Radiology

ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

# Natural History of Colorectal Polyps Undergoing Longitudinal in Vivo CT Colonography Surveillance

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Conflicts of interest are listed at the end of this article.

See also the editorial by Dachman in this issue.

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***Background:*** The natural history of colorectal polyps is not well characterized due to clinical standards of care and other practical constraints limiting in vivo longitudinal surveillance. Established CT colonography (CTC) clinical screening protocols allow surveillance of small (6–9 mm) polyps.

***Purpose:*** To assess the natural history of colorectal polyps followed with CTC in a clinical screening program, with histopathologic correlation for resected polyps.

***Materials and Methods:*** In this retrospective study, CTC was used to longitudinally monitor small colorectal polyps in asymptomatic adult patients from April 1, 2004, to August 31, 2020. All patients underwent at least two CTC examinations. Polyp growth patterns across multiple time points were analyzed, with histopathologic context for resected polyps. Regression analysis was performed to evaluate predictors of advanced histopathology.

***Results:*** In this study of 475 asymptomatic adult patients (mean age, 56.9 years ± 6.7 [SD]; 263 men), 639 unique polyps (mean initial diameter, 6.3 mm; volume, 50.2 $mm^3$) were followed for a mean of 5.1 years ± 2.9. Of these 639 polyps, 398 (62.3%) underwent resection and histopathologic evaluation, and 41 (6.4%) proved to be histopathologically advanced (adenocarcinoma, high-grade dysplasia, or villous content), including two cancers and 38 tubulovillous adenomas. Advanced polyps showed mean volume growth of +178% per year (752% per year for adenocarcinomas) compared with +33% per year for nonadvanced polyps and −3% per year for unresected, unretrieved, or resolved polyps ($P < .001$). In addition, 90% of histologically advanced polyps achieved a volume of 100 $mm^3$ and/or volume growth rate of 100% per year, compared with 29% of nonadvanced and 16% of unresected or resolved polyps ($P < .001$). Polyp volume-to-diameter ratio was also significantly greater for advanced polyps. For polyps observed at three or more time points, most advanced polyps demonstrated an initial slower growth interval, followed by a period of more rapid growth.

***Conclusion:*** Small colorectal polyps ultimately proving to be histopathologically advanced neoplasms demonstrated substantially faster growth and attained greater overall size compared with nonadvanced polyps.

Clinical trial registration no. NCT00204867



*Supplemental material is available for this article.*

Although advances in treatment and screening have improved outcomes, colorectal cancer (CRC) remains a leading cause of cancer death (1), with both incidence and mortality increasing among patients under 55 years of age (2). The pathway from benign precursor polyp to malignant CRC generally takes several years, allowing CRC screening programs to decrease mortality in recent decades (3,4).

Despite these advances, understanding of the natural history of colorectal polyps remains limited. With current endoscopic techniques, over half of adults with average risk undergoing CRC screening with optical colonoscopy will have polyps identified, yet the individual lifetime incidence of CRC is approximately 4% (5). Although small and diminutive colorectal polyps have a low chance of progression to cancer (6–11), the enduring practice of "universal polypectomy" at optical colonoscopy as the clinical standard of care has restricted direct observation of polyps to cross-sectional studies. While there have been some optical colonoscopy–based longitudinal studies (12–15), these have primarily eschewed true screening populations and instead have targeted cancer outcomes in patients who have previously undergone resection, offering limited data on polyp morphologic and histologic characteristics and growth patterns. Other endoscopic studies have relied

### Abbreviations:

CRC = colorectal cancer, CTC = CT colonography


### Summary

Polyp volume and volumetric growth rates were predictive of advanced histology, including cancer, with histologically advanced polyps demonstrating faster growth and attaining an overall larger size than nonadvanced polyps.


### Key Results

- Volumetric polyp growth rates predicted advanced histology, with mean growth of 178% per year for advanced polyps versus 33% per year for nonadvanced polyps ($P < .001$).
- Advanced histology better correlated with polyp volume than linear diameter, as 90% of advanced polyps attained a volume of 100 $mm^3$ and/or growth of 100% per year, compared with 29% of nonadvanced polyps ($P < .001$).
- Among newly detected polyps with a diameter of 6 mm or more, the advanced histology rate did not differ between polyps with (9%) and without (6%) identifiable diminutive (≤5 mm) precursors ($P = .47$).

on sigmoidoscopy (16–18), which offers only limited coverage of the colon, while early radiologic research relied chiefly on barium enema (19,20), which is imprecise for localization and measurement of polyps and difficult to reproduce. Additionally, many early studies offered limited follow-up intervals, at most 1–3 years (12,13,15–18,20).

Over the last 20 years, CT colonography (CTC) has emerged as a viable CRC screening modality (21,22) and is included in official screening recommendations (23,24). Relative to optical colonoscopy, CTC is less invasive and better tolerated by patients (25) and allows for precise polyp localization and measurement of polyp volume, which has been shown to be superior to linear diameter for prediction of advanced histology (26–28). Given these benefits, CTC represents a valuable tool for longitudinal polyp surveillance. A clear understanding of the relationship between polyp behavior and CRC risk is paramount, as not all colorectal polyps have malignant potential. Polyps with advanced histology (adenocarcinoma, high-grade dysplasia, and/or villous content) have a much greater chance of progressing to cancer (3,4,29). Clinicians' having the ability to predict which polyps pose a meaningful risk may spare many patients unnecessary polypectomy, along with the associated risks and costs. Our aim in this 16-year study was to assess the natural history of colorectal polyps identified and followed longitudinally with CTC, with follow-up including volumetric assessment of individual polyps over multiple time points and histopathologic correlation.

## Materials and Methods

### Study Design and Patients

This Health Insurance Portability and Accountability Act–compliant, institutional review board–approved, retrospective longitudinal cohort study was conducted at a single academic institution. An initial patient group provided written informed consent. After the low-risk nature of in vivo CTC surveillance was established (28), the need for written informed consent was waived for subsequent patients entering this clinical innovation pathway. This article was written following Strengthening the Reporting of Observational Studies in Epidemiology, or STROBE, guidelines (30).

The initial study sample included consecutive asymptomatic adult (age, 18 years or older) patients who underwent first-time screening CTC at a single academic center between April 1, 2004, and September 30, 2017. Patients in the study sample were followed through August 31, 2020. Among those with an initial positive screening, patients were excluded if they were ineligible for CTC polyp surveillance (ie, if they had any polyp with diameter ≥ 10 mm or more than two polyps with diameter ≥ 6 mm) or elected against CTC polyp surveillance. Among those with an initial negative screening, patients were excluded if they did not return for subsequent 5-year CTC screening or if subsequent screening was negative. A flow diagram of the study group is provided in Figure 1.

Patients with a negative CTC screening were offered 5-year follow-up screening CTC. Patients with a positive CTC screening with only one or two small (6–9 mm) polyps were offered optical colonoscopy with polypectomy or 3-year polyp surveillance CTC (31). Patients with a positive CTC screening with any polyp with a diameter of 10 mm or more, or more than two polyps with a diameter of 6 mm or more, were offered optical colonoscopy with polypectomy and were excluded from participating in CTC surveillance.

Findings from a subset of patients included in this study were previously reported (11) in a study characterizing polyp growth (eg, growth, stability, and regression) and examining adenoma and advanced adenoma rates among small polyps undergoing CTC surveillance versus those that are immediately resected. While drawing from the same larger patient data set, the present study leverages a larger study group that includes patients with diminutive (≤5 mm) polyps to offer a novel quantitative analysis of polyp volume and growth, including comparison among histologic groups and subgroup analysis of polyps evaluated in three or more CTC examinations.

### Imaging Procedure and Evaluation

The CTC technique used in this study has been previously described (32). Once acquired, images from CTC examinations were interpreted using dedicated standalone software with primary three-dimensional polyp detection and two-dimensional confirmation (33). Examples of CTC surveillance of two different polyps from a single patient are shown in Figure 2. Polyps were prospectively identified during clinical CTC screening by an experienced abdominal radiologist and were recorded in a database. Polyp linear diameter, segmental location within the colon, and morphologic characteristics were prospectively recorded. Of note, diminutive polyps were not routinely reported at screening CTC. Consequently, for polyps meeting inclusion criteria, any prior negative CTC examinations were reviewed to determine if polyps were previously present as diminutive polyps.

Polyp volume was measured using a semiautomated segmentation tool that automatically detects the margins of the polyp but allows for manual adjustment to ensure accurate

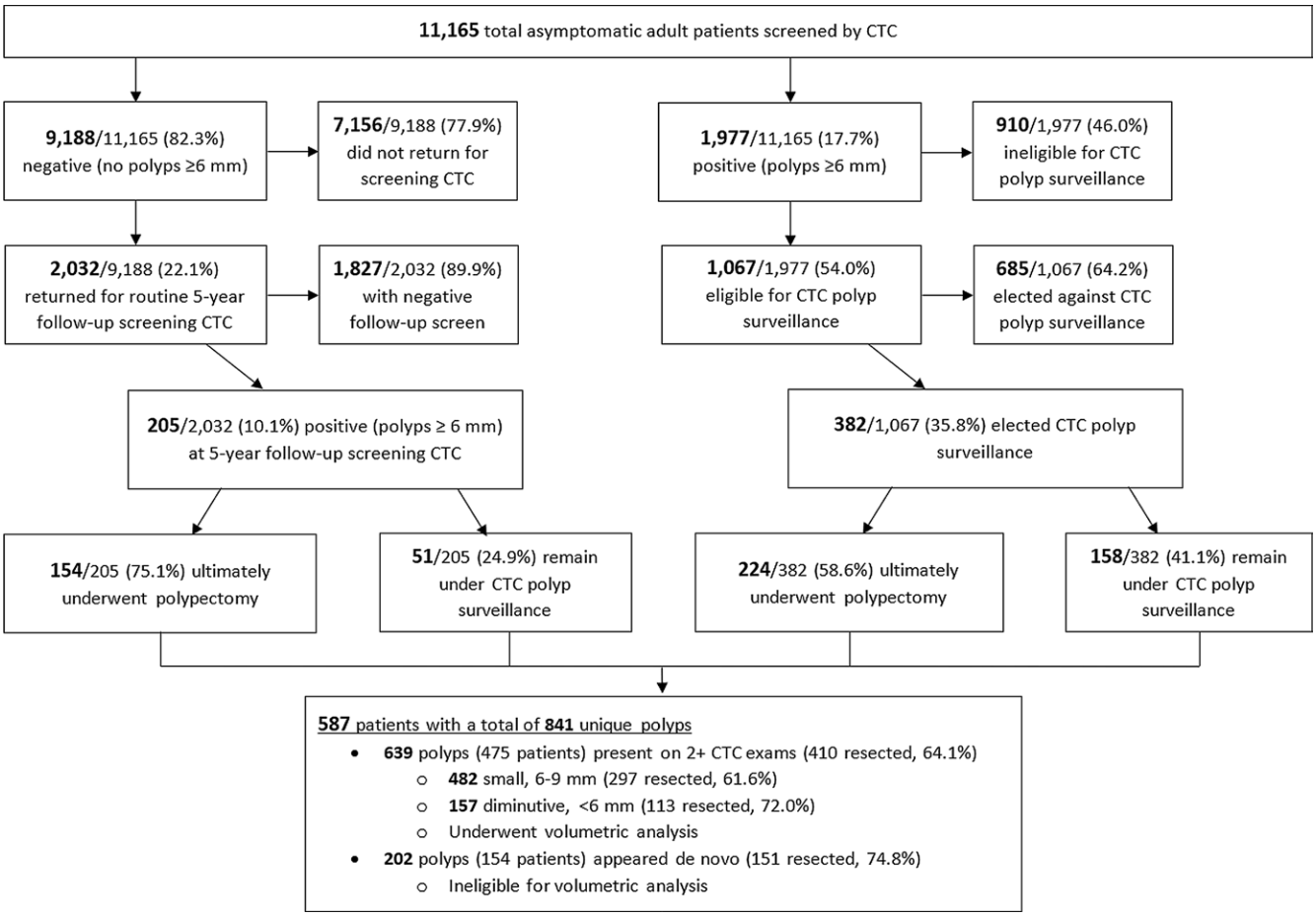


**Figure 1:** Flow diagram of study group. CTC = CT colonography.

volume measurement (26–28). For pedunculated polyps, the pedicle was not included in the volume calculation; this correction was made manually where needed. Reviewers measuring polyp volume (B.D.P., abdominal fellowship-trained attending radiologist with 5 years of experience; D.H.K., abdominal fellowship-trained attending radiologist with 24 years of experience; and P.J.P., attending abdominal radiologist with 24 years of experience) were blinded to any resection or histopathologic data. Polyps resected during the study underwent histopathologic evaluation as part of standard clinical care by gastrointestinal pathologists blinded to polyp growth data at the time of evaluation; histopathologic diagnoses were gathered from the electronic medical record.

### Definitions, Terminology, and Clinical Screening Protocol

Polyps with a diameter of 10 mm or more were defined as large; 6–9 mm, as small; and 5 mm or less, as diminutive. A screening CTC examination where at least one large or small polyp was detected was considered positive, while negative screening CTC examinations were those that detected no large or small polyps, although diminutive polyps could be present. Polyps were defined as histologically advanced if they contained villous components (eg, tubulovillous adenoma), high-grade dysplasia, or adenocarcinoma. Polyps were defined as resolved if they were undetectable at a follow-up examination.

### Statistical Analysis

Statistical analyses were performed by two authors (B.D.P. and M.A.N.). Study data were collected and collated in Microsoft Excel. Single-factor analysis of variance and *t* tests were used to assess differences in continuous variables, and $\chi^2$ analysis was used to assess differences in categorical variables. $P < .05$ was used to define a statistically significant difference. Changes in polyp linear diameter and volume, as well as polyp volume-to-diameter ratio, were calculated for all polyps evaluated at two or more time points. For polyps evaluated at three or more time points, separate interval growth rates and overall growth rates were calculated. Basic descriptive and inferential statistics were calculated using SPSS Statistics (IBM). Ordinal regression was used to assess whether patient demographic or CTC factors in isolation or collectively were predictive of final polyp histology and was performed using *R* (version 4.1.2; R Foundation for Statistical Computing).

## Results

### Patient Characteristics

In total, 11 165 asymptomatic adult patients were initially screened with CTC, of whom 1977 (17.7%) had an initial positive screening CTC examination (Fig 1). Of these 1977 patients, 910 (46.0%) were not eligible for CTC polyp surveillance

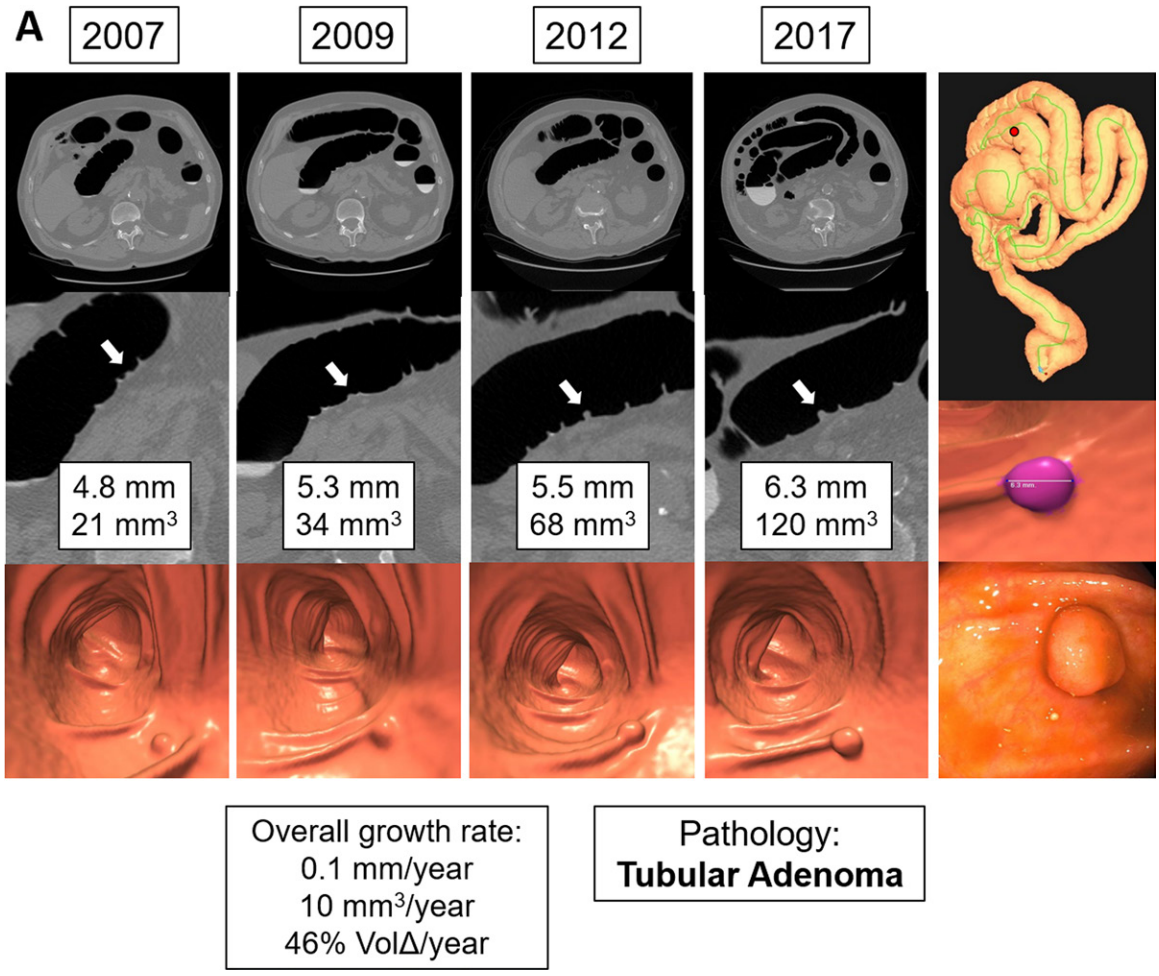


**Figure 2:** In vivo observation of two colorectal polyps over a decade in a man who was aged 71 years at initial CT colonography (CTC) in 2007. **(A)** Two-dimensional (top) and three-dimensional (bottom) CTC images show a subcentimeter sessile polyp (arrow) in the redundant right colon (red dot on colon map) monitored over four examinations. Images on the far right are the colon map (top), a three-dimensional CTC image showing semiautomated segmentation at CTC in 2017 (middle), and an endoscopic image from the time of resection in 2017 (bottom). The polyp was diminutive based on diameter until the final CTC examination, when it surpassed 6 mm. However, note the progressive increase in polyp volume, which increased sixfold despite only a minimal linear size increase. At endoscopic resection the polyp proved to be a tubular adenoma without high-grade dysplasia. *(Fig 2 continues).*

because they had a large polyp or more than two small polyps, leaving 1067 (54.0%) patients who were eligible for CTC polyp surveillance. Of these 1067 patients, 685 (64.2%) elected against CTC polyp surveillance and were excluded, while 382 (35.8%) elected CTC polyp surveillance, with 224 of 382 (58.6%) ultimately undergoing polypectomy and 158 of 382 (41.1%) remaining under CTC polyp surveillance. Of the 9188 of 11 165 (82.3%) patients with an initial negative screening CTC examination, 7156 (77.9%) did not return for subsequent 5-year CTC screening and were excluded, while 2032 (22.1%) returned for routine follow-up CTC screening (mean interval, 5.9 years ± 1.5 [SD]). Of the 2032 patients who returned for 5-year follow-up screening, 1827 (89.9%) had a negative screening and 205 (10.1%) had a positive screening, with 154 of 205 (75.1%) ultimately undergoing polypectomy and 51 of 205 (24.9%) remaining under CTC polyp surveillance.

In total, 382 patients began CTC polyp surveillance at the initial screening, and 205 patients began CTC polyp surveillance at a positive screening examination after an initial negative screening examination. These 587 patients had a total of 841 unique polyps; however, 202 polyps in 154 patients were excluded from volumetric analysis as they arose de novo during the study and were evaluated at only one time point. Thus, a total of 475 patients (mean age at initial CTC examination, 56.9 years ± 6.7; 263 men) had 639 unique polyps that were evaluated in at least two CTC examinations and underwent volumetric analysis. Patient demographic characteristics are summarized in Table 1.

## Volumetric Growth Analysis

Among the 639 unique small and diminutive colorectal polyps identified at two or more CTC examinations during the study period, the mean surveillance interval was 5.1 years ± 2.9 per polyp (range, 0.7–14.9 years), providing 3239.2 total polyp-years of in vivo surveillance. Polyp baseline characteristics, including segmental location and initial morphologic characteristics, are summarized in Table 2. Mean polyp linear size and volume at initial CTC were 6.3 mm ± 1.7 (range, 2–9 mm) and

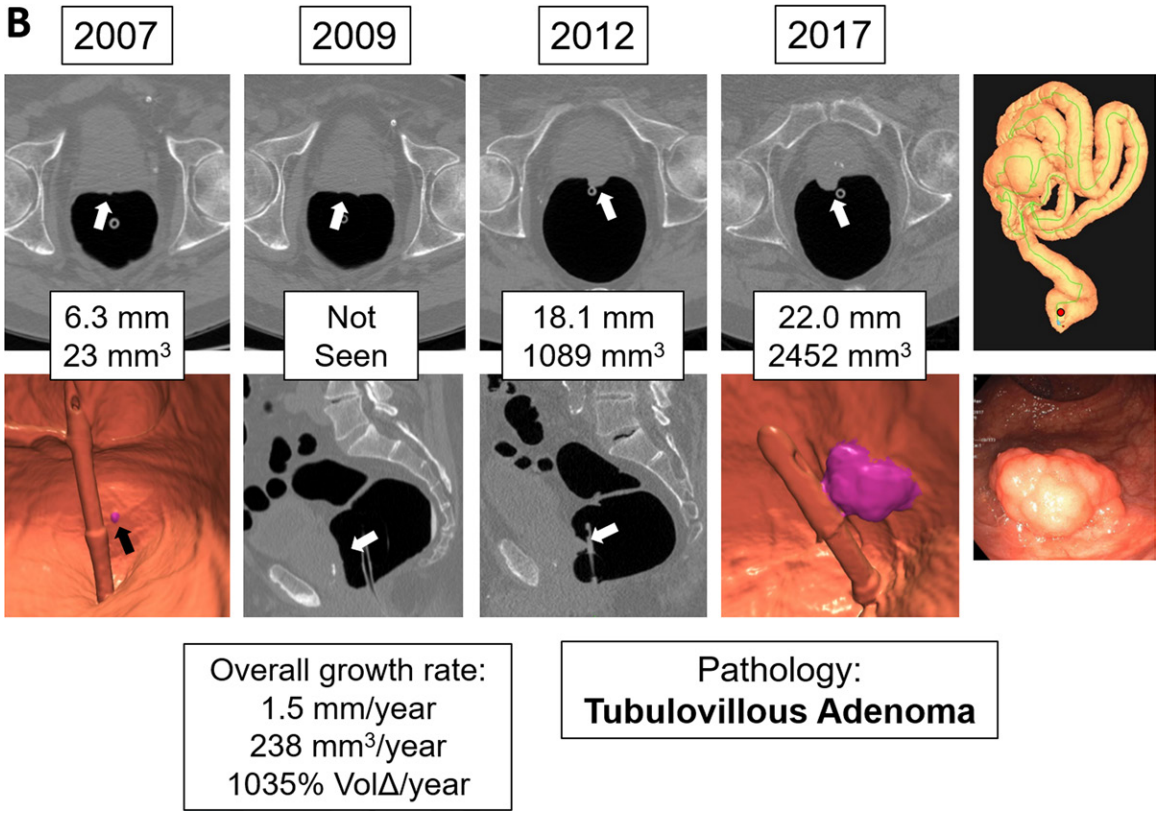


**Figure 2 *(continued)*:** **(B)** Two-dimensional and three-dimensional CTC images show a polyp (arrow; red dot on colon map) monitored over four examinations. Images on the far right are the colon map (top) and an endoscopic image from the time of resection in 2017 (bottom). The polyp was diminutive at the index CTC examination in 2007. In 2009, the balloon from the rectal catheter effaced and obscured the polyp. In 2012, the then large polyp was mistaken for stool at prospective interpretation and therefore not resected. By 2017, further polyp growth suggested a true lesion, confirmed at optical colonoscopy; the lesion proved to be a tubulovillous adenoma. Note the marked volumetric growth after 2009. Despite the delay in polypectomy, cancer prevention was still effective. VolΔ = volume change.

**Table 1: Patient Demographic Characteristics**

| Characteristic | All Screened Patients (*n* = 11 165) | Study Group* (*n* = 587) | Volumetric Analysis Subgroup (*n* = 475) |
|---|---|---|---|
| Age (y) | | | |
| Mean ± SD | 57.5 ± 8.3 | 56.4 ± 6.6 | 56.9 ± 6.7 |
| Median | 56 | 58 | 56 |
| Range | 23–96 | 34–86 | 34–86 |
| Sex | | | |
| Male | 5019 (45) | 323 (55) | 263 (55) |
| Female | 6146 (55) | 264 (45) | 212 (45) |

Note.—Except where noted, data are numbers of patients, with percentages in parentheses.

* Study group includes patients with initial positive screen who were eligible for and elected CT colonography surveillance and patients with initial negative screen and subsequent positive screen at CT colonography.

50.2 mm$^3$ ± 47.3 (range, 2.0–366.0 mm$^3$), respectively. Of the 639 polyps undergoing volumetric growth analysis, 410 (64.2%) were ultimately resected and underwent histopathologic evaluation (although 12 polyps were not retrieved), while 179 (28.0%) remained unresected at the conclusion of the study period, and 50 (7.8%) resolved. Polyp outcome characteristics for polyps undergoing resection (*n* = 410), including final morphologic and histopathologic characteristics, are summarized in Table 3. Mean surveillance interval for resected polyps was 5.1 years ± 2.8 and did not differ significantly from that of unresected polyps (5.1 years ± 0.1; *P* = .97).

Of all 639 polyps identified at two or more CTC examinations, 41 (6.4%) were histologically advanced, with two (0.3%) developing into adenocarcinoma. High-grade dysplasia was present in an additional two (0.3%) polyps (one tubulovillous adenoma and one tubular adenoma). The rate of histologically advanced polyps among those resected and retrieved was 10.3% (41 of 398). Mean initial and final diameter and volume measurements for the major histopathologic types are shown in Table 4, as well as changes in size over time. Mean annualized polyp volume change was 751.6% ± 537.7 for adenocarcinomas, 150.6% ± 195.9 for tubulovillous adenomas, 39.8% ± 76.4 for tubular adenomas, 14.5% ± 23.3 for sessile serrated polyps, and 10.5% ± 24.7 for hyperplastic polyps (*P* < .001) (Fig 3).

Histologically advanced polyps had similar initial mean linear diameter (6.2 mm ± 1.8) compared with nonadvanced polyps (6.3 mm ± 1.8; *P* = .74), but differed significantly in initial volume (advanced, 64.7 mm$^3$ ± 68.4; nonadvanced, 47.4 mm$^3$ ± 45.3; *P* = .03). Annualized volume change differed significantly

**Table 2: Baseline Characteristics of Polyps Evaluated at Two or More CTC Examinations**

| Characteristic | No. of Polyps (*n* = 639) |
|---|---|
| Colorectal segment location | |
| Cecum | 62 (10) |
| Ascending | 147 (23) |
| Transverse | 113 (18) |
| Descending | 52 (8) |
| Sigmoid | 168 (25) |
| Rectum | 107 (17) |
| Morphologic characteristics | |
| Sessile | 355 (56) |
| Flat | 105 (16) |
| Pedunculated | 22 (3) |
| Diminutive (≤5 mm) | 157 (25) |

Note.—Data in parentheses are percentages. CTC = CT colonography.

**Table 3: Outcome Characteristics of Resected Polyps Evaluated at Two or More CTC Examinations**

| Characteristic | No. of Polyps (*n* = 410) |
|---|---|
| Morphologic characteristics at final CTC examination | |
| Sessile | 275 (67) |
| Flat | 83 (20) |
| Pedunculated | 23 (6) |
| Diminutive (≤5 mm) | 29 (7) |
| Histopathology | |
| Adenocarcinoma | 2 (<1) |
| Tubulovillous adenoma* | 38 (9) |
| Tubular adenoma* | 234 (57) |
| Sessile serrated polyp | 64 (16) |
| Traditional serrated adenoma | 2 (<1) |
| Hyperplastic | 48 (12) |
| Other benign nonneoplastic | 10 (2) |
| Not retrieved | 12 (3) |

Note.—Data in parentheses are percentages. CTC = CT colonography.

* High-grade dysplasia present in one tubulovillous adenoma and one tubular adenoma.

between advanced polyps (+76.0 $mm^3$ ± 154.8 per year; +178% ± 247 per year) and nonadvanced polyps (+8.8 $mm^3$ ± 31.4 per year; +33% ± 69 per year; $P < .001$), while unresected, unretrieved, or resolved polyps demonstrated a mean decrease in annualized volume (–5.0 $mm^3$ ± 17.0 per year; –3% ± 34 per year). When polyp linear diameter and volume data were combined into a volume-to-diameter ratio, significant differences between histopathologic groups were observed for the initial and final CTC examinations, as well as for the change in volume-to-diameter ratio over time (Table 4). Ninety percent (37 of 41) of histologically advanced polyps attained a volume of

**Table 4: Change in Polyp Size according to Histopathologic Group for Polyps Evaluated at Two or More CTC Examinations (*n* = 639)**

| Measure and Histopathologic Group | Mean Diameter (mm) | Mean Volume ($mm^3$) | Volume-to-Diameter Ratio |
|---|---|---|---|
| Initial value | | | |
| Adenocarcinoma | 6.5 ± 0.7 | 110.0 ± 49.5 | 17.4 |
| TVA | 6.2 ± 1.8 | 63.7 ± 69.3 | 9.0 |
| TA | 6.0 ± 1.7 | 48.6 ± 46.4 | 7.3 |
| SSP | 7.2 ± 1.8 | 46.1 ± 36.0 | 6.1 |
| Hyperplastic | 6.4 ± 1.6 | 37.5 ± 32.5 | 5.5 |
| Unresected | 6.4 ± 1.5 | 49.8 ± 43.1 | 7.2 |
| Resolved | 6.6 ± 1.3 | 56.3 ± 41.7 | 8.2 |
| Final value | | | |
| Adenocarcinoma | 27.0 ± 11.3 | 3231.5 ± 2216.8 | 112.3 |
| TVA | 10.4 ± 4.1 | 301.0 ± 409.2 | 24.5 |
| TA | 7.5 ± 2.2 | 93.6 ± 105.3 | 11.1 |
| SSP | 9.0 ± 2.6 | 62.0 ± 41.7 | 6.7 |
| Hyperplastic | 7.1 ± 1.7 | 40.4 ± 30.8 | 5.6 |
| Unresected | 6.6 ± 1.5 | 50.6 ± 50.2 | 7.1 |
| Resolved | NA | NA | NA |
| Change in value | | | |
| Adenocarcinoma | 20.5 ± 10.6 | 3121.5 ± 2266.3 | 94.9 |
| TVA | 4.2 ± 4.0 | 237.3 ± 416.9 | 15.5 |
| TA | 1.6 ± 2.4 | 45.1 ± 89.9 | 3.8 |
| SSP | 1.8 ± 2.2 | 16.0 ± 36.4 | 0.6 |
| Hyperplastic | 0.6 ± 1.7 | 2.9 ± 17.0 | 0.1 |
| Unresected | 0.2 ± 1.7 | 0.8 ± 43.3 | –0.1 |
| Resolved | NA | NA | NA |

Note.—*P* values for the comparisons of initial values, final values, and change in values for mean diameter, mean volume, and volume-to-diameter ratio among the histopathologic groups were all <.001, except for the *P* value for the comparison of initial mean volume among the histopathologic groups, which was .03. Comparison included only polyps that were resected and sent for histopathologic examination (ie, unresected, unretrieved, and resolved polyps were not included). CTC = CT colonography, NA = not applicable, SSP = sessile serrated polyp, TA = tubular adenoma, TVA = tubulovillous adenoma.

100 $mm^3$ and/or annualized growth rate of 100% per year (annual volume doubling) at any point in the study, compared with only 29% (102 of 357) of nonadvanced polyps and 16% (39 of 241) of unresected, unretrieved, or resolved polyps ($P < .001$) (Fig 4).

There were 186 polyps (103 resected with histopathologic results and 83 unresected, unretrieved, or resolved by the end of the study period) that underwent CTC evaluation at three or more time points, with comparison between the first and second growth intervals summarized in Table 5. Notably, most tubulovillous adenomas and many tubular adenomas demonstrated substantially faster growth during the second interval compared with the first, while growth curves for sessile serrated and hyperplastic polyps remained comparatively flat (Fig 5).

Ordinal regression confirmed that initial and final volume-to-diameter ratios were predictive of polyp histology and, further, that no other CTC or demographic factors (polyp segmental

location, polyp morphologic characteristics, or patient age or sex) had a significant effect on predictive accuracy after accounting for volume-to-diameter ratio (see Appendix S1).

### Comparison of Previously Diminutive and De Novo Polyps

Over the course of the study period, a total of 359 polyps with a diameter of 6 mm or more were newly detected at a follow-up CTC examination (ie, an examination after the patient's initial screening CTC), including 87 polyps in the 382 patients who began CTC polyp surveillance at the initial screening and 272 polyps in the 205 patients with a positive screening after an initial negative screening. Of these 359 polyps, 157 (43.7%) in 134 patients were retrospectively found as diminutive polyps on images from the prior CTC examination, and 202 (52.3%) in 154 patients were determined to have arisen de novo. At detection, the mean linear diameter was 6.6 mm ± 2.3 for previously diminutive polyps versus 8.9 mm ± 5.2 for de novo polyps ($P < .001$). Resection rates were 72.0% (113 of 157; two were not retrieved) for previously diminutive polyps and 74.8% (151 of 202) for de novo polyps ($P = .63$). Among retrieved polyps, the adenoma rate was 86.4% (96 of 111) for previously diminutive polyps and 77.5% (117 of 151; $P = .08$) for de novo polyps, with corresponding advanced histology rates of 9% (10 of 111) for previously diminutive polyps and 6% (nine of 151; $P = .47$) for de novo polyps. There were no polyps harboring adenocarcinoma or high-grade dysplasia in either group.

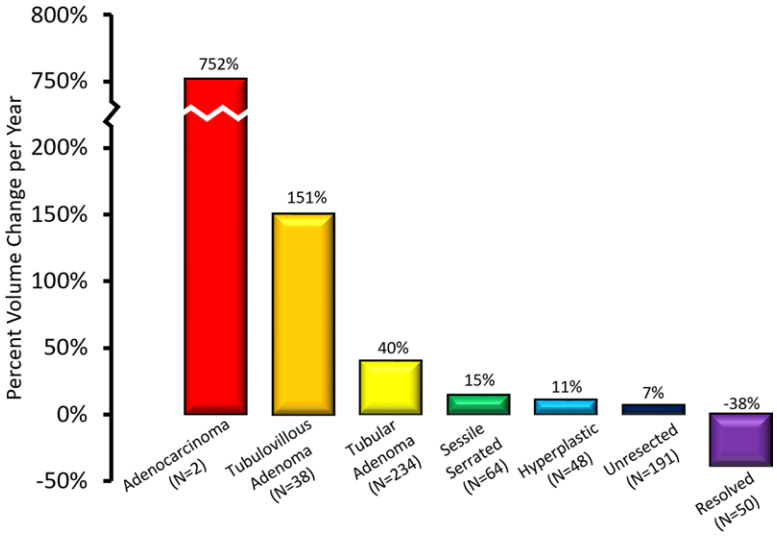


**Figure 3:** Bar graph shows mean polyp volume change per year expressed as a percentage of initial polyp volume. "Unresected" includes unresected ($n = 179$) and unretrieved ($n = 12$) polyps. A scale break is used to accommodate the growth of adenocarcinomas.

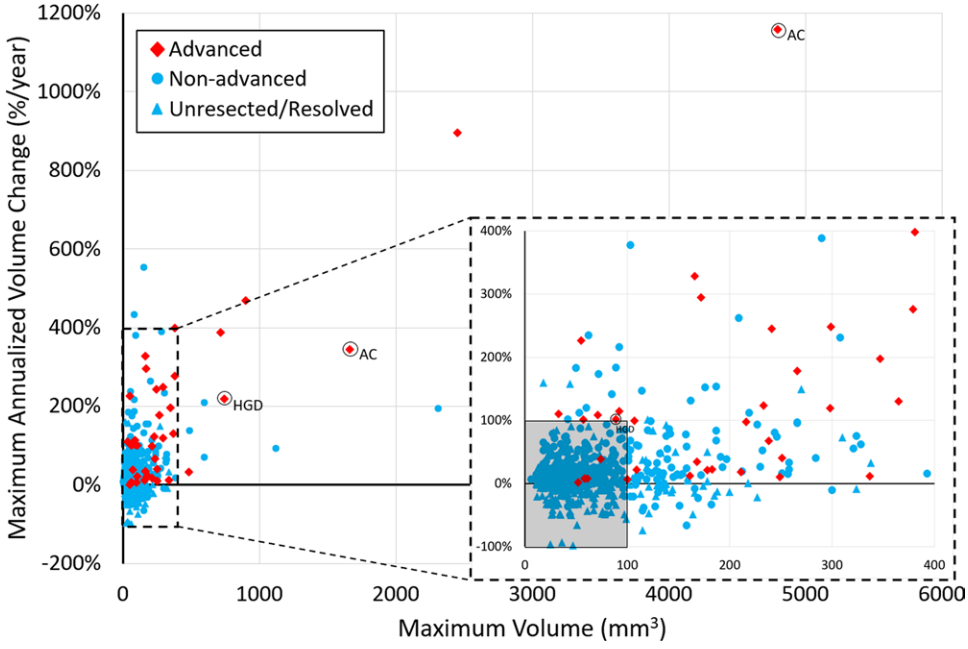


**Figure 4:** Scatterplot of per-polyp volume change versus maximum volume. The data points within the lower range of maximum volume (0–400 $mm^3$) are expanded in the inset (right). Ninety percent of histologically advanced polyps, including all adenocarcinomas (AC) and polyps harboring high-grade dysplasia (HGD), achieved a volume of 100 $mm^3$ and/or volume growth rate of 100% per year (outside the gray box in the expanded view) at any time point in the study. Only 29% of nonadvanced and 16% of unresected, unretrieved, or resolved polyps reached this same threshold.

## Discussion

The natural history of colorectal polyps remains poorly characterized, with limited knowledge regarding their progression and development. To date, large studies of colorectal polyp natural history have not yet been conducted, and our study aimed to evaluate the natural progression of 639 colorectal polyps in 475 patients using CT colonography in a clinical screening program, correlating findings with histopathologic analysis of resected polyps. The results demonstrated that the size and growth rate of polyps were predictive of advanced histology, and histologically advanced polyps exhibited faster growth and reached larger overall sizes than nonadvanced polyps. Advanced polyps showed mean volume growth of +178% per year (752% per year for adenocarcinomas) compared with +33% per year for nonadvanced polyps and −3% per year for unresected, unretrieved, or resolved polyps ($P < .001$).

This study affirms that polyp volume represents a more relevant measure of polyp size than linear diameter, as suggested by prior studies (27,28). All major histologic groups had similar initial subcentimeter mean linear diameters within a narrow 1-mm range; however, histologically advanced polyps had initial volumes and volume-to-diameter ratios significantly

**Table 5: Mean Growth Rates in the First and Second Intervals for Polyps Evaluated at Three or More Time Points**

| Histopathologic Group | No. of Polyps | Interval 1 | | Interval 2 | | *P* Value* |
|---|---|---|---|---|---|---|
| | | Mean Growth Rate ($mm^3$/y) | Mean Interval Length (y) | Mean Growth Rate ($mm^3$/y) | Mean Interval Length (y) | |
| Known histopathology | 103 | | | | | |
| Tubulovillous adenoma | 8 | 12.7 | 2.5 | 45.7 | 4.1 | .48 |
| Tubular adenoma | 68 | 0.3 | 2.9 | 17.9 | 3.6 | <.001 |
| Sessile serrated polyp | 16 | 3.1 | 3.1 | 0.1 | 3.6 | .36 |
| Hyperplastic | 11 | −1.5 | 3.4 | 0.5 | 3.7 | .24 |
| Unknown histopathology | 83 | | | | | |
| Unresected or not retrieved | 70 | −1.1 | 2.8 | −0.9 | 4.3 | .93 |
| Resolved | 13 | −18.5 | 2.9 | −8.3 | 4.0 | .37 |

* *P* values are for comparison of growth rates between intervals 1 and 2.

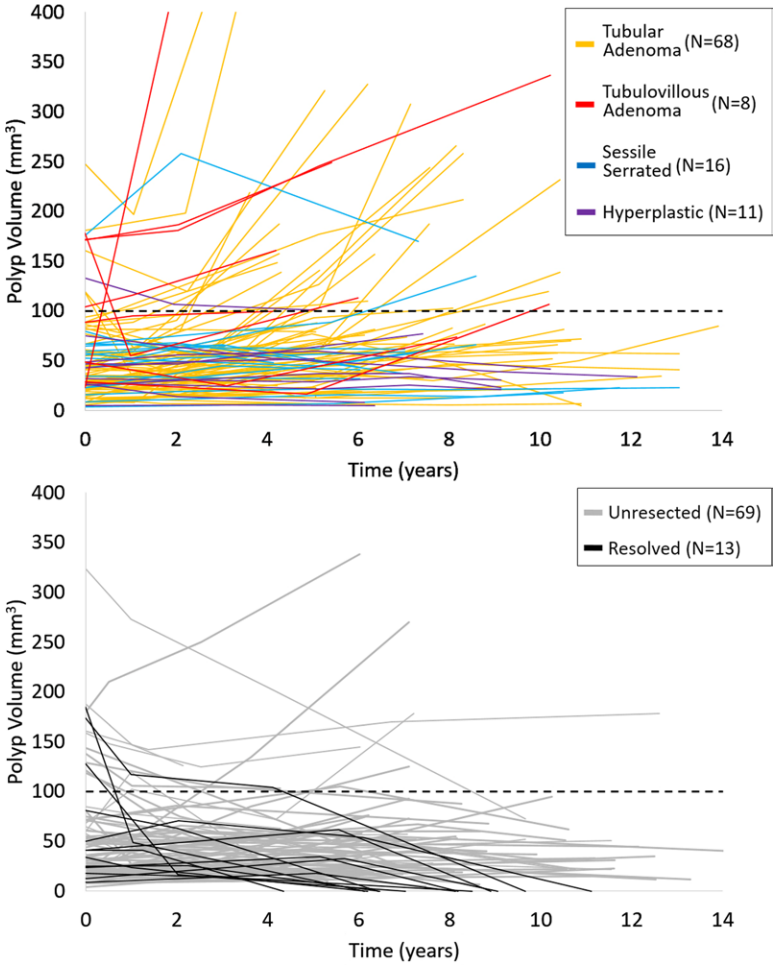


**Figure 5:** Graphs of polyp growth trajectories (volume over time) for polyps evaluated at three or more time points. While overall most polyps remained less than 100 $mm^3$ in total volume (dashed line) and had relatively flat growth trajectories, most tubulovillous adenomas and some tubular adenomas experienced a marked increase in growth rate after an initial period of relatively slow growth (upper panel). Unresected (including unretrieved) and resolved polyps (lower panel) demonstrated overall slower growth trajectories. Of note, the few unresected polyps with more rapid growth were lost to follow-up or the patient deferred resection.

greater than those of nonadvanced polyps. These volume differences were further amplified at follow-up CTC, with upwards of fivefold volume increases for advanced polyps (up to 30-fold for cancers), while nonadvanced polyps had on average less than twofold volume increases. Our study further confirms prior research showing that small and diminutive polyps represent minimal risk to patients (6,8,10,11,28). Of polyps resected and sent for histopathologic analysis following CTC surveillance, only 10% (41 of 398) were histologically advanced, representing only 6% (41 of 639) of all polyps undergoing CTC surveillance; the actual fraction of advanced polyps is likely between these figures, as advanced polyps were more likely to grow and be resected. Only two of 639 (0.3%) polyps undergoing CTC surveillance developed into cancer, with an additional two (0.3%) harboring high-grade dysplasia. Presumably, the removal of advanced adenomas prevented the development of additional cancers. Among small polyps, no significant difference in adenoma or advanced histology rate was observed between those with diminutive precursors retrospectively identified on images from prior examinations and those that appeared to be de novo, suggesting that there may be little difference between a diminutive polyp and no polyp.

Study findings suggest that rapid volumetric growth is suspicious for progression to advanced neoplasia, including cancer. The few polyps that eventually proved histologically advanced demonstrated significantly faster growth than those with nonadvanced histology and attained a larger absolute size. On average, cancers and tubulovillous adenomas more than doubled in volume annually (ie, more than 100% per year increase), while nonadvanced polyps (tubular adenomas, sessile serrated polyps, and hyperplastic polyps) experienced less than 50% increases in volume. Furthermore,

90% (37 of 41) of advanced polyps achieved annual volume doubling and/or attained an absolute volume of 100 $mm^3$ or greater compared with less than 25% of nonadvanced and unresected or resolved polyps. Such thresholds—based on measures other than linear diameter alone—may prove useful in identifying polyps with a greater chance of advanced histopathology while allowing polyps with more benign behavior to be followed up with continued surveillance. Importantly, advanced statistical modeling did not identify patient age, patient sex, polyp segmental location, or subjectively assigned polyp morphologic characteristics as predictive of histology.

This study represents, to our knowledge, the first assessment of individual polyp growth rates across three or more time points. Among such polyps, the most histologically advanced polyps, as well as a substantial minority of nonadvanced tubular adenomas, underwent a relatively slow growth phase followed by a comparatively fast growth phase, a phenomenon previously observed only in animal models (34).

Our study has several limitations. First, because of the clinical standards of care applicable to CRC screening programs, there was an unavoidable bias in patient selection for this study. For example, patients with any polyp with a diameter of 10 mm or more or with more than two polyps with a diameter of 6 mm or more at initial screening were not eligible for CTC surveillance and were not included. Further, a number of patients eligible for CTC surveillance underwent an immediate polypectomy, either as a personal choice or at the direction of their referring physician, and were not included. Second, of all polyps in the study sample, approximately one-third remained unresected at the conclusion of the study, precluding histopathologic evaluation; most of these polyps remained under CTC surveillance because of their indolent growth behavior. Finally, diminutive polyps (≤5 mm) were not routinely reported in our CTC screening program because of their clinical irrelevance and because they approached the practical limits of CT resolution. Consequently, not all diminutive polyps harbored by patients in our study group may have been identified for inclusion.

In conclusion, polyp volume represents a more meaningful measure of polyp size than linear diameter, and in our study volumetric growth rate correlated with advanced histopathology. Further, small and diminutive polyps presented a low risk to patients and may be safely monitored, eliminating the costs and risks associated with unnecessary polypectomy. Finally, colorectal polyps that proved histopathologically advanced demonstrated substantially faster growth and attained greater overall size than nonadvanced polyps, which may be of value in clinical decision-making.

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**Data sharing:** Data generated or analyzed during the study are available from the corresponding author by request.

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