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# Prior Colorectal Neoplasia Is Associated With Increased Risk of Ileoanal Pouch Neoplasia in Patients With Inflammatory Bowel Disease

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**BACKGROUND & AIMS:** Although restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) substantially reduces the risk of colorectal cancer in patients with inflammatory bowel disease (IBD), subsequent pouch neoplasia can develop. There are few data on the incidence of and risk factors for neoplasia, so there is no consensus on the need for pouch surveillance. We aimed to determine the cumulative incidence of pouch neoplasia in patients with IBD and identify risk factors for developing pouch neoplasia. **METHODS:** We searched the Dutch Pathology Registry (PALGA) to identify all patients with IBD and IPAA in The Netherlands from January 1991 to May 2012. We calculated the cumulative incidence of pouch neoplasia and performed a case-control study to identify risk factors. Demographic and clinical variables were analyzed with univariable and multivariable Cox regression analyses. **RESULTS:** We identified 1200 patients with IBD and IPAA; 25 (1.83%) developed pouch neoplasia, including 16 adenocarcinomas. Respective cumulative incidences at 5, 10, 15, and 20 years were 1.0%, 2.0%, 3.7%, and 6.9% for pouch neoplasia and 0.6%, 1.4%, 2.1%, and 3.3% for pouch carcinoma. A history of colorectal neoplasia was the only risk factor associated with pouch neoplasia. Hazard ratios were 3.76 (95% confidence interval, 1.39–10.19) for prior dysplasia and 24.69 (95% confidence interval, 9.61–63.42) for prior carcinoma. **CONCLUSIONS:** The incidence of pouch neoplasia in patients with IBD without a history of colorectal neoplasia is relatively low. Prior dysplasia or colon cancer is associated with an approximate 4- and 25-fold increase in risk, respectively, of developing pouch neoplasia.

*Keywords:* PALGA; Ulcerative Colitis; Ileal Pouch-Anal Anastomosis; Adenocarcinoma.

Despite medical progress, approximately 30% of patients with ulcerative colitis eventually require a colectomy because of refractory disease, intolerance to medication, or complications of the disease.[1] In those cases, restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is the preferred surgical treatment to restore intestinal continuity and fecal continence. Dysplasia or cancer of the colon is one of the UC-related complications that may necessitate a colectomy. It is well established that the risk of colorectal cancer (CRC) is increased in patients with inflammatory bowel disease (IBD).[2] The risk of CRC is especially increased in cases of multifocal low-grade dysplasia (LGD) or high-grade dysplasia (HGD), and these are generally well-accepted indications for proctocolectomy. Restorative proctocolectomy with IPAA substantially reduces the risk of developing CRC; however, malignant degeneration of the pouch may still arise.

The incidence and prevalence of pouch neoplasia in patients with IBD are probably low. According to the latest review, only 42 pouch adenocarcinomas have been described in the literature.[1] A previous study reported a cumulative incidence of pouch neoplasia of 1.9% after 15 years and 5.1% after 25 years.[3] However, these data were collected in a single tertiary pouch referral center and may not be representative of the general IBD population with IPAA. Furthermore, the relatively low incidence makes it difficult to assess risk factors for development of pouch neoplasia.

Given the paucity of data regarding the risk of pouch neoplasia, there is no consensus on the necessity and potential interval of pouch surveillance. The aim of our study was to establish the cumulative incidence of pouch neoplasia in a nationwide cohort of patients with IBD and IPAA.

***Abbreviations used in this paper:*** **ATZ, anal transitional zone; CRC, colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IND, indefinite for dysplasia; IPAA, ileal pouch–anal anastomosis; LGD, low-grade dysplasia.**

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Furthermore, we aimed to identify risk factors for pouch neoplasia to contribute to a recommendation for a more targeted pouch surveillance program in patients with IBD.

# Patients and Methods

## Design

We studied the cumulative incidence of pouch neoplasia using a nationwide established Dutch cohort of patients with IBD. Risk factors for developing pouch neoplasia were identified by adopting a case-control study approach.

## Patient Identification

PALGA, the nationwide network and registry of histopathology and cytopathology, was searched, with approval of their Privacy Commission and Scientific Council, to identify all patients with IBD and IPAA in The Netherlands. PALGA contains pathology reports generated in The Netherlands since 1971 and has complete national coverage since 1991 encompassing all pathology laboratories from all academic and nonacademic hospitals in The Netherlands.[4] A search of PALGA was performed with the following search terms: "ulcerative colitis," "Crohn's disease," "indeterminate colitis," and "chronic idiopathic inflammatory bowel disease" combined with "pouch" or a (Dutch) synonym. The search was performed from January 1991 to May 2012. Cases were further confirmed or excluded after careful evaluation of the individual pathology reports.

## Verification Cohort

To verify the coverage of our PALGA search, we compiled a verification cohort. This cohort consisted of patients with IBD and IPAA from the Radboud University Nijmegen Medical Centre who had at least one outpatient medical contact at the Department of Gastroenterology and Hepatology between 2004 and May 2012. Next, we verified whether pathology reports from examination of gastrointestinal tissue were available in the medical records. Using these pathology reports, we verified whether patients were likewise identified through the PALGA search.

## Inclusion and Exclusion Criteria

Patients with IPAA were identified with PALGA, and those with a diagnosis of ulcerative colitis, indeterminate colitis, or Crohn's disease based on the colonic resection specimen were included. The following exclusion criteria were used: familial adenomatous polyposis, absence of a diagnosis of IBD or IPAA, Kock pouch, ileorectal anastomosis, ileoneorectal anastomosis, or missing follow-up. Furthermore, patients were excluded if the colectomy specimen was not available or if no distinction could be made for the type of pouch or anastomosis despite careful evaluation of the pathology reports. Of note, none of the exclusion groups contained patients with IPAA and pouch neoplasia.

Patients who developed pouch neoplasia, including pouch dysplasia and pouch adenocarcinoma, were identified as cases. Pouch malignancies other than adenocarcinomas were excluded from the case group. Controls for the case-control study were randomly selected (using a 1:3 ratio) from the entire population with IBD and IPAA (identified with PALGA) at the 6 centers that provided the majority (69%) of cases. Because the control group in a case-control study should reflect the entire source population that gave rise to the cases, we did not exclude patients with pouch neoplasia from the control group.[5]

## Data Collection

One author (L.A.A.P.D.) extracted demographic and clinical variables from PALGA and the medical records. Variables identified in PALGA included sex, type of IBD, age at colectomy, date of colectomy, date of last pouch biopsy, and history of colorectal neoplasia. For patients included in the case-control study, additional data were extracted from anonymized patient records. These data included sex, type of IBD based on histopathologic evaluation of the resection specimen, date of diagnosis of IBD, IBD phenotype according to the Montreal Classification, dates of proctocolectomy, pouch configuration (J or S), type of anastomosis (stapled without mucosectomy or hand sewn with mucosectomy), smoking history, family history of CRC, prior colorectal neoplasia, and primary sclerosing cholangitis. Colorectal neoplasia was classified according to Riddell as indeterminate for dysplasia (IND), LGD, HGD, or adenocarcinoma.[6] The diagnosis of primary sclerosing cholangitis was based on the presence of typical abnormalities on cholangiography with compatible clinical, biochemical, and hepatic histological findings.[7] After IPAA construction, the following variables were documented: surveillance pouchoscopy frequencies and intervals, pouchitis, cuffitis, Crohn's disease of the pouch, and development of neoplasia, including the date, location, tumor stage, presence of dysplasia before development of carcinoma, and outcome of pouch neoplasia. Surveillance pouchoscopy was defined as an endoscopic procedure of the pouch regardless of the indication with at least one pouch biopsy. Diagnoses of pouchitis and cuffitis were documented as previously established at the discretion of the treating physician. Relapsing pouchitis was defined as 4 or more episodes of pouchitis per year. Chronic pouchitis was defined as pouchitis failing to respond after $>4$ weeks of treatment with a single antibiotic (ciprofloxacin or metronidazole).[8] The diagnosis of Crohn's disease of the pouch was based on a combined assessment of clinical, endoscopic, histological, or radiographic features.[8]

## Histopathologic Assessment

Pouch neoplasia was defined as dysplasia or carcinoma in the pouch or anal transitional zone (ATZ) (the area between the dentate line and anastomosis, with or without mucosectomy), classified according to Riddell as IND, LGD, HGD, or adenocarcinoma.[6] For the patients with a diagnosis of pouch dysplasia, the pouch biopsy specimens with dysplasia were reevaluated by an expert gastrointestinal pathologist (I.D.N.) blinded to clinical, endoscopic, and radiographic features. The gradation of dysplasia was reassessed, and eventually revised results were used for analysis. The category IND after reevaluation was excluded from the case group in the analysis.

## Statistics

Cumulative incidences were counted with 1 minus Kaplan–Meier curves. Time to event was calculated from the date of pouch construction to the development of pouch neoplasia (cases) or the end of follow-up for patients who did not develop a neoplasia (controls). End of follow-up was

defined as the last gastroenterology-related medical contact, pouch excision, or patient's death. The median time to develop pouch carcinoma and the median survival time, including a minimum to maximum range, were derived from Kaplan–Meier curves. For the variables collected from the total cohort, log-rank analyses were performed to compare the incidence of pouch neoplasia in those subgroups.

$\chi^2$ test or Fisher exact test (if expected cell counts were $<5$) for categorical data and independent Student $t$ test for continuous data were used to compare cases and controls on all selected possible risk factors. Variables with a $P$ value of $<.1$ in univariate analyses were included in a multivariate Cox proportional hazard model with backward sampling to determine which risk factors are independently associated with developing a pouch carcinoma. A $P$ value of $<.05$ (2 sided) was considered to be statistically significant. Cases in the control group were analyzed as cases in the Cox model, resulting in hazard ratios that can be interpreted as relative risks. All missing values were considered to be completely at random and were excluded from analyses. All statistical analyses were performed with IBM SPSS statistics version 20.0 (SPSS Inc, Chicago, IL).

# Results

## Patients

We identified 1200 patients with IBD and IPAA with a median follow-up time of 6.5 years using PALGA. Forty-five of the 1200 patients (3.75%) had an initial histological diagnosis of pouch neoplasia (Figure 1). This



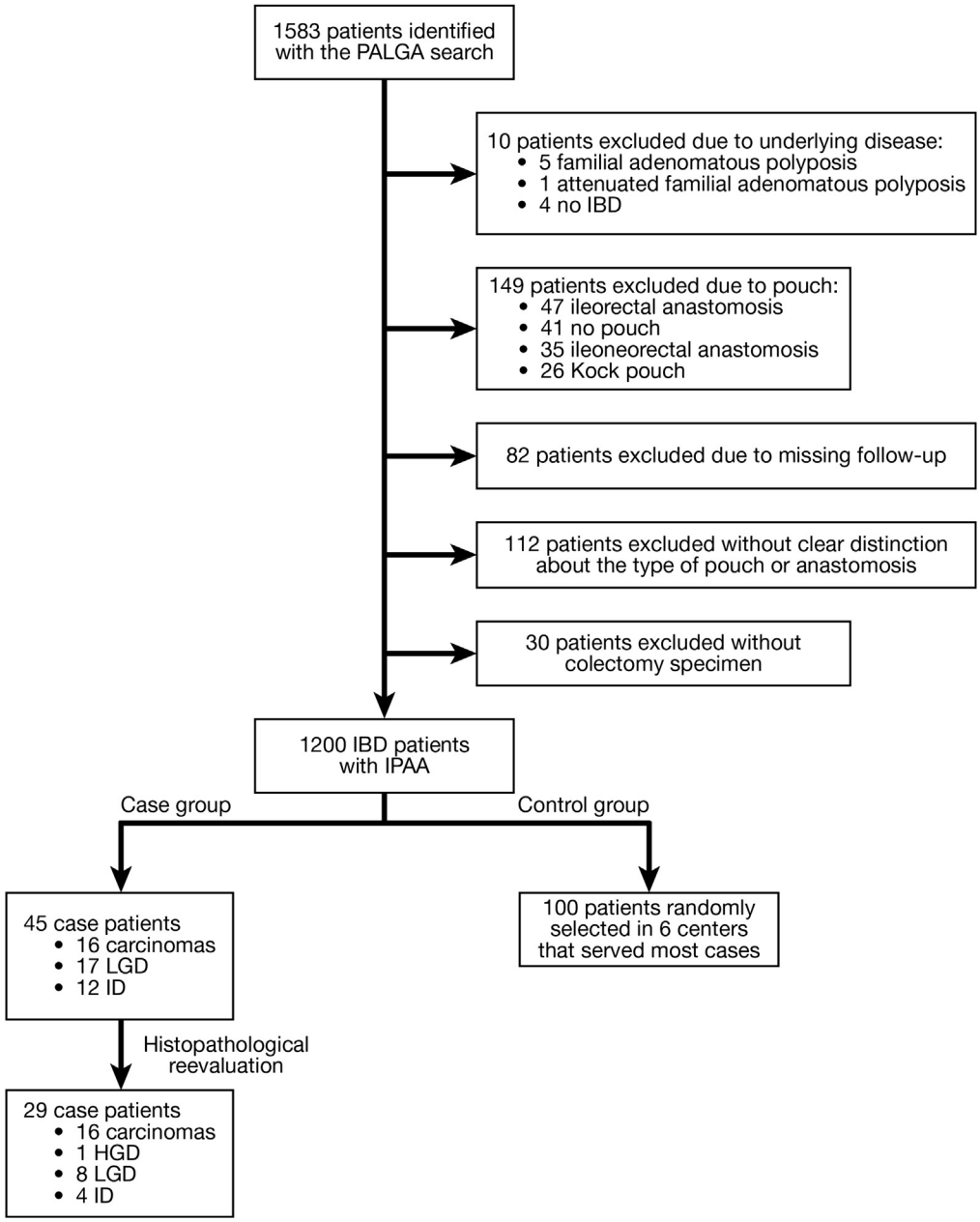


**Figure 1.** Flowchart showing patient inclusion.

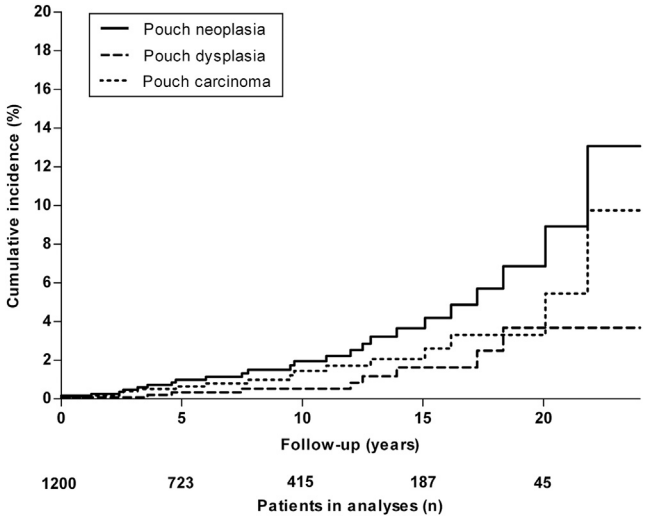


**Figure 2.** Cumulative incidences of pouch neoplasia (both carcinoma and dysplasia), pouch carcinoma, and pouch dysplasia.

group consisted of 12 patients with IND, 17 patients with LGD, and 16 patients with adenocarcinoma. In the latter group, 4 carcinomas were considered to be recurrence of CRC and 2 carcinomas arose after pouch excision. One of the patients with a recurrence previously underwent an incomplete CRC resection and a pouch carcinoma was detected 1 month after pouch construction. In the other 3 cases, recurrences occurred within 1 to 2 years after treatment of CRC. The 2 patients with adenocarcinoma after pouch excision for chronic pouchitis or perianal symptoms developed carcinomas 5 and 6 years after pouch excision. Identified pouch malignancies other than adenocarcinoma included one B-cell non-Hodgkin lymphoma, and this case was excluded from the analysis. The control group was established by random selection of 100 patients from the nationwide cohort. The medical record of one patient could not be retrieved, which resulted in a final control group of 99 patients. This control group included 4 cases with a diagnosis of pouch neoplasia.

## Verification Cohort

Our verification cohort consisted of 93 patients with IBD and IPAA who visited the outpatient clinic at the Radboud University Nijmegen Medical Centre between 2004 and May 2012. Eighty-eight of the 93 patients (95%) were identified on the initial search of PALGA, and the remaining 5 patients (5%) escaped identification by our search. These 5 patients never underwent a pouch biopsy or the PALGA search terms were not mentioned in the pathology reports.

## Histopathologic Reassessment

All pouch biopsy specimens with dysplasia except one were available for reassessment. Re-review of the specimens shifted the grades of dysplasia in 22 of 29 cases. Reassessment resulted in downgrading of dysplasia in 18 patients and upgrading in 4 patients. This resulted in the identification of 4 cases with IND, 8 cases with LGD, 1 case with HGD, and 16 cases with adenocarcinoma (Figure 1).

## Cumulative Incidences

Figure 2 depicts the cumulative incidences of pouch neoplasia (both dysplasia and carcinoma), pouch dysplasia (LGD and HGD), and pouch carcinoma. The cumulative incidences of pouch neoplasia were 1.0%, 2.0%, 3.7%, and 6.9% at 5, 10, 15, and 20 years, respectively. The respective cumulative incidences at 5, 10, 15, and 20 years for pouch dysplasia were 0.3%, 0.5%, 1.6%, and 3.7% and for pouch carcinoma were 0.6%, 1.4%, 2.1%, and 3.3%.

## Risk Factors for Pouch Neoplasia

Table 1 lists the basic variables extracted from PALGA, including age at colectomy, sex, type of IBD, and prior colorectal neoplasia. A history of colorectal neoplasia significantly differed between cases and controls. For this

**Table 1.** Comparison of the Extracted Variables From PALGA Between Patients With Pouch Neoplasia (Both Carcinoma and Dysplasia) and Patients Without Pouch Neoplasia

| Variable | With pouch neoplasia (n = 25) | Without pouch neoplasia (n = 1175) | Univariate analyses (*P* value) | Missing value (n) |
|---|---|---|---|---|
| Age at colectomy (*y*), mean ± SD | 39.7 ± 9.9 | 35.9 ± 12.4 | .123 | 0 |
| Female sex | 8 (32.0) | 559 (47.6) | .157 | 0 |
| IBD type | | | | |
| Ulcerative colitis | 20 (80.0) | 1033 (87.9) | | |
| Crohn's disease | 2 (8.0) | 44 (3.7) | | |
| Indeterminate colitis | 3 (12.0) | 98 (8.3) | .190 | 0 |
| Prior colorectal neoplasia | | | | |
| Without | 10 (40.0) | 1026 (87.4) | | |
| Dysplasia | 6 (24.0) | 107 (9.1) | | |
| Adenocarcinoma | 9 (36.0) | 41 (3.5) | <.001 | 1 |

NOTE. All values are expressed as n (%) unless otherwise noted.

variable, we performed log-rank analyses. Patients with prior colorectal dysplasia or carcinoma had higher cumulative incidences of pouch neoplasia compared with patients without a history of colorectal neoplasia ($P < .001$, log-rank test, Figure 3). After 15 years, the combined cumulative incidence of pouch dysplasia and carcinoma was 29.5% in the subgroup with prior CRC and 2.2% in the subgroup without prior neoplasia (Figure 3).

Clinical and demographic characteristics that were derived from the medical records are described in Table 2. Age at pouch construction, duration of IBD, primary sclerosing cholangitis, and again a history of colorectal neoplasia were significantly different between patients with and without pouch neoplasia ($P = .019$, $P = .001$, $P = .030$, and $P < .001$, respectively). Table 3 shows the results of the multivariate Cox model with all hazard ratios before elimination of nonsignificant variables as well as the final model after backward elimination. Both prior colorectal dysplasia and carcinoma emerged as risk factors with respective hazard ratios of 3.76 (95% confidence interval, 1.39–10.19; $P = .009$) and 24.69 (95% confidence interval, 9.61–63.42;

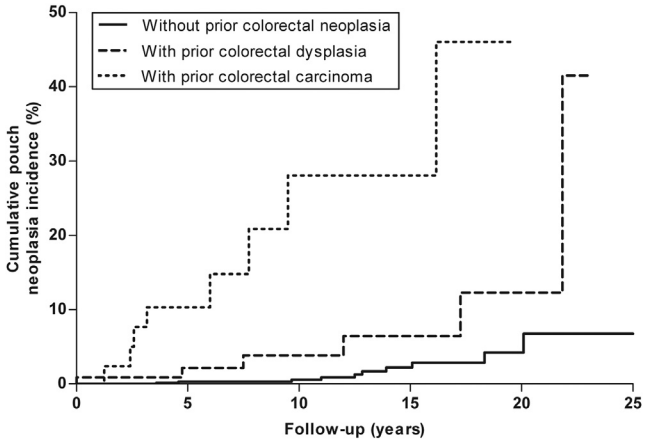


**Figure 3.** Cumulative incidences of pouch neoplasia of subgroups categorized by the presence or absence of prior colorectal dysplasia or cancer, which differ significantly with log-rank analyses ($P < .001$).

**Table 2.** Comparison Between Patients With Pouch Neoplasia (Both Carcinoma and Dysplasia) and the Control Group for Possible Risk Factors and Confounders Extracted From the Medical Records

| Variable | Patients with pouch neoplasia (n = 25) | Control group (n = 99) | Univariate analyses (*P* value) | Missing value (n) |
|---|---|---|---|---|
| Female sex | 8 (32.0) | 41 (41.4) | .494 | 0 |
| Age at diagnosis of IBD (*y*), mean ± SD | 25.7 ± 11.6 | 25.7 ± 12.5 | .984 | 10 |
| Age at pouch construction (*y*), mean ± SD | 39.8 ± 9.9 | 33.0 ± 13.3 | .019 | 0 |
| IBD type | | | | |
| Ulcerative colitis | 20 (80.0) | 89 (89.9) | | |
| Crohn's disease | 2 (8.0) | 3 (3.0) | | |
| Indeterminate colitis | 3 (12.0) | 7 (7.1) | .296 | 0 |
| Extended colitis (Montreal E3) | 22 (91.7) | 78 (89.7) | 1.000 | 13 |
| Duration of IBD from diagnosis to pouch construction (*y*), mean ± SD | 13.3 ± 8.2 | 6.9 ± 6.1 | .001 | 10 |
| Prior colorectal neoplasia (LGD, HGD, carcinoma) | 15 (62.5) | 12 (12.4) | <.001 | 3 |
| J-pouch configuration | 18 (85.7) | 79 (85.9) | 1.000 | 11 |
| Anastomosis type | | | | |
| Hand sewn with mucosectomy | 4 (19.0) | 17 (18.7) | | |
| Stapled without mucosectomy | 17 (81.0) | 74 (81.3) | 1.000 | 12 |
| Pouchitis (chronic or relapsing) | 6 (24.0) | 26 (26.3) | 1.000 | 0 |
| Cuffitis | 4 (16.0) | 10 (10.1) | .479 | 0 |
| Crohn's disease of the pouch | 2 (8.0) | 2 (2.0) | .181 | 0 |
| Primary sclerosing cholangitis | 4 (16.0) | 3 (3.0) | .030 | 0 |
| Ever smoked | 8 (38.1) | 17 (23.6) | .262 | 31 |
| Family history of CRC | 0 (100) | 0 (100) | Not computable | 54 |
| Pouch duration (*y*)[a], mean ± SD | 8.6 ± 6.1 | 8.4 ± 7.0 | .883 | 0 |
| Surveillance frequency (average/year) | 0.43 ± 0.42 | 0.52 ± 0.57 | .470 | 15 |
| Surveillance intervals | | | | |
| No surveillance pouchoscopy | 3 (12.0) | 14 (14.1) | | |
| ≥1 pouchoscopy every 3 y | 8 (32.0) | 26 (26.3) | | |
| ≥1 pouchoscopy every 5 y | 3 (12.0) | 12 (12.1) | | |
| ≥1 pouchoscopy every 10 y | 3 (12.0) | 29 (29.3) | | |
| <1 pouchoscopy every 10 y | 8 (32.0) | 18 (18.2) | .332 | 0 |

NOTE. All values are expressed as n (%) unless otherwise noted.
[a]Pouch duration of cases and controls was calculated from the date of proctectomy to the development of pouch neoplasia (cases) or end of follow-up (controls). End of follow-up for controls was defined as the last gastroenterology-related medical contact, pouch excision, or patient's death.

**Table 3.** Cox Proportional Hazard Model to Identify Risk Factors for Developing Pouch Neoplasia

| | Cox model before backward elimination of nonsignificant variables | | | Final Cox model after backward elimination of nonsignificant variables | | |
|---|---|---|---|---|---|---|
| | Coefficient $\beta$ | Hazard ratio (95% confidence interval) | *P* value | Coefficient $\beta$ | Hazard ratio (95% confidence interval) | *P* value |
| Prior colorectal neoplasia[a] | | | | | | |
| Dysplasia (LGD and HGD) | 0.63 | 1.87 (0.52–6.76) | .341 | 1.33 | 3.76 (1.39–10.19) | .009 |
| Carcinoma | 2.69 | 14.74 (4.96–43.78) | <.001 | 3.21 | 24.69 (9.61–63.42) | <.001 |
| Duration of IBD | 0.03 | 1.03 (0.97–1.10) | .279 | | | |
| Primary sclerosing cholangitis | 0.93 | 2.54 (0.53–12.17) | .244 | | | |
| Age at pouch construction | 0.03 | 1.03 (0.99–1.06) | .137 | | | |

NOTE. n = 112 patients (12 excluded from analyses due to missing variables).
[a]Reference category is patients without prior colorectal neoplasia.

$P < .001$). Most cases of prior colorectal neoplasia were located in the rectosigmoid colon (Table 4).

Inclusion of patients with a recurrence of CRC and thus a prior CRC may give a distorted picture of the identified risk factor "prior colorectal neoplasia." Patients who developed adenocarcinoma after pouch excision may contribute to this effect. To verify the identified risk factors, we performed a sensitivity analysis excluding these patients. A new Cox model confirmed our earlier findings and showed prior colorectal dysplasia and carcinoma as the only risk factors, with respective hazard ratios of 4.17 (95% confidence interval, 1.50–11.62; $P = .006$) and 20.28 (95% confidence interval, 6.71–61.30; $P < .001$).

### *Characteristics and Outcomes of Pouch Neoplasia*

The identified cases of pouch carcinoma and dysplasia were further analyzed, and an overview is presented in Table 4 and Supplementary Table 1. The median time to develop a pouch carcinoma after diagnosis of IBD was 20 years (range, 14–38 years) and 7.0 years (range, 0–22 years) after pouch construction. LGD developed at a median time of 19 years (range, 9–34 years) after diagnosis of IBD and 7.0 years (range, 0–18 years) after pouch construction. Ten of 16 pouch carcinomas were located at the ATZ, and 3 of 8 cases of pouch dysplasia arose at the ATZ.

The endoscopic characteristics at the time of detection of pouch neoplasia were not consistent. Dysplasia and cancer were seen in patients with ulcerated lesions, polypoid lesions, and mass-like lesions, but patients without endoscopic abnormalities also had neoplasia (Table 4 and Supplementary Table 1). For instance, 4 of 16 patients with pouch carcinoma did not have any visible lesions on endoscopy.

Pouch dysplasia rarely progressed during follow-up, and as a result only 3 carcinomas (19%; stage I, n = 2; stage II, n = 1) were preceded by HGD, LGD, and/or IND. In patients with IND or LGD, only 2 of 14 patients progressed to carcinoma during follow-up, whereas 9 of 14 patients with dysplasia had regression on subsequent biopsy specimens. One patient with HGD also showed regression, and no dysplasia was found on subsequent biopsy specimens. In our cohort, 3 patients with pouch dysplasia were not followed up by pouchoscopy. In one patient in the latter group, LGD was detected in the excised pouch specimen.

Most pouch carcinomas were detected at an advanced stage of disease, resulting in a high mortality rate (Table 4). Nine of 16 patients died with a median survival of 11 months (range, 1–20 months) after diagnosis of pouch carcinoma. Three additional patients were lost to follow-up. Two of these patients had metastatic disease at last follow-up. Pouch carcinomas did not recur in 4 patients during a median follow-up of 12 months (range, 11–124 months) after diagnosis of pouch carcinoma.

## Discussion

The key finding of our study is the relatively low incidence of pouch carcinoma, especially in patients without a history of colorectal neoplasia. Only 16 of 1200 patients with IPAA (1.3%) were identified with pouch carcinoma in our nationwide IBD cohort. Of note, most of these carcinomas developed at the ATZ (63%). The cumulative incidence of developing pouch carcinoma reached 3.3% after 20 years. Furthermore, a history of colorectal dysplasia and carcinoma raised the risk of pouch neoplasia by 4- and 25-fold, respectively. After 15 years, the cumulative incidence of pouch neoplasia was 29.5% in the subgroup with a prior CRC and 2.2% in the subgroup without a prior neoplasia.

The relatively low incidence of pouch carcinoma (cumulative incidence of 3.3% after 20 years) in IBD is in line with the findings of another large cohort study. This study evaluated 3202 patients with IBD and IPAA and reported a cumulative incidence of pouch carcinoma of 2.4% after 20 years.[3] Similarly, this cohort study detected 23 patients (0.72%) with pouch dysplasia, while a meta-analysis showed a pooled prevalence of pouch dysplasia of 1.13% in 2040 patients.[3,9] This is in line with data presented in the current study (pouch dysplasia in 9 of 1200 patients [0.75%]).

Prior colorectal neoplasia is a risk factor for development of pouch neoplasia.[3,10–12] The majority of cases

**Table 4.** Overview of All Patients With Pouch Carcinoma

| Patient no. | Type of IBD | Age at diagnosis of IBD (*y*) | Duration of IBD (*y*) | Age at IPAA (*y*) | Indication for proctocolectomy | Type of anastomosis | Pouch duration until carcinoma (*y*) | Tumor location | Tumor stage at diagnosis | | Endoscopic features | Treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pouch carcinomas** | | | | | | | | | | | | | |
| 1 | UC | 17 | 15 | 33 | 2× LGD (location NA) | Stapled without mucosectomy | 4 | ATZ | T4N2M1 | IV | Ulcerative inflammation | Chemoradiation<br>Surgical resection | No recurrence at 11 mo |
| 2 | UC | 17 | 17 | 35 | CRC (T3N1, rectosigmoid colon) | Stapled without mucosectomy | 3 | ATZ | T4N1M1 | IV | No endoscopic abnormalities | Incidental finding in the pouch excision specimen<br>Chemoradiation | Metastases<br>Died at 7 mo |
| 3 | CD | 5 | 28 | 34 | CRC (T4N1, sigmoid colon) | Stapled without mucosectomy | 9 | ATZ | T2N0MX | I | No endoscopic abnormalities | Radiotherapy<br>Surgical resection | Local recurrence at 38 mo<br>Treated with chemoradiation and surgical excision<br>No recurrence at 10.5 y after pouch carcinoma |
| 4 | CD | 28 | 25 | 53 | Medically refractory | Stapled without mucosectomy | 11 | Pouch | T4N2M0 | III | Cobbled lesion | Radiotherapy | Metastases<br>Died at 11 mo |
| 5 | UC | 31 | 4 | 36 | Medically refractory | Stapled without mucosectomy | 12 | ATZ | T3N0MX | II | Ulcerative inflammation with stenosis and fibrosis | Chemoradiation<br>Surgical resection | Metastases<br>Died at 13 mo |
| 6 | UC | 24 | 6 | 31 | Medically refractory | Stapled without mucosectomy | 15 | ATZ | T4N0M0 | II | Mass-like lesion (diameter, 4 cm) | Chemoradiation<br>Surgical resection | No recurrence at 25 mo |
| 7 | UC | 21 | 8 | 30 | Medically refractory, incidental CRC (T2N0, rectosigmoid colon) | Stapled without mucosectomy | 7 | NA | NA | | Mass-like lesion | Surgical resection (incomplete) | Died at 3 mo |
| 8 | UC | 38 | 10 | 48 | CRC (T1N0, rectum) | Stapled without mucosectomy | 15 | ATZ | T2N0M0 | I | Mass-like lesion (diameter, 3 cm) | Chemoradiation<br>Surgical resection | No recurrence at 12 mo |
| 9 | UC | 4 | 22 | 26 | 2× HGD (rectum) | Hand sewn with mucosectomy | 11 | ATZ | T4N0M1 | IV | No endoscopic abnormalities | Radiotherapy | Died at 20 mo |

CLINICAL AT

CLINICAL AT



**Table 4.** Continued

| Patient no. | Type of IBD | Age at diagnosis of IBD (*y*) | Duration of IBD (*y*) | Age at IPAA (*y*) | Indication for proctocolectomy | Type of anastomosis | Pouch duration until carcinoma (*y*) | Tumor location | Tumor stage at diagnosis | Endoscopic features | Treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | UC | 16 | 4 | 20 | Medically refractory | NA | 22 | Pouch | T4N2M1 IV | Circular growing mass | Chemoradiation | Died at 12 mo |
| **Recurrences of CRC** | | | | | | | | | | | | |
| 11 | UC | 29 | 27 | 56 | CRC (T2N0, rectum) | Stapled without mucosectomy | 2 | ATZ | T4N2M0 III | Polypoid lesion | Surgical resection | Died at 4 months |
| 12 | UC | 33 | 14 | 47 | CRC (T1N0, rectum) | Hand sewn with mucosectomy | 1 | ATZ | T3N1MX III | NA | Chemoradiation | Metastases<br>Lost to follow-up |
| 13 | UC | 28 | 18 | 46 | CRC (T3N1, rectum) | NA | 2 | Between pouch and vagina back wall | NA | No endoscopy performed | Chemoradiation<br>Surgical resection | Local recurrence at 8 mo<br>Treated with chemoradiation<br>Died at 13 mo |
| 14 | UC | 10 | 20 | 31 | CRC (T3N2, ascending colon) | NA | 0 | NA | Extended disease | No endoscopy performed | Tumor debulking<br>Chemotherapy | Died at 10 mo |
| **Adenocarcinomas after pouch excision** | | | | | | | | | | | | |
| 15 | IC | 44 | 5 | 49 | Medically refractory | Stapled without mucosectomy | 9 (pouch excision after 3.5 y, pouch carcinoma 5.5 y later) | Prior pouch location, originating from pouch remnant | NA | Mass-like lesion and abscess | Radiotherapy<br>Surgical resection | Metastases<br>Lost to follow-up |
| 16 | IC | 21 | 20 | 42 | CRC (T2N0, rectum) | Hand sewn with mucosectomy | 6 (pouch excision after 0.5 y, pouch carcinoma 5.5 y later | Remnant anal canal | TisN0M0 0 | Inflammation | Incidental finding in the anorectal remnant excision specimen<br>No further treatment | Lost to follow-up |

UC, ulcerative colitis; NA, not available; CD, Crohn's disease.

identified in our cohort (69%) as well as by the most recent review[1] (57%) had a history of colorectal neoplasia. Most pouch carcinomas (63% in our cohort) developed at the ATZ. Although it seems reasonable to remove colonic tissue by mucosectomy, this strategy does not protect against pouch neoplasia.[3,13,14] A possible explanation is the presence of residual colonic mucosa islets that may remain even after "complete" mucosectomy.[15] It could be hypothesized that this residual colonic mucosa bears an increased risk of malignant degeneration, especially in patients with prior colorectal neoplasia. The short interval between pouch construction and development of carcinoma in some patients and the ATZ location of most pouch carcinomas raises the issue whether some pouch carcinomas represent recurrence of CRC rather than a primary pouch carcinoma. Other previously purported risk factors for developing pouch neoplasia include pouchitis,[3,15–17] long duration of IBD,[3,10–12] and primary sclerosing cholangitis.[3,18,19] None of these factors were identified as a risk factor in our study.

A thorough understanding of the natural history of pouch neoplasia is fundamental to the development of an effective strategy for pouch surveillance. In colonic IBD, the surveillance strategy is based on the concept of an inflammation-dysplasia-carcinoma sequence.[20] Whether this sequence also applies to pouch neoplasia is unknown. The fact that pouchitis was not identified as a risk factor as well as the high regression rates and low progression rates of pouch dysplasia both in the literature and in our study suggest that this hypothesis does not hold for pouch carcinogenesis.[1,21] On the other hand, one study identified concurrent LGD or HGD in 10 of 11 (90.9%) pouch carcinomas in the pouch excision specimens.[3] In addition, many clinicopathological and molecular features in pouch carcinoma are shared with IBD-associated CRC, which is in favor of the inflammation-dysplasia-carcinoma sequence.[22]

The underlying purpose of our study was to contribute to a recommendation for a more targeted pouch surveillance program in patients with IBD. Importantly, our nationwide study provides the opportunity to generate data that reflect the IPAA population at large, in contrast to prior studies that stem from tertiary referral centers. Data from the present study suggest that pouch surveillance with close inspection of the ATZ should be considered in patients with IPAA who have a history of colorectal neoplasia. However, it is unknown whether surveillance will indeed detect carcinoma at a less advanced stage and result in an improved prognosis. Most pouch carcinomas in our study were not preceded by dysplasia, and resection of dysplastic lesions might not contribute to the prevention of pouch carcinoma. Furthermore, our data suggest a limited role for pouch surveillance in patients without a history of colorectal neoplasia. This is supported by the relatively low incidence of pouch neoplasia in patients without prior colorectal neoplasia (cumulative incidence of 2.2% after 15 years), especially in comparison with the lifetime incidence of approximately 5% for developing CRC in the general population.[23]

The present study has some limitations. First, the retrospective nature of the study and use of data primarily not intended for research resulted in missing variables. Second, the relatively small number of cases might result in a type II error in determining risk factors. In addition, the current study could represent a slight overestimation of the actual cumulative incidences. The exclusion of patients because of incomplete documentation of the presence of IPAA, as well as pouch patients who never underwent pouch biopsies (and thus escaped identification by our search), could contribute to this effect. However, our verification cohort suggests that only few patients were missed and none of these patients had a diagnosis of pouch neoplasia. It is debatable whether patients with recurrences of CRC and pouch carcinomas after pouch excision should be part of the case group. Because we aimed to formulate a comprehensive surveillance strategy that identifies all pouch carcinomas, we included these carcinomas in our case group. This may influence the identification of risk factors, but sensitivity analyses excluding these patients resulted in identification of similar risk factors. Finally, patients were not subjected to a standardized endoscopic surveillance program. Pouchoscopies were performed by both gastroenterologists and surgeons without standardized biopsy protocol and well-defined intervals. Although the average pouchoscopy rate was once per 5 years and the surveillance intervals were the same between the case and control groups, it is unknown whether a more standardized surveillance program would have picked up more cases of pouch dysplasia in general and before pouch carcinoma. Many cases of dysplasia regressed; this, combined with the absence of a standardized endoscopic surveillance strategy, may have contributed to missed cases of pouch dysplasia. The slightly larger sample size of the pouch carcinoma group compared with the pouch dysplasia group might also reflect missed detection of dysplasia. Patients with a prior CRC could have had a pouchoscopy more frequently; however, this was not seen in the patients included in the case-control study (data not shown).

In conclusion, the incidence of pouch neoplasia in patients with IBD without prior colorectal neoplasia is relatively low. A history of dysplasia and CRC raises the risk of pouch neoplasia significantly. Our data suggest that a limited surveillance program is sufficient for patients with IPAA without a history of colorectal neoplasia. A targeted surveillance program should be considered in patients with a prior colorectal neoplasia. However, prospective studies are required to evaluate the effects of such a surveillance strategy.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.09.047.

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**Conflicts of interest**
The authors disclose no conflicts.

# Supplementary Material

**Supplementary Table 1.** Overview of All Patients With Pouch Dysplasia

| Patient no. | Type of IBD | Age at diagnosis of IBD (*y*) | Duration of IBD (*y*) | Age at IPAA (*y*) | Indication for proctocolectomy | Type of anastomosis | Pouch duration until dysplasia (*y*) | Dysplasia location | Highest-grade dysplasia | Endoscopic features | Treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17 | UC | 26 | 11 | 38 | LGD and IND | Hand sewn with mucosectomy | 0 | Multiple foci (location NA) | LGD | No endoscopy performed | Incidental finding in pouch excision specimen No further treatment | Pouch excision |
| 18 | IC | NA | NA | 48 | Medically refractory, incidental identification (rectum) | Stapled without mucosectomy | 4 | ATZ | LGD | Polypoid lesion | Watchful waiting | Refinding of dysplasia at 3 mo Lost to follow-up |
| 19 | UC | 29 | 20 | 49 | Carcinoma in situ (sigmoid colon) | Stapled without mucosectomy | 12 | Pouch | LGD | 2 erosive lesions | Watchful waiting | Regression of dysplasia at 11, 23 and 35 mo |
| 20 | UC | 18 | 17 | 35 | Multifocal HGD | Stapled without mucosectomy | 17 | Pouch and in random biopsy specimens | LGD | No endoscopic abnormalities | Watchful waiting | Refinding of dysplasia at 7 and 24 mo Regression of dysplasia at 34 mo |
| 21 | IC | 52 | 1 | 53 | Iatrogenic bowel perforation | Stapled without mucosectomy | 18 | ATZ | LGD | Ulcerative inflammation | Watchful waiting | Regression of dysplasia at 3 mo |
| 22 | UC | 34 | 15 | 50 | Repeatedly LGD | Stapled without mucosectomy | 7 | Pouch | LGD | Solitary ulcer | Watchful waiting | Regression of dysplasia at 3 mo |
| 23 | UC | 38 | 5 | 44 | Toxic megacolon | NA | 3 | ATZ | LGD | NA | Watchful waiting | Refinding of dysplasia at 13 mo Lost to follow-up |
| 24 | UC | 32 | 3 | 35 | NA | Stapled without mucosectomy | 13 | NA | LGD | Inflammation | Watchful waiting | Lost to follow-up |
| 25 | UC | 21 | 4 | 25 | Medically refractory | Stapled without mucosectomy | 12 | NA | HGD | Inflammation | Watchful waiting | Regression of dysplasia at 2 mo No visible lesions on endoscopy (biopsy specimens not taken) at 21, 49 and 52 mo |

UC, ulcerative colitis; NA, not available; IC, indeterminate colitis.