Original article

# Advanced age is a risk factor for proximal adenoma recurrence following colonoscopy and polypectomy

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**Background:** **Knowledge of risk factors for recurrence of colorectal adenomas may identify patients who could benefit from individual surveillance strategies. The aim of this study was to identify risk factors for recurrence of colorectal adenomas in a high-risk population.**

**Methods:** **Data were used from a randomized clinical trial that showed no effect of aspirin–calcitriol–calcium treatment on colorectal adenoma recurrence. Patients at high risk of colorectal cancer who had one or more sporadic colorectal adenomas removed during colonoscopy were followed up for 3 years. Independent risk factors associated with recurrence and characteristics of recurrent adenomas were investigated in a generalized linear model.**

**Results:** **After 3 years, the recurrence rate was 25·8 per cent in 427 patients. For younger subjects (aged 50 years or less), the recurrence rate was 19 per cent; 18 of 20 recurrent adenomas were located in the distal part of the colon. For older subjects (aged over 70 years), the recurrence rate was 35 per cent, and 16 of 25 recurrent adenomas were in the proximal colon. Age (odds ratio (OR) 1·04, 95 per cent c.i. 1·01 to 1·07) and number of adenomas (OR 1·27, 1·11 to 1·46) at the time of inclusion in the study were independent risk factors for recurrence.**

**Conclusion:** **In contrast to current guidelines, advanced age is not a reason to discontinue adenoma surveillance in patients with an anticipated live expectancy in which recurrence can arise.**

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## Introduction

Colorectal adenomas are potential precursors of colorectal cancer[1]. The standard treatment is endoscopic polypectomy to prevent the progression to carcinoma[2]. However, following polypectomy the recurrence rate is approximately 50 per cent after 3 years[3]. Chemoprevention may therefore be relevant, and aspirin has proven effective in randomized clinical trials (RCTs)[4,5]. Several studies[6–9] have pointed to an additional benefit when aspirin is combined with calcium and vitamin D. Therefore, the authors designed a double-blind RCT to investigate the effect of oral aspirin, calcitriol (active vitamin D) and calcium treatment or placebo on the colorectal adenoma recurrence rate. The trial was stopped as the treatment had no effect on the primary outcome, colorectal adenoma recurrence after 3 years. Results of the primary analysis have been presented elsewhere[10].

The additional analyses of the trial focus on risk factors for recurrence. Knowledge of risk factors may identify patients who will benefit from an alternative treatment approach and screening/surveillance programme[11]. Several risk factors have already been identified[3,12–18]. However, this has not been investigated in a population with an increased risk of colorectal cancer: those with one adenoma larger than 1 cm in size, multiple adenomas or a family history of colorectal cancer. The aim of this study was to determine risk factors for recurrence of colorectal adenomas 3 years after polypectomy in a high-risk population.

## Methods

Results from a multicentre, randomized, double-blind, placebo-controlled clinical trial are presented. This trial investigated the chemopreventive effects of a 3-year treatment with aspirin, calcitriol and calcium on the

**Table 1** Univariable analyses of patient-related risk factors for recurrence

| | Recurrence ($n = 110$) | No recurrence ($n = 317$) | $P$† |
|---|---|---|---|
| Treatment | | | 0·684 |
| Active | 52 (47·3) | 157 (49·5) | |
| Placebo | 58 (52·7) | 160 (50·4) | |
| Sex ratio (M : F) | 74 : 36 | 173 : 144 | 0·020 |
| Age at screening (years)* | 62 (41–74) | 59 (40–75) | 0·005‡ |
| Smoking status | | | 0·058 |
| Current smoker | 33 (30·0) | 66 of 316 (20·9) | |
| Former smoker | 41 (37·3) | 110 of 316 (34·8) | |
| Never smoked | 36 (32·7) | 140 of 316 (44·3) | |
| No. of cigarettes smoked per day (ever smokers)* | 20 (1–60) | 15 (1–60) | 0·326‡ |
| Time since smoking cessation (former smokers) (years)* | 10 (1–40) | 15 (2–54) | 0·237‡ |
| Duration of smoking (ever smokers) (years)* | 21 (1–55) | 20 (3–50) | 0·094‡ |
| Compliance with trial medications (%)* | 99 (69–117) | 99 (60–115) | 0·142‡ |
| Haemoglobin out of range | | | 0·317 |
| Yes | 8 of 109 (7·3) | 15 of 312 (4·8) | |
| No | 101 of 109 (92·7) | 297 of 312 (95·2) | |
| Alkaline phosphatase out of range | | | 0·125 |
| Yes | 10 of 108 (9·3) | 16 of 312 (5·1) | |
| No | 98 of 108 (90·7) | 296 of 312 (94·9) | |
| Phosphate out of range | | | 0·799 |
| Yes | 11 of 109 (10·1) | 34 of 310 (11·0) | |
| No | 98 of 109 (89·9) | 276 of 310 (89·0) | |
| Creatinine out of range | | | 0·207 |
| Yes | 3 of 109 (2·8) | 18 of 309 (5·8) | |
| No | 106 of 109 (97·2) | 291 of 309 (94·2) | |
| Calcium out of range | | | 0·322 |
| Yes | 8 of 109 (7·3) | 33 of 311 (10·6) | |
| No | 101 of 109 (92·7) | 278 of 311 (89·4) | |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †$\chi^2$ test, except ‡Mann–Whitney $U$ test.

recurrence of adenomas in the colon or rectum. The study was terminated prematurely because a planned interim analysis showed no effect of the treatment (data published elsewhere)[10]. The data presented here are secondary analyses from that study. The study was registered at clinicaltrials.gov (NCT00486512). Approval was obtained from the Danish Data Protection Agency (2002-41-2286), Committee on Health Research Ethics (S-VF-20020028) and the National Board of Health (EudraCT 2004-000693-31).

The investigation included patients aged 40–75 years, of both sexes, who had a sporadic adenoma removed from the colon or rectum within the 3 months before the start of the study. These adenomas were classified as being either tubular, tubulovillous or villous. With the aim of including only patients with an increased risk of colorectal cancer, they had to meet one of three criteria: a single adenoma larger than 1 cm in diameter, multiple adenomas of any size, or an adenoma of any size and family history of colorectal cancer (first-degree relative). Following adenoma removal, the patients were followed up for 3 years, after which the study ended with a final colonoscopy. Patient characteristics and features of adenomas removed at the initial screening were investigated as potential risk factors for adenoma recurrence after 3 years. Pathological classification and dysplasia were graded according to validated measures[19,20].

Study outcomes were the proportion of patients with recurrence, number of recurrent adenomas, and location of recurrence (proximal *versus* distal). Proximal location included the transverse colon, ascending colon, hepatic flexure or caecum, whereas distal location comprised the splenic flexure, descending colon, sigmoid colon or rectum.

## Statistical analysis

Univariable and multivariable analyses were performed. $\chi^2$ test and Mann–Whitney $U$ test were used to test the significance of binary and continuous outcomes respectively in univariable analyses of co-variables. Variables with a potential influence on risk of recurrence were incorporated into a generalized linear model with recurrence as dependent variable. These were age, sex, size of largest adenoma removed at screening, number of adenomas

**Table 2** Univariable analyses of adenoma-related risk factors for recurrence

| | Recurrence ($n = 110$) | No recurrence ($n = 317$) | $P$† |
|---|---|---|---|
| No. of adenomas at screening* | 2 (1–15) | 1 (1–12) | < 0·001‡ |
| Grade of dysplasia at screening | | | 0·255 |
| High-grade dysplasia | 21 (19·1) | 46 (14·5) | |
| Low-grade dysplasia | 89 (80·9) | 271 (85·5) | |
| Histology at screening | | | 0·985 |
| Tubulovillous/villous | 49 (44·5) | 140 of 315 (44·4) | |
| Tubular | 61 (55·5) | 175 of 315 (55·5) | |
| Adenoma size at screening (mm)* | 10 (2–40) | 12 (0·5–67) | 0·170‡ |
| Position of adenoma at screening | | | 0·513 |
| Proximal | 30 of 109 (27·5) | 77 of 316 (24·4) | |
| Distal | 79 of 109 (72·5) | 239 of 316 (75·6) | |
| Advanced adenoma at screening | | | 0·281 |
| Yes | 83 (75·5) | 253 of 315 (80·3) | |
| No | 27 (24·5) | 62 of 315 (19·6) | |
| Endoscopic surgical adenoma removal at screening | | | 0·837 |
| Surgical excision/resection | 5 (4·5) | 12 of 316 (3·8) | |
| Piecemeal resection | 8 (7·3) | 19 of 316 (6·0) | |
| Simple polypectomy | 97 (88·2) | 285 of 316 (90·2) | |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †$\chi^2$ test, except ‡Mann–Whitney $U$ test.

removed at screening, histology of the least favourable adenoma removed at screening (tubular, tubulovillous or villous (least favourable)), grade of dysplasia of the least favourable adenoma removed at screening (low- *versus* high-grade (least favourable)), location (distal *versus* proximal) of the first adenoma removed at screening, representing the most proximally located adenoma, and smoking status (never smoked, former smoker, current smoker). To account for an immeasurable effect of being in the treatment or placebo group, treatment group was included in the model. The reported interaction between non-steroidal anti-inflammatory drugs and smoking on adenoma recurrence[21] was accounted for by incorporating the term treatment × smoking status into the model. Wald statistics were used and estimates reported as odds ratios (ORs) with 95 per cent c.i. A model with the same variables was used for the outcomes number of recurrent adenomas (linear model), location of recurrent adenomas (binary model), histology at recurrence (binary model; tubular *versus* tubulovillous/villous) and size of recurrent adenomas (binary model; 10 mm or greater *versus* less than 10 mm). SPSS® version 20 (IBM, Armonk, New York, USA) was used for statistical analysis. $P \leq 0{\cdot}050$ was considered statistically significant.

## Results

At the time of the interim analysis, 427 patients had completed the study including a colonoscopy after 3 years, and 25·8 per cent of these had adenoma recurrence. Baseline characteristics of the patients and resected adenomas at the time of inclusion colonoscopy are shown in *Tables 1* and *2* respectively.

**Table 3** Patients with adenomas after 3 years according to age at initial screening

| Age (years) | Recurrence | No recurrence | Total |
|---|---|---|---|
| ≤ 50 | 14 | 61 | 75 |
| 51–60 | 33 | 122 | 155 |
| 61–70 | 51 | 112 | 163 |
| > 70 | 12 | 22 | 34 |
| Total | 110 | 317 | 427 |

$P = 0{\cdot}050$ (Fisher's exact test).

### Recurrence

Univariable analysis revealed that male sex, the number of adenomas removed at initial screening and age were risk factors for recurrence (*Tables 1* and *2*). The recurrence rate increased with age ($P = 0{\cdot}050$) (*Table 3*). For younger subjects (aged 50 years or less) the recurrence rate was 19 per cent (14 of 75), whereas for older people (aged over 70 years) it was 35 per cent (12 of 34). In multivariable analysis, age ($P = 0{\cdot}011$) and number of adenomas removed ($P < 0{\cdot}001$) at initial screening were identified as independent risk factors for recurrence (*Table 4*).

There was a significant interaction between smoking and study treatment; the recurrence risk for current smokers *versus* patients who had never smoked was dependent on treatment group (active treatment or placebo) ($P = 0{\cdot}006$). Subgroup analysis showed no effect of smoking status on recurrence for the placebo group. Because of this, $P$ values for smoking status may be misleading and have

**Table 4** Multivariable analysis of risk factors for adenoma recurrence

| | Odds ratio | *P* |
|---|---|---|
| Sex (F *versus* M) | 0·65 (0·40, 1·08) | 0·095 |
| Histology | | |
| Tubular | 0·62 (0·20, 1·95) | 0·415 |
| Tubulovillous | 0·70 (0·22, 2·24) | 0·553 |
| Villous | 1·00 (reference) | |
| Dysplasia (high- *versus* low-grade) | 0·80 (0·41, 1·54) | 0·499 |
| No. of adenomas | 1·27 (1·11, 1·46) | < 0·001 |
| Age | 1·04 (1·01, 1·07) | 0·011 |
| Location (proximal *versus* distal) | 1·16 (0·66, 2·02) | 0·608 |
| Adenoma size | 0·98 (0·95, 1·01) | 0·233 |

Values in parentheses are 95 per cent c.i. Age and adenoma variables refer to the time of screening. A generalized linear model was used; the analysis was adjusted for interaction between treatment and smoking status.

**Table 5** Location of adenomas after 3 years according to age at initial screening

| | No. of adenomas | | |
|---|---|---|---|
| Age (years) | Distal colon* | Proximal colon† | Total |
| ≤ 50 | 18 | 2 | 20 |
| 51–60 | 36 | 33 | 69 |
| 61–70 | 39 | 41 | 80 |
| > 70 | 9 | 16 | 25 |
| Total | 102 | 92 | 194 |

*Rectum, sigmoid colon, descending colon, splenic flexure; †ascending colon/caecum, hepatic flexure, transverse colon. $P = 0·001$ (Fisher's exact test).

been omitted. However, the interaction was included in the analysis and thereby accounted for.

## Location of recurrent adenomas

Eighteen of 20 recurrent adenomas in patients aged 50 years or less at initial screening were located in the distal part of the colon, whereas more than 50 per cent were located in the proximal part in older patients ($P = 0·001$) (*Table 5*). In the youngest age group, the majority of adenomas recurred in the rectum or sigmoid colon, whereas among older patients the recurrences were more widely spread (*Fig. 1*). In multivariable analysis, age (OR 1·08, 95 per cent c.i. 1·02 to 1·14) and proximal location (OR 4·29, 1·35 to 13·69) at initial screening were independent risk factors for subsequent proximal location of recurrent adenomas after 3 years.

## Number of recurrent adenomas

The number of adenomas at initial screening was independently associated with increased number of recurrent adenomas at 3 years (OR 1·16, 95 per cent c.i. 1·07 to 1·25).

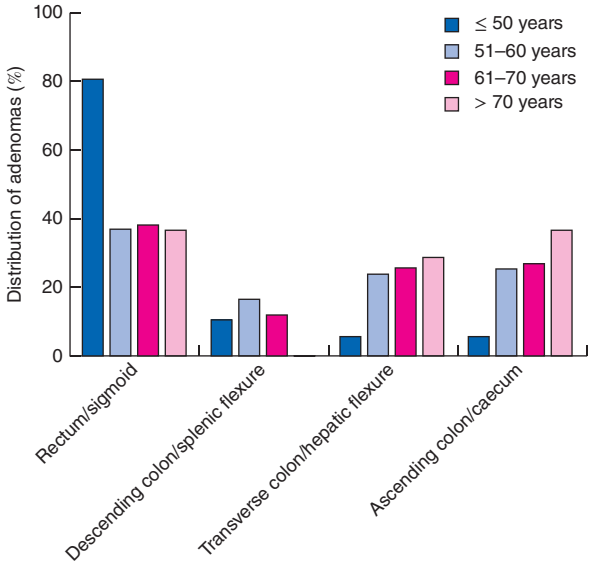


**Fig. 1** Location of adenomas after 3 years according to age at initial screening

## Additional factors

Histology (OR 0·97, 95 per cent c.i. 0·88 to 1·07), number of adenomas (OR 0·98, 0·96 to 1·01) and adenoma size (OR 1·03, 0·96 to 1·11) after 3 years showed no association with age at initial screening in multivariable analyses. The same was true for the remaining variables investigated.

# Discussion

This study found that age and the number of adenomas removed at initial screening were risk factors for adenoma recurrence after 3 years. Age and proximal adenoma location at the time of screening were risk factors for proximal recurrence, and the number of adenomas at screening was associated with the number of recurrent adenomas.

Earlier studies investigated risk factors for adenoma recurrence in the general population. Associations between age and risk of recurrence[14] and risk of proximal recurrence[17] have been shown previously, as has the association between the number of adenomas removed at initial screening and recurrence[3,13,14,16]. The interaction between smoking and study medication found in the present study is supported by the previous finding of an interaction between smoking and aspirin treatment[21]. The literature supports a relationship between smoking and development of colorectal adenomas[22] as well as colorectal cancer[23]. However, no overall effect of smoking on adenoma recurrence was found in two large prospective studies[12,18]. All primary outcome analyses in the present

trial showed no effect of the treatment[10]. It is therefore assumed that the intervention may not have interfered significantly with the present results. An interaction between smoking status and treatment was found, but this was accounted for by incorporating the interaction into the final model.

According to current guidelines, patients with a large number of adenomas are considered to be at high risk of recurrence; this affects the surveillance strategy and such patients have shorter intervals between colonoscopies[24,25]. However, there is insufficient evidence to make recommendations on postpolypectomy surveillance based on age as a risk factor. In fact, some guidelines suggest stopping surveillance at a certain age (75–80 years)[24,26]. In the light of the present results, together with the increased life expectancy of the general population, further consideration should be given to whether age alone should be a valid reason for discontinuation of surveillance.

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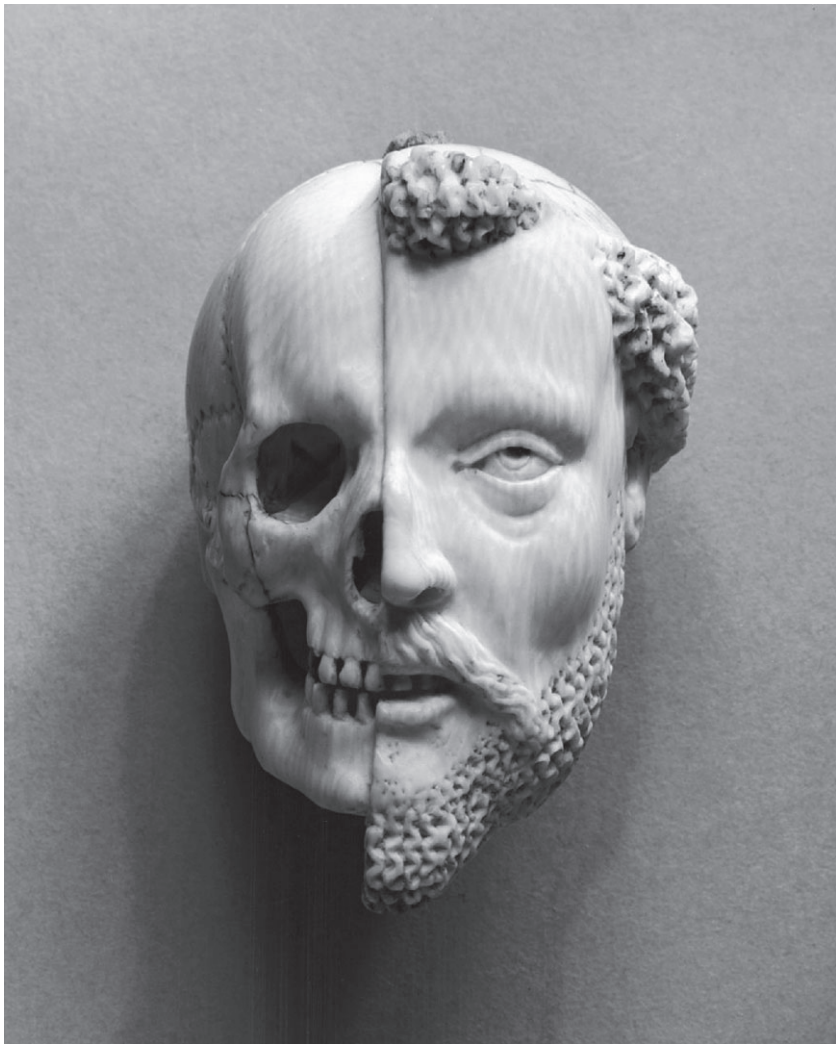
*Disclosure:* The authors declare no other conflict of interest.

## References

1 Midgley R, Kerr D. Colorectal cancer. *Lancet* 1999; **353**: 391–399.
2 Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS *et al.* Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; **329**: 1977–1981.
3 Brand L, Munding J, Pox CP, Ziebarth W, Reiser M, Hüppe D *et al.* β-Catenin, Cox-2 and p53 immunostaining in colorectal adenomas to predict recurrence after endoscopic polypectomy. *Int J Colorectal Dis* 2013; **28**: 1091–1098.
4 Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R *et al.* A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003; **348**: 891–899.
5 Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R *et al.* A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 2003; **348**: 883–890.
6 Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS *et al.* Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 1999; **340**: 101–107.
7 Grau MV, Baron JA, Sandler RS, Haile RW, Beach ML, Church TR *et al.* Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J Natl Cancer Inst* 2003; **95**: 1765–1771.
8 Pommergaard HC, Burcharth J, Rosenberg J, Raskov H. Chemoprevention with acetylsalicylic acid, vitamin D and calcium reduces risk of carcinogen-induced lung tumors. *Anticancer Res* 2013; **33**: 4767–4770.
9 Pommergaard HC, Burcharth J, Rosenberg J, Raskov H. Oral chemoprevention with acetyl salicylic acid, vitamin D and calcium reduces the risk of tobacco carcinogen-induced bladder tumors in mice. *Cancer Invest* 2013; **31**: 490–493.
10 Pommergaard HC, Burcharth J, Rosenberg J, Raskov H. Aspirin, calcitriol, and calcium do not prevent adenoma recurrence in a randomized controlled trial. *Gastroenterology* 2015; [Epub ahead of print].
11 Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J *et al.* Colorectal cancer screening and surveillance: clinical guidelines and rationale – update based on new evidence. *Gastroenterology* 2003; **124**: 544–560.
12 Baron JA, Sandler RS, Haile RW, Mandel JS, Mott LA, Greenberg ER. Folate intake, alcohol consumption, cigarette smoking, and risk of colorectal adenomas. *J Natl Cancer Inst* 1998; **90**: 57–62.
13 Bonithon-Kopp C, Piard F, Fenger C, Cabeza E, O'Morain C, Kronborg O *et al.* Colorectal adenoma characteristics as predictors of recurrence. *Dis Colon Rectum* 2004; **47**: 323–333.
14 Chung SJ, Kim YS, Yang SY, Song JH, Kim D, Park MJ *et al.* Five-year risk for advanced colorectal neoplasia after initial colonoscopy according to the baseline risk stratification: a prospective study in 2452 asymptomatic Koreans. *Gut* 2011; **60**: 1537–1543.
15 Jacobson JS, Neugut AI, Murray T, Garbowski GC, Forde KA, Treat MR *et al.* Cigarette smoking and other behavioral risk factors for recurrence of colorectal adenomatous polyps (New York City, NY, USA). *Cancer Causes Control* 1994; **5**: 215–220.
16 Ji JS, Choi KY, Lee WC, Lee BI, Park SH, Choi H *et al.* Endoscopic and histopathologic predictors of recurrence of colorectal adenoma on lowering the miss rate. *Korean J Intern Med* 2009; **24**: 196–202.
17 Laiyemo AO, Doubeni C, Pinsky PF, Doria-Rose VP, Marcus PM, Schoen RE *et al.* Factors associated with the risk of adenoma recurrence in distal and proximal colon. *Digestion* 2013; **87**: 141–146.
18 Paskett ED, Reeves KW, Pineau B, Albert PS, Caan B, Hasson M *et al.* The association between cigarette smoking and colorectal polyp recurrence (United States). *Cancer Causes Control* 2005; **16**: 1021–1033.
19 Hamilton SR, Aaltonen LA. *Pathology and Genetics of Tumours of the Digestive System*. International Agency for Research on Cancer: Lyons, 2000.

20 Jørgensen OD, Kronborg O, Fenger C. The Funen Adenoma Follow-Up Study. Characteristics of patients and initial adenomas in relation to severe dysplasia. *Scand J Gastroenterol* 1993; **28**: 239–243.
21 Ishikawa H, Mutoh M, Suzuki S, Tokudome S, Saida Y, Abe T *et al.* The preventive effects of low-dose enteric-coated aspirin tablets on the development of colorectal tumours in Asian patients: a randomised trial. *Gut* 2014; **63**: 1755–1759.
22 Botteri E, Iodice S, Raimondi S, Maisonneuve P, Lowenfels AB. Cigarette smoking and adenomatous polyps: a meta-analysis. *Gastroenterology* 2008; **134**: 388–395.
23 Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA* 2008; **300**: 2765–2778.
24 Hassan C, Quintero E, Dumonceau JM, Regula J, Brandão C, Chaussade S *et al.* Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2013; **45**: 842–851.
25 Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS *et al.* Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008; **58**: 130–160.
26 Atkin WS, Saunders BP; British Society of Gastroenterology; Association of Coloproctology of Great Britain and Ireland. Surveillance guidelines after removal of colorectal adenomatous polyps. *Gut* 2002; **51**(Suppl 5): V6–V9.



Pendant with a Monk and Death. Artist unknown. Acquired by Henry Walters. Bequeathed to Walters Art Museum in 1931.