 (0.68–1.25)

In Model 2: red meat and white meat included simultaneously. In Model 3: red meat, fish and poultry included simultaneously.

*Statistically significant at 5% level.

Table 4 Odds ratios (OR) and 95% confidence intervals (CI) (Adjusted for age, sex and group) by quintiles in daily consumption of meat variables (T0 + T1 + T2 + T3 + T4)/4 before colonoscopy

Summary	Q1	Q2 OR (95% CI)	Q3 OR (95% CI)	Q4 OR (95% CI)	Q5 OR (95% CI)
Advanced adenoma recurrence versus no recurrence					
Model 1					
All meat	1.0	0.80 (0.43–1.50)	1.41 (0.79–2.51)	0.79 (0.41–1.50)	0.92 (0.48–1.76)
Model 2					
Red meat	1.0	0.70 (0.38–1.29)	0.67 (0.37–1.23)	0.84 (0.47–1.51)	0.73 (0.38–1.39)
White meat	1.0	0.79 (0.43–1.45)	0.94 (0.52–1.69)	0.92 (0.50–1.68)	1.04 (0.57–1.90)
Model 3					
Red meat	1.0	0.73 (0.40–1.36)	0.69 (0.37–1.27)	0.88 (0.49–1.58)	0.76 (0.40–1.45)
Fish	1.0	0.83 (0.45–1.53)	0.84 (0.45–1.57)	0.92 (0.50–1.71)	1.05 (0.56–1.96)
Poultry	1.0	0.96 (0.53–1.72)	0.83 (0.44–1.53)	0.95 (0.51–1.77)	1.10 (0.60–2.02)
Model 4					
High temp. meat	1.0	0.73 (0.39–1.35)	1.21 (0.69–2.14)	0.87 (0.47–1.59)	0.82 (0.43–1.56)
Model 5					
Processed meat	1.0	0.73 (0.39–1.35)	1.21 (0.69–2.14)	0.87 (0.47–1.59)	0.82 (0.43–1.56)
Multiple adenoma recurrence versus no recurrence					
Model 1					
All meat	1.0	0.72 (0.48–1.07)	0.76 (0.50–1.13)	0.55 (0.36–0.84)	0.71 (0.47–1.07)
Model 2					
Red meat	1.0	0.96 (0.64–1.44)	0.72 (0.47–1.09)	0.65 (0.43–1.01)	0.81 (0.53–1.25)
White meat	1.0	0.68 (0.46–1.03)	0.94 (0.64–1.39)	0.89 (0.60–1.32)	0.55 (0.36–0.86)
Model 3					
Red meat	1.0	1.01 (0.67–1.53)	0.76 (0.49–1.16)	0.69 (0.45–1.07)	0.86 (0.55–1.32)
Fish	1.0	0.54 (0.36–0.81)*	0.58 (0.38–0.87)*	0.79 (0.53–1.17)	0.64 (0.42–0.98)*
Poultry	1.0	0.91 (0.61–1.35)	0.70 (0.46–1.06)	1.05 (0.70–1.57)	0.74 (0.48–1.13)
Model 4					
High temp. meat	1.0	0.95 (0.63–1.42)	1.07 (0.71–1.60)	0.81 (0.53–1.25)	1.00 (0.65–1.52)
Model 5					
Processed meat	1.0	1.02 (0.68–1.53)	0.88 (0.58–1.34)	0.92 (0.61–1.40)	0.88 (0.58–1.33)

In Model 2: red meat and white meat included simultaneously. In Model 3: red meat, fish and poultry included simultaneously.

*Statistically significant at 5% level.

meat or meat-cooking methods such as frying and whether well-done with increased risk of colorectal adenomas (Giovannucci *et al.*, 1994; Sinha *et al.*, 1999). In the present study all the subjects had had at least one adenoma during their lifetime. If diet influenced critical events in colorectal neoplasia at the molecular, cellular or tissue level before the development of first adenoma, then a later change in intake might be ineffective. In a similar vein, if meat intake affected early events in colorectal neoplasia, the relatively short period of dietary intervention (4 years) might be insufficient to allow differences between intervention and control groups to emerge.

In terms of the overall meat consumption pattern, the intervention participants tended to substitute fish and poultry for red, processed meat and high temperature-cooked meat. The percentage reduction in the consumption of red, processed, high temperature-cooked meat among subjects in the intervention group, however, might have been too small to affect the risk of recurrent adenomas. We also cannot preclude the possibility that, in the light of the dietary expectations fostered by the trial, subjects in the intervention group systematically under-reported their intake of meat.

The present analyses hint at the possibility that high intake of fish is associated with a low risk for development of recurrent colorectal adenoma. Given the lack of a dose-response relationship across the quintiles of fish consumption, this result may simply be a chance finding. Alternatively, however, the data may reflect a threshold effect for fish intake. Some epidemiological data do show that a high consumption of fish is associated with a low risk of colorectal adenoma (Haile *et al.*, 1997; Caderni *et al.*, 1999). One study found that omega-3 fatty acid supplementation normalized proliferation in the upper compartment of the crypt among subjects with adenomatous polyps (Anti *et al.*, 1992).

In conclusion, changes in the meat intake seen in the PPT were rapidly made in the 1st year and then remained steady in later years. The analyses provided no evidence to suggest that less red meat intake reduces the risk of recurrent colorectal adenomas.

References

- Anti M, Marra G, Armelao F, *et al.* (1992). Effect of Ω -3 fatty acids on rectal mucosal cell proliferation in subjects at risk for colon cancer. *Gastroenterology* **103**: 883–891.
- Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L (1986). A database approach to diet questionnaire design and testing. *Am J Epidemiol* **124**: 453–469.
- Caderni G, Palli D, Lancioni L, *et al.* (1999). Dietary determinants of colorectal proliferation in the normal mucosa of subjects with previous colon adenomas. *Cancer Epidemiol Biomarkers Prev* **8**: 219–225.
- de-Verdier MG, Hagman U, Peters RK, Steineck G, Overvik E (1991). Meat, cooking methods and colorectal cancer: a case-referent study in Stockholm. *Int J Cancer* **49**: 520–525.
- Flood A, Velie EM, Sinha R, *et al.* (2003). Meat, fat, and their subtypes as risk factors for colorectal cancer in a prospective cohort of women. *Am J Epidemiol* **158**: 59–68.
- Gaard M, Tretli S, Loken EB (1996). Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. *Eur J Cancer Prev* **5**: 445–454.
- Giovannucci E, Rimm EB, Stampfer MJ, *et al.* (1994). Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* **54**: 2390–2397.
- Goldbohm RA, van den Brandt PA, van't Veer P, *et al.* (1994). A prospective cohort study on the relation between meat consumption and the risk of colon cancer. *Cancer Res* **54**: 718–723.
- Haile RW, Witte JS, Longnecker MP, *et al.* (1997). A sigmoidoscopy-based case-control study of polyps: macronutrients, fiber and meat consumption. *Int J Cancer* **73**: 497–502.
- Hill MJ, Morson BC, Bussey HJR (1978). Aetiology of the adeno-carcinoma sequence in the large bowel. *Lancet* **1**: 245–247.
- Hosmer DW, Lemeshow S (1989). *Applied Logistic Regression*. New York: John Wiley & Sons.
- Kampman E, Slattery ML, Bigler J, *et al.* (1999). Meat consumption, genetic susceptibility, and colon cancer risk: a United States multicenter case-control study. *Cancer Epidemiol Biomarkers Prev* **8**: 15–24.
- Kipnis V, Freedman LS, Brown CC, *et al.* (1993). Interpretation of energy adjustment models for nutritional epidemiology. *Am J Epidemiol* **137**: 1376–1380.
- Kulldorff M, Sinha R, Chow WH, Rothman N (2000). Comparing odds ratios for nested subsets of dietary components. *Int J Epidemiol Assoc* **29**: 1060–1064.
- Lanza E, Schatzkin A, Ballard-Barbash R, *et al.* (1996). The polyp prevention trial II. Dietary intervention and baseline participant dietary characteristics. *Cancer Epidemiol Biomarkers Prev* **5**: 385–392 (1996). [Erratum *Cancer Epidemiol Biomarkers Prev* **5**: 584].
- Mares-Perlman JA, Klein BE, Klein R, *et al.* (1993). A diet history questionnaire ranks nutrient intakes in middle-aged and older men and women similarly to multiple food records. *J Nutr* **123**: 489–501.
- Schatzkin A, Lanza E, Freedman LS, *et al.* (1996). The polyp prevention trial I: Rationale, design, recruitment, and baseline participant characteristics. *Cancer Epidemiol Biomarkers Prev* **5**: 375–383.
- Schatzkin A, Lanza E, Corle D and the PPT Study Group (2000). Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* **342**: 1149–1155.
- Sinha R, Chow W-H, Kulldorff M, *et al.* (1999). Well-done, grilled red meat increases the risk of colorectal adenomas. *Cancer Res* **59**: 4320–4324.
- Tangrea JA, Albert PS, Lanza E, *et al.* (2003). Non-steroidal anti-inflammatory drug use is associated with reduction in risk of sporadic colorectal adenomas: a prospective study among participants of the Polyp Prevention Trial. *Cancer Causes Control* **14**: 403–411.
- Voskuil DW, Kampman E, Grubben MJ, *et al.* (2002). Meat consumption and meat preparation in relation to colorectal adenomas among sporadic and HNPCC family patients in The Netherlands. *Eur J Cancer* **38**: 2300–2308.
- Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE (1990). Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* **323**: 1664–1672.

Appendix 1 – PPT Study Group

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