

**Keywords:** colorectal cancer; screening; chemoprevention; aspirin; statins; ACE-inhibitors

# The impact of aspirin, statins and ACE-inhibitors on the presentation of colorectal neoplasia in a colorectal cancer screening programme

D Mansouri<sup>\*1</sup>, D C McMillan<sup>1</sup>, C S D Roxburgh<sup>1</sup>, E M Crichton<sup>2</sup> and P G Horgan<sup>1</sup>

<sup>1</sup>Academic Department of Surgery, School of Medicine—University of Glasgow, Glasgow Royal Infirmary, Glasgow G4 0SF, UK and <sup>2</sup>Department of Public Health Screening Unit, NHS Greater Glasgow and Clyde, West House, Gartnavel Royal Hospital, Glasgow G12 0XH, UK

**Background:** There is increasing evidence that aspirin, statins and ACE-inhibitors can reduce the incidence of colorectal cancer. The aim of the present study was to assess the impact of these medications on an individual's risk of advanced neoplasia in a colorectal cancer screening programme.

**Methods:** A prospectively maintained database of the first round of screening in our geographical area was analysed. The outcome measure was advanced neoplasia (cancer or intermediate or high risk adenomata).

**Results:** Of the 4188 individuals who underwent colonoscopy following a positive occult blood stool test, colorectal pathology was present in 3043(73%). Of the 3043 patients with colorectal pathology, 1704(56%) had advanced neoplasia. Patients with advanced neoplasia were more likely to be older (OR 1.38; 95% CI 1.19–1.59) and male (OR 1.66; 95% CI 1.43–1.94) (both  $P < 0.001$ ). In contrast, those on aspirin (OR 0.68; 95% CI 0.56–0.83), statins (OR 0.65; 95% CI 0.55–0.78) or ACE inhibitors (OR 0.71; 95% CI 0.57–0.89) were less likely to have advanced neoplasia at colonoscopy (all  $P < 0.05$ ).

**Conclusion:** In patients undergoing colonoscopy following a positive occult blood stool test with documented evidence of aspirin, statin or ACE-inhibitor usage, advanced neoplasia is less likely, suggesting that the usage of these medications may have a chemopreventative effect.

Colorectal cancer is the third most common cancer in the Western world and is second only to lung cancer as a cause of cancer death in the combined male and female populations in the United Kingdom. Around 40 000 people are diagnosed with bowel cancer each year in the United Kingdom alone and around 16 000 deaths occur annually from the disease. Incidence increases with age, with over 80% of cases occurring in patients over the age of 60 years (Cancer Research UK).

There is good evidence that screening for colorectal cancer using the guaiac-based faecal occult blood test (gFOBT) increases the number of early-stage cancers diagnosed (Dukes A and B) and

consequently reduces cancer-specific mortality (Mandel *et al*, 1993; Hardcastle *et al*, 1996; Kronborg *et al*, 1996). In addition, there is increasing evidence that screening using the faecal immunochemical test (FIT), where the level of blood in the stool can be quantified, may have improved sensitivity over gFOBT, albeit with higher positivity rates and slight reductions in specificity (Guittet *et al*, 2007; Hol *et al*, 2009; Parra-Blanco *et al*, 2010). This has led to the development of a gFOBT/FIT population-based screening programme in Scotland, where individuals with a weakly positive result on initial gFOBT testing are sent a confirmatory FIT (Fraser *et al*, 2012). Despite this, interval cancers do develop (Steele *et al*, 2009).

\*Correspondence: D Mansouri; E-mail: David.Mansouri@glasgow.ac.uk

Received 14 March 2013; revised 16 May 2013; accepted 17 May 2013; published online 18 June 2013

© 2013 Cancer Research UK. All rights reserved 0007–0920/13

This number appears to increase with successive screening rounds, suggesting that while screening is good at targeting so called screen-detected cancers, a proportion of tumours are resistant to the screening process in its current form (Steele *et al*, 2009, 2012).

Therefore, there is substantial ongoing interest in the field of chemoprevention, with the use of certain drugs to reduce an individual's risk of cancer. For example, there is considerable evidence that aspirin may reduce an individual's likelihood of developing both pre-cancerous adenomata (Baron *et al*, 2003; Benamouzig *et al*, 2003; Sandler *et al*, 2003; Cole *et al*, 2009) and colorectal cancer (Thun *et al*, 1991; Flossmann and Rothwell, 2007). Moreover, it may have an impact on reducing cancer deaths in those with colorectal tumours (Rothwell *et al*, 2010, 2011). The precise mechanism for aspirin's effect is not entirely clear but appears to be due to both its role in modulating the inflammatory response and also through more complex direct effects on tumour cells themselves (Chan *et al*, 2012).

In addition, statins have also been suggested to reduce an individual's risk of developing both colorectal cancer and advanced adenomas. The evidence for this has been variable in individual trials (Poynter *et al*, 2005; Jacobs *et al*, 2011; Simon *et al*, 2012); however, a recent meta-analysis involving 11 randomised control trials, 13 case-control studies and 8 cohort studies concluded that chronic statin usage did indeed have a small protective impact on colorectal cancer occurrence (Bardou *et al*, 2010). The mechanism for its effect is thought to arise through a combination of increased induction of tumour cell apoptosis, inhibition of cell growth or angiogenesis, or through enhancement of the immune response (Gauthaman *et al*, 2009).

Furthermore, some evidence has emerged that angiotensin-converting enzyme inhibitors (ACE-i) may also have a chemopreventative effect (Lever *et al*, 1998), and in particular for colonic cancer their use may reduce the development of pre-cancerous adenomata (Kedika *et al*, 2011). This may be owing to a role of angiotensin-converting enzyme in influencing local tumour growth and neoangiogenesis (Rocken *et al*, 2007).

However, each of these drugs each has their own side-effect profile. This may be magnified when used in high doses, and so far no single agent has been recommended for chemopreventive use in the general population. Use of these drugs for chemoprevention in combination has previously been suggested (Zhou *et al*, 2012) but not studied in a population setting; however, the concept of a 'polypill' to reduce cardiovascular risk has previously been proposed (Wald and Law, 2003; Rodgers *et al*, 2011).

The aim of the present study was to assess the affect of aspirin, statins and ACE-i both in isolation and in combination, on an individual's risk of neoplasia in patients who tested positive in a colorectal cancer screening programme and subsequently underwent colonoscopy.

## PATIENTS AND METHODS

Beginning in April 2009, all males and females between the age of 50 and 74 and registered with a GP in NHS Greater Glasgow and Clyde (NHS GG&C) were identified via their Community Health Index and invited to participate in the Scottish Bowel Screening Programme (SBoSP). Participants were sent a gFOBt kit and asked to provide two samples from three separate faecal specimens. In the case of weakly positive or spoiled kits, participants were sent a FIT kit. Analysis and processing of the gFOBt/FIT kits in the SBoSP has been described previously (Fraser *et al*, 2012). Following a positive result, patients were pre-assessed, either face-to-face or following telephone consultation, by a bowel screening endoscopy nurse and then referred on for colonoscopy if this was deemed

suitable. Details on patient medications were automatically uploaded to the Bowel Screening IT system from the Scottish Care Information Gateway system, which provides an interface between primary and secondary care records. This allows for details of patients regular medication, as held by their General Practitioner to be obtained. As part of the pre-assessment interview, patient medications were checked with this electronic record. A user of medication was defined as an individual who had either aspirin, statin or ACE-i usage at time of pre-assessment documented as per this method. Patient details were obtained from the prospectively maintained Bowel Screening IT system managed by the Public Health Screening Unit at NHS GG&C.

Data on endoscopic findings and pathological diagnosis were obtained retrospectively from clinical information systems. The presence of any colorectal pathology that could account for a positive stool test was noted. This included, but was not limited to, colorectal cancer, dysplastic polyps and non-neoplastic colorectal pathology such as colitis or haemorrhoids. The presence of uncomplicated diverticulosis and hyperplastic polyps were noted as normal findings.

In those patients in whom a pathological diagnosis of dysplastic polyps was reached, they were classified as being of a low risk, intermediate risk or high risk of subsequent development of colorectal cancer as per British Society of Gastroenterology (BSG) guidelines (Atkin and Saunders, 2002) (low risk: 1 to 2 polyps < 1 cm; intermediate risk: 3-4 polyps < 1 cm or ≥ 1 polyp ≥ 1 cm; high risk: ≥ 5 polyps or ≥ 3 polyps of which ≥ 1 is ≥ 1 cm). Advanced neoplasia was defined as patients with either colorectal cancer or dysplastic polyps classified as intermediate or high risk as per BSG guidelines.

Deprivation category was calculated using the Scottish Index of Multiple Deprivation (SIMD), which is an index of relative deprivation combining 38 indicators across 7 domains, namely, income, employment, health, education, skills and training, housing, geographic access and crime. The overall index is a weighted rank for each domain allowing postcodes to be ranked in order of deprivation across Scotland. Quintiles of deprivation were used to assign patients a relative deprivation category based on their postcode at the time of colonoscopy with the first quintile representing the most deprived and the fifth quintile the least deprived (<http://www.scotland.gov.uk/Topics/Statistics/SIMD>).

Permission for the study was granted by the Caldicott Guardian of the data, and data was stored and analysed in an anonymised manner.

**Statistical analysis.** Associations between categorical variables were examined using  $\chi^2$  tests for linear trend unless otherwise specified. Both univariate and multivariate logistical regression was used to calculate odds ratios. A value of  $P < 0.05$  was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

## RESULTS

From April 2009 to March 2011 representing the first complete round of screening in NHS GG&C, 395 096 individuals were invited to participate, 204 461 (52%) responded and 6085 (3%) tested positive. Of those who tested positive, 4631 (76%) patients proceeded to undergo colonoscopy. Complete results on both outcomes following colonoscopy and medications noted at pre-assessment were available for 4188 (90%) patients, which formed the basis of our analysis (Figure 1). The majority of positive results were owing to a positive FIT (3449 (82%) patients).

**Presence of colorectal pathology.** Of the 4188 patients in whom complete results were available, colorectal pathology was identified in 3043 (73%) patients (Figure 2). Patients with colorectal

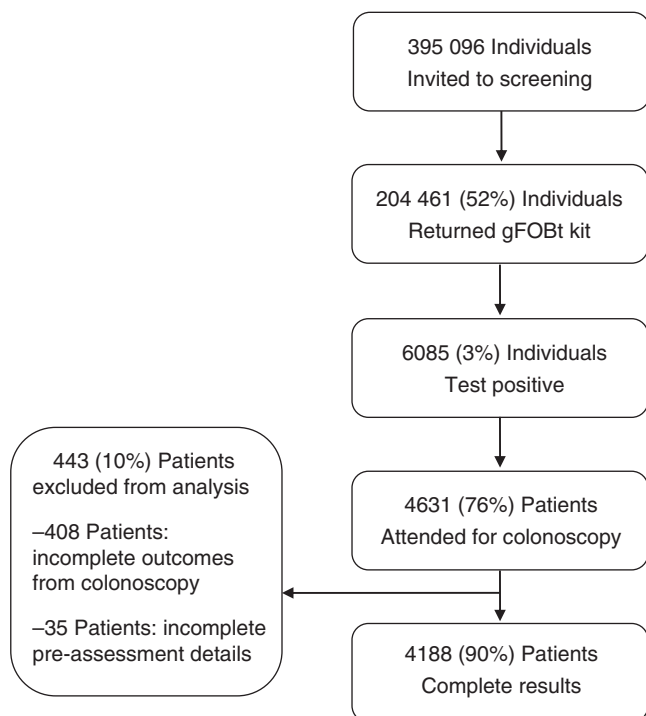
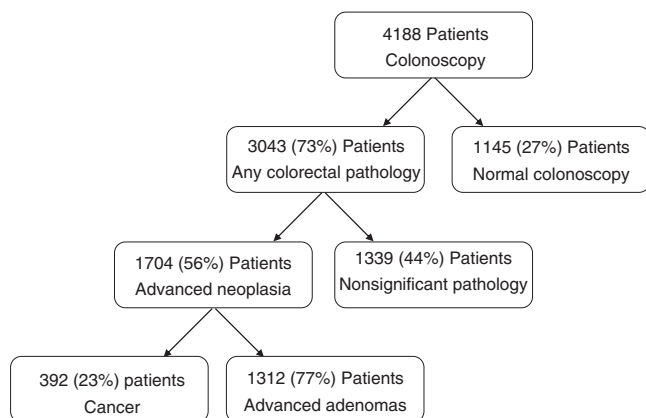


Figure 1. Flow diagram of cohort.



**Figure 2. Outcome from colonoscopies.** Any colorectal pathology is any colorectal pathology that could account for a positive stool test (cancer, dysplastic polyps and non-neoplastic colorectal pathology including, but not limited to, colitis and haemorrhoids). Advanced neoplasia = colorectal cancer, >3 dysplastic polyps <1 cm or >1 dysplastic polyp  $\geq$ 1 cm. Advanced adenomas = 3 dysplastic polyps <1 cm or >1 dysplastic polyp  $\geq$ 1 cm.

pathology were more likely to be older ( $P<0.001$ ), male ( $P<0.001$ ), less deprived ( $P<0.05$ ) and have tested positive through gFOBt route ( $P<0.05$ ) than those without any (Table 1). In contrast, those that were on aspirin were less likely to have colorectal pathology identified at colonoscopy ( $P<0.05$ ). There were no associations between statin or ACE-i usage and the presence of colorectal pathology. On multivariate analysis, older age and male sex remained associated with increased risk of colorectal pathology (both  $P<0.001$ ) and aspirin usage remained associated with a reduced risk of colorectal pathology ( $P<0.001$ ).

**Presence of advanced neoplasia.** Of the 3043 patients with colorectal pathology, advanced neoplasia was identified in 1704 (56%) patients (Figure 2). Patients with advanced neoplasia were more likely to be older, male, less deprived and have tested positive

through the gFOBt route (all  $P<0.001$ ) than those without (Table 2). In contrast, those on aspirin ( $P<0.001$ ), statins ( $P<0.001$ ) or ACE-i ( $P<0.05$ ) were all less likely to have advanced neoplasia at colonoscopy. As the majority of patients on at least one of these medications were in fact on multiple medications for the purposes of multivariate analysis, the variable  $\geq 1$  medication was entered into the model. The associations identified on univariate analysis persisted in the multivariate model. The risk of advanced neoplasia was also then examined in medication combinations (Table 3). Similar odds ratios were seen between combinations of these three medications (OR 0.64; 95% CI 0.50–0.83 to 0.71; 95% CI 0.57–0.89) where the risk of nonsignificant pathology was taken as the reference. Odds ratios for those on  $\geq 1$  medication (OR 0.67; 95% CI 0.56–0.78) or  $\geq 2$  medications (OR 0.67; 95% CI 0.55–0.81) were also similar.

**Presence of cancer.** Of the 1704 patients with advanced neoplasia, colorectal cancer was identified in 392 (23%) patients (Figure 2). Patients with cancer were more likely to be older ( $P=0.001$ ), female ( $P<0.05$ ) and have tested positive through the gFOBt route ( $P<0.001$ ) than those with advanced adenomas only (Table 4). These associations remained significant on multivariate analysis. There was a nonsignificant trend to those with cancer identified being less likely to be on a statin (14% vs 18%,  $P=0.071$ ).

## DISCUSSION

The results of the present study report, for the first time, a reduced incidence of advanced neoplasia in patients who are on a statin or an ACE-i that undergo colonoscopy following a positive stool test within a population-based colorectal cancer screening programme. In addition, it confirms previous work that has shown a reduced incidence of advanced neoplasia in those on aspirin. Overall, the results suggest that there may be role for population-based usage of these medications in reducing the incidence of colorectal neoplasia.

The reduction in the incidence of advanced neoplasia of 33% in those on at least one medication is similar to the 28% reduction seen in a recent meta-analysis of the effect of aspirin in preventing advanced lesions in a non-screened population (Cole *et al*, 2009). Studies have also previously shown a lower yield of neoplasia in those on aspirin who undergo a colonoscopy following a positive gFOBt (Clarke *et al*, 2006; Sawhney *et al*, 2010; Lee *et al*, 2012). However, previous work has been unable to adjust for the false-positive effect of aspirin that can occur with gFOBt tests, and therefore were unable to definitively attribute this to a chemopreventative effect. For example, there is evidence that aspirin can increase gFOBt false positives due to its antiplatelet activity causing occult bleeding in an otherwise normal gastrointestinal tract. In the present study, by removing all those in whom no cause for the positive stool test was found, the impact of this confounding factor was minimised. Furthermore, the majority of our patients tested weakly positive on gFOBt and actually proceeded to colonoscopy only following a confirmatory positive FIT. Indeed, previous authors have reported a limited effect of aspirin usage on FIT specificity (Levi *et al*, 2009; Brenner *et al*, 2010).

In addition, the reduced incidence of advanced neoplasia that was seen in the present study was seen not only in aspirin but in statins and ACE-i that have not previously been reported to cause false-positive stool tests. The present study supports this assumption as aspirin but neither statins nor ACE-i usage was associated with a higher likelihood of having a normal colonoscopy.

The stage at which these medications might impact on the adenoma–carcinoma sequence has been previously speculated (Rocken *et al*, 2007; Gauthaman *et al*, 2009; Chan *et al*, 2012). Of interest, in the present study there was no significant impact of medications on the presence of cancer within those with advanced

Table 1. Study population and risk of detecting any colorectal pathology at colonoscopy following a positive stool test

	All patients		Colorectal pathology		Normal colonoscopy		P-value	Risk of colorectal pathology (multivariate analysis)		
	n	%	n	%	n	%		OR	95% CI	P-value
	4188		3043		1145					
<b>Age</b>										
≤55	877	21	565	19	312	27		1		
56–64	1280	31	925	30	355	31		1.41	1.17–1.71	<0.001
≥65	2031	49	1553	51	478	42	<0.001	1.89	1.58–2.27	<0.001
<b>Sex</b>										
Male	2489	59	1990	65	499	44		1		
Female	1699	41	1053	35	646	56	<0.001	2.49	2.16–2.86	<0.001
<b>Deprivation category</b>										
1 (most deprived)	1506	36	1060	35	446	39		1		
2	785	19	568	19	217	19		1.08	0.88–1.31	0.461
3	666	16	507	17	159	14		1.30	1.05–1.61	0.017
4	527	13	380	13	147	13		1.02	0.81–1.28	0.879
5 (least deprived)	699	17	525	17	174	15	0.017	1.21	0.98–1.49	0.080
<b>Type of positive stool test</b>										
gFOBT	739	18	561	18	178	16		1		
FIT	3449	82	2482	82	967	84	0.029	1.20	0.99–1.45	0.062
<b>Aspirin</b>										
No	3531	84	2592	85	939	82		1		
Yes	657	16	451	15	206	18	0.012	0.67	0.55–0.81	<0.001
<b>Statin</b>										
No	3308	79	2422	80	886	77				
Yes	880	21	621	20	259	23	0.117			
<b>ACE inhibitor</b>										
No	3682	88	2672	88	1010	88				
Yes	506	12	371	12	165	12	0.722			
<b>≥ 1 Medications</b>										
No	3088	74	2271	75	817	71				
Yes	1100	26	772	25	328	29	0.032			

Abbreviations: ACE = angiotensin-converting enzyme; CI = confidence interval; FIT = faecal immunochemical test; gFOBT = guaiac-based faecal occult blood test; OR = odds ratio.

neoplasia. Therefore, it may indicate that rather than affecting cancer progression and growth, these medications exert their influence earlier in the adenoma–carcinoma pathway by preventing adenoma development.

From previous *in vivo* and *in vitro* studies, there is not only debate as to which stage of the adenoma–carcinoma sequence is affected by both aspirin, statins and ACE-i but also the precise mechanism of action. For example, with aspirin, there is evidence for both a direct local effect on tumour cells and the tumour microenvironment, and a systemic effect of the drug on circulating inflammatory cytokines (Chan *et al*, 2012). The clinical limitations with many *in-vitro* studies are that large concentrations of aspirin are required to create a local effect. While not specifically noted, it is likely that the vast majority of patients in the present study were taking low doses designed for cardiac prevention and therefore the local effects on colonic mucosa were likely to be limited. This favours the premise that the reduction in neoplasia seen in the present study is mediated through a systemic effect. If this was

proven to be the case, then the reduction in neoplasia risk detected by the present study is likely to be an underestimation owing to the non-discriminatory use of these medications. There is evidence that an elevated host systemic inflammatory response is associated with the presence of cancer (Proctor *et al*, 2010) and hence it may be that more targeted therapy to those at risk of neoplasia, for example, with an elevated systemic inflammatory response, may yield a greater benefit. It would be of interest to examine medication usage, neoplasia risk and markers of the systemic inflammatory response within population studies and further work is warranted.

It is important to note that conclusions drawn from the present study may not necessarily be representative of the population as a whole who were invited to screening. Only 52% of patients responded to the screening invite and just over three quarters of those who tested positive actually underwent colonoscopy. We have previously reported that those who fail to respond to screening are more likely to be male, younger and more socio-

Table 2. Risk of advanced neoplasia in those with colorectal pathology at colonoscopy

	All patients		Advanced neoplasia		Non-significant pathology		P-value	Risk of advanced neoplasia (multivariate analysis)		
	n	%	n	%	n	%		OR	95% CI	P-value
	3043		1704		1339					
<b>Age</b>										
≤55	565	19	263	15	302	23		1		
56–64	925	30	513	30	412	31		1.48	1.19–1.83	<0.001
≥65	1553	51	928	55	625	47	<0.001	1.89	1.55–2.31	<0.001
<b>Sex</b>										
Male	1990	65	1201	70	780	59		1		
Female	1053	35	503	30	550	41	<0.001	1.70	1.46–1.99	<0.001
<b>Deprivation category</b>										
1 (most deprived)	1060	35	554	33	506	38		1		
2	568	19	324	19	244	18		1.16	0.94–1.43	0.16
3	507	17	278	16	228	17		1.05	0.85–1.31	0.653
4	380	13	232	14	148	11		1.33	1.04–1.70	0.021
5 (least deprived)	525	17	313	18	212	16	<0.001	1.29	1.04–1.60	0.021
<b>Type of positive stool test</b>										
gFOBt	561	18	353	21	208	16		1		
FIT	2482	82	1351	79	1131	84	<0.001	1.39	1.14–1.68	0.001
<b>Aspirin</b>										
No	2592	85	1488	87	1104	82				
Yes	451	15	216	13	235	18	<0.001			
<b>Statin</b>										
No	2422	80	1409	83	1013	76				
Yes	621	20	295	17	326	24	<0.001			
<b>ACE inhibitor</b>										
No	2672	88	1524	89	1148	86				
Yes	371	12	180	11	191	14	0.002			
<b>≥1 Medications</b>										
No	2271	75	1330	78	941	70		1		
Yes	772	25	374	22	398	30	<0.001	0.59	0.50–0.70	<0.001

Abbreviations: ACE = angiotensin-converting enzyme; CI = confidence interval; FIT = faecal immunochemical test; gFOBt = guaiac-based faecal occult blood test; OR = odds ratio.

Table 3. Combinations of medications and risk of advanced neoplasia in those with colorectal pathology at colonoscopy

	Aspirin		Statin		ACE-i		Aspirin and Statin	
All patients, n	451		621		371		371	
OR (95% CI)	0.68 (0.56–0.83) P<0.001		0.65 (0.55–0.78) P<0.001		0.71 (0.57–0.89) P=0.002			
<b>Aspirin, n(%)</b>								
No			250 (40)		170 (46)			
Yes			371 (60)		201 (54)			
OR (95% CI)			0.69 (0.56–0.86) P=0.001		0.67 (0.51–0.90) P=0.006			
<b>Statin, n(%)</b>								
No					93 (25)			
Yes					278 (75)			
OR (95% CI)					0.64 (0.50–0.83) P<0.001			
<b>ACE-i, n(%)</b>								
No							192 (52)	
Yes							179 (48)	
OR (95% CI)							0.66 (0.49–0.90) P=0.007	

Abbreviations: ACE-i = angiotensin-converting enzyme inhibitor; CI = confidence interval; OR = odds ratio. Reference category = non-significant pathology.

Table 4. Risk of cancer in those with advanced neoplasia at colonoscopy

	All patients		Cancer		Advanced adenoma		P-value	Risk of cancer (multivariate analysis)		
	n	%	n	%	n	%		OR	95% CI	P-value
	1704		392		1312					
<b>Age</b>										
≤55	263	15	46	12	217	17	0.001	1	0.82–1.80	0.323
56–64	513	30	104	27	409	31		1.22		
≥65	928	55	242	62	686	52		1.72		
<b>Sex</b>										
Male	1201	70	260	66	941	72	0.04	1	0.59–0.96	0.023
Female	503	30	132	34	371	28		0.75		
<b>Deprivation category</b>										
1 (most deprived)	554	33	118	30	436	33	0.184			
2	324	19	66	17	258	20				
3	278	16	72	19	206	16				
4	232	14	63	16	169	13				
5 (least deprived)	313	18	71	18	242	19				
<b>Type of positive stool test</b>										
gFOBt	353	21	128	33	225	17	<0.001	1	1.87–3.12	<0.001
FIT	1351	79	264	67	1087	83		2.41		
<b>Aspirin</b>										
No	1488	87	349	89	1139	87	0.247			
Yes	216	13	43	11	173	13				
<b>Statin</b>										
No	1409	83	336	86	1073	82	0.071			
Yes	295	17	56	14	239	18				
<b>ACE-i</b>										
No	1524	89	353	90	1171	89	0.652			
Yes	180	11	39	10	141	11				
<b>≥ 1 Medications</b>										
No	1330	78	318	81	1012	77	0.094			
Yes	374	22	74	19	300	23				

Abbreviations: ACE-i = angiotensin-converting enzyme inhibitor; CI = confidence interval; FIT = faecal immunochemical test; gFOBt = guaiac-based faecal occult blood test; OR = odds ratio.

economically deprived, and that those who fail to progress to colonoscopy following a positive test are more likely to be deprived (Mansouri *et al*, 2013). Further work exploring medication usage and subsequent development of neoplasia in those who choose not to participate in screening is required.

A limitation of the present study is that data on dosage, duration or compliance with use of these medications were not collected. Therefore, we were not able to draw conclusions on favoured dosing for chemoprevention, nor were we able to separate those who had taken these medications for a period of weeks from those that had been on them for several years. Furthermore, a potential concern of the present cross-sectional study design is that the medication recorded does not reflect ongoing exposure. Nevertheless, given that the recorded medications are used to treat existing co-morbid disease it is likely that such medication would be taken on an ongoing basis. In addition, the majority of patients who were on at least one of these medications were in fact on several of them. Therefore, performing multivariate analysis to assess which was of most importance with this large degree of

multicollinearity was not meaningful and the effect of an individual medication could not be reliably estimated. However, this represents a real-life population setting where the majority of patients are likely to be on a combination of medications. Analysis of the risk of neoplasia and the association with medication usage, stratified for location within the colon was also not performed. Previous studies have found the greatest risk reduction with aspirin usage and with lesions of the proximal colon (Rothwell *et al*, 2010) and hence examining this in our population may have been of interest. However, there is an inherent problem with using data derived from occult blood stool-based colorectal cancer screening programmes for this, as such screening tests are less sensitive for right-sided lesions (Logan *et al*, 2012). This altered sensitivity creates a skewed study population undergoing colonoscopy where lesions are mainly on the left side of the colon. For example, only 17% of those with significant neoplasia in our study population had isolated right-sided lesions (data not presented). Such sample bias would negate any meaningful conclusions being drawn from subanalysis based on the location of neoplastic lesions and so such

an analysis was not undertaken. Also, while consideration was made to adjust for age, sex and socioeconomic deprivation, there are other potential confounding factors such as a significant family history or previous history of colonic neoplasia that have not been included in the present analysis. In particular, there is now robust evidence that patients with hereditary non-polyposis colorectal cancer or familial adenomatous polyposis may derive substantial benefit from aspirin chemoprophylaxis (Burn *et al*, 2011a,b). However, the overall incidence of these hereditary cancers in our study population is likely to be small (<10%).

In conclusion, we report that there is a reduced incidence of advanced colorectal neoplasia in patients who are on aspirin, statins or ACE-i undergoing colonoscopy following a positive stool test within a population-based screening programme. This effect persists when adjustment is made for the possible false-positivity effect of aspirin on gFOBt testing, suggesting that this reduction may be owing to a chemopreventative mechanism. Overall, this supports the theory that population-based usage of these medications in this age group may reduce the incidence of colorectal neoplasia. Further work is required to explore not only this concept but the perceived association with the host systemic inflammatory response, within the context of a national bowel screening programme.

## REFERENCES

- Atkin WS, Saunders BP (2002) Surveillance guidelines after removal of colorectal adenomatous polyps. *Gut* **51**(Suppl 5): V6–V9.
- Bardou M, Barkun A, Martel M (2010) Effect of statin therapy on colorectal cancer. *Gut* **59**: 1572–1585.
- Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA, Pearson L, Saibil F, van Stolk RU (2003) A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* **348**: 891–899.
- Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, Couturier D, Coste T, Little J, Chaussade S (2003) Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. *Gastroenterology* **125**: 328–336.
- Brenner H, Tao S, Haug U (2010) Low-dose aspirin use and performance of immunochemical fecal occult blood tests. *JAMA* **304**: 2513–2520.
- Burn J, Bishop DT, Chapman PD, Elliott F, Bertario L, Dunlop MG, Eccles D, Ellis A, Evans DG, Fodde R, Maher ER, Möslein G, Vasen HF, Coaker J, Phillips RK, Bülow S, Mathers JC (2011a) A randomized placebo-controlled prevention trial of aspirin and/or resistant starch in young people with familial adenomatous polyposis. *Cancer Prev Res (Phila)* **4**: 655–665.
- Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, Eccles D, Evans DG, Maher ER, Bertario L, Bisgaard ML, Dunlop MG, Ho JW, Hodgson SV, Lindblom A, Lubinski J, Morrison PJ, Murday V, Ramesar R, Side L, Scott RJ, Thomas HJ, Vasen HF, Barker G, Crawford G, Elliott F, Movahedi M, Pylvanainen K, Wijnen JT, Fodde R, Lynch HT, Mathers JC, Bishop DT (2011b) Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* **378**: 2081–2087.
- Cancer Research UK. Available at <http://info.cancerresearchuk.org/cancerstats/> (Accessed January 2013).
- Chan AT, Arber N, Burn J, Chia WK, Elwood P, Hull MA, Logan RF, Rothwell PM, Schror K, Baron JA (2012) Aspirin in the chemoprevention of colorectal neoplasia: an overview. *Cancer Prev Res (Phila)* **5**: 164–178.
- Clarke P, Jack F, Carey FA, Steele RJ (2006) Medications with anticoagulant properties increase the likelihood of a negative colonoscopy in faecal occult blood test population screening. *Colorectal Dis* **8**: 389–392.
- Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, Chaussade S, Baron JA (2009) Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. *J Natl Cancer Inst* **101**: 256–266.
- Flossmann E, Rothwell PM (2007) Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* **369**: 1603–1613.
- Fraser CG, Digby J, McDonald PJ, Strachan JA, Carey FA, Steele RJ (2012) Experience with a two-tier reflex gFOBt/FIT strategy in a national bowel screening programme. *J Med Screen* **19**: 8–13.
- Gauthaman K, Fong CY, Bongso A (2009) Statins, stem cells, and cancer. *J Cell Biochem* **106**: 975–983.
- Guittet L, Bouvier V, Mariotte N, Vallee JP, Arsène D, Boutreux S, Tichet J, Launoy G (2007) Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. *Gut* **56**: 210–214.
- Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, James PD, Mangham CM (1996) Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* **348**: 1472–1477.
- Hol L, Wilschut JA, van Ballegooijen M, van Vuuren AJ, van der Valk H, Reijerink JC, van der Togt AC, Kuipers EJ, Habbema JD, van Leerdam ME (2009) Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. *Br J Cancer* **100**: 1103–1110.
- Jacobs RJ, Kodach LL, Hardwick JC (2011) The potential of statins for individualized colorectal cancer chemoprevention. *Curr Drug Targets* **12**: 1903–1908.
- Kedika R, Patel M, Pena Sahdala HN, Mahgoub A, Cipher D, Siddiqui AA (2011) Long-term use of angiotensin converting enzyme inhibitors is associated with decreased incidence of advanced adenomatous colon polyps. *J Clin Gastroenterol* **45**: e12–e16.
- Kronborg O, Fenger C, Olsen J, Jørgensen OD, Sondergaard O (1996) Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* **348**: 1467–1471.
- Lee CS, McNamara D, O'Morain CA (2012) Aspirin as a chemoprevention agent for Colorectal cancer. *Curr Drug Metab* **13**: 1313–1322.
- Lee TJ, Hull MA, Rajasekhar PT, Clifford GM, Ritchie M, James P, McNally RJ, Rutter MD, Rees CJ (2012) Aspirin users attending for NHS bowel cancer screening have less colorectal neoplasia: chemoprevention or false-positive faecal occult blood testing? *Digestion* **85**: 278–281.
- Lever AF, Hole DJ, Gillis CR, McCallum IR, McInnes GT, MacKinnon PL, Meredith PA, Murray LS, Reid JL, Robertson JW (1998) Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet* **352**: 179–184.
- Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, Birkenfeld S, Lieberman N, Klang S, Niv Y (2009) Sensitivity, but not specificity, of a quantitative immunochemical fecal occult blood test for neoplasia is slightly increased by the use of low-dose aspirin, NSAIDs, and anticoagulants. *Am J Gastroenterol* **104**: 933–938.
- Logan RF, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C (2012) Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. *Gut* **61**: 1439–1446.
- Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F (1993) Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* **328**: 1365–1371.
- Mansouri D, McMillan DC, Grant Y, Crichton EM, Horgan PG (2013) The impact of age, sex and socioeconomic deprivation on outcomes in a colorectal cancer screening programme. *PLoS One*. Article accepted but not yet published.
- Parra-Blanco A, Gimeno-García AZ, Quintero E, Nicolás D, Moreno SG, Jiménez A, Hernández-Guerra M, Carrillo-Palau M, Eishi Y, López-Bastida J (2010) Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. *J Gastroenterol* **45**: 703–712.
- Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, Low M, Greenon JK, Rennert G (2005) Statins and the risk of colorectal cancer. *N Engl J Med* **352**: 2184–2192.
- Proctor MJ, Talwar D, Balmar SM, O'Reilly DS, Foulis AK, Horgan PG, Morrison DS, McMillan DC (2010) The relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters. Initial results of the Glasgow Inflammation Outcome Study. *Br J Cancer* **103**: 870–876.
- Rocken C, Neumann K, Carl-McGrath S, Lage H, Ebert MP, Dierkes J, Jacobi CA, Kalmuk S, Neuhaus P, Neumann U (2007) The gene polymorphism of the angiotensin I-converting enzyme correlates with tumor size and patient survival in colorectal cancer patients. *Neoplasia* **9**: 716–722.
- Rodgers A, Patel A, Berwanger O, Bots M, Grimm R, Grobbee DE, Jackson R, Neal B, Neaton J, Poulter N, rafter N, Raju PK, Reddy S, Thom S, Vander

- Hoorn S, Webster R (2011) An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. *PLoS One* **6**: e19857.
- Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW (2011) Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* **377**: 31–41.
- Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, Meade TW (2010) Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* **376**: 1741–1750.
- Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, Petrelli N, Pipas JM, Karp DD, Loprinzi CL, Steinbach G, Schilsky R (2003) A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* **348**: 883–890.
- Sawhney MS, McDougall H, Nelson DB, Bond JH (2010) Fecal occult blood test in patients on low-dose aspirin, warfarin, clopidogrel, or non-steroidal anti-inflammatory drugs. *Dig Dis Sci* **55**: 1637–1642.
- Simon MS, Rosenberg CA, Rodabough RJ, Greenland P, Ockene I, Roy HK, Lane DS, Cauley JA, Khandekar J (2012) Prospective analysis of association between use of statins or other lipid-lowering agents and colorectal cancer risk. *Ann Epidemiol* **22**: 17–27.
- Steele RJ, McClements P, Watling C, Libby G, Weller D, Brewster DH, Black R, Carey FA, Fraser CG (2012) Interval cancers in a FOBT-based colorectal cancer population screening programme: implications for stage, gender and tumour site. *Gut* **61**: 576–581.
- Steele RJ, McClements PL, Libby G, Black R, Morton C, Birrell J, Mowat NA, Wilson JA, Kenicer M, Carey FA, Fraser CG (2009) Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. *Gut* **58**: 530–535.
- Thun MJ, Namboodiri MM, Heath Jr. CW (1991) Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* **325**: 1593–1596.
- Wald NJ, Law MR (2003) A strategy to reduce cardiovascular disease by more than 80%. *BMJ* **326**: 1419.
- Zhou P, Cheng SW, Yang R, Wang B, Liu J (2012) Combination chemoprevention: future direction of colorectal cancer prevention. *Eur J Cancer Prev* **21**: 231–240.

This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License.