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Incidental findings in the bowel cancer population screening program: other polyps and malignancies – A nationwide study

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Incidental findings in the bowel cancer population screening program: other polyps and malignancies – A nationwide study

The introduction of bowel cancer population screening programs has had a profound impact on gastrointestinal pathology. While the focus is mainly on quality assurance of diagnoses relevant for the outcome of these programs (colorectal cancer and its precursors), incidental findings are increasingly diagnosed. The incidence of such findings is largely unknown. Therefore, we investigated the incidence of incidental findings within the national screening program of the Netherlands. From the Dutch nationwide pathology databank (PALGA), we retrieved all histological diagnoses of patients participating in the national bowel cancer screening program from the start in 2014 until 1/1/2021. Descriptive statistics were used. During these 7 years, in total 9407 other polyps and malignancies (262 per 10,000 colonoscopies) were diagnosed. The majority (65%) were classified as inflammatory polyps. The most common malignancies were neuroendocrine tumours (n = 198, 6 per 10,000 colonoscopies); less common were lymphomas (n = 64) and metastases (n = 33). Mesenchymal polyps, such as leiomyomas and lipomas, were relatively common (27 and 16 per 10,000 colonoscopies, respectively), in comparison with neural polyps such as perineuriomas, ganglioneuromas, and neurofibromas (respectively 3, 2, and 1 per 10,000 colonoscopies). This is the largest study into the incidence of nonconventional colorectal polyps and malignancies in a homogeneous cohort of asymptomatic patients. Several of these diagnoses may have consequences for treatment and follow-up, in particular the malignancies and detection of patients with hereditary cancer syndromes.

Keywords: bowel, colonoscopy, population screening

Introduction

The worldwide implementation of bowel cancer screening programs has led to a steep increase in the number of colorectal biopsies and polypectomies. Not only has there been an initial increase in the number of colorectal cancer (CRC) cases, also numerous precursor lesions have been diagnosed. The increased frequency of these types of diagnoses in combination with several quality improvement strategies[1–3] and increased awareness of pathologists has led to an overall improved quality of diagnosis as well as an

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increased interest in gastrointestinal pathology. Datasets for standardised reporting have been developed and can be used to monitor trends in diagnosis.[4]

Apart from CRC and its precursors (conventional adenomas and serrated polyps), within the population screening other diagnoses are frequently encountered. Inflammation is present in 4–5% of endoscopies within population screening programs.[5] Detection of asymptomatic inflammatory bowel disease (IBD) varied between 0.4 and 50 patients per 10,000 screened persons.[6–8] This development led to intense discussions about clinical management of these asymptomatic patients.

However, several other diagnoses within the screening programs might have clinical consequences as well. Detection of malignancies other than CRC, but also hamartomatous polyps, might require action, since these may be indicators of hereditary cancer syndromes.[9–11] The incidence of these additional findings is not yet known. In the current study, we aimed to gather information on infrequent diagnoses in endoscopic specimens. We selected all histopathological diagnoses within the Dutch bowel cancer screening program and describe the relative incidence in asymptomatic patients and add characteristics of these other diagnoses.

Methods

DUTCH BOWEL CANCER SCREENING PROGRAM

From its implementation in 2014, the population between the ages of 55 and 75 biennially receives an invitation and faecal immunochemical test (FIT) for participation in the Dutch bowel cancer screening program. In case of FIT positivity, subsequent colonoscopy was provided.[12] From the start of the program in 2014 until January 1st 2021, 11,551,878 invitations were sent and 8,584,961 participants were adequately screened (74.3% uptake of primary screening test, all rounds together). Approximately 4.9% (n = 418,129) of the screened participants had an abnormal FIT result. There was an 82.5% uptake of endoscopy (n = 344,917). This resulted in 265,628 pathology reports (77% of all colonoscopies), with an average of 3.6 separate diagnoses per case (SD 2.4, median 3).

PATHOLOGY DATABASE SEARCH

All histopathological diagnoses from colorectal biopsies in the setting of the Dutch population screening program between 2014–2021 were retrieved from the Dutch nationwide pathology databank, PALGA,[13] registered under LZV-2020-116. This study was considered exempt from ethical approval due to anonymous data.

We included all diagnoses that did not belong to the primary endpoints of the population screening program (i.e. colorectal cancer, conventional adenomas, hyperplastic polyps, sessile serrated lesions, and traditional serrated adenomas were all excluded). The flowchart is shown in Figure 1. Exclusion criteria were lack of tissue, no diagnosis, no abnormalities, anal pathology, reactive changes, lymphoid hyperplasia, ischaemia, haematoma and haemangioma, pseudomelanosis, infections, amyloidosis, and endometriosis. Miscoded cases were those that were filed under the "other" category but belonged to the primary endpoints of the program (i.e. serrated polyps, adenomas, and adenocarcinomas).

The results are described as frequency, linked to location and size, as well as to clinical parameters such as gender and age. When possible, incidence is given as number of cases per 10,000 colonoscopies. No additional statistics were performed. In the Results section, comparison with the existing literature is made for incidence and clinicopathological features.

Results

From our original 63,263 included cases, we excluded 54,216 cases according to the exclusion criteria (Figure 1), leaving 9,047 cases for further analysis. This translates to a prevalence of 262 other polyps and malignancies per 10,000 colonoscopies. The most common specific findings are summarised in Table 1.

SPECTRUM OF INFLAMMATORY POLYPS

The most common polyps were inflammatory polyps (Figure 2A), over 65% of cases (n = 5950, 173 per 10,000 colonoscopies). These were not directly associated with the presence of IBD in other biopsies from the same patients. However, no clear definition of this type of polyp is available, resulting in a wide variety of histological morphologies.

Inflammatory fibroid polyps are a distinct entity, with a well-described morphology and accompanying molecular aberrations, and should be classified as a mesenchymal polyp. These most frequently present in the stomach or small bowel.[14] Only one case was diagnosed in our cohort (Table 2). No PDGFRA

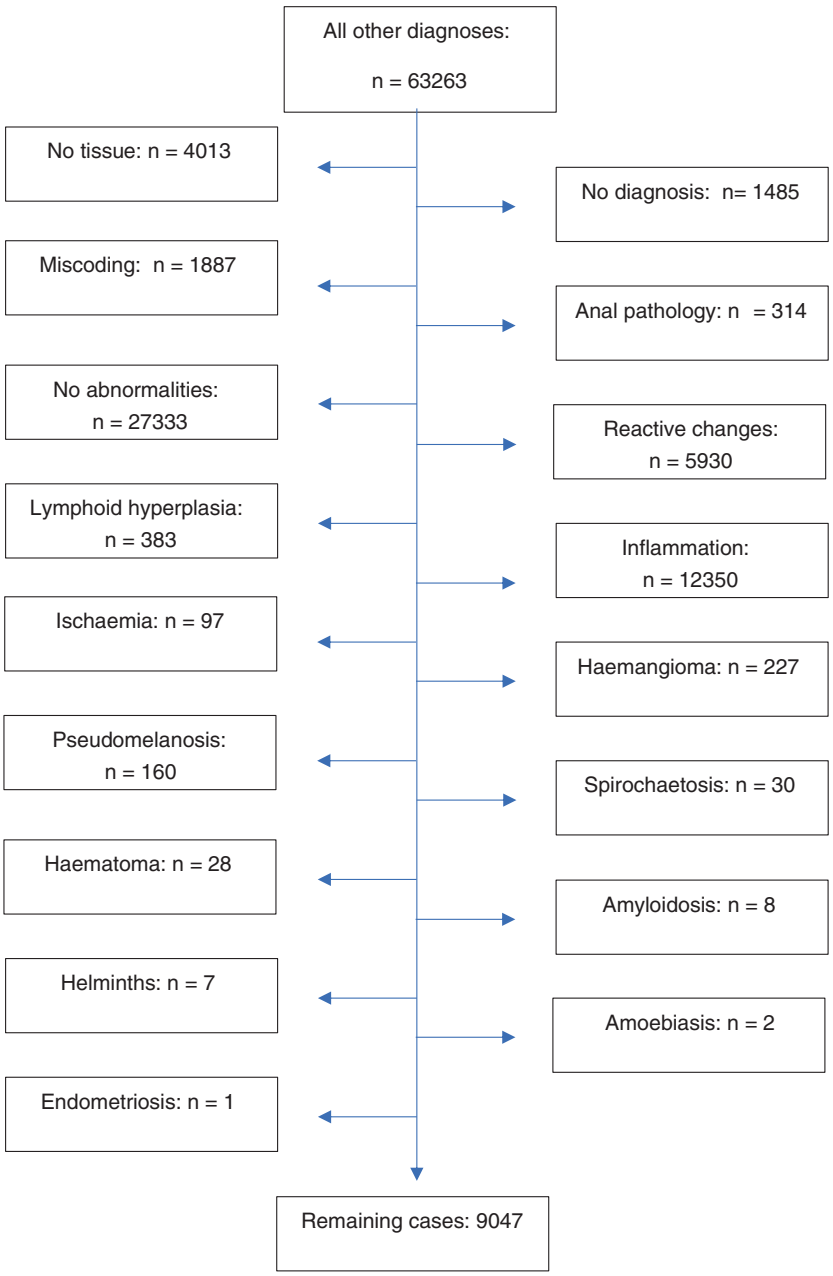

Figure 1. Flowchart of case selections.

mutation was present, but the diagnosis was confirmed in the regional soft tissue expert panel.

Prolapse-related polyps were present in 12 per 10,000 colonoscopies (n = 400). These were located mainly in the sigmoid (44%) and rectum (46%) (Figures 2B and 3I), the former suggesting a relation with diverticular disease and the latter likely due to a multiplicity of causes, including mucosal prolapse and local trauma (obstipation, straining).

MESENCHYMAL POLYPS

Twenty-seven mainly small leiomyomas were detected per 10,000 colonoscopies, most frequently in the sigmoid colon (Table 1, Figure 2B, and Figure 3A). In 12 patients, two leiomyomas were present, and in 147 cases this was the only diagnosis in the patient. They are benign proliferations derived from the muscularis mucosae, and are negative for

Table 1. Clinical data per polyp diagnosis

Diagnosis	*N* Polyps	*N* Patients	Gender % female	Age Mean	Size Mean	Size Range	Incidence Per 10,000 colonoscopies
Leiomyoma	941	929	31%	65.6	0.6	0.1–5.0	27
Lipoma	558	555	39%	66.1	1.1	0.1–7.0	16
Juvenile polyp	438	426	32%	64.7	1.4	0.1–7.0	12
Prolapse-related polyp	400	380	40%	64.7	0.9	0.1–4.1	12
Perineurioma	113	109	37%	66.4	0.6	0.2–3.0	3
Ganglioneuroma	93	70	34%	64.4	0.5	0.1–1.9	2
Hamartoma n.o.s.	71	58	32%	64.7	1.3	0.1–2.8	1.7
Peutz–Jeghers polyp	42	40	31%	66.3	1.7	0.4–3.3	1
Xanthoma	40	40	23%	66.3	0.4	0.2–0.8	1
Neurofibroma	34	34	56%	65.3	0.5	0.2–1.7	1
Schwann-cell hamartoma	20	19	20%	64.8	0.5	0.2–1.7	0.6
Granular cell tumour	14	14	36%	61.0	0.6	0.3–1.1	0.4

N: Number, NOS not otherwise specified. age range is 55–75 according to inclusion for population screening. Size in cm, age in years.

gastrointestinal stromal tumour-specific immunohistochemistry.[15] In line with the literature,[15] our cases were most common in the rectosigmoid and rectum.

Sixteen lipomas were detected per 10,000 colonoscopies, most frequently in the caecum and ascending colon, in line with the literature[16] (Table 1, Figure 2B, and Figure 3B). This might be an underestimation, since these can be recognised by their endoscopic features and will not be sent for diagnosis. One case was diagnosed as an angiolipoma and another case as an intramucosal lipoma. Larger lipomas (over 4 cm in size) were present in the sigmoid ($n = 4$) and transverse colon ($n = 3$). In 73 patients, lipoma was the only diagnosis; the majority of those were small.

A specific subgroup in the mesenchymal polyp category is formed by the neural polyps. The most common neural polyp is perineurioma (Figure 3C), with 3 per 10,000 colonoscopies. The coincidence of perineuriomas with sessile serrated lesions[17] might be responsible for inflated numbers, as in particular the smaller perineuriomas often present with serrated crypts. The original title, benign fibroblastic polyp, was used 29 times.

Ganglioneuromas were detected in 2 per 10,000 colonoscopies, most frequently in the sigmoid colon (Figure 2B, Table 1, and Figure 3D). Seven patients presented with multiple ganglioneuromas, ranging from 2 to 11. In all seven patients a genetic predisposition was suggested in the conclusion of the report.

Neurofibroma (1 per 10,000 colonoscopies, Figure 3E), Schwann-cell hamartoma (0.6 per 10,000 colonoscopies, Figure 3F), and granular cell tumour (0.4 per 10,000 colonoscopies) are very rare.

HAMARTOMAS

Juvenile(-like) polyps were the most frequently diagnosed hamartomas (12 per 10,000 colonoscopies, $n = 438$). In 19, polyps dysplasia was present. Twelve patients presented with two juvenile polyps, one of them also had a dysplastic juvenile polyp (Figure 3G). Juvenile polyps occurred most frequently in the sigmoid (Figure 2B), just like the juvenile polyps with dysplasia (11/19). Peutz–Jeghers(-like) polyps were diagnosed in 1 in 10,000 colonoscopies. On average, these were the largest polyps, with a mean size of 13 mm (Table 1, Figure 3H). There was also a rather large group of hamartomas that could not be further classified (1.7 per 10,000 colonoscopies); five patients with two hamartomas, one with three, and one with eight hamartomas.

RARE DIAGNOSES

Small xanthomas (Figure 3J) were mainly diagnosed in the rectosigmoid, with an incidence of 1 in

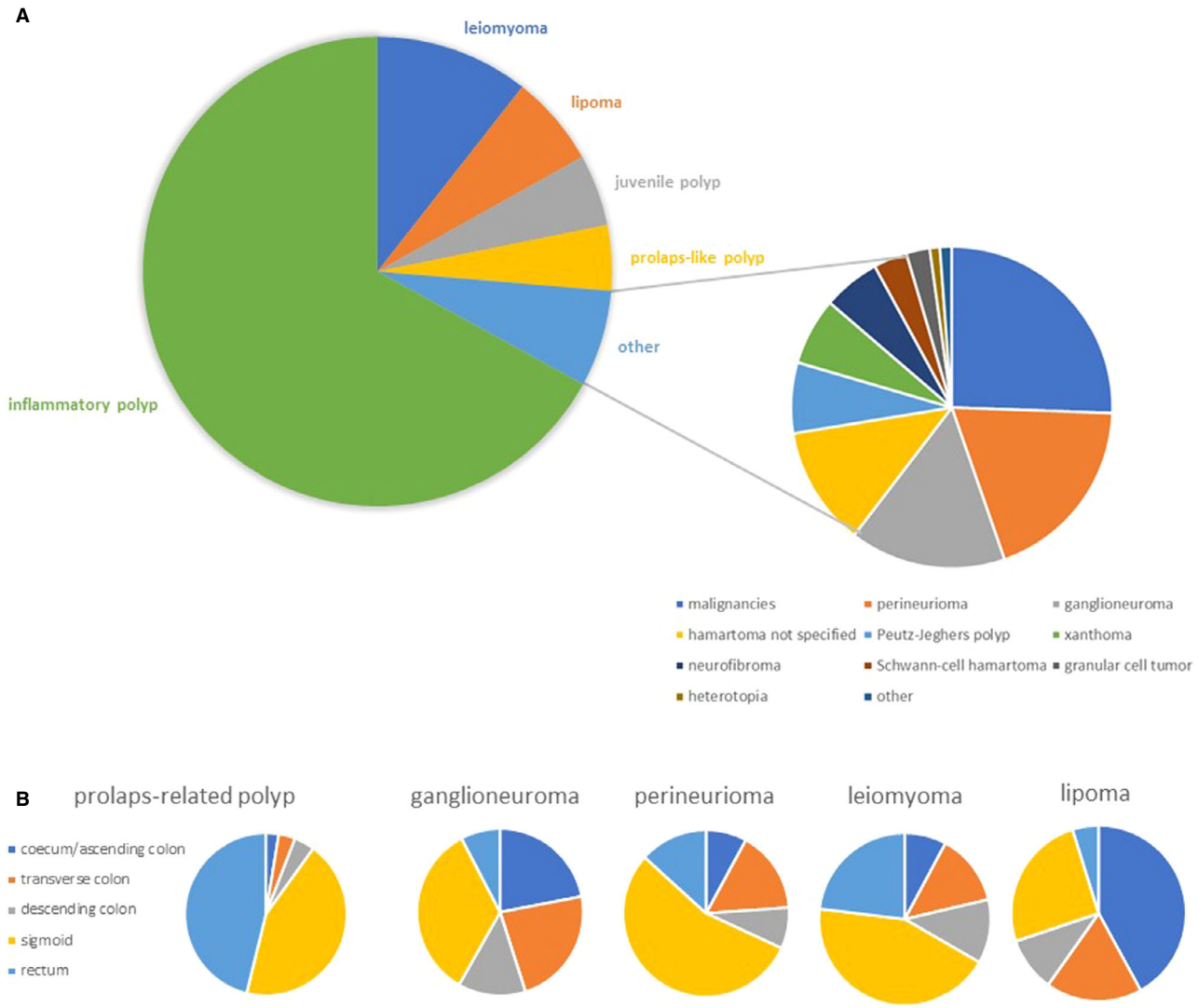

Figure 2. Distribution of polyp diagnoses. **A**: Relative frequency of the different diagnosis on a per-polyp basis. **B:** Distribution according to location in the bowel.

10,000 colonoscopies. In six cases this was the only diagnosis.

Heterotopias were diagnosed very rarely (Table 2), and were located mainly in the rectum, in line with the literature.[18]

HAEMATOLOGICAL MALIGNANCIES

The most common haematological malignancies (Table 3) were mantle cell lymphoma (Figure 3K) and MALT lymphoma (Figure 3L), with an incidence of 0.7 and 0.6 per 10,000 colonoscopies, respectively. In particular, mantle cell lymphoma presented as polyposis, in line with the literature.[19]

NEUROENDOCRINE TUMOURS

Neuroendocrine tumours (NET, also including neuroendocrine carcinomas in this paragraph, Table 3, Figure 3M,N) presented in 6 per 10,000 colonoscopies, which is similar to the incidence in the English population screening program.[20] Most of these were grade 1 NET (82%), and most were located in the rectum (58%).

METASTASES

In 33 patients metastatic disease (Table 3, Figure 3O, P) was present in the colon (1 per 10,000 colonoscopies). However, in a number of cases it was not

Table 2. Summary of very rare diagnoses on a per-patient basis

Diagnosis		Gender	Age	Location	Size
Heterotopia	Bone	Male	69	Descending colon	
	Pancreas	Male	67	Rectum	0.9
	Bronchus	Male	58	Sigmoid	
	Gastric	Female	55	Rectum	
	Gastric	Female	61	Rectum	
	Gastric	Male	73	Rectum	
Langerhans histiocytosis		Female	62	Transverse colon	0.9
Inflammatory fibroid polyp		Male	57	Ascending colon	3.0

entirely clear during colonoscopy whether direct ingrowth in the bowel wall was present. In at least five patients the primary cancer was already known. In line with the literature, gynaecological metastases were the most common.[21] In four patients, the origin of the metastasis was not clear based on histology alone.

OTHER MALIGNANCIES

The other malignancies were three gastrointestinal stromal cell tumours, all low risk. One case with an atypical mesenchymal proliferation in the caecum was, after external consultation, booked out as a low-grade leiomyosarcoma in a 70-year-old female and one Kaposi sarcoma was diagnosed in a 55-year-old male. This patient also presented with a high-grade diffuse large B-cell lymphoma. We do not have information on his HIV status.

Discussion

This study provides an up-to-date overview of the incidence of relatively a rare colorectal diagnoses in a homogeneous group of asymptomatic patients within the setting of FIT-based population screening. For most of these entities, these kinds of data are not or rarely available, or derived from historical large autopsy series. With the increased technical possibilities in modern endoscopy, more and smaller lesions are detected, necessitating information derived from a recent large patient series. Analysis of population screening cohorts, using structured reports from our national database, provides reliable data in large, relatively homogeneous cohorts.

In the Results section, we already provided some background references linked to the specific diagnoses. In general, by the detection of lesions in asymptomatic patients, one could wonder about the clinical impact of our diagnoses. First of all, it is important to note that most of these lesions in general do not warrant follow up. Second, the detection of malignancies other than CRC has a direct impact for patients and their treatment. While the majority of NETs are adequately treated by polypectomy, and chronic lymphocytic leukaemia might not need treatment in all cases, other patients might have received their treatment earlier due to detection in the population screening program.

Finally, there is a small group of patients in whom their hamartomatous polyps might point towards the presence of a hereditary cancer syndrome. For the diagnosis of juvenile polyposis, more than three juvenile polyps are necessary.[10] In 12 patients, two juvenile polyps were diagnosed. So, based on the histological diagnosis alone, these patients were not yet diagnosed with juvenile polyposis. The presence of dysplasia in a juvenile polyp is not part of the definition, but dysplasia is not described in sporadic juvenile polyps.[22] Additional staining for SMAD4 expression might also be helpful in the determination of a syndromic origin of juvenile polyps.[23]

Patients with Peutz–Jeghers polyps, as well as patients with hamartomas that cannot be further classified are also candidates for a more thorough workup for a potential hereditary polyposis syndrome. For the former, the characteristic mucocutaneous pigmentation might be the key to the diagnosis of Peutz–Jeghers syndrome. Nonclassifiable hamartomas can be part of several syndromes, but are particularly often present in Cowden syndrome.[24] In the context of this syndrome, a wide variety of lesions can be observed, including lipomas and lymphoid polyps.

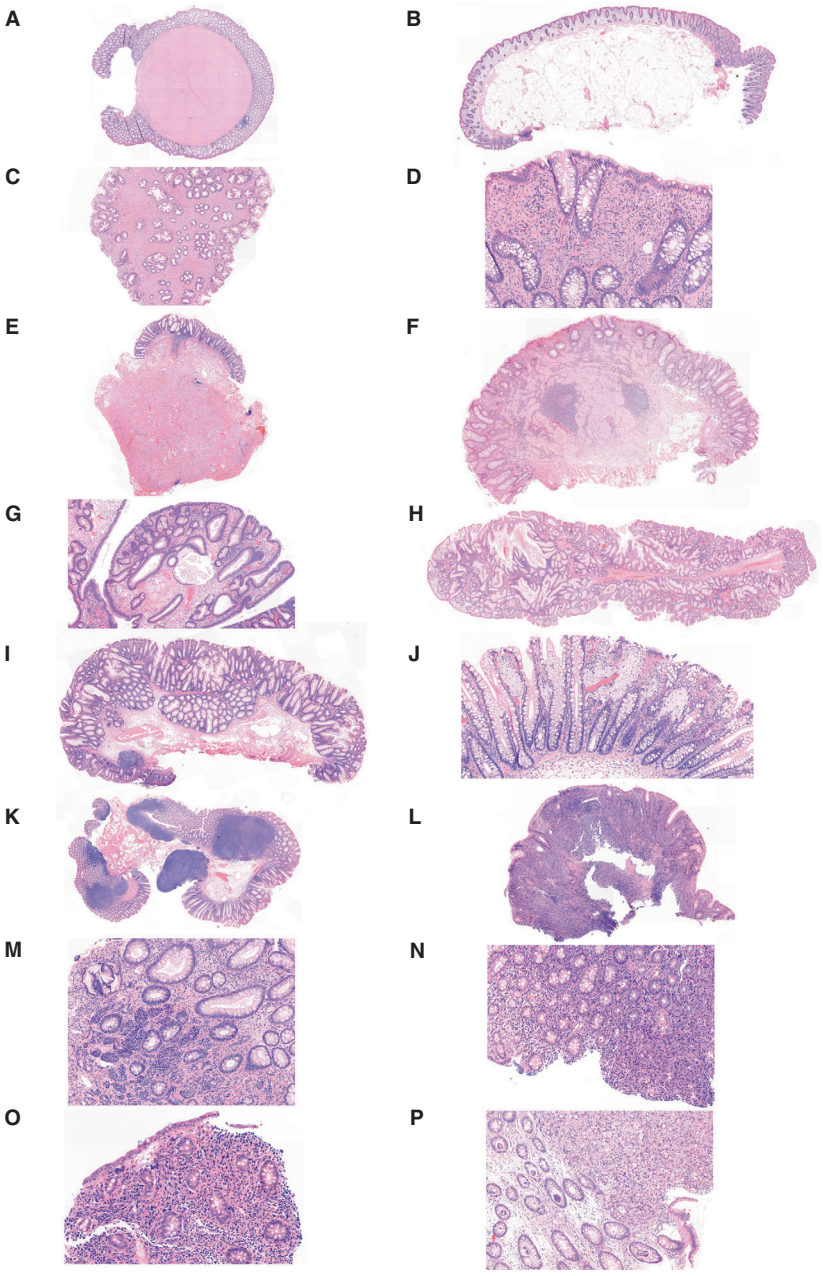

Figure 3. A: Leiomyoma, B: lipoma, C: Perineurioma, D: ganglioneuroma, E: neurofibroma, F: Schwann-cell hamartoma, G: juvenile polyp with dysplasia, H: Peutz–Jeghers polyp, I: prolapse-related polyp, J: xanthoma, K: mantle cell lymphoma, L: MALT lymphoma, M: neuroendocrine tumour, N: neuroendocrine carcinoma, O: Metastasis of cutaneous melanoma, P: Metastasis of gastric cancer.

The presence of multiple ganglioneuromas, as observed in seven of our patients, is considered a major criterion for this diagnosis.[25] This was well considered by the reporting pathologists, as evident by additional remarks in the conclusion of their reports, suggesting genetic counselling.

However, the distinction between postinflammatory polyps and hamartomatous polyps might be impossible. One could argue that, based on the age of the screening population, the chances of discovering a hereditary cancer syndrome (i.e. juvenile polyposis or Peutz–Jeghers syndrome) are low. Indeed, the majority of patients with Peutz–Jeghers syndrome are diagnosed before their thirties.[26] Careful review can distinguish between Peutz–Jeghers polyps and mimics,[27] but true sporadic Peutz–Jeghers polyps are extremely rare. Additional clinical information is essential for the final diagnosis. The overlap between juvenile polyps and inflammatory polyps is evident, and some pathologists do not diagnose juvenile polyps in older patients, but refer to "inflammatory polyp, juvenile type" instead.[28] For juvenile polyposis,

Table 3. Summary of malignant diagnoses per patient

Diagnosis	Type/origin	Number of patients	Patients with more than 1 localisation
Hematologic	Mantle cell lymphoma	25	8
	MALT lymphoma	16	1
	Diffuse large B-cell lymphoma	11	1
	CLL-SLL	4	2
	Follicular lymphoma	3	—
	Undefined lymphoma	2	—
	T-cell lymphoma	1	—
	EBV-B-LPD	1	—
	Plasmacytoma	1	—
Soft tissue	GIST	3	—
	Leiomyosarcoma	1	—
	Kaposi sarcoma	1	—
Neuroendocrine	NET G1	163	3
	NET G2	15	—
	NET G3	5	—
	NET unspecified	3	—
	NEC	12	—
Metastases	Breast	6	2
	Lung	2	1
	Ovary*	8	2
	Pancreas	1	1
	Melanoma	6	3
	Urinary bladder	2	1
	Prostate*	3	—
	Cervix*	1	-—
	Cancer of unknown primary	4	—

CLL-SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; EBV-B-LPD, Epstein–Barr virus-associated lymphoproliferative diseases, B cell type; GIST, gastrointestinal stromal tumour; MALT, mucosa-associated lymphoid tissue; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour.
*Distinction between direct invasion and metastasis was not clear on biopsy.

the mean age of diagnosis is 25 years, with a wide age range (0–86 years).[29] However, juvenile polyps can also occur as part of Cowden syndrome, which is more difficult to diagnose.[30] In order to distinguish simple postinflammatory polyps from these specific hamartomas, careful histological review in combination with clinical examination and (family) history is necessary. It might well be that most cases would be better diagnosed as postinflammatory polyps.

Another potential pitfall is the recognition of prolapse-related polyps. In particular in the rectum, these might be misdiagnosed as serrated polyps.[31–33] While prolapse-related polyps fall into the spectrum of solitary ulcer syndrome, these are characterised by

elongated and distorted crypts, with hyperplastic features, surrounded by proliferation of smooth muscle fibres from the muscularis mucosa. The presence of these stromal changes should prevent the diagnosis of a sessile serrated lesion,[31] which can be supported by the lack of BRAF mutations.[32]

It is well known that colorectal cancer and precursors can be detected by (microscopic) blood in the stool. For other malignancies and the larger polyps, blood loss can also be expected. In addition, most patients with other polyps presented with colorectal cancer or precursors as well. However, small numbers of patients present with only minute lipomas or xanthomas (no other synchronous lesions present) that are most probably not the cause of a positive FIT. Potential causes include the coexistence of haemorrhoids, medications,[34] as well as, rarely, upper gastrointestinal cancers.[35] However, the incidence of the latter is too low to warrant standard workup of these patients.

In this study, we present a timely overview of relatively rare diagnosis on colorectal biopsies and polypectomies in the setting of a national FIT-based CRC screening program to provide incidence data and speculate about clinical consequences.

Author contributions

IN: designed the study, analysed the data, and wrote the article, MEVB: critically reviewed the article and provided the illustrations, CCHJK: provided and analysed the data and critically reviewed the article, ED and NAS: critically reviewed the article. No funding was obtained for the current study.

Conflict of interest

No conflict of interest declared

Data availability statement

The data that support the findings of this study are available from PALGA, but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data, however, are available from the authors upon reasonable request and with permission of PALGA.

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