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Lessons from Lynch syndrome: a tumor biology-based approach to familial colorectal cancer

Daniel D Buchanan, PhD,

Familial Cancer Laboratory, QIMR, Herston Q 4006, Australia, Tel.: +61 733 620 498

Aedan Roberts, BSc (Hons),

Familial Cancer Laboratory, QIMR, Herston Q 4006, Australia, Tel.: +61 733 620 493

Michael D Walsh, BSc,

Familial Cancer Laboratory, QIMR, Herston Q 4006, Australia, Tel.: +61 738 453 775

Susan Parry, MBChB, FRACP, and

Genetic Services, Auckland City Hospital, & Department of Gastroenterology & Hepatology, Middlemore Hospital, Auckland, New Zealand, Tel.: +64 930 749 49

Joanne P Young, PhD[†]

Associate Professor, Familial Cancer Laboratory, QIMR, Herston Q 4006, Australia, Tel.: +61 733 620 490, Fax: +61 733 620 108

Daniel D Buchanan: daniel.buchanan@qimr.edu.au; Aedan Roberts: aedan.roberts@qimr.edu.au; Michael D Walsh: michael.walsh@qimr.edu.au; Susan Parry: sparry@adhb.govt.nz; Joanne P Young: joanne.young@qimr.edu.au

Abstract

Colorectal cancer (CRC) develops within precursor lesions in the single-celled epithelial lining of the gut. The two most common epithelial lesions are the adenoma and the serrated polyp. CRC is also one of the most familial of the common cancers, and just as there are syndromes associated with increased risk of CRC arising in adenomas, there are also syndromes with increased CRC risk associated with serrated polyps. In this article, we describe the features of such a syndrome, familial serrated neoplasia, which distinguish it from the well-characterized condition Lynch syndrome (or hereditary nonpolyposis CRC), and show that the molecular pathology of tumors forms the basis for this distinction. Lynch syndrome CRC arises almost exclusively within adenomatous precursor lesions, in contrast with familial serrated neoplasia where at least half of the cancers develop in serrated polyps. Finally, rare families exist in which both conditions segregate independently, producing a difficult diagnostic picture.

Keywords

familial serrated neoplasia; hyperplastic polyposis; Lynch syndrome; *MUTYH*-associated polyposis; Somatic *BRAF* mutation

[†]Author for correspondence: Familial Cancer Laboratory, QIMR, Herston Q 4006, Australia • Tel.: +61 733 620 490 • Fax: +61 733 620 108 • joanne.young@qimr.edu.au.

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Lynch syndrome, a familial cancer predisposition associated with defective DNA mismatch repair (MMR) and consequent increased risks for colorectal and endometrial malignancy in particular, was first recognized in a large family by Warthin in the early 20th Century. Clinical definitions for the recognition of Lynch syndrome, such as the Amsterdam I Criteria, had previously been based on the pattern of occurrence of cancers in multicase families [1,2]. However, it quickly became apparent that only half of the families meeting the Amsterdam Criteria demonstrated DNA MMR deficiency in their tumors [3,4]. Conversely, with both modern trends towards smaller and more scattered families, as well as the recognition of lower penetrance mutations, patients who have Lynch syndrome may not meet the clinical criteria for its recognition. Today, Lynch syndrome is largely defined by the MMR-deficient biology of its tumors, thus largely overcoming these previous limitations. Recognition of Lynch syndrome has become a paradigm for an evolving set of clinical criteria based on increasing understanding of the condition over time [5].

As a consequence, the definition of familial colorectal cancer (CRC) type X has emerged in recent times as an Amsterdam I familial configuration in the absence of MMR deficiency to account for the balance of Amsterdam I families who do not have Lynch syndrome [6]. Type X CRC has become synonymous with unexplained familial CRC that is microsatellite stable, and its criteria are also likely to follow a path of evolution over time, although the retention of stringency, at least in the initial stages, may serve to limit the background noise for gene discovery. A familial CRC that fits neither of these categories, but is sometimes mistakenly included in both, was reported from New Zealand in 1996, in which the most striking feature was ‘giant hyperplastic polyps’ in multiple family members [7]. In this landmark publication, Jass and colleagues not only prepared the ground for the recognition of the serrated pathway of CRC development at a fundamental level, but also described a novel syndrome of CRC predisposition completely distinct from our current understanding of what constitutes either Lynch syndrome [8,9] or familial CRC type X [6,10]. Importantly, it was the detailed examination of multiple tumors in this initial family that was crucial to its recognition as a separate syndrome.

The CRC-affected members of the New Zealand kindred comprised a mother and five of her ten offspring. Both the mother and one of her children developed CRC before the age of 50 years, thereby meeting the Amsterdam Criteria of the day for hereditary nonpolyposis CRC (or Lynch syndrome). However, pathology review and molecular analysis revealed several features that deviated from the accepted presentation of Lynch syndrome, specifically, multiple large hyperplastic and mixed hyperplastic/adenomatous polyps, as well as the majority of CRC demonstrating no ‘replication errors’ (now known as microsatellite instability [MSI]). One exceptional family member presented with two synchronous CRCs, and a large hyperplastic polyp, all with some evidence of MSI, although the level of the MSI was not clear. Hyperplastic polyps varied in size among affected family members, with the largest measuring 40 mm. Furthermore, two out of five offspring in the third generation of this family had multiple polyps, including ten hyperplastic, one tubular and a mixed polyp, at younger ages of onset than would be expected in the general population [11]. Importantly, at least two members of the family in the second generation had a colonic landscape consistent with hyperplastic polyposis, demonstrating multiple large hyperplastic polyps. Details of the pedigree are given in Figure 1, and of the affected family members in Table 1.

Diverse presentations of hyperplastic polyposis

Hyperplastic polyposis syndrome (HPS) is a colonic polyposis condition presenting at a wide range of ages (11–83 years) [12–15], with the bulk of patients reported to be in the sixth or seventh decades of life [16,17]. HPS has been recognized since the late 1970s but has not, until

very recently, been widely considered to be a pathologic or a genetic entity. The polyposis in HPS is frequently pancolonic [18]; however, polyps may be concentrated in either the distal or proximal colon [19]. Current evidence suggests that HPS [18], and serrated polyps in general [20,21], are more common in Europeans, and this may account for its apparent rarity in some populations. In addition, an association between current cigarette smoking and serrated polyps also increases the probability that HPS has at least one environmental modifier [21–24]. The fundamental defect in HPS has yet to be elucidated; however, the involvement of widespread DNA methylation in the normal mucosa of patients with HPS suggests deregulation of an epigenetic control mechanism [25].

The current WHO criteria for the recognition of HPS (a condition that was first described in 1977 by Spjut and Estrada [26]) are any of the following symptoms (Box 1) [27]:

- At least five histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, two of which are greater than 10 mm in diameter;
- Any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis;
- More than 30 hyperplastic polyps of any size but distributed throughout the colon.

Box 1

WHO criteria for hyperplastic polyposis syndrome

- At least five histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, two of which are greater than 10 mm in diameter; or
- Any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis; or
- More than 30 hyperplastic polyps of any size but distributed throughout the colon

Data from [27].

Clinical descriptions as well as the WHO criteria for the recognition of HPS were reported and proposed, respectively, for several important reasons. First, since HPS was once considered an innocuous condition of young males [28], it was important to delineate it from the clearly penetrant and clinically severe condition of familial adenomatous polyposis. Second, the foundation criteria were necessarily stringent to ensure that the diminutive hyperplastic polyps observed relatively often in the distal colon of older patients, including those that cluster around rectal cancers, were not included in the definition [29,30].

Although HPS was previously considered to have no significant clinical consequences [28], today, with the wider description of larger numbers of cases, it is now thought to be associated with an increased risk of CRC [17], although quantitation of this risk remains problematic [29,30]. In published series of more than five cases taken together, approximately 40% of HPS patients will present with synchronous CRC [15–19,26,28,31–37]. This has been recently confirmed by a large series in Europe, where 27 out of 77 (35%) of HPS patients presented with CRC [38]. A further important clinical consequence associated with HPS is the increased risk of both CRC [7,39,31,33,36] and possibly extracolonic cancers [40] in the wider family setting of HPS patients. WHO Criterion 2, while at first counterintuitive, addresses the considerable evidence that HPS occurs frequently in a familial context [19,31,33,34,36,37, 41], rather than simply conferring the label of HPS to an individual with a single proximal hyperplastic polyp, and elevates the significance of smaller numbers of hyperplastic polyps in a first-degree relative of an individual with HPS. The risk of CRC to relatives in the families

of individuals with HPS appears to be increased; however, the penetrance for CRC is not as high as in Lynch syndrome [42].

As with the original Amsterdam Criteria for Lynch syndrome, families with serrated neoplasia in multiple kindred members have been described in which no affected individual meets the criteria for HPS [43]. That serrated neoplasia families can be divided about this somewhat arbitrary delineation but share so many features suggests a need for a more expansive approach to this spectrum of presentations based on a constellation of tumor biology features, which has served so well to identify Lynch syndrome. Other problems that arise in the approach to the patient with serrated neoplasia predisposition include the historical under-reporting of hyperplastic polyps, the difficulty in obtaining accurate or cumulative polyp counts, histological subtype designation and distribution within the colon, as well as the need to obtain a detailed personal and family history of CRC and polyps in newly presenting CRC patients. Such data are not always readily available. In addition, the emphasis placed by the WHO criteria on proximal disease in HPS (Box 1) [27] distracts from increasing evidence that in the younger onset HPS patient, distal malignancy is more likely to occur [31,44], suggesting that in patients aged under 50 years, multiple distal neoplasia may also be worthy of notice as well as prompting investigation of family history.

Role of the adenoma in serrated neoplasia predisposition

The complex biology of serrated neoplasia and the plasticity of its developmental pathway, which can give rise to CRC with variable MSI status, and to small numbers of apparently traditional adenomas, in addition to multiple serrated polyps, further contribute to the difficulties in recognizing this condition, and necessitate a more tumor-focused approach. It has been estimated that adenomatous lesions, including those with villous components, are seen in up to 90% of HPS cases [16,17], raising the notion that lesser numbers of traditional adenomas are part of the syndrome. In the New Zealand family described in the opening paragraphs of this review, mixed serrated adenomatous polyps were a prominent feature. Examples of histological subtypes of colorectal polyps are given in Figure 2.

Adenomatous lesions in a serrated neoplasia predisposition may evolve from advanced serrated polyps. The first detailed histological description of HPS was published in 1977, where the observation that adenomatous foci could arise within serrated lesions was made [26]. The presence of such mixed polyps, which demonstrate a very high rate of somatic *BRAF* mutation (80–90%) [45], and therefore by implication, origin in a serrated polyp, provides a plausible precursor lesion for the CRC that arises in HPS [12,26,46–48]. By contrast, traditional adenomas almost never harbor a *BRAF* mutation [49]. CRC in HPS have shown somatic *BRAF* mutation in two out of six cases (33%) in a published report [50], and in eight out of 19 (42%) of a case series [Walsh MD & Young JP, Unpublished Data].

The balance of CRC in HPS demonstrates either somatic *KRAS* mutation or is oncogene-mutation null, and may arise, in the manner of common CRC, from the traditional adenomas that frequently co-exist in patients with HPS [17,18]. Indeed, in reporting the first autosomal dominant family with serrated neoplasia, Jass and colleagues made note of an adenomatous precursor in contiguity with a small CRC, and concluded that the CRC in HPS arises through both the development of dysplasia in serrated polyps, as well as through co-incident traditional adenomas [7].

Somatic *KRAS* mutation straddles the divide between serrated and adenomatous polyps and is mutually excluded in lesions bearing a *BRAF* mutation [51]. It is observed in goblet cell hyperplastic polyps [52], which rarely undergo malignant transformation; however, its presence, albeit less common, in advanced serrated polyps [49], in rare contiguous serrated polyps attached to CRC [Young JP, Unpublished Data] and in the lesions present in bi-allelic mutation

carriers for *MUTYH* [53] suggest that serrated lesions with *KRAS* mutations are not completely devoid of malignant potential. However, *KRAS* mutation exerts its strongest effects on the development of CRC within the adenoma–carcinoma developmental sequence through its acquisition by villous components of adenomas [49,54], ultimately giving rise to approximately a third of all CRC [55].

***MUTYH*-associated polyposis & HPS**

KRAS-mutated serrated polyps are less frequently observed among lesions removed for histological examination in the general population [49]. Consistent with this finding, HPS patients with predominantly *KRAS*-mutated polyps constitute a minor subgroup of HPS and have been reported on at least two previous occasions [19,56]. Current evidence suggests that in at least some [31,53], but not all [19], of these patients, bi-allelic common germline mutation of *MUTYH* may be responsible. Importantly, these cases can be distinguished from the bulk of HPS patients by the demonstration of numbers of adenomas well in excess of those observed in the majority of HPS patients (>25 adenomas). Although germline bi-allelic mutation in *MUTYH* accounts for only 1% of all HPS cases [57], when bi-allelic *MUTYH* mutation carriers are assessed, 18% meet the WHO criteria for HPS [53]. The question now arises as to whether patients such as these are segregating more than one disorder, with concomitant clinical implications.

In contrast to HPS, where first-degree relatives are at increased risk for CRC, the risk to *MUTYH* single-mutation carriers is not substantial, and colonoscopic surveillance is not generally advised for their parents or children. A recent report from Parry *et al.* presents some evidence that individuals with both *MUTYH*-associated polyposis (MAP) and HPS may be segregating two conditions with differing modes of inheritance [58]. In this particular report, they describe a 56-year-old Caucasian male with more than 100 colonic polyps, (10–15-mm adenomas predominating in the proximal colon and <5-mm serrated polyps in the distal colon and rectum) who was demonstrated to be a bi-allelic mutation carrier for the two common European mutations in *MUTYH* [58]. His mother had CRC of the sigmoid colon at the age of 70 years. Interestingly, his 17-year-old symptomatic son had multiple 4-mm hyperplastic polyps in the rectosigmoid, suggesting that an independently segregating predisposition to serrated neoplasia may be present in this family, and that screening therefore needs to also consider the risk to first-degree relatives that serrated neoplasia can present in this setting. For this reason, detailed pathological examination of the polyps in patients with MAP is warranted.

Lynch syndrome & serrated neoplasia in mixed lineage families

An additional scenario that is likely to arise in northern European populations, albeit infrequently, is that of a family with independent segregation of both serrated neoplasia and Lynch syndrome [59,60]. The identification of Lynch syndrome has been greatly assisted by the advent of tumor MSI testing and immunohistochemistry for MMR proteins. More recently, the presence of acquired somatic *BRAF* mutation has been used as a negative predictive test for Lynch syndrome, since the CRC in Lynch syndrome arises within traditional adenomas, a lesion that almost never demonstrates this mutation [61].

However, somatic *BRAF* mutation is not only present in sporadic MMR-deficient CRC but may also be present in the tumors of families with a serrated neoplasia predisposition. Such families have been reported previously [39,43,62], and in a subset of these probands, high-level MSI tumors arise where *MLH1* is methylated and therefore absent on immunohistochemical tests. Such findings may increase the probability that the family could be incorrectly diagnosed as having Lynch syndrome [43]. Furthermore, the presence of a somatic *BRAF* mutation in a tumor from an individual family member could result in their CRC being designated ‘sporadic’ [63]. Therefore, any family in which Lynch syndrome is

suspected or confirmed, but in which a *BRAF* mutation is detected in a young-onset CRC patient, is likely to be segregating two independent CRC predispositions and would benefit from expanded surveillance. Although not all high-level MSI CRC occurring outside Lynch syndrome are sporadic, those which occur in individuals older than 70 years are less likely to be associated with a familial risk of CRC [64].

Conclusion

Colorectal cancer is one of the most familial of the common cancers [5]. It has been estimated that 15% of all CRC is associated with familial aggregation. However, we can definitively identify the underlying genetic cause in only 2% of CRC cases. Just as there are syndromes associated with increased risk of CRC arising in adenomas (Lynch syndrome), there are also syndromes with increased CRC risk associated with serrated polyps. Subsequent to the first report of familial serrated neoplasia, other families have been reported, including 11 from Australia [43], 26 from Sweden [40] and seven from the USA [59]. Further examples of families with serrated neoplasia from the Genetics of Serrated Neoplasia (GSN) study are given in Figures 3 & 4 [101]. Characterization of the genetic basis of serrated neoplasia predisposition is a necessary requirement for assessment of risk to both patients and their relatives. Until a genetic mechanism for HPS is uncovered, with subsequent penetrance and risk assessment studies at a population level, the minimal requirements of what constitutes a serrated neoplasia predisposition will remain undefined. In the interim, the role of genetics departments in assembling the clinical picture of families such as these is likely to become increasingly important [65]. A more complete assessment, including pedigree analysis, pathology review and molecular and immunohistochemical phenotyping on multiple cases, may be of benefit to the diagnosis and management of some families, rather than the diagnosis of a family being based on assessment of a single individual. This is especially true in families with serrated neoplasia where the presence of MSI or immunohistochemical absence of *MLH1*, coupled with an Amsterdam-like pedigree structure, can erroneously lead to a diagnosis of Lynch syndrome [43].

The lack of recognition that accompanies serrated neoplasia and its ability to complicate the presentation of at least *MYH*-associated polyposis [31] and Lynch syndrome [60] constitutes a potential problem in the management of CRC families. Importantly, patients with multiple or advanced serrated polyps may originate from CRC families who fall short of the WHO criteria. Some of these familial configurations are currently included by default under familial CRC type X, and the inclusion of these families within this category is likely to introduce further heterogeneity [66], thus hampering efforts to find the underlying genetic cause of both type X families and those with serrated neoplasia predisposition. The recognition of familial serrated neoplasia as a concept in its own right, and its distinction from Lynch syndrome [67] and MAP (Table 2) is an important step in the wider understanding and characterization of its genetics and biology.

Future perspective

Approximately two-thirds of familial CRC has neither an identified genetic basis nor a defined mode of inheritance, making the management of families particularly difficult. An under-recognized syndrome, familial serrated neoplasia, is associated with northern European ancestry and can present alone or in combination with other syndromes. Important in its recognition is a detailed analysis of both its pathology and molecular features in multiple affected family members, since the plasticity of the familial serrated neoplasia phenotype does not lead to characteristic presentations in individuals, unless the proband has hyperplastic polyposis. With the advances in mutation-finding technologies, it is likely that the genetic basis for familial serrated neoplasia will be identified in the next 5 years, allowing population studies

of genetic penetrance, personal and familial risk of CRC, and interactions with environmental agents such as cigarette smoking, all of which will contribute to optimal management for patients with this condition and their families.

Executive summary

Introduction to familial serrated neoplasia

- Familial colorectal cancer is heterogeneous.
- Serrated neoplasia can occur in a familial setting.
- Approaches to nonsyndromic forms should include a pathology review.
- It has been recognized that familial serrated neoplasia can present in a variety of pedigree configurations.

Hyperplastic polyposis

- Hyperplastic polyposis is associated with personal and familial risks for colorectal cancer.

Role of the adenoma in familial serrated neoplasia

- Adenomas co-occur with multiple or advanced serrated polyps in a family setting and are associated with an increased risk for colorectal cancer.

Serrated neoplasia can interact with other syndromes

- *MUTYH*-associated polyposis.
- Lynch syndrome.

Conclusion

- Unless a familial syndrome is clearly identifiable, pathology review of lesions from more than one affected family member is recommended.

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Bibliography

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

1. Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res* 1998;58:5248–5257. [PubMed: 9823339]
2. Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. *J Natl Cancer Inst* 1997;89:1758–1762. [PubMed: 9392616]
3. Jass JR, Cottier DS, Jeevaratnam P, et al. Diagnostic use of microsatellite instability in hereditary non-polyposis colorectal cancer. *Lancet* 1995;346:1200–1201. [PubMed: 7475662]

4. Jass JR, Pokos V, Arnold JL, et al. Colorectal neoplasms detected colonoscopically in at-risk members of colorectal cancer families stratified by the demonstration of DNA microsatellite instability. *J Mol Med* 1996;74:547–551. [PubMed: 8892060]
5. Castells A, Castellvi-Bel S, Balaguer F. Concepts in familial colorectal cancer: where do we stand and what is the future? *Gastroenterology* 2009;137:404–409. [PubMed: 19540838]
6. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA* 2005;293:1979–1985. Original report of familial colorectal cancer type X. [PubMed: 15855431]
7. Jeevaratnam P, Cottier DS, Browett PJ, Van De Water NS, Pokos V, Jass JR. Familial giant hyperplastic polyposis predisposing to colorectal cancer: a new hereditary bowel cancer syndrome. *J Pathol* 1996;179:20–25. Original case report of New Zealand family with serrated neoplasia. [PubMed: 8691339]
8. Jass JR. Hereditary non-polyposis colorectal cancer: the rise and fall of a confusing term. *World J Gastroenterol* 2006;12:4943–4950. [PubMed: 16937488]
9. Lynch HT, Lynch JF, Lynch PM. Toward a consensus in molecular diagnosis of hereditary nonpolyposis colorectal cancer (Lynch syndrome). *J Natl Cancer Inst* 2007;99:261–263. [PubMed: 17312298]
10. Llor X, Pons E, Xicola RM, et al. Differential features of colorectal cancers fulfilling Amsterdam criteria without involvement of the mutator pathway. *Clin Cancer Res* 2005;11:7304–7310. [PubMed: 16243801]
11. Pendergrass C. Occurrence of colorectal adenomas in younger adults: an epidemiologic necropsy study. *Clin Gastroenterol Hepatol* 2008;6:1011–1015. [PubMed: 18558514]
12. Bengoechea O, Martinez-Penuela JM, Larrinaga B, Valerdi J, Borda F. Hyperplastic polyposis of the colorectum and adenocarcinoma in a 24-year-old man. *Am J Surg Pathol* 1987;11:323–327. [PubMed: 3565675]
13. Cohen SM, Brown L, Janower ML, McCready FJ. Multiple metaplastic (hyperplastic) polyposis of the colon. *Gastrointest Radiol* 1981;6:333–335. [PubMed: 7308714]
14. Keljo DJ, Weinberg AG, Winick N, Tomlinson G. Rectal cancer in an 11-year-old girl with hyperplastic polyposis. *J Pediatr Gastroenterol Nutr* 1999;28:327–332. [PubMed: 10067739]
15. Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. *Gastroenterology* 1996;110:748–755. [PubMed: 8608884]
16. Leggett BA, Devereaux B, Biden K, Searle J, Young J, Jass J. Hyperplastic polyposis: association with colorectal cancer. *Am J Surg Pathol* 2001;25:177–184. [PubMed: 11176066]
17. Rubio CA, Stemme S, Jaramillo E, Lindblom A. Hyperplastic polyposis coli syndrome and colorectal carcinoma. *Endoscopy* 2006;38:266–270. [PubMed: 16528654]
18. Yeoman A, Young J, Arnold J, Jass J, Parry S. Hyperplastic polyposis in the New Zealand population: a condition associated with increased colorectal cancer risk and European ancestry. *NZ Med J* 2007;120:U2827.
19. Carvajal-Carmona LG, Howarth KM, Lockett M, et al. Molecular classification and genetic pathways in hyperplastic polyposis syndrome. *J Pathol* 2007;212:378–385. [PubMed: 17503413]
20. English DR, Young JP, Simpson JA, et al. Ethnicity and risk for colorectal cancers showing somatic *BRAF* V600E mutation or CpG island methylator phenotype. *Cancer Epidemiol Biomarkers Prev* 2008;17:1774–1780. [PubMed: 18628431]
21. Wallace K, Grau MV, Ahnen D, et al. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. *Cancer Epidemiol Biomarkers Prev* 2009;18:2310–2317. [PubMed: 19661090]
22. Ji BT, Weissfeld JL, Chow WH, Huang WY, Schoen RE, Hayes RB. Tobacco smoking and colorectal hyperplastic and adenomatous polyps. *Cancer Epidemiol Biomarkers Prev* 2006;15:897–901. [PubMed: 16702367]
23. Morimoto L, Newcomb P, Ulrich C, et al. Risk factors for hyperplastic and adenomatous polyps: evidence for malignant potential? *Cancer Epidemiol Biomarkers Prev* 2002;11:1012–1018. [PubMed: 12376501]

24. Shrubsole MJ, Wu H, Ness RM, Shyr Y, Smalley WE, Zheng W. Alcohol drinking, cigarette smoking, and risk of colorectal adenomatous and hyperplastic polyps. *Am J Epidemiol* 2008;167(9):1050–1058. [PubMed: 18304959]
25. Minoo P, Baker K, Goswami R, et al. Extensive DNA methylation in normal colorectal mucosa in hyperplastic polyposis. *Gut* 2006;55:1467–1474. [PubMed: 16469793]
26. Spjut H, Estrada RG. The significance of epithelial polyps of the large bowel. *Pathol Annu* 1977;12 (Pt 1):147–170. [PubMed: 917590]
27. Burt R, Jass JR. Hyperplastic polyposis. In: Hamilton SR, Aaltonen LA, editors. *Pathology and Genetics of Tumours of the Digestive System*. IARC Press; Lyon, France: 2000. p. 135–136. Criteria for the recognition of hyperplastic polyposis syndrome
28. Williams GT, Arthur JF, Bussey HJ, Morson BC. Metaplastic polyps and polyposis of the colorectum. *Histopathology* 1980;4:155–170. [PubMed: 7358345]
29. Jass JR. Gastrointestinal polyposis: clinical, pathological and molecular features. *Gastroenterol Clin North Am* 2007;36:927–946. viii. [PubMed: 17996798]
30. Jass JR. Colorectal polyposis: from phenotype to diagnosis. *Pathol Res Pract* 2008;204:431–447. [PubMed: 18541388]
31. Chow E, Lipton L, Lynch E, et al. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. *Gastroenterology* 2006;131:30–39. [PubMed: 16831587]
32. Ferrandez A, Samowitz W, DiSario JA, Burt RW. Phenotypic characteristics and risk of cancer development in hyperplastic polyposis: case series and literature review. *Am J Gastroenterol* 2004;99:2012–2018. [PubMed: 15447765]
33. Hyman NH, Anderson P, Blasyk H. Hyperplastic polyposis and the risk of colorectal cancer. *Dis Colon Rectum* 2004;47:2101–2104. [PubMed: 15657661]
34. Lage P, Cravo M, Sousa R, et al. Management of Portuguese patients with hyperplastic polyposis and screening of at-risk first-degree relatives: a contribution for future guidelines based on a clinical study. *Am J Gastroenterol* 2004;99:1779–1784. [PubMed: 15330918]
35. Place RJ, Simmang CL. Hyperplastic-adenomatous polyposis syndrome. *J Am Coll Surg* 1999;188:503–507. [PubMed: 10235578]
36. Rashid A, Houlihan PS, Booker S, Petersen GM, Giardiello FM, Hamilton SR. Phenotypic and molecular characteristics of hyperplastic polyposis. *Gastroenterology* 2000;119:323–332. [PubMed: 10930367]
37. Renaut AJ, Douglas PR, Newstead GL. Hyperplastic polyposis of the colon and rectum. *Colorectal Dis* 2002;4:213–215. [PubMed: 12780620]
38. Boparai KS, Mathus-Vliegen EM, Koornstra JJ, et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. *Gut*. 2009 (Epub ahead of print). 10.1136/gut.2009.185884
39. Jass JR, Cottier DS, Pokos V, Parry S, Winship IM. Mixed epithelial polyps in association with hereditary non-polyposis colorectal cancer providing an alternative pathway of cancer histogenesis. *Pathology* 1997;29:28–33. [PubMed: 9094174]
40. Vandrovcova J, Lagerstedt-Robinson K, Pahlman L, Lindblom A. Somatic BRAF-V600E mutations in familial colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2006;15:2270–2273. Suggests that families with serrated neoplasia may have a general cancer predisposition. [PubMed: 17119056]
41. Azimuddin K, Stasik JJ, Khubchandani IT, Rosen L, Riether RD, Scarlatto M. Hyperplastic polyps: “more than meets the eye”? Report of sixteen cases. *Dis Colon Rectum* 2000;43:1309–1313. [PubMed: 11005503]
42. East JE, Saunders BP, Jass JR. Sporadic and syndromic hyperplastic polyps and serrated adenomas of the colon: classification, molecular genetics, natural history, and clinical management. *Gastroenterol Clin North Am* 2008;37:25–46. v. [PubMed: 18313538]
43. Young J, Barker MA, Simms LA, et al. Evidence for *BRAF* mutation and variable levels of microsatellite instability in a syndrome of familial colorectal cancer. *Clin Gastroenterol Hepatol* 2005;3:254–263. Describes 11 families with serrated neoplasia. [PubMed: 15765445]
44. Yantiss RK, Goodarzi M, Zhou XK, et al. Clinical, pathologic, and molecular features of early-onset colorectal carcinoma. *Am J Surg Pathol* 2009;33:572–582. [PubMed: 19047896]

45. O'Brien MJ, Yang S, Mack C, et al. Comparison of microsatellite instability, CpG island methylation phenotype, *BRAF* and *KRAS* status in serrated polyps and traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. *Am J Surg Pathol* 2006;30:1491–1501. [PubMed: 17122504]
46. Cooper HS, Patchefsky AS, Marks G. Adenomatous and carcinomatous changes within hyperplastic colonic epithelium. *Dis Colon Rectum* 1979;22:152–156. [PubMed: 446245]
47. McCann BG. A case of metaplastic polyposis of the colon associated with focal adenomatous change and metachronous adenocarcinomas. *Histopathology* 1988;13:700–702. [PubMed: 2466756]
48. Sumner HW, Wasserman NF, McClain CJ. Giant hyperplastic polyposis of the colon. *Dig Dis Sci* 1981;26:85–89. [PubMed: 7460710]
49. Spring KJ, Zhao ZZ, Karamatic R, et al. High prevalence of sessile serrated adenomas with *BRAF* mutations: a prospective study of patients undergoing colonoscopy. *Gastroenterology* 2006;131:1400–1407. [PubMed: 17101316]
50. Beach R, Chan AO, Wu TT, et al. *BRAF* mutations in aberrant crypt foci and hyperplastic polyposis. *Am J Pathol* 2005;166:1069–1075. [PubMed: 15793287]
51. Yuen ST, Davies H, Chan TL, et al. Similarity of the phenotypic patterns associated with *BRAF* and *KRAS* mutations in colorectal neoplasia. *Cancer Res* 2002;62:6451–6455. [PubMed: 12438234]
52. O'Brien MJ, Yang S, Clebanoff JL, et al. Hyperplastic (serrated) polyps of the colorectum: relationship of CpG island methylator phenotype and *K-RAS* mutation to location and histologic subtype. *Am J Surg Pathol* 2004;28:423–434. [PubMed: 15087661]
53. Boparai KS, Dekker E, Van Eeden S, et al. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. *Gastroenterology* 2008;135:2014–2018. [PubMed: 19013464]
54. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988;319:525–532. [PubMed: 2841597]
55. Weisenberger DJ, Siegmund KD, Campan M, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with *BRAF* mutation in colorectal cancer. *Nat Genet* 2006;38:787–793. [PubMed: 16804544]
56. Wynter CV, Walsh MD, Higuchi T, Leggett BA, Young J, Jass JR. Methylation patterns define two types of hyperplastic polyp associated with colorectal cancer. *Gut* 2004;53:573–580. [PubMed: 15016754]
57. Buchanan D, Young J. A perspective on bi-allelic *MUTYH* mutations in patients with hyperplastic polyposis syndrome. *Gastroenterology* 2009;136(7):2407–2408. [PubMed: 19406141]
58. Parry, S.; Woodall, S.; Walsh, M., et al. Surveillance recommendations for individuals with *MUTYH*-associated polyposis and hyperplastic polyps: the dilemma. Presented at: InSiGHT Meeting; Dusseldorf, Germany. 23–27 June (2009);
- 59•. Jarrar A, Church JM, Fay S, Kalady M. Is the phenotype mixed or mistaken? Hereditary nonpolyposis colorectal cancer and hyperplastic polyposis syndrome. *Dis Colon Rectum* 2009;52(12):1949–1955. Deals with the question of misdiagnosed colorectal cancer families. [PubMed: 19934914]
- 60•. Walsh MD, Buchanan DD, Walters R, et al. Analysis of families with Lynch syndrome complicated by advanced serrated neoplasia: the importance of pathology review and pedigree analysis. *Fam Cancer* 2009;8(4):313–323. Demonstrates the co-existence of distinct syndromes in a single family. [PubMed: 19241144]
61. Loughrey MB, Waring PM, Tan A, et al. Incorporation of somatic *BRAF* mutation testing into an algorithm for the investigation of hereditary non-polyposis colorectal cancer. *Fam Cancer* 2007;6:301–310. [PubMed: 17453358]
62. Lagerstedt Robinson K, Liu T, Vandrovcova J, et al. Lynch syndrome (hereditary nonpolyposis colorectal cancer) diagnostics. *J Natl Cancer Inst* 2007;99:291–299. [PubMed: 17312306]
63. Ang PW, Li WQ, Soong R, Iacopetta B. *BRAF* mutation is associated with the CpG island methylator phenotype in colorectal cancer from young patients. *Cancer Lett* 2009;273:221–224. [PubMed: 18778891]
64. Samowitz WS, Sweeney C, Herrick J, et al. Poor survival associated with the *BRAF* V600E mutation in microsatellite-stable colon cancers. *Cancer Res* 2005;65:6063–6069. [PubMed: 16024606]

65. Jaspersion KW, Blazer KR, Lowstuter K, Weitzel JN. Working through a diagnostic challenge: colonic polyposis, Amsterdam criteria, and a mismatch repair mutation. *Fam Cancer* 2008;7(4):281–285. [PubMed: 18176851]
66. Lipkin SM, Afrasiabi K. Familial colorectal cancer syndrome X. *Semin Oncol* 2007;34:425–427. Details the heterogeneity in familial colorectal cancer type X. [PubMed: 17920898]
67. Jass JR, Walsh MD, Barker M, Simms LA, Young J, Leggett BA. Distinction between familial and sporadic forms of colorectal cancer showing DNA microsatellite instability. *Eur J Cancer* 2002;38:858–866. [PubMed: 11978509]
68. Iino H, Simms L, Young J, et al. DNA microsatellite instability and mismatch repair protein loss in adenomas presenting in hereditary non-polyposis colorectal cancer. *Gut* 2000;47:37–42. [PubMed: 10861262]
69. Young J, Simms LA, Biden KG, et al. Features of colorectal cancers with high-level microsatellite instability occurring in familial and sporadic settings: parallel pathways of tumorigenesis. *Am J Pathol* 2001;159:2107–2116. [PubMed: 11733361]
70. Dunlop MG, Farrington SM. *MUTYH*-associated polyposis and colorectal cancer. *Surg Oncol Clin N Am* 2009;18:599–610. Important review of the features of *MUTYH*-associated polyposis. [PubMed: 19793568]
71. Jass JR, Iino H, Ruszkiewicz A, et al. Neoplastic progression occurs through mutator pathways in hyperplastic polyposis of the colorectum. *Gut* 2000;47:43–49. [PubMed: 10861263]
72. Iino H, Jass JR, Simms LA, et al. DNA microsatellite instability in hyperplastic polyps, serrated adenomas, and mixed polyps: a mild mutator pathway for colorectal cancer? *J Clin Pathol* 1999;52:5–9. [PubMed: 10343605]
73. Colebatch A, Hitchins M, Williams R, Meagher A, Hawkins NJ, Ward RL. The role of MYH and microsatellite instability in the development of sporadic colorectal cancer. *Br J Cancer* 2006;95:1239–1243. [PubMed: 17031395]
74. Kambara T, Simms LA, Whitehall VL, et al. *BRAF* mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. *Gut* 2004;53:1137–1144. [PubMed: 15247181]

Website

101. Genetics of Serrated Neoplasia. <http://gsn:qimr.edu.au/index.html>

Figure 1. Familial serrated neoplasia pedigree

I, II and III refer to generations.

†Clear colonoscopy.

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Figure 2. Polyp histological subtypes

(A) Traditional adenoma. (B) Tubulovillous adenoma. (C) Serrated adenoma. (D) Mixed polyp with dysplastic and nondysplastic elements. (E) Sessile serrated adenoma demonstrating bizarre serrated architecture, including lateral branching. (F) Hyperplastic polyp (common serrated polyp).

Figure 3. Familial serrated neoplasia pedigree with no individuals meeting the criteria for hyperplastic polyposis (see Figure 2)

The family demonstrates two young-onset *BRAF*-mutated CRC in a cousin pair.

Solid black symbol: CRC; dotted symbol: advanced serrated polyps; blue top left: stomach cancer; yellow bottom right: cervical cancer; yellow top right: breast cancer; pink bottom right: lung cancer; arrowed individual: proband with advanced serrated polyps.

CRC: Colorectal cancer; MSI-H: High-level microsatellite instability; MSS: Microsatellite stable.

Figure 4. Serrated neoplasia pedigrees where a single individual (indicated by an arrow) meets the criteria for hyperplastic polyposis (see Figure 2)

(A) Recessive-like familial configuration with individual with hyperplastic polyposis and CRC accompanied by only extracolonic cancers in relatives. **(B)** Recessive-like familial configuration with individual with hyperplastic polyposis (no CRC) and no affected relatives. **(C)** Codominant-like familial configuration with individual with hyperplastic polyposis (no CRC), and multiple relatives affected with CRC.

Solid black symbol: CRC; dotted symbol: advanced serrated polyps; blue top left: stomach cancer; yellow top right: breast cancer; red bottom left: pancreatic cancer; pink bottom right: lung cancer.

CRC: Colorectal cancer.

Table 1

Details of affected members of familial serrated neoplasia pedigree.

Individual	Age at presentation (years)	Sex	Polyps	Cancer
I-1	34	F	Unknown	1 × colonic
II-5	64	F	One (30-mm HP)	1 × transverse colon
II-6	73	F	Multiple Eight sampled for histology (three HP and five MP up to 40 mm)	1 × cecum
II-7	68	M	Multiple Ten sampled for histology (two tubular adenomas and eight HP up to 20 mm)	2 × ascending colon
II-8	55	M	Multiple Four sampled for histology (HP up to 25 mm)	1 × ascending colon
II-9	49	F	Unknown	1 × colonic
III-4	43	M	Ten (one MP and HP up to 8 mm)	
III-6	40	F	Two (one tubular adenoma and one HP)	

F: Female; HP: Hyperplastic polyp; M: Male; MP: Mixed adenomatous hyperplastic polyp.

Adapted with permission from [7].

Table 2Distinction of Lynch syndrome from familial serrated neoplasia and *MUTYH*-associated polyposis.

Feature	Familial serrated neoplasia	Lynch syndrome	<i>MUTYH</i> -associated polyposis	Ref.
CRC precursors	Polyps are usually commonly serrated, with fewer atypical serrated polyps and adenomas; 50% of CRC arise in serrated precursors	Almost exclusively traditional adenomas	Traditional adenomas give rise to most of the CRC in MAP	[7,43,68,69]
Excess polyps	Yes; variable numbers up to several hundred	No	In approximately two-thirds of patients with bi-allelic mutation, there is an excess of adenomas; in 18%, there is also an excess of serrated polyps	[7,43,53]
CRC site	Proximal > distal in age ≥ 50 years Distal > proximal in age < 50 years	Proximal > distal	Proximal > distal	[70]
MSI in CRC	MSI-variable; majority are MSS	Almost completely MSI-H	Majority are MSS	[43,71]
MSI in precursors	Rare	Up to 80% are MSI-H	Rare	[43,68,71,72]
MMR IHC	MSI-H only associated with MLH1/PMS2 loss	Any of MSH2, MLH1, MSH6 and PMS2 may be missing from the CRC and approximately 70–80% of the precursors	Very rare, MSI-H only associated with MLH1/PMS2 loss	[73]
<i>BRAF</i> mutation	In approximately 40% CRC	No	Unknown	[74]
Familial configuration	Variable Recessive (HPS with no family history) Codominant (HPS with family history of polyps and CRC) Dominant (multicase CRC and serrated polyp family with no case of HPS) Penetrance for CRC is less than 50%	Mostly autosomal dominant; highly penetrant for CRC; rare double heterozygotes with severe phenotypes	Recessive	[19,31,33,34,36,37,41]
Ethnicity	More common in northern Europeans	Occurs across many ethnicities	Occurs across many ethnicities	[18]
Genetic etiology	Unknown at time of writing	Single germline mutation in <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> or <i>PMS2</i> ; rare double heterozygotes	Bi-allelic germline mutation in <i>MUTYH</i>	

CRC: Colorectal cancer; IHC: Immunohistochemistry; HPS: Hyperplastic polyposis syndrome; MAP: *MUTYH*-associated polyposis; MMR: Mismatch repair; MSI: Microsatellite instability; MSI-H: High-level microsatellite instability; MSS: Microsatellite stable.