

# Assessment of volumetric growth rates of small colorectal polyps with CT colonography: a longitudinal study of natural history



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## Summary

**Background** The clinical relevance and in-vivo growth rates of small (6–9 mm) colorectal polyps are not well established. We aimed to assess the behaviour of such polyps with CT colonography assessments.

**Methods** In this longitudinal study, we enrolled asymptomatic adults undergoing routine colorectal cancer screening with CT colonography at two medical centres in the USA. Experienced investigators (PJP, DHK, JLH) measured volumes and maximum linear sizes of polyps in vivo with CT colonography scans at baseline and surveillance follow-up. We defined progression, stability, and regression on the basis of a 20% volumetric change per year from baseline (20% or more growth classed as progression, 20% growth to –20% reduction classed as stable, and –20% or more reduction classed as regression). We compared findings with histological subgroups confirmed after colonoscopy when indicated. This study is registered with ClinicalTrials.gov, number NCT00204867.

**Findings** Between April, 2004, and June, 2012, we screened 22 006 asymptomatic adults and included 243 adults (mean age 57·4 years [SD 7·1] and median age 56 years [IQR 52–61]; 106 [37%] women), with 306 small colorectal polyps. The mean surveillance interval was 2·3 years (SD 1·4; range 1–7 years; median 2·0 years [IQR 1·1–2·3]). 68 (22%) of 306 polyps progressed, 153 (50%) were stable, and 85 (28%) regressed, including an apparent resolution in 32 (10%) polyps. We established immediate histology in 131 lesions on colonoscopy after final CT colonography. 21 (91%) of 23 proven advanced adenomas progressed, compared with 31 (37%) of 84 proven non-advanced adenomas, and 15 (8%) of 198 other lesions ( $p < 0\cdot0001$ ). The odds ratio for a growing polyp at CT colonography surveillance to become an advanced adenoma was 15·6 (95% CI 7·6–31·7) compared with 6–9 mm polyps detected and removed at initial CT colonography screening (without surveillance). Mean polyp volume change was a 77% increase per year for 23 proven advanced adenomas and a 16% increase per year for 84 proven non-advanced adenomas, but a 13% decrease per year for all proven non-neoplastic or unresected polyps ( $p < 0\cdot0001$ ). An absolute polyp volume of more than 180 mm<sup>3</sup> at surveillance CT colonography identified proven advanced neoplasia (including one delayed cancer) with a sensitivity of 92% (22 of 24 polyps), specificity of 94% (266 of 282 polyps), positive-predictive value of 58% (22 of 38 polyps), and negative-predictive value of 99% (266 of 268 polyps). Only 16 (6%) of the 6–9 mm polyps exceeded 10 mm at follow-up.

**Interpretation** Volumetric growth assessment of small colorectal polyps could be a useful biomarker for determination of clinical importance. Advanced adenomas show more rapid growth than non-advanced adenomas, whereas most other small polyps remain stable or regress. Our findings might allow for less invasive surveillance strategies, reserving polypectomy for lesions that show substantial growth. Further research is needed to provide more information regarding the ultimate fate of unresected small polyps without significant growth.

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## Introduction

The idea that colorectal cancer generally develops slowly over time from benign precursor lesions has become widely accepted in the past few decades, and most benign polyps are thought not to progress to cancer.<sup>1,2</sup> Unlike breast or lung cancer, this prolonged sequence of events for colorectal cancer has provided a unique opportunity for prevention through the detection and removal of relevant precancerous polyps.<sup>3,4</sup> In particular, advanced neoplasms are the ideal target for colorectal cancer screening and prevention, from both clinical and economic perspectives.<sup>5–7</sup>

Prevalence, histology, and immediate cancer risk of colorectal polyps according to linear size within

asymptomatic screening cohorts have been established in several studies.<sup>8–10</sup> However, findings from these studies have only provided static cross-sectional data with no information about past or future behaviour because polyps are generally removed at the time of initial detection. Although the clinical importance of large colorectal polyps ( $\geq 10$  mm) and the benign nature of diminutive polyps ( $\leq 5$  mm) are generally accepted, elucidation of the in-vivo behaviour and clinical significance of small polyps (6–9 mm), for which treatment decisions are contentious, could have an enormous effect on colorectal cancer screening, irrespective of modality. Previous attempts to investigate

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the longitudinal natural history of small colorectal polyps *in vivo* have used barium enemas,<sup>11</sup> flexible sigmoidoscopy,<sup>12</sup> and optical colonoscopy.<sup>13</sup> Unfortunately, these methods all have notable shortcomings in terms of *in-vivo* localisation, verification, and measurement of polyps, which restrict their utility as investigative tools. CT colonography, in conjunction with selective colonoscopy for polypectomy, is a good method for investigation of polyp natural history, allowing for precise reproducible non-invasive localisation, assessment of actual lesion volume, and direct side-by-side comparison in longitudinal studies. In particular, volumetric measurement is a more reliable means for assessment of interval change over time and can substantially amplify small or imperceptible changes in linear size.<sup>14</sup>

We report the results of a prospective polyp natural history study that assessed the growth rates of small (6–9 mm) colorectal polyps with longitudinal *in-vivo* assessment with CT colonography. We aimed to determine whether growth rates were predictive of neoplasia, advanced adenomas, and clinical importance.

## Methods

### Study design and participants

We enrolled asymptomatic adults undergoing routine colorectal cancer screening with CT colonography at one of two sites in the USA (University of Wisconsin Hospital and Clinics, WI, and the National Military Medical Center in Bethesda, MD). Eligible patients were aged at least 50 years (unless family history warranted earlier screening) and had one or two small colorectal polyps, measuring 6–9 mm in maximum linear size, prospectively identified at CT colonography. Patients with more than two small polyps who refused colonoscopy were also allowed to enter the study. We excluded patients with coexisting large ( $\geq 10$  mm) polyps, masses, or related symptoms.

This study was approved by the institutional review boards at the two participating institutions, and all patients provided written informed consent.

### Procedures

The CT colonography techniques used for bowel preparation, colonic distention, and CT scanning at both screening centres share a common origin and have remained much the same over time.<sup>7,15,16</sup> Briefly, patients underwent a low-volume cathartic preparation the evening before examination, coupled with oral contrast agents to tag stool and fluid. During the examination, colonic distention was achieved with automated low-pressure carbon dioxide delivery, immediately followed by breath-hold supine and prone imaging with multidetector CT scanners. The protocol for initial (index) and surveillance CT colonography examinations was held constant. Patients received no oral or intravenous sedation, pain medication, or spasmolytics. Experienced radiologists prospectively interpreted all

assessments with dedicated CT colonography software (V3D Colon, Viatronix, Stony Brook, NY, USA). We prospectively recorded linear size, morphology (sessile, flat, or pedunculated), and segmental location of the small polyps. We defined flat polyps as superficially elevated lesions that were raised less than 3 mm from the surrounding mucosa.<sup>17</sup>

We set an initial surveillance interval for polyp follow-up of 1–2 years, but after patient safety of short-term *in-vivo* polyp follow-up was shown with no adverse outcomes in the first 100 patients enrolled, the initial interval was expanded to 3 years by the end of the trial period to allow for more extended observation. All patients had the option of colonoscopy for polypectomy immediately after CT colonography follow-up. For some stable or regressing polyps, continued CT colonography surveillance was allowed up to a maximum interval of 5 years. Polypectomy was indicated for all lesions showing linear growth of 1 mm or more at interval CT colonography. We reported histological changes for all resected polyps. For inclusion of histological data to correlate with the CT colonography growth pattern, polypectomy had to be done within 1 year of the final CT colonography. We defined advanced neoplasms according to the presence of a prominent ( $\geq 25\%$ ) villous component, high-grade dysplasia, or invasive cancer at histology, or by a large lesion size ( $\geq 10$  mm).<sup>5,7</sup>

Dedicated retrospective polyp assessment with the same CT colonography software system (Viatronix) was done by PJP, DHK, and JLH, each of whom have extensive experience interpreting CT colonography ( $>1000$  cases each). In addition to confirming linear size, we also did volumetric measurement for each small polyp at the index CT colonography and, if still present, at the surveillance CT colonography. PJP, DHK, and JLH were masked to any relevant clinical, endoscopic, or histopathological data. The maximum linear polyp size was confirmed at CT colonography with a validated approach that combines 2D and 3D assessment.<sup>18,19</sup> We derived polyp volume with a semi-automated technique that segments the lesion but requires that the user confirms or appropriately adjusts the included voxels by manipulation of the region of interest on each individual 2D slice.<sup>14</sup> For pedunculated polyps, the stalk was excluded from measurement. All measurements for each individual polyp were done by the same expert reader to reduce interobserver variability in growth classification. We have previously shown that the error in volumetric polyp measurement relative to underlying volume changes is substantially lower than the error in linear measurement relative to the smaller changes in linear size.<sup>14</sup>

### Statistical analysis

For data analysis, we divided polyp growth into categories of progression, stability, and regression according to measured changes at longitudinal CT colonographies. A threshold of 20% change (growth or reduction) per year

in polyp volume was chosen as the baseline categorisation into the three groups (20% or more growth classed as progression, 20% growth to -20% reduction classed as stable, and -20% or more reduction classed as regression), because this value is beyond the expected range of CT measurement error and should therefore constitute a real change.<sup>14</sup> The baseline threshold for linear size change was set at 1 mm (growth or reduction) per year. We used varying threshold definitions for volumetric and linear size changes in sensitivity analysis. In general, because interval volume changes are amplified compared with one dimensional measurement, volumetric assessment should provide a better indication of growth.

Polyp histology was primarily divided into neoplasms (advanced and non-advanced), non-neoplastic lesions (eg, hyperplastic), and unresected (including resolved) lesions where histology was unknown. To compare the histological results of this longitudinal surveillance cohort against a cross-sectional reference standard, we used non-surveillance histology data from 464 small (6–9 mm) polyps—identified within the same general asymptomatic population at initial CT colonography screening—that were immediately removed at colonoscopy.<sup>20</sup> This cross-sectional data provides a static baseline for comparison because lesions were removed at the time of initial detection and thus lack any natural history data. All statistical analyses were done with R version 2.12.2.

This study is registered with ClinicalTrials.gov, number NCT00204867.

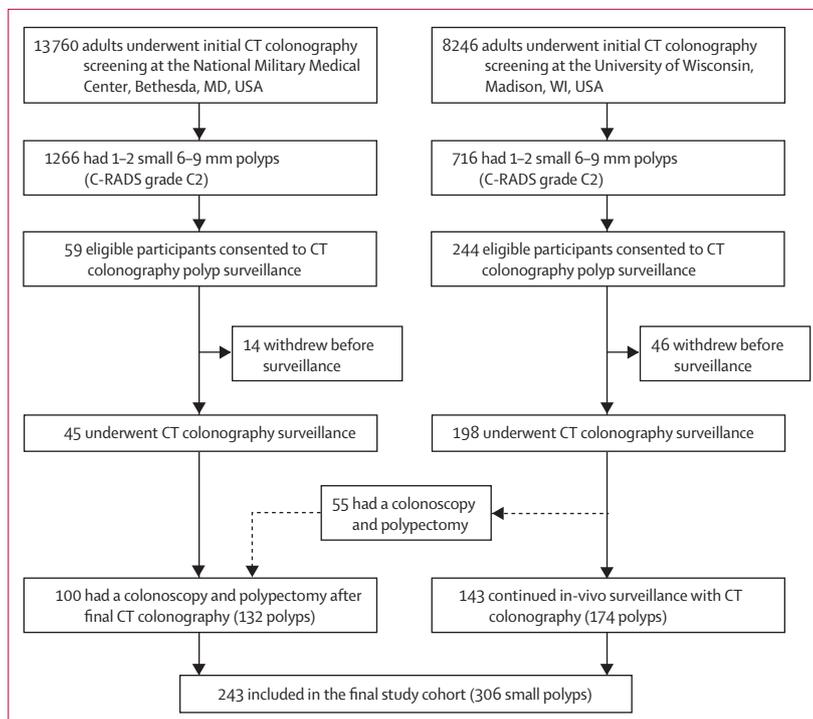
### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had full access to all the data in the study.

### Results

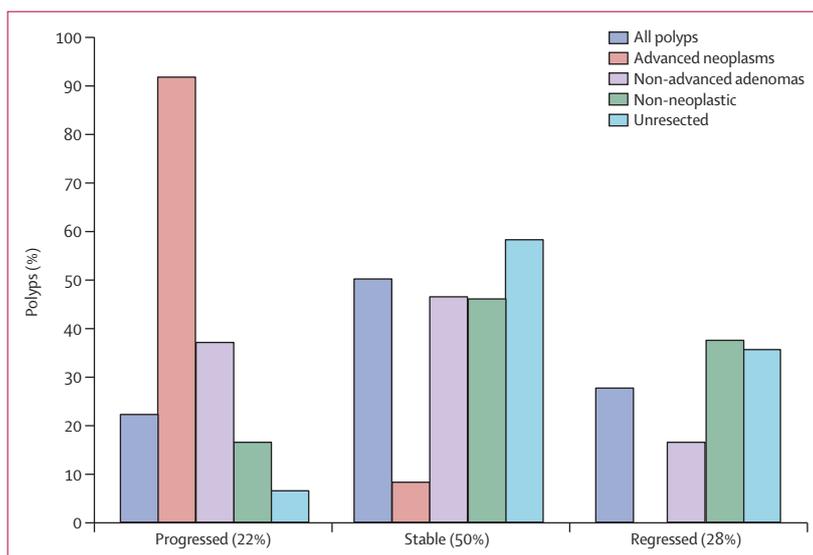
Between April, 2004, and June, 2012, we screened 22 006 adults undergoing CT colonography at the two centres. The final patient cohort consisted of 243 asymptomatic adults (mean age 57.4 years [SD 7.1] and median age 56 years [IQR 52–61]; 106 [37%] women), with 306 small colorectal polyps at the initial CT colonography screening examination (figure 1). Initial screening and enrolment into the trial spanned from April, 2004, to June, 2010. Mean polyp linear size was 7.2 mm (SD 1.1) and mean volume at the index CT colonography was 83.4 mm<sup>3</sup> (60.4). Most polyps were sessile in morphology (237 polyps [77%]), with some appearing flat (36 [12%]) or pedunculated (33 polyps [11%]). Anatomical segmental location included the rectum (46 polyps [15%]), sigmoid (87 polyps [28%]), descending (27 polyps [9%]), transverse (64 polyps [21%]), ascending (58 polyps [19%]), and caecum (24 polyps [8%]).

The mean surveillance interval for the 306 polyps was 2.3 years (SD 1.4; range 1–7 years; median 2.0 [IQR 1.1–2.3]), providing data for 712.7 polyp-years of in-vivo surveillance. 30 patients with 45 small (6–9 mm) polyps underwent two surveillance CT colonography examinations because of stable intermediate findings at the first prospective follow-up assessment. 68 (22%) of 306 polyps



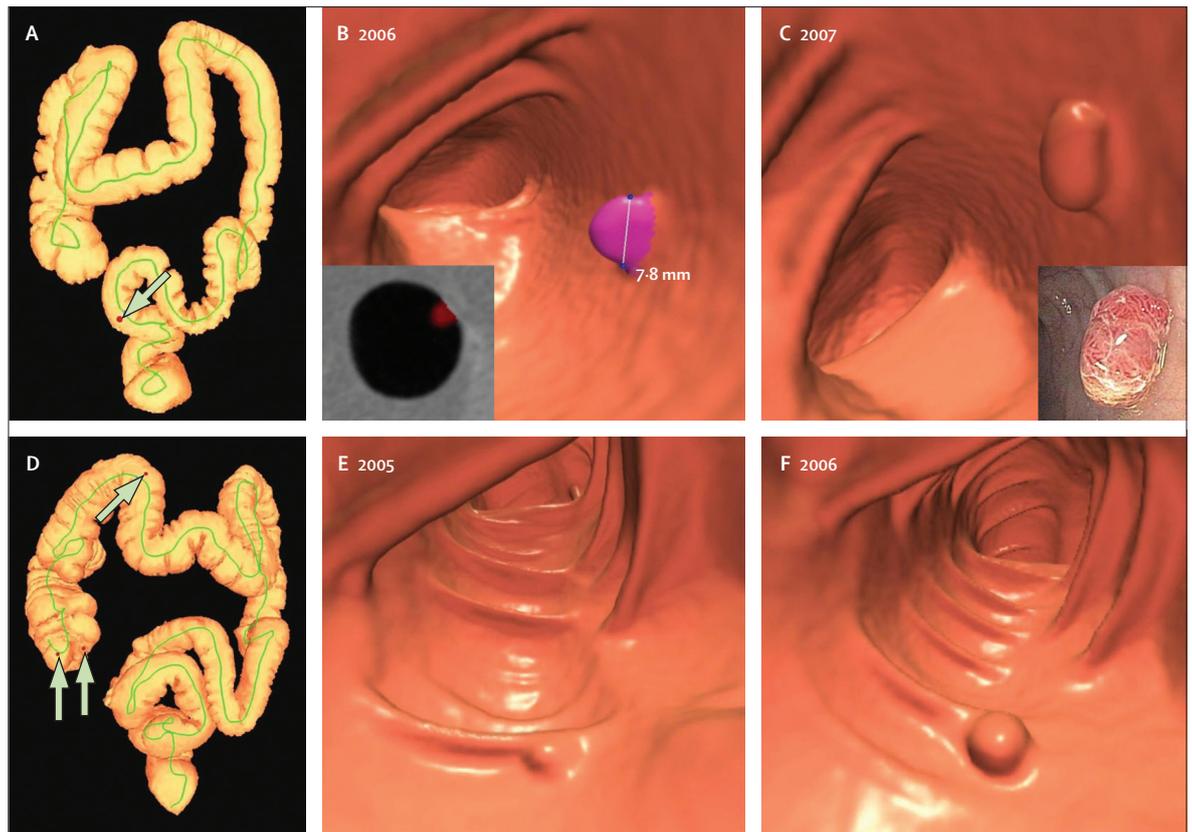
**Figure 1: Study profile**

C-RADS=CT colonography Reporting and Data System.



**Figure 2: Polyp growth according to histological subgroup**

Polyp growth categories are shown according to the baseline assumption of at least 20% volume change per year as progression or regression.



**Figure 3: Interval progression of small colorectal polyps in two patients**

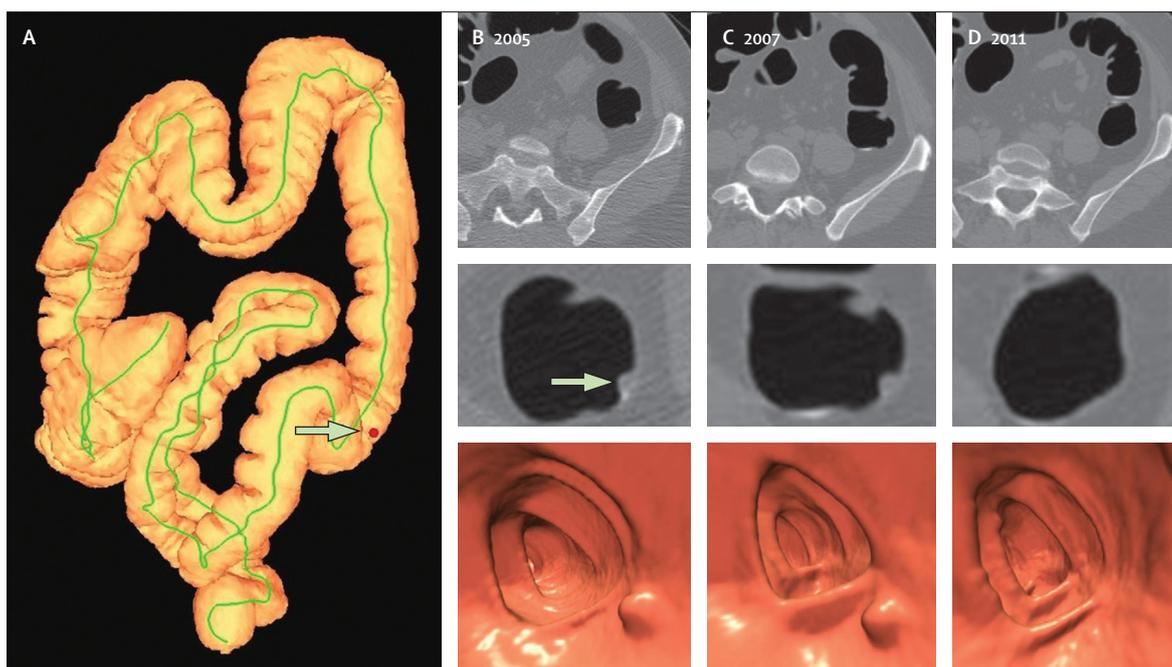
3D colon map from CT colonography (A) showing the location of a small sigmoid polyp (arrow, red dot), which measured 7.8 mm at the index screening examination (B). Polyp segmentation for volume measurement is shown on both 3D and 2D (inset) views. At follow-up CT colonography 1 year later (C), the polyp grew only 0.8 mm but showed a 50% increase in volume (to 205 mm<sup>3</sup>). The lesion proved to be a tubulovillous adenoma after polypectomy at same-day colonoscopy (inset). 3D colon map (D) showing the location of three small polyps in the right colon (arrows, red dots). The patient was enrolled in the study after declining same-day colonoscopy. 3D images from the index CT colonography (E) and surveillance CT colonography 16 months later (F) show a small sessile polyp in the proximal transverse colon that increased from 6.0 mm to 8.0 mm, and increased in volume by 203% (153% per year). Similar growth was seen with the two caecal polyps. The polyp in the transverse colon was a tubular adenoma (the fastest-growing non-advanced adenoma in the study), whereas the caecal lesions were advanced (tubulovillous) adenomas.

progressed according to the defined baseline threshold of 20% change per year, 153 (50%) were stable, and 85 (28%) regressed at CT colonography surveillance (figures 2–4).

Histological analysis of 131 polyps resected immediately after the final surveillance CT colonography identified 107 benign neoplasms, 24 non-neoplastic lesions, and no cancer in 99 patients (mean age 56.1 years [SD 6.9]; median 55 years [IQR 51–60]; 33 [33%] women). 23 (21%) of the 107 proven neoplasms were advanced adenomas, with 13 polyps of large size ( $\geq 10$  mm), 13 polyps with tubulovillous histology, and one polyp with high-grade dysplasia (table 1). The other 84 neoplasms were non-advanced adenomas, including 83 small tubular adenomas and one serrated lesion. 20 (83%) of 24 proven non-neoplastic polyps were hyperplastic; two others were inflammatory, one was juvenile, and one was mucosal. Notably, one patient with a progressing pedunculated rectal polyp at CT colonography surveillance was lost to follow-up but returned 5.5 years after the index examination with

a symptomatic invasive cancer. The remaining polyps with unproven histology either completely regressed by CT colonography (32 polyps) or are under continued CT colonography surveillance (142 polyps).

Of 56 polyps with proven histology that progressed and were immediately removed (figure 2), 52 (93%) were neoplastic, including 21 (40%) advanced adenomas, 31 (60%) non-advanced adenomas, and no cancers. 12 polyps with progression by volume were not immediately resected. Of 75 resected polyps that were not progressing according to the baseline volumetric criterion, only two (4%) of 52 stable lesions were advanced adenomas and none of the regressing lesions were advanced adenomas. The two stable advanced adenomas each had a positive volume change of about 8% per year (table 1). Therefore, all 23 proven advanced adenomas showed positive volume growth at follow-up (table 1), with 21 (91%) progressing according to the 20% per year threshold, compared with 31 (37%) of 84 non-advanced adenomas, four (17%) of 24 non-neoplastic lesions, and 11 (6%) of



**Figure 4: Polyp regression**

3D colon map (A) showing the location of a 6.2 mm polyp in the descending colon (arrows, red dot) detected at screening CT colonography in 2005 (B). Surveillance CT colonography in 2007 (C) showed no interval change in size. By the time of continued surveillance in 2011 (D), 6.4 years after the initial CT colonography, the polyp had completely resolved (a trait noted in 10% of small polyps overall). Detection of the small polyp on the intermediate CT colonography in 2007 essentially excludes the possibility of a false-positive interpretation.

174 polyps with unproven histology ( $p < 0.0001$ ). 32 (38%) of 85 polyps that regressed showed complete resolution by CT colonography (figure 4), representing 10% of all 306 polyps.

The cross-sectional reference standard cohort of patients with 464 small polyps had a similar demographic composition (mean age 58.9 years [SD 8.6]; 140 [40%] women) to the surveillance cohort. 18 (4%) of these polyps were histologically advanced adenomas, 258 (56%) were any adenoma, and no polyps were cancer.<sup>20</sup> By comparison, in all 131 immediately resected polyps in our surveillance cohort, 14 (11%) were histologically advanced adenomas, 23 (18%) were any advanced adenoma (including by size), 107 (82%) were any adenoma (including tubular), and none was cancer.

The overall prevalence of proven advanced histology was much the same for both cohorts (18 [4%] of 464 polyps in the reference standard cohort vs 14 [5%] of 306 polyps in the surveillance cohort), but overall, 21 (38%) of the 56 progressing polyps with proven histology were advanced adenomas (including size). Within the surveillance cohort for resected polyps that were progressing, the odds ratio for an advanced adenoma was 15.6 (95% CI 7.6–31.7) and any adenoma was 10.6 (3.8–29.7) compared with polyps in the cross-sectional cohort.

In the sensitivity analysis, we noted striking differences in growth between the histological subsets, irrespective of the specific volumetric threshold applied (table 2).

Changes in linear size were also notable, although the magnitude was blunted, leading to an increased proportion of stable lesions (table 2). For example, the percentage of advanced neoplasms categorised as stable by the three linear size criteria used (changes of  $>1$  mm per year,  $>10\%$  per year, and  $>25\%$  total) in table 2 ranged from 38% to 58%, compared with only 8–12% for three volumetric criteria (changes of  $>20\%$  per year,  $>15$  mm<sup>3</sup> per year, and  $>30\%$  total; table 2). In general, advanced adenomas grew more rapidly than did non-advanced adenomas, with a strong tendency for overall stability or regression in the remaining subgroups. The mean annual change in polyp volume (figure 5) was an increase of 77% for advanced adenomas, an increase of 16% for non-advanced adenomas, a decrease of 5% for non-neoplastic lesions, and a decrease of 14% for unresected polyps ( $p < 0.0001$ ). Use of an absolute polyp volume threshold of 180 mm<sup>3</sup> at surveillance CT colonography to identify proven advanced neoplasia (including the delayed cancer diagnosis) had a sensitivity of 92% (22 of 24 polyps), specificity of 94% (266 of 282 polyps), positive predictive value of 58% (22 of 38 polyps), and negative predictive value of 99% (266 of 268 polyps). Overall, 123 polyps (40%) in the surveillance cohort had a negative overall growth by volume.

Compared with volumetric assessments, interval changes in linear polyp size were small, often within the expected margin of measurement error. Mean linear changes were increases of 1.1 mm per year for advanced

	Segment	Morphology	Index analysis		Surveillance interval (years)	Surveillance analysis		Linear change per year	Volume change per year	Histology
			Linear size (mm)	Volume (mm <sup>3</sup> )		Linear size (mm)	Volume (mm <sup>3</sup> )			
1	Caecum	Sessile	8.4	42	2.0	14.4	381	35.3%	398.4%	TVA
2	Rectum	Pedunculated	6.8	90	1.0	7.8	220	15.0%	147.4%	TVA
3	Sigmoid	Sessile	7.4	122	2.2	11.5	490	25.0%	136.4%	TA
4	Caecum	Sessile	6.5	88	1.3	8.4	233	21.9%	123.6%	TVA
5	Sigmoid	Sessile	6.0	33	2.8	10.1	123	24.7%	98.5%	TA
6	Caecum	Sessile	6.7	94	1.3	8.0	216	14.6%	97.3%	TVA
7	Transverse	Pedunculated	6.7	160	1.0	8.3	317	23.2%	95.3%	TVA
8	Sigmoid	Pedunculated	8.3	134	1.3	10.1	292	17.3%	94.2%	TA
9	Sigmoid	Pedunculated	8.3	183	1.0	10.2	324	22.3%	75.0%	TA
10	Rectum	Sessile	9.6	283	1.1	12.1	485	24.4%	66.8%	TVA
11	Sigmoid	Pedunculated	8.6	196	1.0	8.6	327	0.0%	65.1%	TVA
12	Sigmoid	Sessile	6.6	67	6.2	10.1	328	8.5%	62.8%	TA
13	Sigmoid	Sessile	7.8	135	1.0	8.6	205	9.8%	49.6%	TVA
14	Ascending	Sessile	9.4	155	2.1	10.6	284	6.2%	40.3%	TA
15	Rectum	Sessile	9.3	85	4.3	10.4	224	2.7%	37.9%	TA
16	Ascending	Pedunculated	9.8	280	1.0	10.4	380	6.4%	37.5%	TVA
17	Transverse	Pedunculated	9.2	248	4.1	14.1	607	13.0%	35.3%	TA
18	Sigmoid	Pedunculated	8.7	366	1.0	10.2	484	17.1%	31.9%	TVA
19	Ascending	Sessile	9.0	150	1.1	10.2	193	12.1%	25.9%	TA
20	Rectum	Sessile	8.4	296	1.0	9.5	366	13.1%	23.7%	TA/HGD
21	Descending	Pedunculated	7.2	109	3.1	9.1	183	8.6%	22.0%	TVA
22	Rectum	Sessile	6.8	171	5.4	9.0	249	6.0%	8.4%	TVA
23	Transverse	Sessile	6.0	53	2.0	6.0	61	0.0%	7.6%	TVA

TVA=tubulovillous adenoma. TA=tubular adenoma. HGD=high-grade dysplasia.

**Table 1: Characteristics of 23 proven advanced adenomas resected after surveillance with CT colonography**

adenomas and 0.1 mm for non-advanced adenomas and decreases of 0.4 mm for non-neoplastic lesions and 0.8 mm for lesions without histology. 16 (6%) polyps exceeded 10.0 mm in linear size at follow-up, of which 14 (88%) were proven advanced neoplasms. In general, polyp volume assessment amplified subtle, imperceptible, or even discordant linear changes, because 74% of all polyps would be categorised as stable with a linear threshold of 1 mm (growth or reduction) per year (table 2, figure 3). In all cases where the direction of the measured volumetric and linear changes (ie, positive vs negative growth) were discordant, subjective visual assessment at CT colonography favoured the volumetric result. 11 of 12 polyps that increased in volume by more than 20% per year at CT colonography follow-up but were not immediately removed grew by less than 1 mm per year. This absence of discernible linear growth at prospective CT colonography interpretation was the primary reason immediate polypectomy was not done at the time of surveillance. For the small pedunculated rectal polyp that ultimately progressed to invasive cancer, the linear growth at 2 year CT colonography follow-up measured only 0.4 mm, but the polyp volume had increased by 59%. By the time of symptomatic cancer presentation, the mass had increased more than 6000% in volume from the index examination.

With the baseline volume threshold of 20% growth or reduction per year, 15 (45%) of 33 pedunculated polyps progressed at surveillance CT colonography, compared with 50 (21%) of 237 sessile polyps and three (8%) of 36 flat lesions (p<0.0001). We noted the highest rates of progression at surveillance in caecal (nine [38%] of 24) and rectal (16 [35%] of 46) polyps, compared with polyps in the descending (seven [26%] of 27), sigmoid (20 [23%] of 87), ascending (nine [16%] of 58), and transverse (six [10%] of 63) colon. For 45 small polyps in 30 patients who had two follow-up CT colonography studies, 38 polyps (84%) remained stable on the final surveillance CT colonography, whereas five (11%) progressed and three (7%) regressed.

### Discussion

We showed that volumetric growth could be a useful biomarker for assessment of the clinical relevance of small colorectal polyps. In particular, proven advanced adenomas grew faster than did non-advanced adenomas, whereas most other small polyps remained stable or regressed over time. Ongoing surveillance of unresected small polyps that did not show substantial growth to date at follow-up CT colonographies might help explain what ultimately happens to these less aggressive lesions.

	Volumetric threshold			Linear threshold		
	±20% per year*	±15 mm <sup>3</sup> per year	±30% total	±1 mm per year	±10% per year	±25% total
<b>Advanced neoplasms (n=24)†</b>						
Progressing	22/24 (92%)	22/24 (92%)	21/24 (88%)	14/24 (58%)	15/24 (63%)	10/24 (42%)
Stable	2/24 (8%)	2/24 (8%)	3/24 (13%)	10/24 (42%)	9/24 (38%)	14/24 (58%)
Regressing	0	0	0	0	0	0
<b>Non-advanced adenomas (n=84)</b>						
Progressing	31/84 (37%)	28/84 (33%)	31/84 (37%)	8/84 (10%)	18/84 (21%)	12/84 (14%)
Stable	39/84 (46%)	42/84 (50%)	40/84 (48%)	67/84 (80%)	56/84 (67%)	69/84 (82%)
Regressing	14/84 (17%)	14/84 (17%)	13/84 (15%)	9/84 (11%)	10/84 (12%)	3/84 (4%)
<b>Non-neoplastic polyps (n=24)</b>						
Progressing	4/24 (17%)	5/24 (21%)	4/24 (17%)	0	1/24 (4%)	0
Stable	11/24 (46%)	12/24 (50%)	15/24 (63%)	20/24 (83%)	15/24 (63%)	22/24 (92%)
Regressing	9/24 (38%)	7/24 (29%)	5/24 (21%)	4/24 (17%)	8/24 (33%)	2/24 (8%)
<b>Unresected polyps (n=174)</b>						
Progressing	11/174 (6%)	10/174 (6%)	16/174 (9%)	3/174 (2%)	6/174 (3%)	3/174 (2%)
Stable	101/174 (58%)	107/174 (61%)	76/174 (44%)	130/174 (75%)	114/174 (66%)	126/174 (72%)
Regressing	62/174 (36%)	57/174 (33%)	82/174 (47%)	41/174 (24%)	54/174 (31%)	45/174 (26%)
<b>All polyps (n=306)</b>						
Progressing	68/306 (22%)	65/306 (21%)	72/306 (24%)	25/306 (8%)	40/306 (13%)	25/306 (8%)
Stable	153/306 (50%)	163/306 (53%)	134/306 (44%)	227/306 (74%)	194/306 (63%)	228/306 (75%)
Regressing	85/306 (28%)	78/306 (25%)	100/306 (33%)	54/306 (18%)	72/306 (24%)	50/306 (16%)

\*>20% change (growth or reduction) in volume per year was the baseline used in this study. †Includes one delayed cancer and 23 advanced adenomas.

Table 2: Change in polyp size according to linear and volumetric thresholds

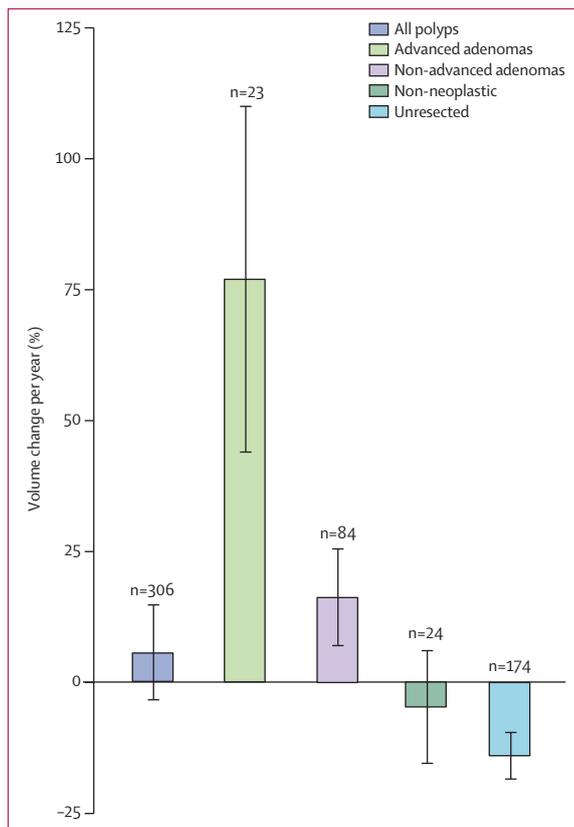
The clinical relevance and management of small colorectal polyps, sometimes referred to as medium-sized or intermediate polyps, is controversial, especially with regard to emerging non-invasive screening strategies such as CT colonography and stool DNA tests (panel).<sup>9,21–25</sup> The perceived dearth of high-quality data about the natural history of these polyps has been regarded as the missing link to improved understanding. Several studies in the past 50 years have tried to investigate the longitudinal behaviour of small colorectal polyps (<10 mm) with various endoscopic and barium techniques.<sup>11–13,26–30</sup> Despite restrictions in terms of in-vivo localisation and measurement of small polyps, overall these studies suggested a very benign and indolent clinical course, which is in line with the long-held tenets of the adenoma-carcinoma sequence.<sup>2</sup> Previous studies notwithstanding, a more precise understanding of the natural history of small colorectal polyps could benefit clinical management and associated economic burden of these colorectal polyps.

Use of CT colonography in conjunction with selective colonoscopy as an improved approach for investigation of polyp natural history allowed us to confirm the general conclusions from previous studies and, for the first time to our knowledge, directly show the strong relation between volumetric growth and clinical relevance. In particular, the positive growth behaviour of advanced neoplasms, which are the primary target of colorectal cancer screening, allows for their non-invasive identification among the larger pool of small polyps. Volumetric growth of colorectal

polyps seems to be a powerful biomarker, which can concentrate the lesions of clinical significance, potentially leaving behind most unimportant lesions.

The issue of whether colorectal polyps truly regress has also been debated.<sup>27,30,31</sup> In our study, 10% of small lesions seemed to completely resolve according to CT colonography, and 40% showed an overall negative growth by volume. In view of the precise localisation ability of CT colonography, the presence or absence of a polyp identified on previous examination can generally be ascertained with high confidence (figure 3). Furthermore, because of the high concordance between CT colonography findings and subsequent colonoscopy in our practice (with a PPV for 6–9 mm polyps of >90%),<sup>32</sup> we probably did not have many false-positive findings, especially because some polyps were confirmed at intermediate CT colonography surveillance (figure 3). Although a lower CT colonography sensitivity for 6–9 mm polyps has been reported in some validation studies, another important difference with our study is that all small polyps were initially detected at the index CT colonography. Therefore, we believe our results also show the most clear-cut proof to date of polyp regression.

Another finding from our study was the relative lack of progression of flat lesions compared with polypoid lesions. This finding is in agreement with our earlier report<sup>17</sup> and the National Polyp Study,<sup>33</sup> that suggested flat lesions show a less aggressive histology than do sessile and pedunculated polyps. Further study is needed in terms of the clinical



**Figure 5: Polyp volume change according to histological subgroup**  
 Bars show 95% CIs. One patient with delayed cancer diagnosis was not included in the graph, because it was not only an extreme outlier but also because tissue diagnosis was established several years after surveillance CT colonography.

significance and natural history of polyps according to morphology. The increased rate of progression of small caecal and rectal polyps relative to other colonic segments also warrants further investigation.

CT colonography is a promising technique for non-invasive in-vivo investigation of colorectal polyps, especially if supplemented by colonoscopy for polypectomy. The ability of CT colonography to precisely and retrospectively localise and measure polyps across more than one examination is a key advance over previously used surveillance modalities. The ability to obtain reliable polyp volume measurements is crucial for identification of the most biologically aggressive lesions. However, in-depth discussion of the potential clinical ramifications of our results in terms of screening and surveillance strategies is beyond the scope of this work. Nonetheless, our findings support the current CT colonography reporting and data system (C-RADS) recommendations that allow for either polypectomy referral or 3 year CT colonography surveillance for individuals with one or two small (6–9 mm) polyps identified at CT colonography,<sup>34</sup> which is our current practice. The costs and risks of an aggressive strategy of colonoscopic polypectomy for all benign polyps smaller

than 10 mm detected at CT colonography must be balanced against the presumed benefit, which might be small. Although CT surveillance of small polyps might ultimately prove to be a clinical efficacious and cost-effective strategy,<sup>21</sup> whether this screening modality will achieve widespread adoption remains to be seen.

Our study had limitations. Despite the key contribution of polyp volume assessment to our results, this measure is not yet routinely used in present clinical CT colonography practice, and the technique itself is not yet widely implemented for colorectal screening apart from in a few centres. In general, volumetric assessment at CT is a relatively straightforward measure and might prove useful for various clinical indications, such as tumour response to cancer treatment. 174 (57%) of 306 polyps in our study had unproven histology, largely because of either continued in-vivo surveillance or resolution. However, by comparing our results for advanced adenomas by histology against the expected prevalence from our cross-sectional non-surveillance CT colonography screening cohort data,<sup>20</sup> we showed that about the same percentage of adenomas with proven advanced histology (4% vs 5%) were highly concentrated within the progressing polyps in the surveillance cohort. These figures suggest that all the unresected polyps might not have important histological changes, although we cannot absolutely exclude the possibility that additional advanced lesions persist in stable or regressing unresected polyps. Lack of future growth detected on continued surveillance would further strengthen this supposition. We did not investigate diminutive lesions ( $\leq 5$  mm), in part because of the logistical difficulties in detection and correlation with colonoscopy, but also because their indolent behaviour would probably require assessment of many more lesions over a longer period of observation.<sup>9,10</sup> 5-year follow-up of patients with a negative CT colonography screening examination (ie, no polyps or only diminutive lesions)<sup>35</sup> suggested a benign course for diminutive lesions, with fewer interval cancers at follow-up compared with experience at colonoscopy screening. Finally, we had only one proven serrated polyp in this study (which showed a 33% decrease in volume per year). Therefore, we cannot provide any further insight into this alternative pathway to cancer, which might be more prolonged than the classic adenoma-carcinoma sequence. In our experience, most right-sided serrated polyps detected at CT colonography tend to be larger in size ( $\geq 10$  mm).

One patient who had delayed rectal cancer but did not return for scheduled follow-up was an outlier in terms of ultimate growth and histological changes of the polyp, and had a clinical course that we have not noted before or since. Presumably, the small polyp was benign at the initial CT colonography surveillance study, but the increase in polyp volume (59% from index) suggested that it might already have been histologically advanced

**Panel: Research in context****Systematic review**

We searched Medline for reports published between Jan 1, 1950, and Dec 31, 2012, without language restrictions on in-vivo surveillance of small colorectal polyps to study their behaviour and natural history. We identified several studies published in 1963–2010 that used either barium enemas or endoscopy as the surveillance technique, both of which have important restrictions in terms of confident localisation and accurate measurement of polyps. No previous study used CT colonography for in-vivo surveillance of small polyps.

**Interpretation**

To our knowledge, our study is the first prospective assessment of polyp natural history to use CT colonography as a non-invasive technique for in-vivo surveillance, supplemented by colonoscopy for polypectomy as indicated. The ability of CT colonography to precisely and retrospectively localise and measure polyps across several examinations is a major advance over previously used surveillance modalities. We noted that volumetric growth assessment of small (6–9 mm) colorectal polyps with CT colonography is a good biomarker for determination of clinical importance. In particular, proven advanced adenomas showed more rapid growth than non-advanced adenomas, whereas most other small polyps remained stable or regressed over time. These findings could allow for less invasive surveillance strategies of small colorectal polyps, reserving polypectomy for lesions that show substantial growth.

(eg, tubulovillous or high-grade dysplasia). The massive growth reported subsequent to the surveillance CT colonography implies malignant transformation, but the precise timing could not be ascertained.

In conclusion, longitudinal in-vivo volumetric assessment of small colorectal polyps at CT colonography seems to be a biomarker that is predictive of clinical relevance. Advanced adenomas usually manifest with measurable interval growth, whereas non-advanced adenomas tend to show intermediate behaviour, and most other benign small polyps tend to remain stable or regress over time.

**Contributors**

PJP and BDP designed the study and did the primary data analysis. PJP and DHK did the literature search. All authors were involved in clinical conduct of the trial. PJP, DHK, and JLH acquired polyp measurement data. BDP did the statistical analysis. PJP wrote the report, which was edited by all authors.

**Conflicts of interest**

PJP and DHK cofounded VirtuoCT colonography (an educational website) and have consulted for Viatronix. PJP is also a consultant for Bracco, Check-Cap, and iCAD.

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