COLON

Does a family history of cancer increase the risk of occurrence, growth, and recurrence of colorectal adenomas?

K Almendingen, B Hofstad, M H Vatn

Gut 2003;**52**:747–751

See end of article for authors' affiliations

Correspondence to: M H Vatn, Medical Department, Rikshospitalet, N-0027 Oslo, Norway; morten.vatn@klinmed.uio.no

Accepted for publication 29 November 2002

Background: Familial history of colorectal cancer (FHCRC) is a recognised risk factor for sporadic CRC. The relationship to the growth rate of adenomas is largely unknown. Lifestyle related factors, which may also cluster in families, are also recognised risk factors for adenomas and CRC.
Aims: To study the relationships between FHCRC and family history of other cancers (FHOC) among first degree relatives in relation to occurrence, growth, and recurrence of adenomas.
Patients and methods: Eighty seven patients with adenomas, participating in a double blind, three year, placebo controlled, endoscopic follow up and intervention study of growth and recurrence of polyps (50% men, 50–76 years). Polyps >9 mm were removed whereas the remainder and newly discovered polyps <10 mm were left in situ for three years before removal and histological diagnosis. Data were collected by means of dietary records, interviews, and questionnaires.
Results: The adenoma cases with FHCRC had a fourfold higher risk of adenoma growth. In contrast, no significant association was found for adenoma recurrence. FHOC was not significantly related to increased risk of growth or recurrence. Family history showed no significant association with the risk of baseline adenoma occurrence. Adjustment for CRC risk factors, also known to cluster in families, did not alter the results.
Conclusions: FHCRC seems to be a strong risk factor for adenoma growth, but not for the earlier phases of CRC development such as the initiation of adenomas.

First degree relatives of individuals with colorectal cancer (CRC) are known to have an approximately twofold increased risk of sporadic CRC.[1–5] Even higher risks have been reported among individuals with two or more affected relatives.[6] Familial clustering may be due to a combination of environmental and genetic factors.[7–12] It has been suggested that for a substantial proportion of sporadic CRCs inheritance determines the individual susceptibility whereas lifestyle is important for expression of the cancer.[8]

Different types of studies have suggested that an "unhealthy diet"[13–17] and the use of tobacco[13 18 19] are associated with the occurrence of adenomas less than 1 cm in diameter. The malignant potential however increases with the size of the adenoma as less than 1% of polyps <1 cm in diameter show malignant change while 10–50% of polyps >2 cm in diameter are malignant.[20] Growth of adenomas followed up in situ is thus considered a very good surrogate for CRC risk.[20] Against this background, it seems important to identify factors affecting the growth rate of polyps. Evidence exists that different lifestyle related factors are related to the adenoma growth phase[21–23] but the number of polyp growth studies is limited. This may be due to the fact that technical problems related to in situ measurements, redetection, and reidentification of polyps, or ethical considerations, make studies of polyp growth difficult to accomplish.[20]

The incidence rate of CRC in Norway has risen from a low level in the 1950s to the highest rate among the five Nordic countries over the past decades.[24] The increasing incidence of CRC during the past decades coincides with several changes in lifestyle habits in the Norwegian population during the same time period.[25] It is thus important to evaluate to what extent familial predisposition is involved in both early and late stages of colorectal neoplasia.

The aims of the present study were to observe the relationships between a familial history of CRC (FHCRC) and a familial history of other cancers (FHOC) among first degree relatives in relation to occurrence, growth, and recurrence of colorectal adenomas in a Norwegian cohort of polyp bearing outpatients. We also wished to see if the study outcomes were dependent on choice of control group. Our assessments of lifestyle related habits in this material[17 19 22 23] allowed for control of potential confounders that may also cluster in families. This is relevant as such variables are found to be associated with both adenomas and CRC in different types of studies.[13 14]

PATIENTS AND METHODS

Patients

The study was primarily designed to investigate the effects of intervention medication on growth and recurrence of colorectal polyps. The present data were thus derived from a double blind, three year, placebo controlled, follow up and intervention study of growth and recurrence of polyps.[26–31] Patients received placebo (lactose) or a mixture of calcium (1.6 g) and antioxidants (150 mg vitamin C, 75 mg α-tocopherol, 15 mg β-carotene, 101 μg selenium). They were stratified according to polyp size and block randomised in order to test whether the active medication could reduce polyp growth or recurrence.[27]

Patients were consecutively recruited from gastroenterological outpatients who had been referred for colonoscopy for a variety of abdominal symptoms prior to inclusion. Subjects with CRC, familial polyposis coli (FAP), hereditary non-polyposis colorectal cancer (HNPCC), inflammatory bowel

Abbreviations: BMI, body mass index; CRC, colorectal cancer; FAP, familial polyposis coli; FHCRC, family history of colorectal cancer; FHOC, family history of other cancers; HNPCC, hereditary non-polyposis colorectal cancer; OR, odds ratio.

disease, renal or heart failure, or inability to undergo colonoscopy or dietary assessment were excluded. We defined FAP as >100 polyps and HNPCC according to the Amsterdam criteria I.[32] No eligible patients were excluded due to these syndromes.[26] Thus subjects with a first degree relative with CRC were regarded as having FHCRC in this study. Of the 116 polyp patients (50% men, 50–76 years) who were included in the intervention study, eight were non-compliers with lifestyle assessments. Twenty one patients had hyperplastic polyps only, and they were excluded due to the low malignant potential of such polyps.[33 34] The remaining 87 patients all had histologically confirmed adenomas at inclusion, and it was 48 of these patients who received placebo during the three years of intervention.

All large sized polyps were removed whereas the remainder and newly discovered polyps of <10 mm maximum diameter were left in situ for up to three years with annual colonoscopic follow up examinations. At the end of the study, all polyps were removed and subjected to histological examination, which was performed by a single experienced histopathologist. Polyps were classified according to WHO criteria.[35] Change in polyp size after three years was assessed. When patients had multiple polyps that were followed up, the diameters of all of the different polyps in each patient were added together to give an estimation of net growth, whether positive or negative. Net growth was defined as an increase in diameter of at least 1 mm. Forty per cent of adenomas increased in size over three years by 1–4 mm.[29] Further details of patients, design, methods, and endoscopic results have been presented elsewhere.[26–31]

Controls

Polyp free controls were recruited to investigate the effects of risk factors on the prevalence of polyps. To minimise the risk of control selection bias,[36] two separate sets of unrelated controls matched for sex (50% men) and age (±5 years) were recruited.[17] The same eligibility criteria were applied for controls as for cases. Both sets of controls were recruited from the same geographic area as the cases. As for the cases, none of the controls was hospitalised but lived at home. As adenomas are usually diagnosed in older adults who undergo colonoscopy for symptoms usually unrelated to their adenoma, it was considered necessary to obtain a control group selected in the same way. A "hospital" control group of 35 outpatients referred for colonoscopy to the same gastroenterological department as the cases were included after colonoscopic verification of polyp free status. Additionally, a healthy control group of 35 persons were recruited from a centre for elderly people and two large insurance companies. It was intended that the healthy controls should have no abdominal symptoms to warrant colonoscopy, and they were proven to be free of adenomatous polyps by screening colonoscopy.

Registration of data

Immediately after the baseline colonoscopy, subjects were asked to complete a questionnaire which also included information on FHCRC and FHOC in first degree relatives. The questionnaires were checked to eliminate errors, inconsistencies, and misunderstandings. Information regarding second degree relatives was not collected. FHCRC was defined as at least one first degree relative with a history of CRC, and FHOC as at least one first degree relative with a history of cancer other than CRC.

Self administered questionnaires, structured interviews, and a five day dietary record by weighing were used to collect information on lifestyle related habits and other demographic data.[17 19 22 23] After one year, no major dietary changes were found.[37] Weight and height were measured, and body mass index (BMI) was calculated as: BMI=weight (kg)/height $(m)^2$. Subjects were not given any dietary or lifestyle advice during the study.

Colonic examinations were performed by a single endoscopist and the lifestyle assessments by a single clinical nutritionist. As a consequence, the endoscopist was blind to the results of the lifestyle assessments. The nutritionist was blind to the FHCRC and FHOC status of the subjects. The endoscopist, nutritionist, and cases were all blind to the adenoma status of the cases during these registrations as the histological examination of the polyps was performed after three years when all polyps were removed.

Safety of the study

The protocol and aims were explained to the subjects who had to give their consent before inclusion. Approval of the study was obtained from the regional ethical committee. The safety aspect of leaving adenomas <10 mm maximum diameter in situ for three years, rather than performing polypectomy at diagnosis, has previously been discussed in detail.[20 26–31]

Statistical methods

This study is a supplementary study to an intervention trial.[27] The primary end point of that study was to examine the effect of trial medication on growth and recurrence of colorectal polyps, and the size of the study group was determined as described previously.[27]

Statistical analysis was performed using the SPSS statistical package version 8.0. Analyses were carried out separately for the two different control groups to provide an indication of the differences in risk estimates introduced by control sources. All reported p values were two sided, and a level of significance was set at $p \leq 0.05$. Non-parametric statistical methods were applied for exposure variables as a consequence of their generally skewed values. Continuous data were analysed by the Mann-Whitney *U* test for comparisons of groups whereas χ^2 tests were used for categorised data. Univariate logistic regression was used to estimate crude odds ratios (ORs) including the 95% confidence intervals (95% CI), and multiple logistic regression was performed to estimate adjusted ORs, adjusting for potential confounders, including smoking habits, BMI, alcohol intake, and dietary variables (fat, carbohydrates, vegetables, vitamins, etc). These variables were chosen because of their associations with adenomas in these data.[17 19 22 23] In the adjusted analyses, the primary exposure of interest was categorised, and the other variables were used continuously. The category of lowest intake was used as reference. Adjusted p for trend was tested by including the exposure categories as continuous in the logistic model.

RESULTS

Background characteristics

Fourteen cases (16%) reported having FHCRC, none with more than one first degree relative, and 37 cases (43%) FHOC (table 1). Six cases had combined FHCRC and FHOC. Only one of these was a HNPCC spectrum cancer (cancer of the uterus). None had more than one first degree relative with HNPCC spectrum cancers. The number of cases with FHCRC and FHOC did not differ between the groups receiving placebo and active medication (p=0.7 and p=0.5). The median baseline number of adenomas was 1.5 among cases with FHCRC and 1.0 among cases without FHCRC (p=0.7).

Cases did not differ from the two sets of controls with respect to FHCRC, FHOC, age, sex, alcohol intake, or BMI. Several differences were however observed between cases and controls with regard to the use of tobacco and dietary habits, with the cases presenting several indicators of having a poorer diet[17] and more extensive use of tobacco.[19]

Relationship between reported disposition for familial cancer and baseline adenoma occurrence

The risk of having adenomas (that is, adenoma occurrence) was not related to FHCRC when the 87 adenoma cases were

Table 1 Background characteristics of adenoma cases, "hospital" controls, and healthy controls

	Adenoma cases (n=87)	"Hospital" controls* (n=35)	p Value†	Healthy controls* (n=35)	p Value‡
Age (y)§	66	64	0.7	66	0.9
Body mass index (kg/m^2)	24.8	25.6	0.2	25.4	0.2
FHCRC (%)	16	14	0.8	17	0.9
FHOC (%)	43	31	0.3	34	0.4
Alcohol intake (g/day)	5	5	0.7	5	0.6
Never smokers (%)	23	43		43	
Ex-smokers (%)	33	43		37	
Current smokers (%)	44	14	0.006	20	0.03
Type of intervention (%)¶					
Active	45	—		—	
Placebo	55	—		—	

Values are medians or percentage of study group.
*Both sets of controls were sex (50% men) and age matched (±5 years) to cases and proven to be free of polyps by colonoscopy.
†Adenoma cases versus "hospital" controls; ‡adenoma cases versus healthy controls.
§Range at inclusion: 50–76 years.
¶The active medication consisted of vitamin C (150 mg), α-tocopherol (75 mg), β-carotene (15 mg), selenium (101 μg), and calcium (1.6 g), and the placebo medication consisted of lactose.[27] The controls did not participate in the intervention study.
FHCRC, familial history of colorectal cancer in first degree relatives; FHOC, familial history of other cancers in first degree relatives.

Table 2 Odds ratios (ORs) with 95% confidence intervals (CIs) for risk of adenoma occurrence by familial history of colorectal cancer (FHCRC) and other cancers (FHOC) in first degree relatives

	Cases	Hospital controls (n=35)*					Healthy controls (n=35)*				
	n	n	Crude OR (95% CI)	Adjusted† OR (95% CI)	Adjusted‡ OR (95% CI)	Adjusted§ OR (95% CI)	n	Crude OR (95% CI)	Adjusted† OR (95% CI)	Adjusted‡ OR (95% CI)	Adjusted§ OR (95% CI)
FHCRC											
No	73	30	1.0	1.0	1.0	1.0	29	1.0	1.0	1.0	1.0
Yes	14	5	1.2 (0.4–3.5)	1.2 (0.4–3.8)	1.1 (0.3–3.5)	1.1 (0.4–3.5)	6	0.9 (0.3–2.7)	0.9 (0.3–2.8)	0.9 (0.3–2.8)	0.9 (0.3–2.7)
FHOC											
No	50	24	1.0	1.0	1.0	1.0	23	1.0	1.0	1.0	1.0
Yes	37	11	1.6 (0.7–3.7)	1.6 (0.7–3.7)	1.6 (0.7–3.8)	1.6 (0.7–3.7)	12	1.4 (0.6–3.2)	1.5 (0.6–3.5)	1.5 (0.6–3.5)	1.4 (0.6–3.2)

*Both sets of controls are sex (50% men) and age matched (±5 years) to the cases and proven to be free of polyps by colonoscopy.
†Adjusted for smoking status.
‡Adjusted for smoking status and intake of alcohol (g/day).
§Adjusted: FHCRC for FHOC and FHOC for FHCRC.

compared with the "hospital" and healthy controls (table 2). The crude ORs for FHCRC were 1.2 (95% CI 0.4–3.5) and 0.9 (95% CI 0.3–2.7), respectively. The crude ORs for FHOC were 1.6 (95% CI 0.7–3.7) and 1.4 (95% CI 0.6–3.2), respectively. Further adjustments (other than those shown in table 2) for BMI and intakes of vegetables, cruciferous vegetables, carbohydrates, fat, cereals, and number of polyps found at inclusion did not affect any of these risk estimates.

We distinguished cases according to the size of the largest adenoma (table 3). However, no significant associations were found for either FHCRC or FHOC.

The number of cases with multiple large adenomas (n=18) did not differ significantly from those with a single small adenoma (n=13) with regard to FHCRC or FHOC (p<0.7) (data not shown).

Relationship between reported disposition for familial cancer and adenoma recurrence after three years of endoscopic follow up

Neither FHCRC nor FHOC significantly increased the risk of formation of new adenomas in either crude or adjusted analyses (adjusted OR 0.7, 95% CI 0.1–4.8 and adjusted OR 1.8, 95% CI 0.4–7.1, respectively). Further adjustments for number of polyps found at inclusion, BMI, and intake of carbohydrates, starch, cholesterol, and cruciferous vegetables did not affect these risk estimates (data not shown). Only the placebo cases (n=48) were included in these analyses to avoid bias due to possible effects of the intervention medication.[27]

Relationship between reported disposition for familial cancer and adenoma growth after three years of endoscopic follow up

FHCRC was positively associated with adenoma growth in all analyses (table 4). However, significance was only reached after inclusion of the active medication receivers (n=87) in both crude (OR 4.2, 95% CI 1.3–13.9) and adjusted analyses. In contrast, FHOC did not increase the risk of growth. Further adjustments for number of polyps found at inclusion, BMI, carbohydrates, starch, cholesterol, and cruciferous vegetables did not affect these risk estimates.

DISCUSSION

In the present study, FHCRC was a strong risk factor for adenoma growth after three years of endoscopic follow up. In contrast, no such association was seen for adenoma recurrence or baseline adenoma occurrence.

Whereas small adenomas are rarely malignant, malignant potential increases with the size of the polyp.[33 34] Previous studies[1 3 7] have suggested that the presence of FHCRC in first degree relatives is a risk factor for CRC. In particular, a French study[4] found that the risk of CRC in subjects with FHCRC was doubled, as was the risk of large adenomas, whereas the risk

Table 3 Odds ratios (ORs) with 95% confidence intervals (CIs) for the risk of having small, medium, or large adenomas by familial history of colorectal cancer (FHCRC) and other cancers (FHOC) in first degree relatives

	Adenoma cases (n)	Healthy controls* (n)	Crude OR (95% CI)	Adjusted† OR (95% CI)	Adjusted‡ OR (95% CI)
Occurrence of small sized adenomas (maximum diameter <5 mm)					
FHCRC					
No	11	29	1.0	1.0	1.0
Yes	3	6	1.3 (0.3–6.2)	1.5 (0.3–7.8)	1.6 (0.3–8.1)
FHOC					
No	9	23	1.0	1.0	1.0
Yes	5	12	1.1 (0.3–3.9)	0.9 (0.2–3.9)	0.9 (0.2–3.7)
Occurrence of medium sized adenomas (maximal diameter 5–9 mm)					
FHCRC					
No	33	29	1.0	1.0	1.0
Yes	7	6	1.1 (0.3–3.4)	1.2 (0.3–4.2)	1.2 (0.3–4.2)
FHOC					
No	23	23	1.0	1.0	1.0
Yes	17	12	1.4 (0.6–3.6)	1.8 (0.6–4.9)	1.8 (0.6–4.9)
Occurrence of large sized adenomas (maximum diameter ⩾10 mm)					
FHCRC					
No	29	29	1.0	1.0	1.0
Yes	4	6	0.7 (0.2–2.6)	0.6 (0.1–2.4)	0.6 (0.2–2.5)
FHOC					
No	18	23	1.0	1.0	1.0
Yes	15	12	1.6 (0.6–4.3)	1.5 (0.5–4.0)	1.4 (0.5–3.8)

*The healthy controls were sex (50% men) and age matched (±5 years) to cases and proven to be free of polyps by colonoscopy.
†Adjusted for smoking status.
‡Adjusted for smoking status and intake of alcohol (g/day).

Table 4 Familial predisposition of colorectal cancer (FHCRC) and other types of cancers (FHOC) among first degree relatives and risk of net growth of adenomas <10 mm followed up in situ three years after inclusion

	Cases with net adenoma growth* (n)	Cases with no net adenoma growth† (n)	Crude OR (95% CI)		Adjusted OR (95% CI)¶		Adjusted OR (95% CI)** (All‡)	Adjusted OR (95% CI)†† (All‡)
			All‡	Placebo§	All‡	Placebo§		
FHCRC								
No	22‡/13d§	51‡/28§	1.0	1.0	1.0	1.0	1.0	1.0
Yes	9/5	5/2	4.2 (1.3–13.9)	5.4 (0.9–31.5)	3.7 (1.1–12.5)	4.3 (0.7–26.5)	3.8 (1.1–12.8)	3.9 (1.2–13.4)
FHOC								
No	19/13	31/16	1.0	1.0	1.0	1.0	1.0	1.0
Yes	12/5	25/14	0.8 (0.3–1.9)	0.4 (0.1–1.5)	0.7 (0.3–1.8)	0.3 (0.1–1.1)	0.7 (0.3–1.8)	0.9 (0.3–2.1)

*Net growth=more than 1 mm increase in total adenoma diameter after three years.
†No net growth=less than 1 mm increase in total adenoma diameter after three years; no detectable change or regression.
‡Data for the whole study group of 87 adenoma cases
§Data for the 48 adenoma cases who only received placebo during the three years of intervention.[27]
¶Adjusted for smoking status.
**Adjusted for type of intervention and smoking status.
††Adjusted for type of intervention and number of polyps found at inclusion.

of small adenomas was not affected. In accordance with these studies, we may suggest that the genetic background for colorectal adenomas influences adenoma growth but has less influence on initial adenoma formation.

A major strength of the study was that we were able to follow up adenomas <10 mm left in situ for three years, and that a histological diagnosis was available for all polyps. Furthermore, both cases and controls underwent colonoscopy, which was performed by a single experienced endoscopist. Therefore, misclassification was reduced to a minimum, which is essential for studies of this sample size. The ORs were approximately 4 in some of the analyses and failure to detect significance may have been due to the low sample size. To obtain a more reliable result, a larger study population should be investigated in future studies. However, the findings were consistent, even after adjustments for potential behavioural confounders which are likely to aggregate in families and which are also associated with both adenomas and CRC in different types of studies.[13 14] Moreover, the choice of controls did not affect the results. Generally, in case control studies the validity of the results is increased if they are similar, regardless of choice of controls. In contrast, the validity of the results is reduced if it is dependent upon this choice.[36] A limitation of the present study is that we defined family predisposition only on the basis of self reported presence or absence of FHCRC and FHOC. This was not checked in the cancer registry or hospital records. However, family history appears to be reported with high sensitivity and specificity.[38–40] Generally, in clinical long term studies, a tendency for self selection bias and recall bias cannot be excluded.[36] Cases may have belonged to a health conscious group of the population. However, these patients had a baseline diet high in fat and cholesterol and low in fibre and antioxidants, and the number of smokers was high. Nevertheless, the overall consistency of the data with previous studies and the lack of association with FHOC may indicate a minor influence of bias on the present results.

The present data may suggest that at some point in the sporadic development of CRC, FHCRC becomes more important as a risk factor than common environmental risk factors. Despite the low number of polyp growth studies, evidence

suggests that indicators of an "unhealthy lifestyle" may also be risk factors for adenoma growth.[21–23] One may hypothesise that the different lifestyle related risk factors play an individual role among patients without inherited risk factors.[8 10] This is supported by our previous finding that the intervention medication (calcium and antioxidants) was only found to have an effect on adenoma recurrence in low risk individuals without FHCRC.[27] In any case, the present and previous findings [21–23] may suggest that a combination of inherited and environmental risk factors is active. Future studies should include examination of gene-lifestyle related risk factor interactions at different stages of CRC development.

Various studies have suggested that a "healthy" lifestyle may be protective in the development of early stages of sporadic neoplastic lesions.[13 14] In order to prevent initiation of the premalignant stages of CRC, and also development of other lifestyle related diseases, a preventive lifestyle should therefore be recommended in general from an early age.

In conclusion, the presence of FHCRC among first degree relatives was strongly associated with growth of colorectal adenomas followed up in situ for three years. This finding was consistent after adjustment was made for potential behavioural confounders that are likely to aggregate in families, and choice of controls. These results are important because the malignant potential increases with the size of the adenoma. The study suggests that at some point in the development of CRC, FHCRC may become an important risk factor, superimposed on the common environmental factors which may play a stronger role in the earlier phases. These questions should be studied more closely in the future.

ACKNOWLEDGEMENTS

This study was supported financially by the Norwegian Cancer Society and Pronova a/s.

Authors' affiliations
K Almendingen, M H Vatn, Medical Department, Rikshospitalet University Hospital, Oslo, Norway
B Hofstad, Medical Department, Ullevål University Hospital, Oslo, Norway

REFERENCES

1 **Cannon-Albright LA**, Skolnick MH, Bishop DT, *et al*. Common inheritance of susceptibility to colonic adenomatous polyps and associated colorectal cancers. *N Engl J Med* 1988;**319**:533–7.
2 **Vogelstein B**, Fearon ER, Hamilton SR, *et al*. Genetic alterations during colorectal- tumor development. *N Engl J Med* 1988;**319**:525–32.
3 **Fuchs CS**, Giovannucci El, Coldiz GA, *et al*. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med* 1994;**331**:1669–74.
4 **Boutron MC**, Faivre J, Quipourt V, *et al*. Family history of colorectal tumours and implications for the adenoma-carcinoma sequence: a case control study. *Gut* 1995;**37**:830–4.
5 **Kerber RA**, Slattery ML, Potter JD, *et al*. Risk of colon cancer associated with a family history of cancer or colorectal polyps: the diet, activity, and reproduction in colon cancer study. *Int J Cancer* 1998;**78**:157–60.
6 **St John DJ**, McDermott FT, Hopper JL, *et al*. Cancer risk in relatives of patients with common colorectal cancers. *Ann Intern Med* 1993;**118**:785–90.
7 **Slattery ML**, Mineau GP. Kerber RA. Reproductive factors and colon cancer: the influences of age, tumour site and family history on risk (Utah, United States). *Cancer Causes Control* 1995;**6**:332–8.
8 **Fernandez E**, La Vecchia C, D'Avanzo B, *et al*. Risk factors for colorectal cancer in subjects with family history of the disease. *Br J Cancer* 1997;**75**:1381–4.
9 **Rafter J**, Glinghammar B. Interactions between the environment and genes in the colon. *Eur J Cancer Prev* 1998;**7**:S69–74.
10 **Sellers TA**, Bazyk AE, Bostick RM, *et al*. Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). *Cancer Causes Control* 1998;**9**:357–67.
11 **La Vecchia C**, Gallus S, Talamini R, *et al*. Interaction between selected environmental factors and familial propensity for colon cancer. *Eur J Cancer Prev* 1999;**8**:147–50.
12 **Lichtenstein P**, Holm NV, Verkasalo PK, *et al*. Environmental and heritable factors in the causation of cancer. *N Engl J Med* 2000;**343**:78–85.
13 **WCRF and AICR Report**. In: *Food, Nutrition and the Prevention of Cancer: a Global Perspective*. Washington, DC: World Cancer Research Fund/American Institute for Cancer Research, Menasha, 1997.
14 **Scheppach W**, Bingham S, Boutron-Ruault M-C, *et al*. WHO Consensus statement on the role of nutrition in colorectal cancer. *Eur J Cancer Prev* 1999;**8**:57–62.
15 **Faivre J**, Boutron MC, Senesse P, *et al*. Environmental and familial risk factors in relation to the colorectal adenoma-carcinoma sequence: results of a case-control study in Burgundy (France). *Eur J Cancer Prev* 1997;**6**:127–31.
16 **Hoff G**, Moen IE, Trygg K, *et al*. Epidemiology of polyps in the rectum and sigmoid colon. Evaluation of nutritional factors. *Scand J Gastroenterol* 1986;**21**:199–204.
17 **Almendingen K**, Hofstad B, Trygg K, *et al*. Current diet and colorectal adenomas: a case-control study including different sets of traditionally chosen control groups. *Eur J Cancer Prev* 2001;**10**:395–406.
18 **Hoff G**, Vatn MH, Larsen S. Relationship between tobacco smoking and colorectal polyps. *Scand J Gastroenterol* 1987;**22**:13–16.
19 **Almendingen K**, Hofstad B, Trygg K, *et al*. Smoking and colorectal adenomas: a case- control study. *Eur J Cancer Prev* 2000;**9**:193–203.
20 **Hofstad B**, Vatn M. Growth rate of colon polyps and cancer. Evolving issues in colon endoscopy. *Gastrointest Endosc Clin North Am* 1997;**7**:345–63.
21 **Hoff G**, Moen IE, Trygg K, *et al*. Colorectal adenomas and food. A prospective study of change in volume and total mass of adenomas in man. *Scand J Gastroenterol* 1988;**23**:1253–8.
22 **Almendingen K**, Hofstad B, Vatn MH. Does high body fatness increase the risk of presence and growth of colorectal adenomas followed up *in situ* for 3 years? *Am J Gastroenterol* 2001;**96**:2238–46.
23 **Almendingen K**, Hofstad B, Vatn MH. Does intake of alcohol increase the risk of presence and growth of colorectal adenomas followed up *in situ* for 3 years? *Scand J Gastroenterol* 2002;**37**:80–7.
24 **Møller B**, Fekjñr H, Hakulinen T, *et al*. Prediction of cancer incidence in the Nordic countries up to the year 2020. *Eur J Cancer Prev* 2002;**11**:S27–9.
25 **Johansson L**, Drevon CA, Bjørneboe G-E Aa. The Norwegian diet during the last hundred years in relation to coronary heart disease. *Eur J Clin Nutr* 1996;**50**:277–83.
26 **Hofstad B**, Vatn MH, Hoff G, *et al*. Growth of colorectal polyps. Design of a prospective, randomised, placebo-controlled intervention study in patients with colorectal polyps. *Eur J Cancer Prev* 1992;**1**:415–22.
27 **Hofstad B**, Almendingen K, Vatn M, *et al*. Growth and recurrence of colorectal polyps. A double-blind 3-year intervention with calcium and antioxidants. *Digestion* 1998;**59**:148–56.
28 **Hofstad B**, Vatn M, Larsen S, *et al*. Growth of colorectal polyps: recovery and evaluation of unresected polyps of less than 10 mm, 1 year after detection. *Scand J Gastroenterol* 1994;**29**:640–5.
29 **Hofstad B**, Vatn M, Andersen SN, *et al*. Growth of colorectal polyps: redetection and evaluation of polyps for a period of three years. *Gut* 1996; **39**:449–56.
30 **Hofstad B**, Vatn M, Larsen S, *et al*. Reliability of *in situ* measurements of colorectal polyps. *Scand J Gastroenterol* 1992;**27**:59–64.
31 **Hofstad B**, Vatn M, Larsen S, *et al*. *In situ* measurement of colorectal polyps to compare video and fiberoptic endoscopes. *Endoscopy* 1994;**26**:461–5.
32 **Vasen HF**, Mecklin JP, Khan PM, *et al*. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 1991;**34**:424–5.
33 **Morson B**. The polyp-cancer sequence in the large bowel. *Proc R Soc Med* 1974;**67**:451–7.
34 **Faivre J**, Hill MJ. *Causation and Prevention of Colorectal Cancer. ECP Symposium/4*. Amsterdam: Experta Medica, 1987.
35 **Jass JR**, Sobin LH. *Histological Typing of Intestinal Tumors. WHO International Histological Classification of Tumours*. Berlin: Springer, 1989.
36 **Altmann DG**. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1991.
37 **Almendingen K**, Trygg K, Hofstad B, *et al*. Results from two repeated 5-day dietary records with a one year interval among patients with colorectal polyps. *Eur J Clin Nutr* 2001;**55**:374–9.
38 **Aitken J**, Bain C, Ward M, *et al*. How accurate is self-reported family history of colorectal cancer? *Am J Epidemiol* 1995;**141**:863–71.
39 **Kerber RA**, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. *Am J Epidemiol* 1997; **146**: 244–8.
40 **Bonelli L**, Martines H, Conio M, *et al*. Family history of colorectal cancer as a risk factor for benign and malignant tumours of the large bowel. A case-control study. *Int J Cancer* 1988;**41**: 513–17.