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# Hereditary Non-polyposis Colorectal Cancer as a Model for Early Colorectal Cancer

**Jeremy R. JASS**

Department of Pathology, School of Medicine, University of Auckland, Auckland, New Zealand

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***Summary.*** **An understanding of the early morphogenesis of hereditary non-polyposis colorectal cancer (HNPCC) is relevant to screening strategies. If most cancers in HNPCC were to evolve through the classical adenoma-carcinoma sequence, screening and removal of adenomas at relatively long intervals might be a safe and cost-effective approach. 131 cancers from 117 affected members of 34 HNPCC families were reviewed. 104 cancers were initial symptomatic lesions, eight were cancers detected in asymptomatic screened individuals, one was a synchronous cancer and 18 were metachronous cancers. None of the 131 cancers was a small, superficial type. Residual adenoma was present in 3/3 (100%) in-situ cancers, 8/9 (89%) cancers involving only submucosa, 4/14 (29%) cancers limited to the muscle coat and 13/105 (12%) cancers extending beyond the muscle coat. 21/28 (75%) residual adenomas had a villous component. Only one was flat. Of the eight asymptomatic cancers, seven arose within tubular[2] or tubulovillous adenomas.[5] The eighth was not associated with an adenoma but was 35 mm in diameter and extended through the bowel wall. Discrete adenomas (contiguous excluded) were present in 22% of surgical specimens and in 31% of specimens from subjects older than 50 years. A relatively high proportion (30%) had a villous component and 43% were at least 10 mm in diameter. Patients with one or more discrete adenoma in their first surgical specimen were more likely to develop multiple cancers. The findings are consistent with the view that adenomas do not occur with increased frequency in HNPCC but are more likely to be large and adopt a villous configuration. There is little evidence for morphogenetic pathways involving flat adenomas or de novo carcinoma in HNPCC.**

**Key words**—HNPCC, early cancer, morphogenesis, adenoma-carcinoma sequence, de novo cancer.

Correspondence: Prof. Jeremy R Jass, Department of Pathology, School of Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand.

## INTROCUCTION

The morphogenesis of colorectral cancer remains controverisal. There can be no doubt, however, that size, gross appearance and extent of spread of a particular cancer is not merely a factor of the span of time between the dates of initiation and clinical presentation. A small, ulcerating cancer associated with diffuse infiltration and multiple lymph node involvement and a large, protuberant cancer showing no evidence of lymphatic spread represent the extreme ends of a spectrum of pathobiological types of colorectal cancer. These contrasting types of colorectal cancer presumably differ in their morphogenesis and in the nature, order and timing of the molecular events underlying their evolution. By analogy, the precursor lesion, or adenoma, also may range in appearance from a small, flat[1] or depressed[2] lesion showing severe dysplasia to a large, protuberant and mildly dysplastic villous adenoma. Particular types of adenoma and carcinoma may be related histogenetically. The flat adenoma may be the precursor of the small, superficial cancer.[3] Flat adenomas and small, superficial carcinomas share a relative infrequency of K-ras mutations.[4,5] Conversely, villous adenoma is known to be associated with well and moderately differential mucinous adenocarcinoma.[6] Small, superficial cancers have been considered to arise de novo,[7] but it is impossible to exclude the possibility of a pre-existing microadenoma.

Tht evolution of colorectal cancer may also be influenced by particular precancerous conditions. For example sporadic bowel cancer, colitic cancer, hereditary non-polyposis colorectal cancer (HNPCC)[8] and cancer in familial adenomatous polyposis (FAP)[9] may differ in their evolutionary predilection. An understanding of the morphogenesis of cancer in

HNPCC is of practical importance as it relates to screening strategies. If most cancers in HNPCC were to evolve slowly through the classical adenoma-carcinoma sequence, long screening intervals would be relatively safe. Conversely, if significant numbers of high grade cancers apparently arose de novo, screening intervals would need to be shortened. The aim of this study was to review the adenoma-carcinoma sequence in specimens of large bowel cancer obtained from members of HNPCC families.

## SUBJECTS, MATERIALS AND METHODS

Subjects included 117 (61 males and 56 females) with bowel cancer who were members of 34 HNPCC families fulfilling the Amsterdam criteria.[10] Of 131 cancers, 104 were the initial symptomatic lesions, eight were asymptomatic cancers detected at the time of the first colonoscopy, one was a synchronous cancer and 18 were metachronous cancers. 248 affected or at-risk individuals have been colonoscoped on at least one occasion. Three of the screened cancers were malignant adenomas removed by polypectomy. The remaining cancers were contained within surgical specimens.

The prevalence of residual adenoma was related to the extent of direct spread in continuity as achieved for sporadic colorectal cancer.[11,12] Additional discrete adenomas were grouped by size and type and compared with findings in sporadic colorectal cancer.[13,14] The number of adenomas in the initially presenting specimen was related to the risk of multiple colorectal cancer.

**Table 1.** Incidence of contiguous residual adenoma related to depth of malignant invasion

| Depth of invasion | HNPCC | Sporadic CRC* | Sporadic CRC** |
|---|---|---|---|
| In-situ (Tis) | 3/3(100%) | — | — |
| Submucosa (T1) | 8/9 (89%) | 57% | 57% |
| Muscle coat (T2) | 4/14 (29%) | 18% | 43% |
| Beyond muscle coat (T3) | 13/105 (12%) | 11% | 17% |

*Muto et al., 1975[11]; **Eide et al., 1983[12]

## RESULTS

Of the 131 cancers, none was a small, superficial cancer. The frequency of residual adenoma was related to the depth of malignant invasion as shown in Table 1. Seven out of eight cancers detected by screening contained residual adenoma (Table 2). Three were in-situ and four were limited to the submucosa. The cancer with no residual adenoma had extended beyond the bowel wall. The distribution of contiguous adenoma by type is shown in Table 3. The frequency of specimens (initially presenting surgical specimens) harbouring discrete adenomas (contiguous residual adenomas excluded) is shown in Table 4. The distribution of discrete adenomas by type and size is shown in Tables 5 and 6, respectively. The frequency of multiple cancer according to the number of adenomas in the initially presenting surgical specimen is shown in Table 6. A focus of early cancer (synchronous) limited to the submucosa was present in one of the discrete adenomas.

## DISCUSSION

A group of screened patients at high risk of developing colorectal cancers serves as a useful model of the

**Table 2.** Cancers detected colonoscopically in at-risk members of HNPCC families

| Age | Gender | Site | Appearance | Type and size of contiguous adenoma | Spread of cancer | Treatment |
|---|---|---|---|---|---|---|
| 29 | M | Rectum | Sessile polyp | TVA 15mm | T1 | Colectomy & IRA |
| 36 | F | TC | Plaque (35mm) | — | T3 | Colectomy & IRA |
| 64 | M | DC | Polypoid | TVA 30mm | Tis | Resection |
| 54 | M | SC | Polypoid | TA 10mm | T1 | Polypectomy |
| 51 | M | TC | Polypoid | TVA 25mm | Tis | Polypectomy |
| 40 | F | AC | Polypoid | TVA 10mm | T1 | Polypectomy |
| 28 | M | TC | Polypoid | TA 20mm | T1 | Resection |
| 55 | F | AC | Sessile polyp | TVA 50mm | T1 | Colectomy & IRA |

AC: ascending; TC: transverse; DE: descending; SC: sigmoid colon; TA: tubular adenoma; TVA: tubulovillous adenoma; IRA: ileorectal anastomosis

morphogenesis of early colorectal cancer. In this study of patients with hereditary non-polyposis colorectal cancer (HNPCC), seven of eight cancers detected colonoscopically were found to arise within relatively large tubular (two) or tubulovillous (five) adenomas (Table 2). The eighth cancer was a 35 mm plaque that extended through the bowel wall. Within overall series of 131 cancers there was a clear correlation between the presence of residual adenomatous tissue and the depth of malignant invasion (Table 1). This is in keeping with similar observations in sporadic colorectal cancer[11,12] and accords with the view that adenomatous remnants would be destroyed as cancers advance. It is suggested that the classical adenoma-carcinoma sequence serves as the major morphogenetic pathway in HNPCC. It is conceivable, however, that the adenoma-carcinoma sequence would be more evident in a population with a very high incidence of colorectal cancer, as occurs in New Zealand.

The adenoma-carcinoma sequence may show particular modifications in HNPCC. It has been suggested that the frequency and distribution of adenomas in HNPCC may be the same as in the general population.[15] However, the HNPCC mutator genes appear to promote adenoma growth and the development of villosity.[15,16] In the present study, discrete adenomas occurred less frequently in surgical specimens for HNPCC than in specimens of sporadic bowel cancer (Table 4). On the other hand, HNPCC adenomas were more likely to include a villous component (Table 5) and to achieve a larger size (Table 6) than adenomas in sporadic bowel cancer specimens. These effects of the HNPCC genes upon adenomas are presumably exaggerated in the proximal colon, thereby accounting for the well known excess of proximal cancers.

The penetration of HNPCC genes is virtually 100% in high risk countries for colorectal cancer. This means that most individuals must develop at least one adenoma and that the rate of conversion of adenoma to carcinoma must be relatively high. It is evident from autopsy studies that adenomas are uncommon before the age of 50 years,[17] yet cancers in HNPCC usually present in the fifth decade. It is now appreciated, however, that for every macroscopically visible adenoma, there are probably numerous microadenomas or aberrant crypt foci.[18] It is suggested that these begin to develop relatively early in life and that only small numbers will become visible as adenomas. HNPCC genes will presumably accelerate the growth of microadenomas.

It is likely that independent genetic factors will influence the number and growth potential of microadenomas. This would account for the extreme phenotypic variability of HNPCC, such as age of presentation of cancer and frequency of multiple cancers. In this study patients with multiple adenomas in their first surgical specimen were more likely to develop metachronous cancer. Due to the

**Table 3.** Types of contiguous residual adenoma in HNPCC

| Flat adenoma | TA | TV | VA | UN |
|---|---|---|---|---|
| 1 | 5 | 13 | 8 | 1 |

TA: tubular adenoma; TV: tubulovillous adenoma; VA: villous adenoma; UN: undiagnosable

**Table 4.** Percentage of initially presenting specimens harbouring one more discrete adenomas (contiguous adenomas excluded)

| HNPCC (all) | HNPCC (>50 yrs) | Sporadic CRC* | Sporadic CRC** |
|---|---|---|---|
| 22.2% | 30.8% | 35% | 36% |

*Eide, 1986[13] (prospective study); **Chu et al, 1986[14] (retrospective study)

**Table 5.** Types of discrete adenomas (contiguous adenomas excluded) in surgical specimens

| | HNPCC* | Sporadic CRC** |
|---|---|---|
| TA | 31 (70%) | 130 (98%) |
| TV | 11 (25%) | 2 ( 2%) |
| VA | 2 ( 5%) | 0 ( 0%) |

*Initial surgical specimen only; **Eide, 1986[13]

**Table 6.** Size of discrete adenomas in surgical specimens

| Diameter (mm) | HNPCC* | Sporadic CRC** |
|---|---|---|
| 1-4.9 | 11 (25%) | 55 (42%) |
| 5-9.9 | 14 (32%) | 62 (47%) |
| 10-14.9 | 10 (23%) | 8 ( 6%) |
| 15+ | 9 (20%) | 7 ( 5%) |

*Initial surgical specimen only; **Eide, 1986[13]

**Table 7.** Frequency of subjects with multiple cancer according to number of discrete adenomas in initially presenting specimen (adenomas contiguous with cancer excluded)

| No. of adenomas | No. of subjects | Multiple cancer |
|---|---|---|
| 0 | 84 | 9 (10.7%) |
| 1 | 14 | 2 (14.3%) |
| 2+ | 10 | 3 (30.0%) |

Fisher's exact test $p=0.19$ (subjects with adenomas combined)

small number of observations, this trend did not reach statistical significance (Table 7).

The findings of this study do not negate the importance of flat adenomas in the evolution of colorectal cancer. However, they indicate that the preferred morphogenetic pathology in HNPCC is through the polypoid adenoma-carcinoma sequence, at least within a country with a high incidence of colorectal neoplasia.

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