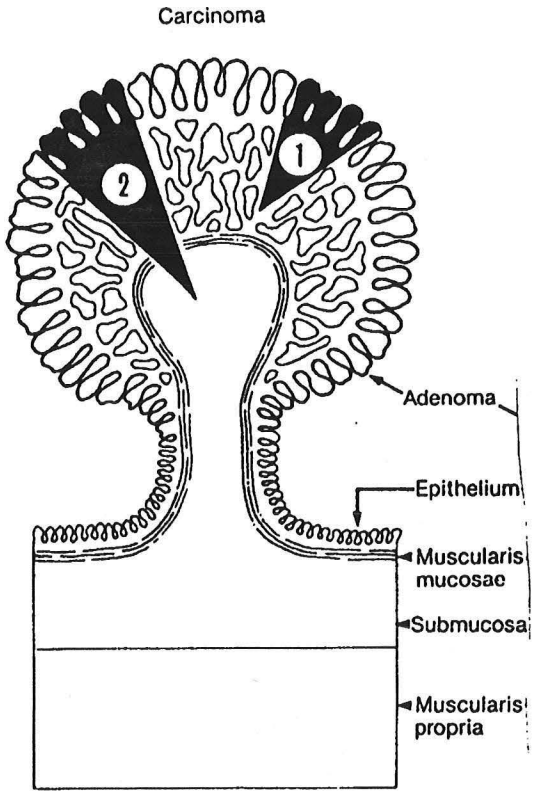
# COLON CANCER

## The Role of Screening and Surveillance

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Colon cancer remains the leading cause of gastrointestinal malignancies and is the second most frequent cause of cancer-related mortality after lung cancer(1). There is now convincing evidence that most colon cancers arise in adenomatous polyps which are therefore considered to be premalignant lesions. Removal of adenomatous polyps by colonoscopic polypectomy before they have reached a malignant stage leads to a substantial decrease in the incidence of colon cancer(2). Since it is not possible to perform colonoscopy on the entire population over a certain age for practical and economic reasons it is necessary to identify risk factors for polyp formation and enroll persons at risk into currently recommended screening and surveillance programs.

It is the purpose of these grand rounds to review our current knowledge of colonic adenoma formation with an emphasis on the molecular events in the adenoma-carcinoma sequence and also to review the results of recently completed prospective and retrospective studies of the effect of screening and surveillance for colon cancer in persons without or with identifiable risk factors.

Colon cancer incidence and mortality

The estimated incidence of colorectal cancer in the U.S. in 1995 was a total of 138,000 new cases with an almost similar incidence among males and females for colon cancer (M:49,000; F:51,000) and a lower incidence for females of rectal cancer (16,500) than males (21,700)(1).

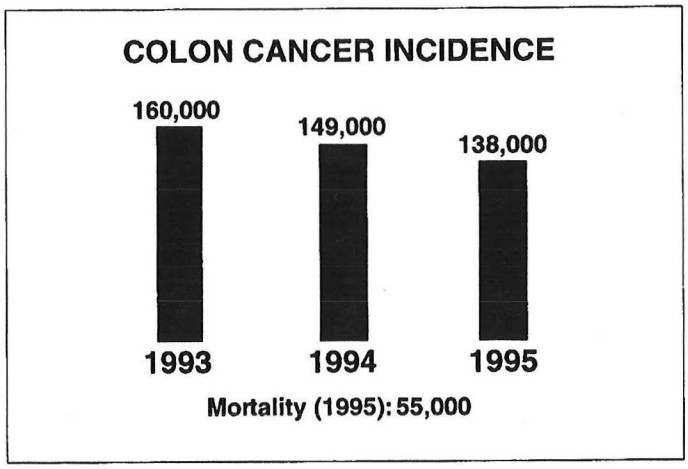


Fig. 1 Incidence and mortality of colorectal cancer (U.S.)

Surprisingly, the incidence of colorectal cancer appears to be decreasing if these numbers are to be trusted. The estimated incidence for colorectal cancer in 1994 was 149,000 and in the preceding years the incidence was around 160,000. The SEER data upon which these numbers are based are collected from nine population-based cancer registries which cover about 10% of the U.S. population (1). It should also be emphasized that the SEER data used for calculation of estimates are at least three years old and thus should be interpreted with caution.

The estimated number for cancer death from colorectal cancer in 1995 was 55,000 and an almost identical number was predicted for 1994. There is however a difference between females and males in age-adjusted cancer death rates as seen in Fig. 2 where the rates per 100,000 have been plotted as a function of time since 1930 (age-adjusted to the 1970 U.S. standard population).

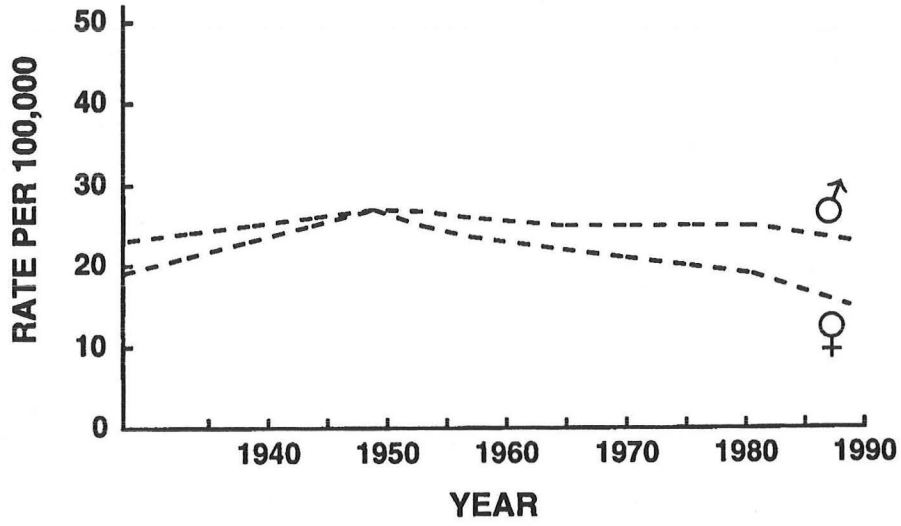


Fig. 2 Age-adjusted cancer death rates in women and men (U.S.)

The rates for both females and males peaked in the late 40's and have since remained fairly constant for males but have shown a steady decrease for females (1). The difference in age-adjusted death rates between males and females and the reason for the continued decrease in rates for females are so far unexplained.

Sporadic and hereditary types of colon cancer

The most common type of colorectal cancer is sporadic where no risk factors for colon cancer can be identified. Sporadic colon cancer accounts for about 80 to 85% of all colorectal cancers (Fig. 3)

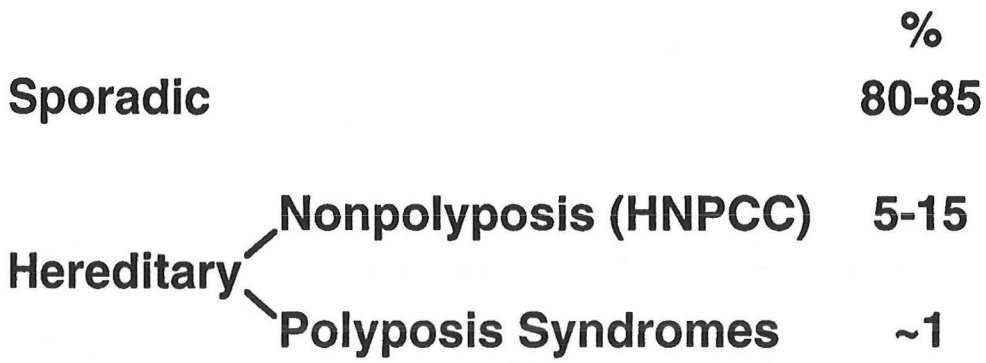


Fig. 3 Case distribution among sporadic and hereditary colon cancer

The hereditary types of colorectal cancers are divided into two major groups: hereditary nonpolyposis colon cancer (HNPCC) and the polyposis syndromes: familial adenomatous polyposis (FAP), Gardner's and Turcot's syndromes. HNPCC accounts for 5 to 15% and the polyposis syndromes account for 1% of all colorectal cancers.(3,4) Hereditary nonpolyposis colon cancer, previously called cancer family syndromes or the Lynch syndromes, is defined by family history and must fulfill strict criteria (Amsterdam criteria) to meet the diagnosis of HNPCC. The criteria were established by an International Collaborative Group in 1991 (5) and are as follows: 1. Three or more

two generations; and 3. At least one case of colorectal cancer should be diagnosed before the age of 50 years (Fig. 4).

- Three or more relatives with colon cancer spanning two generations
- One case a first-degree relative of the other two
- One person diagnosed with colon cancer before age 50

Fig. 4 Amsterdam criteria for diagnosis of HNPCC

Both HNPCC and the polyposis syndromes are inherited in an autosomal dominant fashion and the family history is therefore a very important clue to diagnosis. The polyposis syndromes are characterized by the development of hundreds of adenomatous polyps in the early teens and almost invariably lead to colon cancer in one or more of the adenomatous polyps in the third to fourth decade if diagnosis and treatment are delayed. Colon cancer in patients with HNPCC also arises in adenomatous polyps. Despite the name 'nonpolyposis' HNPCC patients have an increased propensity for adenomatous polyp formation but much fewer than patients with the polyposis syndromes. Adenoma formation in HNPCC tends to occur at a younger age than adenoma formation in the general population and they are predominantly found in the right colon. There are important distinctions between colorectal cancers in HNPCC and sporadic cases that reflect adenoma development and distribution in these two groups of patients as outlined in Fig. 5.

| | HNPCC | Sporadic |
|---|---|---|
| Mean age at diagnosis (yr) | 45 | 67 |
| Multiple cancers (%) | 35 | 4-11 |
| Proximal to splenic flexure (%) | 72 | 35 |
| Excess cancers at other sites | YES | NO |

Fig. 5 Characteristics of colon cancer in HNPCC and sporadic cases.

Colorectal cancers in HNPCC occur at a significantly younger age than sporadic cases, are often multiple and two-thirds of the cancers are found proximal to the splenic flexure. In addition, HNPCC is associated with an excess rate of cancers at other sites (endometrium, ovary, stomach; Lynch II) which is not typical of sporadic colon cancer. Thus, adenomatous polyps in

both HNPCC and the polyposis syndromes are the precursors for development of colon cancers in these hereditary syndromes.

There is now overwhelming evidence that adenomatous polyps are also the precursors of cancer in sporadic colon cancers. The evidence has been accumulating over the past decade and is based on the following observations: 1. The prevalence of colonic adenomas parallels the prevalence of colon cancer. Adenoma development precedes colon cancer by 5 to 10 years; 2. The site distribution and frequency of adenomatous polyps within specific colon segments parallel those of colon cancer; 3. Carcinoma in situ is most often observed in an adenomatous polyp and is rarely found within normal colon mucosa; 4. Adenomatous tissue is often found within or surrounding a colon cancer; 5. The molecular changes observed in adenomas are also found in colon cancers; and 6. Removal of adenomas reduces the risk of development of colon cancer (Fig. 6)(6).

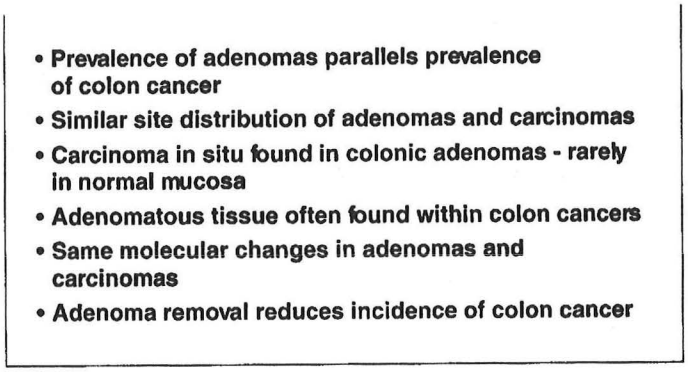


Fig. 6 Evidence for adenoma-carcinoma sequence.

These observations have led to the formulation of the 'adenoma-carcinoma sequence'. The only exception to the rule is colon cancers in patients with chronic ulcerative colitis. These cancers arise in a dysplastic lesion and do not go through an adenoma stage.

Adenoma formation and characterization

Adenomatous polyps are neoplastic lesions of the epithelial cells of the colon which lead to abnormal cellular proliferation and differentiation. A postulated scheme for polyp formation is illustrated in Fig. 7 which shows five colonic crypts(7).

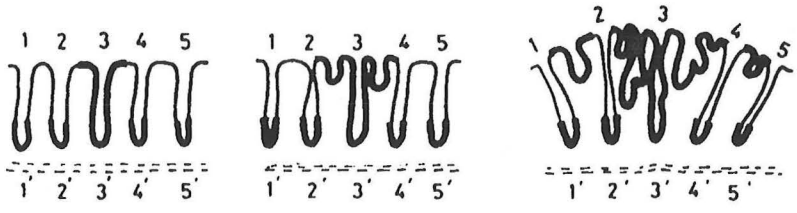


Fig. 7 Proposed scheme for colonic polyp formation.

The proliferative zone is restricted to the lower one-third of normal crypts (1,2,4 & 5). New cells are continuously formed in the crypts and march up the crypt and finally undergo apoptosis and are sloughed off at the crypt opening. Crypt 3 is abnormal (neoplastic) and the proliferative zone has expanded to the entire crypt length. The continuous proliferation of the abnormal cells results in formation of tubular structures and protrusion into the lumen. Further growth of the neoplastic cells leads to branching and infolding of the tubular structures with formation of villus-like structures.

Adenomas are characterized by size, histology and the degree of dysplasia. Histologically, adenomatous polyps are divided into three types, tubular, tubulovillous and villous adenomas according to the predominant structural features and the amount of the villous component(8). Adenomatous polyps are by definition dysplastic lesions and the degree of dysplasia is commonly divided into mild, moderate and severe dysplasia according to the degree of cytological atypia and structural abnormalities of the glands according to established criteria (9). The characteristics of colonic adenomatous polyps in terms of size, histology and degree of dysplasia is shown in Fig. 8. The data stems from a large prospective study of colonic polyps, the National Polyp Study, which was initiated in 1980 and include data from seven centers in the U.S. (10).

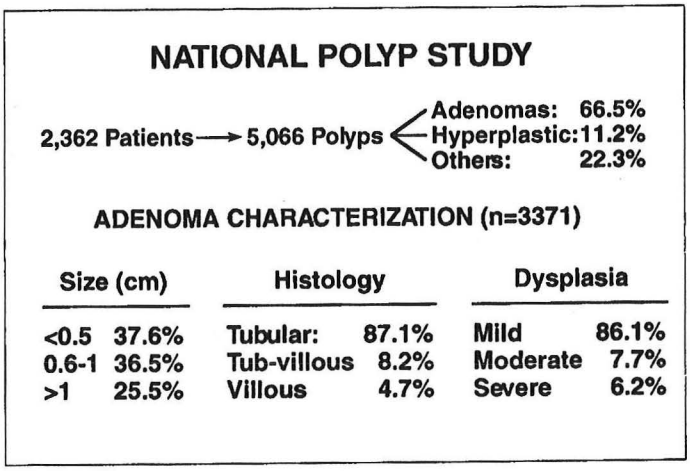


Fig. 8 Size, histology and degree of dysplasia in adenomatous polyps

It is apparent that most polyps are small to medium sized ( <1cm) tubular adenomas with mild grade dysplasia. The frequency of high grade dysplasia was related to both adenoma size and the villous component as shown in Fig. 9 & 10.

Thus, as an adenoma grows in size it attains more villous characteristics and an increasing degree of dysplasia. The presence of multiple adenomas and increasing age also increased the risk of high grade dysplasia (10). The concept that high grade dysplasia is a precursor for malignant transformation is supported by several studies (11).

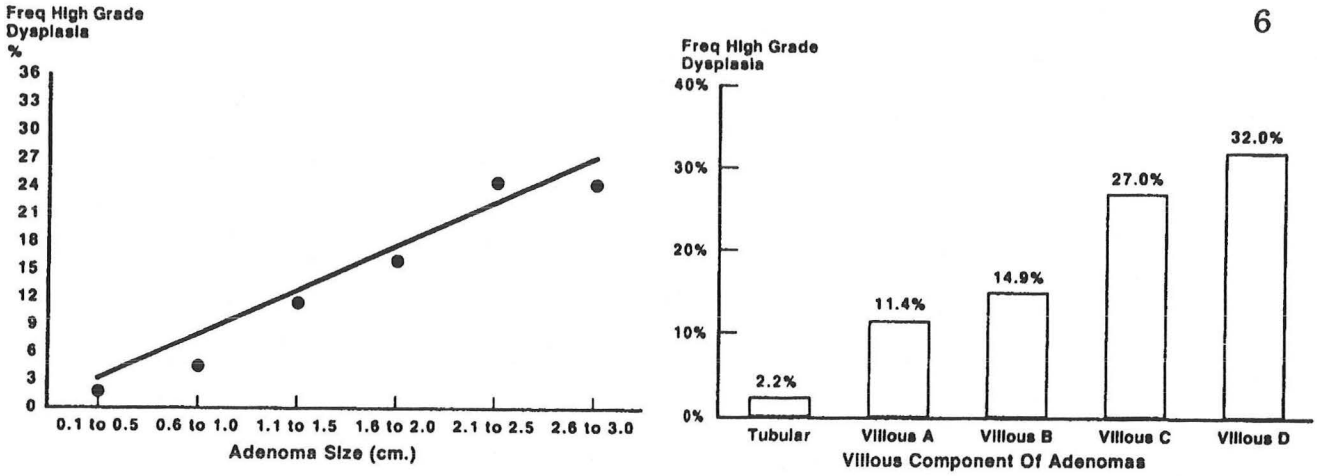


Fig. 9 & 10 Correlation between frequency of high-grade dysplasia and adenoma size and percent villous component.

Molecular changes in the adenoma-carcinoma sequence

The biochemical changes that result in uncontrolled cellular proliferation have long remained an enigma. There has however been a remarkable advance in knowledge of genetic and biochemical alterations in neoplasia over the past decade due to the advent of powerful molecular biology techniques. Vogelstein and his collaborators at Johns Hopkins have been at the forefront of unraveling genetic alterations in colorectal tumorigenesis. In a landmark study in 1988 they demonstrated that several genetic alterations are observed in the progression from adenoma to carcinoma (12). The study looked for ras-gene mutations and allelic deletions on chromosome 5, 17 and 18 in colonic adenomas and carcinomas. The percent of tumors with genetic alterations of these four markers in three classes of adenomas and carcinomas are shown in Fig. 11

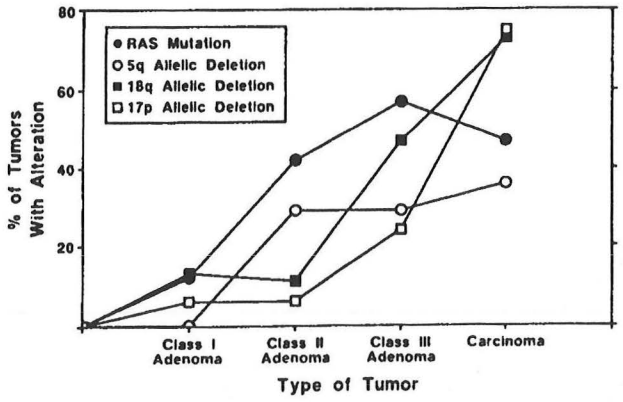


Fig. 11 Frequency of genetic alterations in colonic adenomas and carcinomas.

It is apparent that the number of genetic alterations increases as an adenoma progresses from class I to III and to carcinoma. It was concluded that the development of colon carcinoma in an adenomatous polyp is the result of several genetic alterations that accumulate during progression from adenoma to carcinoma. A recent study has substantiated these observations with a detailed analysis of the sequence and rate of allelic losses in colonic adenomas and carcinomas using microdissection and markers for loci on chromosome 5, 17 and 18 (13). The results of these studies are shown in Fig. 12.

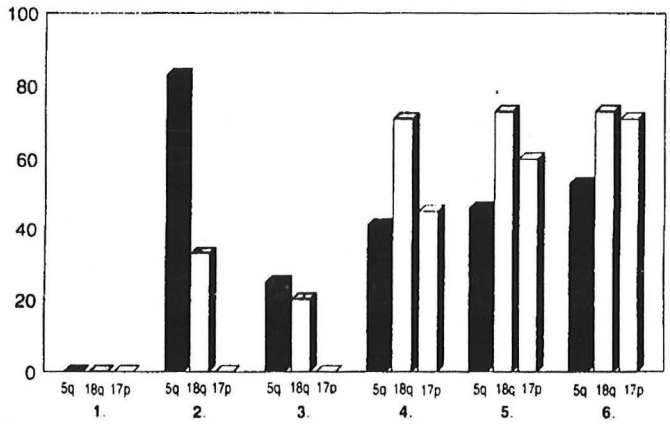


Fig. 12 Allelic losses in adenomas with increasing degree of dysplasia and in carcinomas

Allelic losses or loss of heterozygosity (LOH) in percent are illustrated in normal mucosa (1), adenomas with low grade dysplasia (2), moderate and high grade dysplasia (3 & 4), invasive cancer (5) and adenocarcinoma (6). Loss of heterozygosity in normal colonic mucosa was never observed even though the tissue was adjacent to either adenoma or carcinoma. LOH on chromosome 5q appears to be an early event in adenoma formation and LOH of 17p was never observed in mild and moderate degree of dysplasia. In high grade dysplasia, invasive cancer and carcinoma there was a progressive increase in LOH at 5q, 17p and 18q. The authors proposed a model for neoplastic progression as shown in Fig. 13.

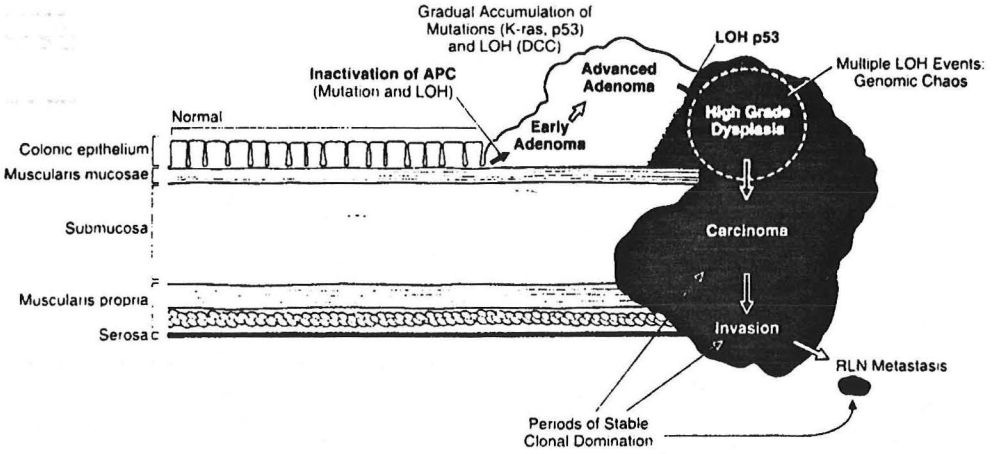


Fig. 13 Genetic events in progression from early adenoma to carcinoma.

The earliest change observed in this study was LOH at the 5q locus in the transition from normal mucosa to adenomatous polyps with low grade dysplasia. In addition, LOH at the 17p locus was only observed in polyps with high grade dysplasia and later stages. It was proposed that the initial event in adenoma formation is inactivation of the locus on 5q which endows the cells arising from that clone with a growth potential. Additional genetic alterations such a ras mutations, which were not studied, may lead to further cell proliferation and increased susceptibility to other mutations. Inactivation of the locus on 17p appears to be a crucial step in the transition from high grade dysplasia to invasive cancers.

Many of the genes involved in colonic tumorigenesis have now been identified. There are two genes on chromosome 5q which are altered in colon

cancer: the APC (adenomatous polyposis coli) and the MCC (mutated in colon cancer) genes. The two genes are in close proximity to each other (14). The protein product of the APC gene interacts with ß-catenin and E-cadherin in zonula adherens on the lateral cell membranes. The complex functions as a cell adhesion molecule (15-18). Inactivation of the APC gene may therefore lead to uninhibited cell growth. The product of the MCC gene has not been identified. It is speculated that it also has a role in cell adhesion. Ras genes (K-ras, N-ras and H-ras) are located on chromosome 12. These genes encode small membrane bound proteins with GTP-ase activity(19). Mutations of these genes may result in absent enzymatic activity of the protein product and signal transduction by GTP remains constantly turned on which has been shown to transform certain cultured cell lines (19). K-ras mutations in colon adenomas and carcinomas are typically found in codon 12 and 13 of the gene. It has recently been shown that APC alterations precede ras mutations in small adenomas (20). The genetic alterations observed on chromosome 17p are found within the gene p53. The protein product of p53 functions as a regulator of the cell cycle and stops cells with abnormal DNA in cell cycle progression and directs these cells into an apoptotic pathway(21). Loss of p53 function is a common observation in many cancers. Finally, the locus tested on chromosome 18q encodes a gene called DCC (deleted in colon cancer). The product of this gene has not been characterized but it may also have a function in cell adhesion (Fig. 14).

**ONCOGENES AND TUMOR SUPRESSOR GENES INVOLVED IN COLON CARCINOGENESIS**

| Gene | Locus | Function |
|---|---|---|
| APC | 5q21 | Cell adhesion |
| MCC | 5q21 | Cell adhesion? |
| K-ras | 12p12 | Signal transduction |
| p53 | 17p53 | Cell cycle regulator |
| DCC | 18q21 | Cell adhesion? |

Fig. 14 Oncogenes and tumor supressor genes in colonic carcinogenesis.

The genetic alterations in hereditary nonpolyposis colon cancer have been discovered within the past two years. In 1993 Vogelstein's group in collaboration with Finnish investigators reported a linkage analysis of two large kindreds of HNPCC patients, where they explored the whole genome with a large set of microsatellite markers and found a highly significant linkage to chromosome 2 (22). Microsatellites are short dinucleotide repeats (CA)n scattered throughout the genome and usually found in introns and between genes. There are 50,000 to 100,000 (CA)n repeats in the genome. (23). In 11 of 14 tumor tissues longer or shorter alleles of microsatellites than the alleles in normal tissue were observed which suggested a replication error in the tumor tissue (24).

Errors in DNA may arise during DNA duplication in mitosis and elaborate repair systems for error correction have been identified in bacteria, yeast and humans. A mismatch repair system found in bacteria is shown in Fig. 15

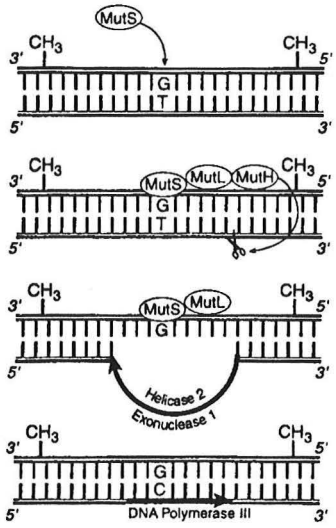


Fig. 15 Mismatch repair system in bacteria.

which shows two DNA strands where a wrong base (T) has been inserted opposite G(25, 26). The mutS protein recognizes and binds to the mismatched sequences followed by mutL and mutH proteins which nicks the incorrect strand. Helicase 2 unwinds the strand and the sequence with incorrect base is removed by an exonuclease and finally the gaps is filled with correct bases by DNA polymerase (27). Within a few months Vogelstein and another group reported that the human homolog of mutS called hMSH2 was mutated in HNPCC and that the gene was located on chromosome 2 as previously shown by linkage analysis (28, 29). Three additional genes involved in mismatch repair in humans, hMLH1, hPMS1 and hPMS2, have now been identified in tumors from HNPCC patients( 30,31, 32). These three genes are all related to the prokaryotic mutL gene. The chromosomal location of the four genes are shown in Fig. 16.

**MISMATCH REPAIR GENES**

| Prokaryotic | Human | Human Locus |
|---|---|---|
| mutS | hMSH 2 | 2p22 |
| mutL | hMLH1 | 3p21 |
| | hPMS1 | 2p31 |
| | hPMS2 | 7p22 |
| mutH | ? | |

Fig. 16 Human homologues of bacterial mismatch repair genes.

Patients with HNPCC have a germline mutation in one of the four replication repair genes and subsequently lose the other allele by somatic mutation. Cells that retain one allele remain repair sufficient. Loss of both alleles increase the mutation rate 100 fold and thus make these cells more susceptible for other genetic alterations (33). Genetic alterations of APC, p53

and DCC are observed with the same frequency in colorectal cancers that develop in HNPCC patients as in sporadic colon cancer (34, 35). Germline mutation of the mismatch repair genes are found in about 70% of HNPCC kindreds(34). It is very possible that there are other genes involved in the mismatch repair process ( 36, 37, 38). With the rate this field of investigation is advancing we can expect to learn more about colon tumorigenesis in the near future.

Geographic variations in the prevalence of adenomatous polyps

There is a substantial variation in the prevalence rate of colonic adenomas in different parts of the worlds. Importantly, the prevalence rates correlate with the observed frequency of colon cancer as shown in Fig. 17

| Population | Colon Cancer Frequency | Prevalence rate (%) | | |
|---|---|---|---|---|
| | | Age | | |
| | | 20-39 | 40-59 | 60+ |
| Hawaiian–Japanese | Very High | 50 | 69 | 64 |
| New Orleans | High | 0 | 39 | 47 |
| Brazil | Intermediate | 5 | 14 | 30 |
| Colombia | Low | 2 | 7 | 18 |

Fig. 17 Frequency of colon cancer and prevalence of adenomatous polyps in four risk groups

which illustrates colon cancer frequency and prevalence rates of colon adenomas in four different populations.(39) Colon cancer is very frequent in Hawaiian Japanese and more than two-third of that population over the age of 50 have colon adenomas. Colombia is at the other end of the spectrum with a low colon cancer frequency and only about one-fifth of the population over the age of 60 have adenomatous polyps. New Orleans and Brazil have high and intermediate colon cancer frequency, respectively, and have likewise high and intermediate prevalence rates for colonic adenomas. The data are derived from autopsy studies. The differences in prevalence rates in various parts of the world are presumably determined by both genetic and environmental factors.

Prevalence of adenomatous polyps in asymptomatic persons

Previous prevalence data for colonic adenomatous polyps were estimated from autopsy studies and ranged from 21 to 47% (40,41,42). Autopsy data are inherently biased and do not represent a random sample of asymptomatic persons. There are now six published studies of screening colonoscopy in asymptomatic persons over the age of 50 years (43-48). The studies include a total of 1417 persons, 952 males and 465 females, who had negative family histories for colon cancer, HNPCC, familial adenomatous polyposis and inflammatory bowel disease. All were hemoccult negative on proper testing for fecal occult blood. The prevalence data for these six studies are shown in Fig. 18.

| (n=1417) | | | | | |
|---|---|---|---|---|---|
| | | | Prevalence % | | |
| n | M/F | Age | Total | M/F | Ref |
| 90 | 61 / 29 | 50-80+ | 24 | 27 / 14 | 43 |
| 105 | 105 / 0 | 50-76 | 41 | | 44 |
| 119 | 119 / 0 | 50-79 | 41 | | 45 |
| 397 | 207 / 190 | 50+ | 39 | 46 / 32 | 46 |
| 210 | 150 / 60 | 50-75 | 25 | | 47 |
| 496 | 310 / 186 | 50-75 | 27 | 31 / 18 | 48 |

Fig. 18 Prevalence of adenomatous polyps in average risk, asymptomatic persons.

Five of studies were performed in the U.S. and one in Italy. All studies had a male predominance. The five U.S. studies are not representative of a random sample of the general U.S. population (almost exclusively Caucasians). With these limitations in mind it is still possible to conclude that the prevalence of adenomatous polyps in asymptomatic persons over 50 years old is surprisingly high (25 to 41% for males and 14 to 32% for females). The higher prevalence of adenomatous polyps in males was also observed in the National Polyp Study where the male/female ratio for removed polyps was 1.6 (10). A statistical analysis of the largest study (n:496) showed that the prevalence rate was significantly correlated with age (48). Multiple adenomas were observed in 45 and 49%, respectively, of persons with adenomas in two of the studies, where these data were specifically stated (45,46). This observation is also corroborated by the National Polyp Study where 41% had multiple adenomas (10). In addition in two of the studies 28 and 36%, respectively of the adenoma bearing persons had only adenomatous polyps proximal to the splenic flexure i.e. beyond the reach of the flexible sigmoidoscope (44,47).

Risk factors in adenoma formation

The currently recognized risk factors in adenoma development are hereditary factors, age and diet.

a. Hereditary factors

The concept that a genetic susceptibility exists for adenoma formation, apart from the genetic alterations in familial adenomatous polyposis and HNPCC, was originally suggested by a study of one large Utah pedigree with many cases of adenomatous polyps and colon cancer (49). The same authors expanded the study to include 34 kindreds with clusters of family members with adenomatous polyps or colon cancer with spouses serving as controls. All underwent flexible sigmoidoscopy and polypectomy if polyps were found. Genetic analysis was most compatible with a dominantly inherited susceptibility gene with a gene frequency of 19% (50). The postulated susceptibility gene(s) has so far not been identified. The relative risk of adenoma formation in asymptomatic persons with one first degree relative with colon cancer has been estimated to be increased 2 to 3 fold as compared to persons with a negative family history (51,52,53). The risk of developing colon cancer is similarly increased 2 to 3 fold in persons with a positive family

history (one or more first degree relatives with colon cancer) (54,55). Conversely, first degree relatives of persons with adenomatous polyps have an increased of developing colon cancer (relative risk 1.8) (56). These observations serve to emphasize that still unidentified genetic risk factors are involved in adenoma formation and that a positive family history of colonic adenomas or colon cancer is an important determinant for screening of family members.

b. Age

The yield of adenoma detection in asymptomatic persons under the age of 50 years is low. There are currently no published data on adenoma prevalence in the age groups from 30 to 49 years but it is probably in the range of 5 to 10%. The abrupt increase in prevalence in persons over 50 years probably reflect that many years are required for accumulation of genetic alterations in a clone of colonic epithelial cells and subsequent polyp formation in the non-inherited forms of colon adenomas. The prevalence of colon adenomas was positively correlated with age in one study (48). Furthermore, in the National Polyp Study age was shown to be a risk factor for high-grade dysplasia independent of adenoma size or amount of villous component (10). It is for these reasons that screening is usually recommended to start at age 50.

c. Dietary factors

It has long been suspected that diet composition plays a major role in causing colon cancer (57,58). The incidence rates of colon cancer varies at least ten fold on a world wide basis when Western countries are compared with Far Eastern and developing countries (59). The major reason for these variations in incidence rates is best explained by variation in diet. It was proposed that a high intake of animal fat increased the risk of colon cancer and that a high intake of fiber reduced the risk. These hypotheses were recently tested in a large prospective study of women (n=88,000) and confirmed that animal fat intake was positively associated with a risk of colon cancer. A low intake of fiber appeared to contribute to the risk (60). These observations have also been confirmed for men(61). There are currently several ongoing phase II and phase III trials of the effect of a low fat, high fiber diet on the recurrence of adenomatous polyps in persons with resected polyps (62). In a study of 424 polypectomized persons the combination of a low fat diet (25% of energy as fat) and 25 g wheat bran significantly reduced the development of larger adenomas (>10 mm) whereas the recurrence rates an only low fat or only high fiber were similar to persons on a control diet (63).

**EFFECTS OF LOW FAT, HIGH FIBER ON ADENOMA FORMATION (n=424)**

| Low Fat | Bran | Adenomas >1cm (No. Subjects) 2 yrs | 4 yrs |
|---|---|---|---|
| No | No | 6 (99) | 6 (80) |
| Yes | No | 5 (98) | 4 (76) |
| No | Yes | 7 (96) | 7 (75) |
| Yes | Yes | 0 (97) | 0 (75) |

Fig. 19 Effect of a low fat, high fiber diet on adenoma growth

The effect of diet is perhaps best illustrated by an autopsy study of the Bantu tribe in South Africa (64). A total of 14,000 autopsies were performed in the period from 1956 to 1968. Over this period a total of 96 colorectal cancers were found and not a single adenomatous polyp! The main constituent of the Bantu diet is maize, which is mainly carbohydrate (75%) with a low fat content (2%). The absence of adenomatous polyps and the extremely low incidence of colon cancer are remarkable and serve to emphasize the role of diet in adenoma formation. African Americans have the same incidence of colon cancer as Caucasians in the U.S. (65).

Risk factor modification

The only risk factor that is amenable for modification is diet. There is little we can do about family history and age. The study outlined in the preceding section and the findings from the Bantu study certainly suggest that a low fat, high fiber diet may have a role in decreasing the rate of adenoma formation or growth. The ongoing studies on the effect of these dietary modifications on colonoscopic determined adenoma recurrence should provide definite answers when these studies are completed.

Screening for sporadic colon cancer

The goal of screening is to detect colorectal cancers or adenomatous polyps at an early stage of their development in asymptomatic persons in order to reduce morbidity and mortality (66,67,68). The current recommendations of the American Cancer Society for screening for colorectal cancer in asymptomatic persons with average risk factors are outlined in Fig. 20.

**SCREENING OF ASYMPTOMATIC PERSONS**
**American Cancer Society**

- **Annual FOBT from age forty**
- **Flexible sigmoidoscopy at age 50**
  **Q 3 years after two negative tests**

Fig. 20 Recommendations for screening of average risk, asymptomatic persons.

Fecal occult blood testing (FOBT) should begin at age 40 and be repeated annually. Flexible sigmoidoscopy should be performed at age 50 and after two negative tests one year apart be repeated every third year. Fecal occult blood testing is an inexpensive test and it is easy to perform. There are currently five large ongoing studies of the effect of FOBT in detection of colorectal cancer in asymptomatic persons. The total number of persons enrolled is about 320,000 in centers in the U.S., England and Scandinavia as shown in Fig. 21.

| Site | # | Positive FOBT (%) | Dukes' stage A or B (%) | |
|---|---|---|---|---|
| | | | Screened | Controls |
| New York | 22,000 | 1.7 | 66 | 33 |
| Minnesota | 47,000 | 2.4 | 61 | 58 |
| England | 143,000 | 2.1 | 76 | 46 |
| Sweden | 51,000 | 1.9 | 64 | 35 |
| Denmark | 62,000 | 1.0 | 81 | 46 |

Fig. 21 Effect of screening with FOBT in asymptomatic persons

The study design was very similar in the five trials in that 50% were enrolled in study groups and offered FOBT annually or biannually and the other 50% were in control groups where FOBT was not performed. The FOBT positivity in the five studies was in the same range from 1.0 to 2.4% using non rehydrated hemoccult slides. The use of rehydrated slides in the later part of the Minnesota study increased the positivity from 2.4 to 9.8% (70). In all five studies more colon cancers detected in the screened groups were at an earlier stage (Duke's A or B) than in the control groups. The Minnesota study which is now completed showed a significant decrease in mortality of about 30% from colorectal cancer in those screened on an annual basis as compared to controls. There was no difference in mortality between those screened every other year and the control groups. The results of the New York study showed an insignificant decrease in mortality from colon cancer in the screened group. The other trials are still in progress. A common observation in all five studies was a progressive decrease in compliance to less than 50% of those originally enrolled.

The positive predictive value of FOBT for both adenomas and cancers in the five studies ranged from 22 to 58% (66). It is obvious that FOBT is imperfect and that a number of colonic lesions are missed even on repeated testing because they do not bleed. (74) FOBT is of little use in adenoma detection, which is illustrated by the adenoma prevalence data where more than 1400 persons tested negative despite the fact that a substantial number had one or more adenomas. It is probably fair to conclude that FOBT on an annual basis results in a moderate reduction in colorectal cancer mortality by detecting cancer at an earlier stage.

There are no prospective, randomized studies of the effect of screening with flexible sigmoidoscopy on the incidence or mortality of colorectal cancers. A few retrospective studies have examined the effect of rigid sigmoidoscopy in a study group compared to a control group matched for sex and age (case control studies) (69,75,76,77). The results of these studies are outlined in Fig. 22 .

| Screened | Controls | Decrease in mortality (%) |
|---|---|---|
| 5,800 | 6,700 | 43 |
| 261 | 868 | 59 |
| 66 | 196 | 80 |
| | | Decrease in incidence (%) |
| 18,200 | – | 85 |

Fig. 22 Effect of screening with rigid sigmoidoscopy in asymptomatic persons.

The limitations of retrospective studies are well recognized. Nonetheless, the results are noteworthy. Three studies showed a reduction in mortality of 43, 59 and 80%, respectively. The last study which comprised 18,158 persons who underwent annual sigmoidoscopy over a 25 year period, showed an 85% reduction in rectosigmoid cancers compared to historical controls. A similar reduction in incidence of rectosigmoid cancers was observed in 1618 persons who underwent sigmoidoscopy with polypectomy and were followed for up to 30 years (78). In light of the fact that rigid sigmoidoscopy only examines the distal 20 to 25 cm of the rectosigmoid area the results of these retrospective studies suggest that screening with a 60 cm flexible sigmoidoscope will yield even better data. It is estimated that 50 to 60% of all colorectal adenomas and cancers are found within the reach of a flexible sigmoidoscope. A randomized controlled trial of the benefits of flexible sigmoidoscopy is a major undertaking. In the UK where screening for colorectal cancer is not recommended such a trial was recently proposed. It was estimated that it was necessary to enroll 120,000 persons (60,000 study subjects and 60,000 controls) to demonstrate a statistical significant difference in mortality. It was further assumed that a 15 year follow-up would be required for a meaningful statistical analysis.(79)

It is not known what proportion of the U.S. population over the age of 50 years is currently enrolled in a screening program. The expense for screening is not covered by Medicare but there are efforts underway to introduce a bill to provide Medicare coverage for colorectal cancer screening.

The benefit of two flexible sigmoidoscopies a year apart has been questioned. In a study of 259 persons who had an initial negative flexible sigmoidoscopy the yield of a second sigmoidoscopy at least 2 years later was 15 persons (6%) with adenomas (80). None of the adenomas were large or had severe dysplasia and no cancers were found. It was concluded that a 5 year interval between the first and second sigmoidoscopy would be safe for average risk, asymptomatic persons.

Finally, colonoscopy should be performed on persons who have adenomatous polyps identified on flexible sigmoidoscopy to clear the rest of the colon for possible synchronous lesions. Colonoscopy is currently not recommended as a screening procedure in asymptomatic persons due to expense and lack of manpower. The effect of colonoscopic polypectomy on the incidence of colorectal cancer was documented in a recent report from the National Polyp Study (2). A total of 1418 patients underwent colonoscopic polypectomy and were followed with periodic colonoscopies for 6 years. Only

5 patients developed early stage colorectal cancer. The expected incidence derived from three historical control groups was 48, 43 and 21 cases which translates into a reduction of incidence of 90, 88 and 76%, respectively.

The W.H.O. has recently issued new guidelines for screening for colorectal cancer (81). The recommendations for average risk persons are FOBT and flexible sigmoidoscopy every 3 to 5 years starting at age 50.

Screening of high risk persons

A family history of one or more first degree relatives with colon cancer places an asymptomatic person in a high risk group. It is currently recommended that such persons should be enrolled in a screening program starting at age 35 to 40. Screening should include FOBT and flexible sigmoidoscopy every 3 to 5 years.

If the family history includes a case of colon cancer before the age of 50 or if there are three or more family members with colon cancer a diagnosis of HNPCC should be considered and colonoscopy should be the screening tool because of the high frequency of right-sided colon lesions in HNPCC.

Surveillance of HNPCC families

HNPCC is inherited in an autosomal dominant manner and 50% of the offspring in a family are at risk of having a germline mutation of one of the mismatch repair genes. So far the identification of an HNPCC family has been based solely on family history which should fulfill the Amsterdam criteria. These criteria have been criticized for being too strict and also for not including the increased risk of extracolonic cancers (Lynch II) (82). The prevalence of HNPCC has been estimated to be 5-10% of all colorectal cancers but this estimate may be too low. The advent of markers for microsatellite instability which is the characteristic phenotype of HNPCC tumors, has permitted testing of sporadic colon cancers and 10 to 15% of these show microsatellite instability (83,84). In a recent study of 189 patients with colonic cancers and without a family history suggestive of HNPCC it was found that 18 of 31 patients under the age of 35 had microsatellite instability (85). In 12 of those 18 a search for germline mutations was undertaken which was positive in 5(42%). The reason why germline mutations could not be detected in 7 of the 12 tested was possibly due to the assays employed. At any rate it is likely that the prevalence of HNPCC will be redefined with the use of genetic markers. The suggested guidelines for surveillance of HNPCC families are outlined in Fig. 23.

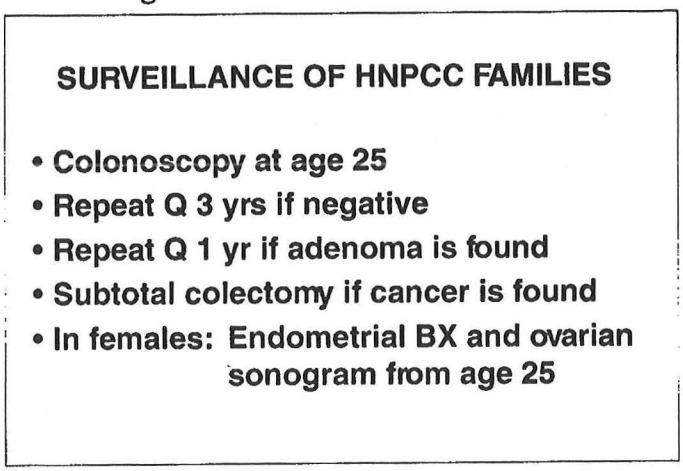


Fig. 23 Recommendations for surveillance of HNPCC families.

These guidelines were proposed by Lynch who originally defined the cancer family syndrome as HNPCC was previously called (3). Because colon cancer develops at a young age and is frequently right-sided, surveillance in first degree relatives is initiated at age 25 with colonoscopy. Colonoscopy is repeated every 2 to 3 years if negative and every year if adenomas are found. In women the surveillance should include endometrial biopsies and ovarian ultrasound also starting at age 25. Subtotal colectomy is recommended for those who develop colorectal cancer because of risk of metachronous lesions.

Surprisingly, a controlled but not randomized study of the benefit of surveillance in HNPCC relatives has been performed in Finland (86). The study persons (n=133) underwent colonoscopy every three years and the control group (n=118) was not screened. The controls had refused screening. Six study patients developed colorectal cancer over the 10 year study period compared to 14 in the control group which is a 62% reduction in incidence. The six colon cancers in the study patients were all early stage (Duke's A and B) and none died, whereas 5 of the 14 controls with colorectal cancer died from disseminated disease. A large international study of 165 HNPCC families is currently evaluating the optimal surveillance programs (87).

Genetic testing for germline mutations of the mismatch repair genes is still not available. A number of different mutations at different locations in the four genes have been identified which hinder the development of a simple genetic test. (88) In Finland, however, it was recently found that two mutations of the hMLH1 gene account for 63% of kindreds with HNPCC and this allowed the development of PCR based tests for screening purposes (89). Whenever genetic screening becomes available in the U.S. it will be possible to identify persons at risk and thus reduce the number of relatives who need to be enrolled in a surveillance program.

Finally, the issue of insurance coverage for surveillance is still problematic. Some insurance carriers refuse payment for surveillance and some may cancel insurance coverage for persons at risk which in turn may lead to low compliance with surveillance programs (3).

Surveillance of FAP families

Familial adenomatous polyposis, Gardner's syndrome and the rare Turcot's syndrome are all characterized by the development of hundred of colonic polyps in the early teens (4,90). They are all inherited in an autosomal dominant fashion. Many countries have now polyposis registries where data on polyposis families are collected. It is important to emphasize that about 25% of patients, who are diagnosed with FAP, are new mutations of the APC gene, i.e. the family history is negative (91). The guidelines for surveillance of first degree relatives of patients with the polyposis syndromes are outlined in Fig. 24.

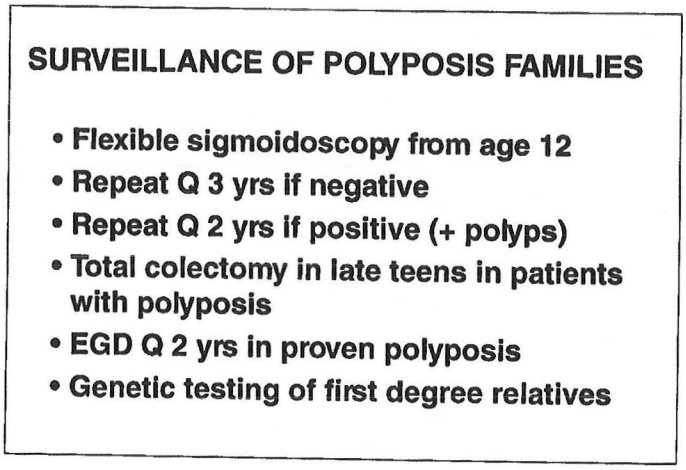


Fig. 24 Recommendations for surveillance of polyposis families

Flexible sigmoidoscopy should start at age 12 and be repeated every two years if polyps are found. The procedure is repeated every three years in those without polyps until the age of 40. Patients who have or develop polyps should undergo total colectomy with ileoanal anastomosis. The timing of surgery is usually delayed to the late teens if possible unless removed polyps have unfavorable histologic characteristics. Patients with documented polyposis will also need surveillance endoscopy on a regular basis because of a high incidence of gastroduodenal adenomatous polyps. A recent report has also documented a high incidence of small ileal adenomatous polyps in patients who had total colectomy for FAP (92). These observations need to be confirmed before ileoscopy is included in the surveillance program. Genetic testing for the polyposis syndromes is now a possibility. Vogelstein's group has devised a PCR based test that detected germline mutations in the APC gene in 54 of 62 FAP patients (93). When the test becomes commercially available testing can be offered to affected families so that only the first degree relatives with germline mutations are enrolled in a surveillance program. Unnecessary surveillance of unaffected relatives can then be avoided.

Surveillance of patients with adenomas or colorectal cancer

The recurrence rate of adenomatous polyps is substantial. Two recent colonoscopic studies of a large number of patients found recurrent polyps after three years in 32 and 42%, respectively (94,95). The current recommendations for follow-up colonoscopy in patients with removed polyps are outlined in Fig. 25.

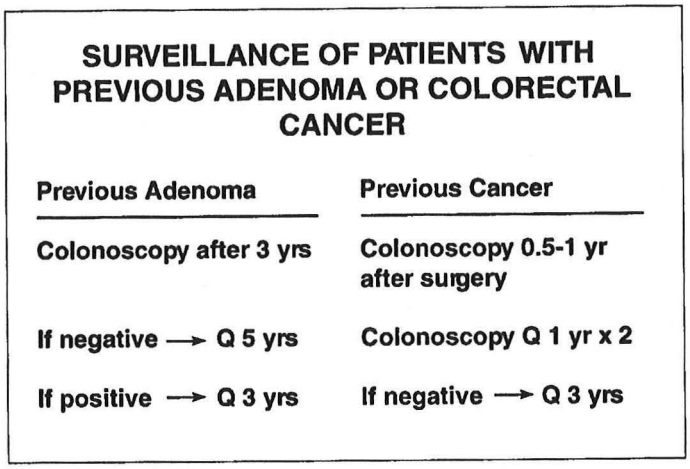


Fig. 25 Surveillance of patients with previous adenomas or colorectal cancer.

The first follow-up colonoscopy should be done at three years. If negative, the next colonoscopy can be postponed to 5 years. If positive, follow-up colonoscopy should be repeated after another three years. The schedule may of course be individualized dependent on the findings. Malignant polyps, large sessile adenoma and multiple adenomas may require more frequent examinations.

Patients who have been operated for colorectal cancer with a presumed curative resection should be colonoscoped within 6 months to 1 year following the operation. If negative then follow-up examination is performed after one and two years and then with three years interval (96).

Surveillance of patients with ulcerative colitis

The risk of colon cancer in patients with ulcerative colitis is well documented (97). The risk increases with disease duration, activity and extension which place patients with chronic active pancolitis of more than 8 years duration at a high risk. The role of surveillance of patients with ulcerative colitis has been a controversial issue and has been much debated (98,99). The most recently recommended guidelines by W.H.O. are as follows (Fig. 26.

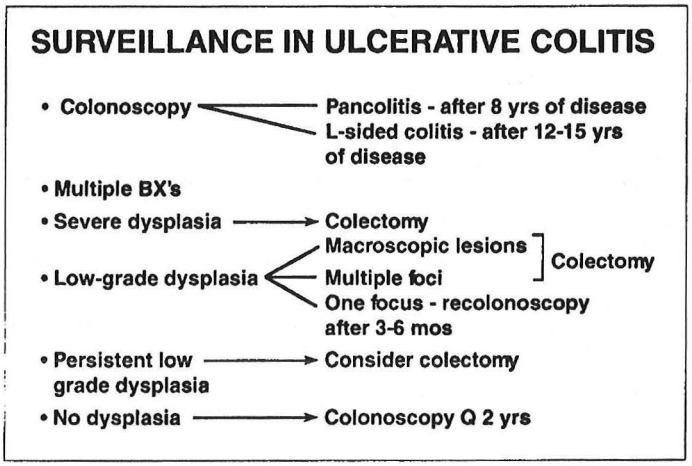


Fig. 26 Surveillance of patients with ulcerative colitis

Colonoscopy should be performed after 8 years of disease in patients with pancolitis and after 12 to 15 years in patients with left-sided colitis. Multiple biopsies (>33) should be obtained at 10 to 12 cm intervals throughout the colon for evaluation of dysplasia by an expert pathologist. If biopsies are negative for dysplasia colonoscopy should be repeated with 1-2 years interval. Colectomy is indicated if biopsies show high grade dysplasia. Follow-up colonoscopy should be performed within 3-6 month if biopsies show low-grade dysplasia. Colectomy is recommended if low grade dysplasia persists or if there are multiple foci or flat lesions with low grade dysplasia. It is obvious that the benefit of surveillance depends to a large extent on the experience of the pathologist. There is still considerable interobserver variations in the recognition of dysplasia even among experienced pathologists (99). The benefit of surveillance in terms of reducing mortality or early detection of cancer has been documented in several large studies (100,101,102). It must be emphasized, however, that some colon cancers in ulcerative colitis arise from a nondysplastic area (99). In patients with chronic active disease of long duration it might be prudent to recommend proctocolectomy rather than life long surveillance.

Currently, the only method to assess risk of colorectal cancer in ulcerative colitis is by colonoscopic biopsies. Only a minority (<10%) of surveilled patients will have dysplasia (102). Thus, it would be desirable to develop less invasive and less expensive test to identify patients at risk for development of dysplasia. It was recently reported that germline mutations of the hMSH2 gene was three times more frequent in patients with ulcerative colitis and high grade dysplasia or carcinoma than in patients without dysplasia or cancer (103). The mutations, however, were only observed in 26% of the affected patients. It is not clear why mutations in only one of the mismatch repair genes were searched for. This finding opens up the possibility that risk factors for dysplasia may in the future be identified by a simple blood test.

Future prospects

The desired goal of screening and surveillance is to reduce morbidity and mortality. The vast majority of colorectal cancers are sporadic and arise in a benign adenomatous polyp. Two-thirds of the population over 50 do not have colonic adenomas and 80-90% of the polyps in the polyp-bearing population are small tubular adenomas with minimal malignant potential. A test that could identify persons at risk, i.e., those with large tubulovillous or villous adenomas with moderate or high grade dysplasia would be highly desirable. The sequential genetic alterations in the adenoma-carcinoma sequence make these changes an obvious target. An assay for ras-mutations in the stool correctly identified identical mutations in the stool and in the tumors in 8 of 9 patients with proven ras-mutations (104). The tumors included 2 adenomas and 7 cancers. Unfortunately, only about 50% of adenomas have ras-mutations. APC gene mutations are early events in adenoma formation and detectable in most adenomas. A stool assay for APC mutations are currently too cumbersome to be of clinical value. It is probably not too far-fetched to predict that a stool assay for genetic alterations of the known genes or not yet identified genes involved in adenoma formation will be available in the future.

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