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Interference with the Adenoma–Carcinoma Sequence

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Epidemiological, pathological, and genetic studies indicate that most colorectal cancers arise in benign neoplastic polyps (adenomas). The likelihood of malignant change increases with adenoma size and volume of villous tissue. Adenomas are monoclonal products of a single stem cell mutation. Acquired genetic mutations and chromosomal deletions that occur late in the polyp–cancer sequence have been well described, although the initiating events leading to micro-adenoma formation are still unknown. Both inherited and environmental factors are implicated. Although the evidence in support of the adenoma–carcinoma sequence is indirect, it is compelling. Chemoprevention trials have not yet identified effective methods of primary prevention. Colonoscopic resection of adenomas (secondary prevention) plus post-polypectomy surveillance markedly decreases the incidence of colorectal cancer.

Key words: colorectal adenoma, carcinoma, polyp, aetiology, primary and secondary prevention, colonoscopy, polypectomy
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INTRODUCTION

EPIDEMIOLOGICAL, pathological and genetic studies indicate that most colorectal cancers arise in previously benign neoplastic polyps (adenomas) [1, 2]. Adenomas morphologically are classified as pedunculated, sessile, or flat, and histologically are classified as tubular, tubulovillous, and villous [3]. They comprise approximately 70–80% of all polyps resected at colonoscopy [4]. Non-neoplastic polyps have no malignant potential and include mucosal excrescences, hyperplastic polyps, lymphoid aggregates, and inflammatory polyps.

HISTOLOGICAL AND MORPHOLOGICAL CLASSIFICATION

Tubular adenomas, which appear to have a low but definite malignant potential, comprise 70–85% of adenomas. Tubulovillous and villous adenomas, which have a much higher malignant potential, comprise about 25 and 5%, respectively, of all adenomas. By definition, according to the World Health Organization classification, tubular adenomas contain 0–25%, tubulovillous adenomas contain 25–75%, and villous adenomas contain 75–100% of villous tissue [2]. Tubular adenomas are composed mainly of straight or branched tubules of dysplastic tissue, and villous adenomas contain finger-like projections of dysplastic epithelium.

Some degree of dysplasia exists in all adenomas. Most pathologists now prefer to grade dysplasia as either low- or high-grade; the latter includes the histological mucosal changes previously called "focal", "superficial", or "intra-epithelial" carcinoma, or "carcinoma *in situ*". Because these latter terms imply an incorrect impression of clinical malignancy often leading to over treatment, they have largely been abandoned in clinical practice. Approximately 5–7% of adenomas have high-grade dysplasia, and 4–7% have invasive carcinoma (carcinoma penetrating into the submucosa) at the time of resection [5].

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AETIOLOGY AND PATHOGENESIS OF ADENOMAS

Adenomas are monoclonal, being derived from a single stem cell mutation [6]. The initial acquired genetic events leading to adenoma formation have not been well-defined, but may involve the FAP locus on the long arm of chromosome 5. Gross adenomatous polyps appear to be preceded by "microadenomas" consisting of only one or a few crypts [7]. The aetiology of colorectal adenomas involves both inherited genetic factors and acquired, environmentally induced genetic alterations [8, 9]. Most simple small tubular adenomas appear to remain static, while a few grow and develop villous changes and high-grade dysplasia. As these advanced adenomas develop, cellular proliferation is followed by recently identified oncogene activation and chromosomal deletions. Extensive pathological studies of adenomas resected in the multicentre U.S. National Polyp Study indicate that increasing villous component and increasing size are independent multiplicative predictors of high-grade dysplasia, and presumably of the eventual development of carcinoma, in an adenoma [2].

ADENOMA–CARCINOMA SEQUENCE

Although the adenoma-carcinoma relationship can probably not be proved directly, persuasive data indicate that colorectal neoplasia proceeds through a continuous process from normal mucosa, to a "field defect" of increased proliferation, to benign adenoma, to carcinoma [1]. Evidence of this adenoma–cancer sequence includes the following observations:

1. A parallel prevalence of adenomas and carcinomas exists, with the average age of patients with adenomas being 5–7 years younger than that of patients with carcinoma [10, 11].
2. Benign adenomatous tissue is often contiguous with carcinoma, while in Western countries small carcinomas without adenomatous components are rarely identified [12].
3. Carcinomas arising in families with both familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer syndromes (HNPCC) are preceded by histologically typical adenomas [13].
4. As adenomas grow, they exhibit increasing signs of malignant change, including villous transformation, high-grade dysplasia, and acquired genetic alterations [2].
5. The anatomical distribution of adenomas and cancers is virtually identical in both sporadic cancers (70% located in the left colon), and HNPCC (70% located in the right colon) [14, 15].
6. Synchronous adenomas are found in 30–40% of patients who have a colorectal cancer; following curative resection, metachronous adenomas develop in a similar fraction [16].

PRIMARY PREVENTION OF ADENOMAS AND CANCER

Epidemiological studies and studies of migrating populations clearly indicate the importance of environmental influences on the incidence of colorectal cancer. Several dietary habits have been implicated including excess fat consumption and insufficient intake of fruits, vegetables, and dietary fibre [17]. In addition, several vitamins (A, E, C, and folate), minerals (calcium, selenium), and drugs (aspirin and other nonsteroidal anti-inflammatory agents) may protect individuals from development of colorectal cancer [18].

Reducing fat intake and increasing the consumption of fruits, vegetables, and fibre are likely to improve the overall quality of an average individual's diet. However, specific recommendations about vitamins and other micronutrients are premature, since controlled chemoprevention studies proving their value have not been completed or have failed to demonstrate benefit in reducing the recurrence rate of polyps, or improvement in the incidence or mortality of colorectal cancer. A recent multicentre controlled trial in the U.S.A. failed to demonstrate a favourable effect on adenoma recurrence of daily ingestion of the antioxidants, vitamins E, C and A [19]. Similar studies employing calcium, aspirin, folate, fibre, and reduced fat intake are in progress.

SECONDARY PREVENTION OF CARCINOMA

Colonoscopy is the procedure of choice for the detection and resection of colorectal adenomas. It is much more accurate than barium enema for the detection of small polypoid lesions even when high quality, double contrast techniques are employed [20, 21]. The entire colon can be thoroughly examined by experienced endoscopists using modern instruments with great safety and minimal discomfort in over 95% of cases. Most importantly, colonoscopy allows the immediate biopsy of suspicious lesions and complete resection of most polyps that are detected.

Clinical proof of the adenoma–carcinoma relationship requires showing that removal of adenomas will reduce the incidence and mortality of colorectal cancers. This chance to interfere with or interrupt the adenoma–cancer sequence is called "secondary prevention", and is an opportunity that is somewhat unique among the major malignancies. This clinical opportunity adds a major component of urgency to screening and surveillance strategies. Pathological estimates, plus observations from the U.S. National Polyp Study, indicate that it takes a relatively long time, 10–12 years on average, for a polyp to develop, grow to a clinically significant size, and degenerate into a gross cancer [1, 11]. Therefore, there is ample opportunity for screening and surveillance methods to detect the developing neoplasm while it is still clinically benign and easily treated.

PROCTOSIGMOIDOSCOPY SCREENING STUDIES

Colonoscopy has not been available long enough to prove that resecting all adenomas from a given population will reduce mortality from colorectal cancer. Cohort and case–control studies of the effect of screening proctosigmoidoscopy, however, suggest that removing all distal adenomas will substantially reduce both the subsequent incidence and mortality from rectal cancer.

Gilbertsen and Nelms at the University of Minnesota, performed annual rigid proctosigmoidoscopy and removed all detected adenomas on a group of over 21 000 volunteers who were followed over a 20-year period [22]. Compared to the known incidence and mortality of colorectal cancer in Minnesota, this follow-up experience indicated a reduction in the incidence of rectal cancer of over 85% and virtual elimination of death from distal cancer. Selby and colleagues performed a retrospective nested case–control study in which the previous incidence of screening rigid proctosigmoidoscopy was determined for a group of patients dying of distal colorectal cancer compared with a group of carefully matched control subjects without cancer [23]. Their analysis suggested that proctosigmoidoscopy with removal of all distal adenomas reduced subsequent mortality from distal cancer by about 60%, and that this protective effect appeared to last for up to 10 years. As a useful internal control that suggests minimal problems with selection bias, the mortality from more proximal colonic cancers, which could not be influenced simply by proctosigmoidoscopy alone, was identical in the two groups.

A second case–control study by Newcomb and associates that had a similar design, reported a reduction of mortality from distal cancer as the result of prior screening proctosigmoidoscopy of up to 80% [24].

PROSPECTIVE STUDY OF COLONOSCOPY

A recent landmark report from the U.S. National Polyp Study addressed the hypothesis that resecting all colorectal polyps in a well-defined population would reduce the total incidence of colorectal cancer [25]. All patients enrolled in the study were pooled for the sake of this analysis. Patients were eligible for the study if they did not have a family or personal history of familial polyposis, inflammatory bowel disease, or history of polypectomy or colorectal cancer. On colonoscopy they were required to have at least one histologically documented adenoma, and no malignant polyps, or sessile polyps greater than 3 cm in diameter. In addition, the colonoscopist had to be confident that all polyps had been removed during complete colonoscopy. All study patients underwent a second colonoscopy after the first and third years, or at 3 years, and then every 3 years. Average follow-up which was 97% complete at the time of this analysis was 5.9 years in 1418 patients (8401 person-years).

Five asymptomatic early-stage cancers (four Dukes' A, one Dukes' B) were detected. All were malignant polyps which were successfully resected (four by surgery, one by colonoscopy alone). Three of the cancers were detected at 3 years, one at 6 years, and one at 7 years after the index polypectomy. This low rate of metachronous cancer was compared with that of three

separate reference populations, a group of adenoma patients from both the Mayo Clinic, U.S.A. and St. Mark's Hospital, London, U.K. and the U.S. National Cancer Institute SEER population (which provides the average incidence of colorectal cancer in the U.S.A.) [26–28]. After statistical correction for polyp size and for cancers that might have occurred during the first 2 years of follow-up, the age and sex-specific incidence of cancer predicted in 8401 person-years by the Mayo Clinic, St. Mark's and NCI reference groups was 48.3, 43.4, and 20.7, respectively. Therefore, the effect of removing all adenomas at the time of enrolment in the National Polyp Study, plus removing adenomas found during subsequent surveillance colonoscopy was to reduce the incidence of metachronous cancer from 76 to 90%, a highly clinically and statistically ($P<0.001$) significant reduction.

Further follow-up of the National Polyp Study cohort is also expected to show a polypectomy-induced reduction in colorectal mortality, since only a few cancers have occurred and all have been early-stage.

CONCLUSIONS AND CONTROVERSIES

Most colorectal carcinomas arise in benign adenomas. Resection of adenomas interferes with this adenoma–carcinoma sequence and, therefore, prevents cancer. Colonoscopy provides a very safe and effective method to treat most adenomas. Most adenomas are detected during screening or surveillance for colorectal cancer, or as the result of structural examination of the large bowel performed for other reasons. Whether primary chemopreventive measures can also prevent cancer by reducing adenoma formation or growth awaits the results of current trials.

Whether clinically inconspicuous small or flat adenomas appreciably contribute to the development of colorectal cancers in Western countries is not known. The rarity of finding such lesions during carefully performed colonoscopy on large numbers of patients, and the failure to detect unexpected cancer in large prospective follow-up studies such as the National Polyp Study suggest that these "de novo" cancers are very rare in the U.S.A. compared with those reported from Japan [20].

While much has been learned about the genetic events that occur with advanced adenomas and carcinomas, very little is known about how inherited genetic factors and environmental influences initiate adenoma formation and promote growth. Whether proliferation markers or other genetic characteristics of resected adenomas or of mucosal biopsies in patients with adenomas will provide new ways to intervene in the adenoma–cancer sequence is an additional important area for study [8, 30].

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