
5 Colorectal Cancer Screening and Surveillance

Introduction

Colorectal cancer is the most preventable neoplasm of the digestive organs and one of the most preventable of all [1]. This is mainly due to the existence of well-defined premalignant lesions – the adenomatous polyps – which take years to transform into carcinoma [2], thus allowing their early detection and removal through endoscopy [3]. Colorectal tumors occur extremely frequently in Western society, with crude incidence rates of the order of 40–70 new cases/100,000 inhabitants/year and a lifetime probability for an individual of developing this malignancy of 4%–6% [4, 5]. In other words, approximately 150,000 new colorectal cancer cases are diagnosed annually in the USA, and 30,000 in countries such as Italy or Britain [6]. There is evidence, however, that the survival of patients with colorectal cancer is gradually increasing [7], a result which can be attributed to many factors, including better screening procedures.

Although colorectal cancer screening is an old problem, which has been debated for years [8], the general impression is that we are moving from a long “incubation” phase of controlled and uncontrolled studies to the time in which we are called to apply this accumulated knowledge to the general population or at least to high-risk individuals [9]. Indeed, several medical societies – including the American Cancer Society – advocate screening for colorectal neoplasms [10], and an interdisciplinary panel of health care professionals came to the conclusion that all screening strategies were found to have a net benefit [11].

Screening for colorectal tumors involves the use of appropriate tests in order to identify individuals likely to have malignant or premalignant (adenomatous polyps) lesions in their bowel. At present, either lower endoscopy (colonoscopy and sigmoidoscopy) or fecal occult blood tests have been found to be effective in reducing the incidence and mortality of colorectal neoplasms and appear to be suitable tools for screening the general population [12]. Some persons, however, are at higher risk for colorectal cancer and may require a closer examination of the large bowel [13, 14]; this approach is referred to as *surveillance*.

Colorectal Cancer Screening in the General Population

Colorectal cancer screening is probably unwarranted in many Asian and African countries, where the disease is relatively rare, with incidence rates as low as 5 new cases/100,000 inhabitants/year [15, 16]. In Western society, the disease has the dimension of an epidemic, and “it is a cruel irony that billions of dollars are spent treating patients with colorectal cancer when the disease is almost entirely preventable” [17]. Moreover, there is evidence that colorectal cancer detected by screening is usually found at an earlier stage, and that patients in whom cancer is diagnosed at these stages have a more favorable outcome [18]. One more reason for promoting screening is that the main causes associated with an increased risk for colorectal malignancies are closely related to our diet and lifestyle [19], two factors that can hardly be modified in a society in which people are becoming progressively more wealthy, sedentary and overweight [20].

Despite the evidence, mass screening remains a difficult objective to achieve. Probably the guidelines on colorectal cancer are still imprecise or may appear redundant; for example, what should general physicians suggest to their patients? Search of fecal occult blood starting at age 45 for all individuals? Flexible sigmoidoscopy or, even better, colonoscopy for all their patients irrespective of their risk? And why not combine a Haemoccult test with endoscopy when approaching 50? A more scrupulous physician will attempt to stratify his/her patients according to different risk levels, in order to subject various subgroups to different screening procedures.

Patients may resist mass screening for colorectal neoplasia, probably because they do not feel like a “patient” but are invited to behave like one. Many individuals – at least in some countries – continue to adopt a “fatalistic attitude” towards diseases (especially cancer) and, in their irrational thinking, believe that certain diseases happen to others but not to themselves. In addition, dealing with feces or undergoing lower endoscopy is undoubtedly unpleasant, especially compared with measuring blood pressure or taking a blood sample for glucose or cholesterol levels. Selecting a high-risk group might have more success, but this is not always the case. In a recent study [21], 223 individuals were identified as at risk for hereditary colorectal cancer by their position in the family tree; of these, only 86 (38.6%) underwent colonoscopy, after recommendation by the interviewer. In a similar investigation [22], a higher compliance (63%) was obtained in a different population (Finnish), but once again the response rate was lower than expected.

Despite these limitations, evidence has been accumulated – in the last 10 years – indicating that mortality for colorectal neoplasms can be reduced through mass screening in the general population, using either a search for fecal occult blood or lower endoscopy (sigmoidoscopy or colonoscopy).

Role of Fecal Occult Blood Testing

The best investigated of several fecal occult blood test methods is the guaiac impregnated slide test, where the peroxidase activity of hemoglobin is the basis for a true positive result. Although the method is widely diffused, there are many important causes of false-positive and false-negative results [23]. The former occur more often from other, non-neoplastic sources of bleeding in the gastrointestinal tract (inflammation, diverticula, hemorrhoids, etc.) or from foods containing peroxidase-like activity. False-negative tests are due to intermittently bleeding or non-bleeding tumors. According to the most common tests, bleeding from the gastrointestinal tract must exceed physiological bleeding 5 to 10 times for a positive test [24]. New methods have been developed for detecting blood in the stools, such as tests based on the porphyrin-like moiety of hemoglobin or on the assay of human hemoglobin [25, 26]. Although these new tests may be more useful than the conventional guaiac assay, they have not yet been investigated in large-scale clinical trials, especially regarding their cost/benefit aspects [27].

Five case-control studies [28–32] and three randomized controlled trials [33–35] showed a reduction in the mortality for colorectal cancer by fecal occult blood test screening. In addition, a meta-analysis of six controlled Haemoccult screening studies found a net 16% reduction in mortality for colorectal malignancies [36]. Since screening may also detect large and bleeding adenomas – the natural precursor of carcinoma – this approach, if pursued for years, might also lead to a reduction in the colorectal cancer incidence rate. In one of these studies [33], 46,551 subjects between the ages of 50 and 80 years were invited to participate; individuals were followed for 13 years, and in this period nearly half of them (i.e. 46.2% of those screened annually and 59.7% of those screened biannually) completed the tests required by the protocol; on average, 6 samples were submitted for each patient. Almost 10% of samples were positive, and 80% of patients with positive tests underwent colonoscopy. In the screening group, cumulative mortality for colorectal cancer during this follow-up period was 5.88/1,000 for individuals screened annually versus 8.83/1,000 in the control group, which means a highly significant 33% reduction of mortality among screened subjects. Most of the lesions detected through screening were Dukes' A or B neoplasms, i.e. those associated with a more favorable clinical outcome, a factor which explains the lower mortality rate in the screened group.

Yet, despite the undoubted evidence of success, fecal occult blood tests have not gained widespread diffusion among the medical community, and there is some resistance – in most countries – to performing mass screening. Though the test is simple, safe, acceptable and relatively inexpensive, lack of accuracy remains the main problem. It has recently been shown that after 5–10 years, patients' compliance with the screening program falls to below 50%, and that too many patients leave the project long before its completion [23]. The high rate of false-positive tests leads many individuals to undergo colonoscopy which in many cases may appear unnecessary or redundant. Even more important, a false-negative test may induce a false sense of security in patients with colorectal

lesions, which postpones the execution of more appropriate diagnostic procedures. In this respect, physicians play a crucial role in explaining to patients the advantages but also the many limitations of the test, that does exclude the presence of polyps or cancer, unlike colonoscopy, but may at most raise a suspicion, and that only in a minority of cases. Moreover, the test cannot be proposed to patients at major risk for colorectal cancer development – such as individuals with a strong family history of cancer or patients with inflammatory bowel diseases – in whom colonoscopic surveillance is mandatory [37].

In conclusion, despite the many supporters of fecal occult blood test screening – because of its efficacy in reducing colorectal cancer mortality [38] – many physicians remain skeptical and suggest different screening procedures.

Role of Sigmoidoscopy

Flexible sigmoidoscopy allows the visualization of the lower portions of the large bowel, i.e. rectum, sigmoid and descending colon. Owing to the limited value of the fecal occult blood test, this technique has been proposed as a mass-screening procedure for colorectal tumors. The American Cancer Society recommends periodic sigmoidoscopy beginning at the age of 50 years and repeated at 3- to 5-year intervals for screening of all average-risk subjects [39]; however, only 15%–30% of eligible persons undergo such testing [40].

Sigmoidoscopy has several advantages over a fecal occult blood test; being an endoscopic investigation, it allows direct visualization and removal of polypoid lesions, with specificity and sensitivity for the detection of distal tumors of the order of 95% or more [41]. The main benefits of sigmoidoscopy, in screening for colorectal tumors, are the detection and removal of non-malignant precursor lesions – thus preventing colorectal cancer development – and the detection of early lesions (Dukes' A and B), which are usually associated with a more favorable clinical outcome. Sigmoidoscopy, however, is an invasive technique which may be embarrassing for many patients, especially when their risk of cancer is relatively low. Moreover, flexible sigmoidoscopy does not provide information on lesions of the proximal colon, where more than 30% of colorectal tumors are localized, and with an increasing frequency [42]; indeed, some authors commented that sigmoidoscopy is “as clinically logic as performing mammography of one breast to screen women for breast cancer” [43] since it explores only a limited portion of the large bowel. Finally, one might argue that sigmoidoscopy actually produces frequent false-positive results when taking into account the very low malignant potential of small (less than 0.5 cm) and hyperplastic polyps [44].

Despite these limitations, two case-control studies showed that the risk of death from colorectal malignancies was reduced by 70%–80% for those individuals who had at least one sigmoidoscopic investigation within the previous 10 years compared with subjects who were not examined [45, 46]. In one of these studies, colorectal cancer developed in 8.8% of patients who reported undergoing at least one sigmoidoscopy (within the previous 10 years) versus 24.2% among individuals who were not investigated ($p < 0.0001$) [45]. In another inves-

tigation [47], 1,618 patients were followed up for 14 years (on average) after polypectomy by rigid sigmoidoscopy. For those individuals in whom polyps had completely been removed, the risk of subsequent colorectal cancer was nearly one-half that of the general population; the observed findings lend further support to the possible role of sigmoidoscopy in reducing the incidence and, presumably, mortality of colorectal neoplasms through the removal of precursor lesions. This contention has recently been confirmed by a prospective investigation in which endoscopic screening was able to reduce the incidence of colorectal cancer in a normal Norwegian population [47a].

Role of Colonoscopy and Barium Enema

Periodic examination of the whole colon by colonoscopy appears to be the most effective tool for mass screening for colorectal cancer. The best evidence supporting this approach comes from the National Polyp Study [48, 49]. The investigation included 1,418 patients who had undergone a colonoscopy at the beginning of the study; of these, 1,210 were followed with colonoscopies at regular intervals until the end of the study (average follow-up 5.9 years). At the time of enrolment, 494 patients (35%) had adenomas larger than 1 cm, and 137 (10%) had adenomatous lesions with high-grade dysplasia. Five completely asymptomatic colorectal malignancies (Dukes' A or B carcinoma) were detected at follow-up endoscopy in five different patients. The numbers of colorectal neoplasms expected on the basis of reference groups [50, 51] were 48.3, 43.4 and 20.7, corresponding to a reduction in the incidence of cancer of 76%–90%. The authors concluded that the incidence rates of colorectal malignancies can be significantly reduced by colonoscopic surveillance and polypectomy; this provides further evidence in favor of the adenoma-carcinoma sequence and supports the current practice of removing adenomatous lesions in the colon.

The main problems associated with colonoscopy screening are cost, discomfort for the patients and risk of major complications (such as bowel perforation), which are estimated at 2/1,000 procedures [52]. Moreover, colonoscopy is more difficult to learn and to perform than flexible sigmoidoscopy. For all these reasons, some authors consider colonoscopy unsuitable for general screening, but the investigation of choice for testing high-risk patients [53]. In a recent investigation, Sonnenberg et al. [54] compared the cost-effectiveness of fecal occult blood testing, sigmoidoscopy and colonoscopy; they concluded that colonoscopy represents a cost-effective means of screening for colorectal neoplasms, since it reduces mortality rates at relatively low incremental costs. Compared with colonoscopy, an annual Haemocult test costs less but saves fewer life-years.

Single contrast barium enema is inadequate for detecting polyps, but the results improve remarkably with the double-contrast technique, the accuracy of which in screening for colorectal lesions larger than 1 cm is of the order of 90%–95% [55]. Colonoscopy is undoubtedly more sensitive for polyps smaller than 1 cm; moreover, the main limitation of barium enema remains the impossibility to carry out biopsies or polypectomy (Table 5.1).

Table 5.1. Colorectal cancer screening in the general population: options

Investigation	Frequency	Age (years)	Reference
Fecal occult blood test	Annual	50	[28–35]
Sigmoidoscopy	3–5 year interval	50	[39, 40]
Sigmoidoscopy	“Once only”	50	[45, 46, 47]
Colonoscopy	Every 5 years	45–60	[48, 49]

New Screening Procedures Based on Molecular Analysis

A novel approach to the early detection of colorectal neoplasms is the use of sensitive molecular methods based on polymerase chain reaction (PCR) and other modern technologies [56]. Thus, Sidranski and collaborators [57] showed that *k-ras* gene mutations could be detected in the colonoscopy effluent of patients with colorectal cancer, while with similar techniques other authors found p53 mutations in approximately 30% of these patients [58]. In fact, colorectal tumorigenesis is characterized by the accumulation of mutations in many cancer-related genes [59]; since cells from neoplastic tissues shed rapidly into the colonic lumen, these mutations can be detected in the cellular debris of feces. This concept represents the basis for a potentially more accurate colorectal cancer screening approach, which might overcome the many limitations of fecal occult blood testing. In a recent investigation [60], the stools from 40 individuals were examined for *k-ras*, p53 and APC genes: mutations were found in 16 of 21 patients with colorectal cancer (76%), and in 7 of 9 subjects with adenomas of various size (78%), but in none of the controls. Rather interestingly, the fecal occult blood tests were negative in all patients with adenomas. Although these techniques are exciting, and further refinement of the methods is under way, at present two main points should be taken into consideration. First, not all colorectal tumors, but only a fraction of them, show mutations in the above-mentioned genes, and in turn, these genes appear frequently mutated in non-neoplastic clinical conditions, such as ulcerative or Crohn's colitis [61]. Second, no study has so far demonstrated any reduction in the incidence or mortality of colorectal cancer with the use of these molecular screening procedures.

Screening in Individuals with Familial Colorectal Cancer

Together with breast neoplasms, colorectal cancer is probably the most “familial” of all human tumors. By recording an accurate family history of patients with colorectal malignancies, it is easy to see how these tumors tend to aggregate in families, affecting first- and second-degree relatives of the proband [19]. In most series, some 10%–20% of colorectal cancer patients show a more or less marked site-specific familiarity [62–64]. In other words, first-degree relatives of patients with colorectal cancer have a 2–3-fold increased risk for site-specific malignan-

cies compared with the general population [65]. Moreover, close relatives of individuals with adenomas have an increased risk of colon cancer [66], and first-degree relatives of patients with colon cancer tend to have an increased risk of adenomatous polyps compared with controls [67]. The number of affected relatives and the age of onset of the neoplasms are also related to the severity of risk. Thus, if two or more close relatives had colon cancer, the risk of these tumors for other family members is higher than if only one first-degree relative was affected; the risk is four times higher if the diagnosis of cancer in the first-degree relative was reached before the age of 45 [68].

Understanding the Nature of the Familial Risk

The nature of the commonly observed familial risk remains unknown; however, since no Mendelian pattern of inheritance may explain cancer aggregation in these families, the most likely explanation seems to be a multifactorial origin, which implicates a close interaction between genes and environmental factors. Familial colorectal malignancies pose a series of relevant problems. At variance with truly hereditary cases – which represent less than 5% of all patients [69] – familial cases are extremely more common, and their prevention or early detection might save thousand of lives, especially in Western countries, where these lesions are more frequent [19]. Moreover, the identification of familial cases can be difficult, owing to the poor attention frequently given to the family history and to the small size of most modern families. Finally, due to our limited knowledge, screening recommendations or appropriate guidelines for individuals with a familial risk of cancer are lacking or should be considered empirical.

A recent study, however, offered some clues towards a better understanding of familial colorectal cancer; indeed, a few genetic alterations have been described that seem to be implicated in this mild to moderate level of cancer predisposition. Laken et al. [70] reported a constitutional mutation in the APC gene (I1307 K) that does not alter the function of the encoded protein but generates an impermutable microsatellite (a short poly-A), thus causing an increased predisposition to cancer. Although this alteration was described in Ashkenazi Jews, it is likely that the mutation contributes to a large fraction of colorectal tumors also in other ethnic groups [71]. Similarly, mutations of the MSH6 gene (a DNA mismatch repair gene, implicated in the pathogenesis of HNPCC) have recently been detected in 7.1% of patients with a family history of colorectal cancer [72]. This suggests that mutations of the MSH6 gene could be responsible for a fraction of familial colorectal malignancies that occur at somewhat older ages and do not meet the clinical criteria usually employed for defining hereditary colorectal cancer [69].

In a recent editorial, R.L. White [73] proposed the new concept of “strongly” or “weakly” predisposing alleles. The former include APC mutations which lead to FAP, alterations of mutator genes (MSH2, MLH1, PMS1–2) that are responsible for HNPCC, or mutations of BRCA1 and 2 genes, associated with hereditary breast cancer. The I1307 K APC mutation and MSH6 alterations might be exam-

ples of weakly predisposing alleles, which might be much more common than the strongly predisposing mutations and may account for a relevant fraction of those cancers at present labeled as familial.

Screening Recommendations for Individuals with Familial Risk

Despite the lack of solid guidelines, the presence of a more or less marked family history of colorectal cancer suggests a more aggressive screening procedure than for the general population. In a recent editorial, R. W. Burt [74] reports the suggestions of a multidisciplinary panel of experts who recommended that individuals with close relatives affected by colorectal cancer should undergo the same screening procedures outlined for average risk, except that it should begin at the age of 40 years. This means annual fecal occult blood testing, sigmoidoscopy every 5 years, and colonoscopy or barium enema (as an option) every 5–10 years.

According to the American Cancer Society, pancolonoscopy should be recommended when colorectal cancer, or adenomatous polyps, are detected in a first-degree relative younger than 60 years, or when two or more first-degree relatives of any age are affected by colorectal cancer. The screening should begin at age 40, or 10 years before the youngest case within a given family, and should be repeated every 3–5 years [75].

Many endoscopists would favor the ample use of colonoscopy – with little or no emphasis on fecal occult blood tests or sigmoidoscopy – for individuals with a family history of colorectal cancer [62, 76].

Surveillance After Endoscopic Polypectomy

Some of the patients who have undergone removal of one or more colorectal adenomas are at increased risk for the development of subsequent benign or malignant lesions and may benefit from endoscopic surveillance [77]. Unfortunately, we do not know in which individuals polyps will recur and in which individuals polyps appear only once in their lifetime. Some clues can be inferred from polyp size and histology; thus, there are studies suggesting that persons with only a single small polyp detected at sigmoidoscopy have no increased subsequent risk of developing cancer when compared with the risk of the general population [78, 79]. Polyps with a diameter of 5 mm or less are defined as “diminutive” [80]. In a recent study, the large majority of these diminutive polyps were hyperplastic (37%) or adenomatous (41%), and only 0.26% of 1,964 resected and examined lesions showed severe dysplasia [81]. The available evidence suggests that small adenomas grow slowly – over the course of years – into large and dysplastic adenomas, and that large adenomas take 5–10 years to develop into infiltrating carcinoma [62, 82]. It follows that when accurate methods – such as colonoscopy – are available, surveillance does not have to be carried out frequently. Indeed, the main objective of surveillance is not just to find and resect

small adenomas – the large majority of which will not progress to larger lesions – but to remove recurrent polyps before they grow to a clinically important size, when they are likely to undergo malignant changes.

Until a few years ago, surveillance was much more “aggressive”, with annual colonoscopic investigations and removal of all lesions. The present approach is towards larger intervals and individualization of follow-up. At the initial endoscopy, the entire colon should be explored and cleaned of polyps. After removal of large (> 1 cm), multiple, villous or dysplastic adenomas, the first surveillance colonoscopy should be carried out after 3 years [83]. For lesions smaller than 1 cm, that are tubular or hyperplastic and with mild or no dysplasia, most endoscopists would recommend surveillance, with sigmoidoscopy or colonoscopy after 3–5 years [84], while for others the follow-up surveillance should be individualized [77]. After normal results of one 3-year control, further surveillance should take into account the patients’ age and anxiety, concomitant diseases, discomfort of endoscopy, and cost-benefit ratio. Surveillance should be discontinued when its benefits are no longer evident for a given patient.

The first evidence of success of endoscopic removal of polyps was found by Gilbertsen in 1974 [85]; after a 25-year study of periodic sigmoidoscopy and polyp resection in a group of more than 18,000 patients, the author was able to demonstrate a significant reduction in the expected number of infiltrating carcinomas. Although the investigation was criticized owing to the lack of a control group and the large fraction of patients lost to follow-up, it remains the first experimental evidence that periodic screening might lower the mortality rate for colorectal carcinoma. Further evidence favoring endoscopic polypectomy was obtained through the National Polyp Study [48, 49, 86]: individuals who underwent regular endoscopic controls at 3-year intervals showed a subsequent frequency of colorectal carcinoma which was only 10%–20% of that predicted for the control populations. However, since the follow-up was relatively short in this study, confirmatory investigations with longer follow-up times might be helpful.

Surveillance After Surgery for Colorectal Cancer

In 20%–30% of all cases, colorectal cancer is diagnosed at an advanced stage, with little or no possibility of radical intervention [87]. In most cases however (70%–80%), apparently curative surgery can be carried out (Dukes’ A, B and C carcinoma), and in these patients the prospect of cure is much more favorable. Colorectal malignancies, however, tend to recur either at the site of previous surgery (local recurrence, especially for rectal cancer) or with a metastatic spread to the liver, lung and, more rarely, other organs. In addition, metachronous lesions in the remaining large bowel tracts are particularly frequent [88, 89].

The main objective of postoperative surveillance is to detect recurrent or metastatic disease as early as possible and to prevent the development of new infiltrating lesions in the large bowel. Although these purposes are sound, their

scientific basis well-grounded, and the technological advancements available to implement this approach, there is no evidence that a close postoperative surveillance may reduce the mortality rate for colorectal neoplasms, simply because curative treatment for recurrent or metastatic disease is rarely possible [90]. Moreover, two recent studies showed the lack of consensus regarding the optimal strategy for cancer surveillance after surgery, as well as the enormous economic impact of such programs [91, 92].

Despite all of these uncertainties and the lack of controlled trials, most surgeons and oncologists recommend some sort of surveillance after curative resection for cancer of the large bowel. PET scanning is useful for an early detection of local recurrences [93, 94]. Abdominal ultrasound, liver enzymes and chest X-ray are recommended for the diagnosis of distant metastasis, especially in the liver and lungs [95]. Colonoscopy is usually carried out during the peri-operative period to clear the colon of all resectable lesions and to exclude the presence of synchronous malignancies. Repeated colonoscopies are executed at various intervals after the resection, depending on the type of patient (and lesion) and the personal belief of the endoscopist; in many European centers, colonoscopy is performed at the 1-year follow-up and then repeated every 3–5 years [96]. It should be stressed that most recurrences (both local and distant) occur within the first 2 years after surgery and that surveillance should be concentrated during that time. In a recent study, Golandiuk et al. [97] evaluated the pattern of recurrence in a large series of patients who underwent curative resection for large-bowel cancer; the median time to recurrence for all patients was 16.7 months. Metachronous colorectal lesions may occur at any time, so colonoscopy screening should be continued for many years.

Surveillance in Patients with Inflammatory Bowel Disease

Patients with ulcerative colitis have an increased risk of colorectal cancer [98]. The incidence of cancer increases progressively with extension and duration of the disease and has been estimated to be of the order of 0.5% per year after 8–10 years of disease [77]. Cancer may develop from polyps or other visible lesions but, more frequently, it appears to originate in colonic epithelium that has undergone dysplastic changes. Dysplastic alterations may precede or be associated with carcinoma, and their identification during routine biopsies forms the basis of surveillance in these patients [99]. Morson et al. were the first, in the late 1960s [100], to draw attention to the predictive value of dysplasia in the large bowel; the introduction of colonoscopy, in the 1970s, had a profound effect on the management of these patients.

According to the most recent guidelines, all patients with ulcerative colitis should undergo colonoscopy at various intervals of time, to control the extent and activity of the disease [101]. At 8–10 years after the diagnosis of pancolitis, surveillance should become more frequent: the current recommendation is endoscopic controls at 1–2 year intervals. During colonoscopy, a full examination should be executed, with inspection of the entire mucosa (from rectum to

caecum), and taking random biopsies at 10-cm intervals along the colon [102]. The endoscopist should examine with particular attention elevated mass-like lesions (Dysplasia Associated Lesions or Masses, DALM), since these areas are at particular risk of harboring dysplasia or carcinoma [103]. For the same reason, further biopsies should be taken from irregular plaques, polyps or pseudo-polyps, unusual ulcers or strictures [101, 103, 104].

Despite the well-grounded scientific approach and the availability of appropriate techniques, evidence of the efficacy of surveillance in ulcerative colitis is still lacking. Various studies have shown that surveillance led to the detection of early-stage carcinoma in only a minority of patients, resulting in a high cost-to-benefit ratio; indeed, a significant number of screened individuals developed advanced lesions despite surveillance [105, 106]. This can be due to the long period of observation in order to demonstrate an effect on cancer stage and survival, to the frequent low compliance, and to the fact that not all patients are ready to accept colectomy with ileoanal anastomosis (one of the current surgical approaches) if severe dysplasia is detected in one or more lesions. Other studies favored surveillance [107, 108]. In the experience of Choi et al. [107], for instance, data of an 18-year surveillance program were collected prospectively, and carcinomas were detected at an early stage (Dukes' A and B) in 15 of 19 patients (79%).

The risk of carcinoma among patients affected by Crohn's colitis is, again, related to the extent and duration of active disease [109]. The relation between cancer risk and dysplasia has not been investigated in detail as for ulcerative colitis; consequently, no specific indications are available to guide practice [77]. Despite this lack of information, most endoscopists recommend periodic colonoscopic surveillance after 10 years of disease for patients with extensive colitis. Particular attention should be given to newly developed symptoms and to the occurrence of strictures that might be caused by infiltrating carcinomas.

To summarize, cancer surveillance in long-standing ulcerative colitis and Crohn's colitis was introduced without the evidence of controlled studies, and it remains of unproven value in terms of cost-effectiveness. However, coupling common sense with the available scientific evidence, most endoscopists recommend surveillance for these patients; this approach, at least in some studies, has led to a more frequent detection of early-stage lesions and to a significant improvement of survival [110].

Surveillance in Hereditary Cancer Syndromes

Among hereditary colorectal cancer syndromes, familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) have been extensively investigated, especially recently, and will be discussed for the surveillance of high-risk individuals. Surveillance in other, rarer hereditary cancer syndromes – such as Turcot syndrome, Cowden disease, Peutz-Jeghers disease, juvenile familial polyposis, etc. [111] – follows, in general terms, the same guidelines as for FAP and HNPCC (see also chapter 12).

Although usually executed in specialized laboratories, genetic tests are now available for the diagnosis of FAP, HNPCC and other related polyposis syndromes [112, 113]. Genetic testing – commonly carried out using DNA from peripheral mononuclear cells – can be applied for two main purposes: (1) to test individuals at risk in a given family owing to their position in the genealogical tree; (2) to confirm the clinical diagnosis in a subject suspected of having FAP or HNPCC. In daily practice, an individual (the proband) with relevant symptoms and signs suggestive of an inherited syndrome is examined first. If a mutation in one of the genes associated with the disease is found, then other family members are tested; when the genetic test is negative in the proband, there is no reason to screen other family members, unless there is the suspicion of a phenocopy in the proband (i.e. a sporadic case occurring, by chance, in a familial setting). When a mutation is not found, this does not allow us to exclude the syndrome, since the available analytic techniques do not identify all relevant mutations and other genes can be implicated in the pathogenesis of the disease (especially for HNPCC). Genetic counseling – defined as the provision of genetic education coupled with psychosocial counseling [114] – is a fundamental part of genetic testing. Counseling should be provided by a clinician with a large experience of family cancer syndromes and should include education on the disease, recommendations on management and surveillance, details on the genetic nature of the syndrome, possible consequences of genetic testing, suggestions on diet and lifestyle, and informed consent.

Familial Adenomatous Polyposis

FAP arises from constitutional mutations of the APC gene (stands for adenomatous polyposis coli) and is inherited in an autosomal dominant fashion [115]. According to the Knudson hypothesis [116], when the corresponding normal allele is lost or mutated, the complete inactivation of APC is followed by the appearance of typical signs and symptoms. FAP is characterized by the presence of hundreds or thousands of polyps of various dimensions scattered in the colorectal tracts and usually appearing during adolescence; if the colon is not removed, colorectal carcinoma almost invariably develops by the age of 30–45 years [117]. Extracolonic manifestations are frequent and include gastric polyps, duodenal periampullary adenomas, desmoid tumors, osteomas, odontomas, epidermoid cysts, retinal spots and, more rarely, other lesions. Many of these changes correlate with location of mutations in the APC gene [118].

All individuals with clinical features of FAP and their first-degree relatives should be offered genetic counseling and genetic testing, beginning at the age of 10–14 years. APC gene mutations can be detected in 80%–90% of families with the present technology [119]; once the mutation is found in the index case, other family members can be studied, and surveillance can be directed to those who test positive for the mutation. These individuals should be examined with colonoscopy annually or biannually until adenomas appear; the optimal timing for colectomy depends on several factors (size, distribution and degree of dys-

plasia of polyps), but in most cases is between the ages of 16 and 20 years [117]. When a mutation is not found, then all family members at risk should undergo endoscopic screening. Upper endoscopy is also recommended for affected and high-risk individuals, at regular intervals of time, for the surveillance of premalignant gastric and especially duodenal lesions [120]. Though prospective controlled studies are lacking, there is evidence from cancer registries indicating that mortality from colorectal cancer can be reduced with an appropriate surveillance of FAP families [121].

Hereditary Non-polyposis Colorectal Cancer

HNPCC poses more problems than FAP, since there are no specific phenotypic manifestations of the disease, and the accurate examination of the family tree represents the basis for a proper diagnosis [122]. HNPCC is an autosomal dominant disease characterized by an early appearance of tumors (more often of the right colon), common occurrence of synchronous or metachronous neoplasms of the large bowel, and frequent association with malignancies of other organs, in particular endometrium, stomach, ovary and urogenital tract [123]. A large fraction (30%–70%) of HNPCC arises from inherited mutations in any of the several known mismatch repair genes, whose function is to maintain DNA integrity during cell replication. Two of these genes – hMSH2 and hMLH1 – account for more than 90% of the constitutional mutations detected in HNPCC families [124]. Inactivation of mismatch repair genes induces a certain type of DNA mutation – called replication errors – which accumulate throughout the genome of involved tumors. These alterations are most easily identified in short DNA segments called “microsatellites” (since many of them are outside the coding region of the genes) which consist of sequences of repeating DNA bases (mono-, di- or polynucleotides) [125]. In the presence of multiple microsatellite errors, the tumor exhibits the “microsatellite instability” (MSI) phenotype; as expected, almost all colorectal malignancies in HNPCC show the MSI phenotype, compared with only 10%–15% of sporadic tumors [126].

In approaching HNPCC surveillance, the first step is to design an accurate genealogical tree, extended to second- and third-degree relatives. Whenever two or three relatives on one side of the family have colorectal cancer (or HNPCC-related neoplasms) – especially when this is located in the right colon and develops before the age of 50 years – the syndrome should be taken into consideration. In families that satisfy the clinical criteria for HNPCC [124], MSI testing should be executed on colon cancer tissue (fresh or paraffin embedded) from one of the affected individuals. If the tumor is unstable (MSI), then the probability that the given family has HNPCC is much greater. The subsequent step is to perform genetic testing on constitutional DNA, in order to find mutations in one of the mismatch repair genes.

Those individuals in a HNPCC family who are positive for mutations need close colonoscopic surveillance at least every 2 years, starting at the age of 20–25 years or 5 years earlier than the youngest individual with cancer in the

Table 5.2. Colorectal cancer surveillance in individuals at risk: recommendations

Clinical condition	Investigation	Frequency	Age	Reference
Familial colorectal cancer	Colonoscopy	5–10 year intervals	40–45	[74, 77]
Endoscopic polypectomy	Colonoscopy	3 year intervals	After polypectomy	[84, 86]
Surgery for colorectal cancer	Colonoscopy	1, 3, 5 years	After surgery	[96, 97]
Inflammatory bowel disease	Colonoscopy	1–2 year intervals	After 10 years of disease	[101, 102]
Hereditary non-polyposis colorectal cancer (HNPCC)	Colonoscopy	2–3 year intervals	20–25 years	[122, 129, 130]
Familial adenomatous polyposis (FAP)	Colonoscopy	1–2 year intervals	14–16 years	[117, 119, 120]

family [122]. Owing to the frequency of endometrial carcinoma, pelvic evaluation (gynecological examination and ultrasound) beginning at 18 years of age is recommended for women. The same approach (colonoscopic surveillance) is also indicated: (1) in families with a strong clinical suspicion of HNPCC (on the basis of clinical findings) but who do not fulfil the standard criteria for HNPCC [127]; (2) in HNPCC – or suspected HNPCC [128] – families who do not show positive results on genetic tests. A surveillance strategy in HNPCC families showed some efficacy in reducing the burden of colorectal cancer. In a large series of HNPCC families, Jarvinen et al. [129] reported the occurrence of fewer colorectal malignancies and fewer cancer-related deaths among HNPCC family members who accepted endoscopic screening every 3 years compared with those who declined this surveillance program. The same authors [130] reassessed their families after completion of a 15-year follow-up and confirmed the excellent results of surveillance: colorectal cancer developed in 8 screened subjects (6%) compared with 19 control subjects (16%, $p < 0.014$; a reduction in cancer rate of 62%). Moreover, all colorectal malignancies in the study group were localized (Dukes' A or B), causing no deaths, compared with 9 cancer-related deaths among controls (Table 5.2).

Conclusion: Media, Society and Colorectal Cancer Screening

As we entered the last decade of the twentieth century, the benefits of colorectal cancer screening were uncertain. The key questions were: can screening the general population reduce colorectal cancer mortality? Can society afford the cost of screening programs? Entering the new millennium, the available literature and the results of many controlled studies seem to suggest that screening asymptomatic

matic individuals can lower the incidence and mortality of colorectal malignancies [131], and that the cost of screening per added years of life does not exceed that of other well-accepted prevention programs, as in the case of hypertension or coronary artery disease [132]. We might, of course, discuss whether a fecal occult blood test is more convenient or feasible when compared with other procedures, such as sigmoidoscopy or colonoscopy; but there is no doubt that the currently available techniques might all be effective in reducing the incidence and mortality of colorectal cancer if applied in large-scale projects. In a recent study, Slusser et al. [133] evaluated the efficacy of a television-advertised screening program for colorectal cancer using a fecal occult blood test. The results showed that this approach was effective in recruiting a large number of participants; moreover, patients diagnosed with colorectal cancer through the television program tended to have early stage disease and improved 5-year survival.

March 2000 was called the “Month of Colorectal Cancer Awareness” by some American cancer foundations [74]. On that occasion, President Clinton gave a speech strongly in favor of colorectal cancer screening, as shown in this sentence: “I encourage health care providers, advocacy groups, policymakers, and concerned citizens across the country to help raise public awareness of the risk and methods of colorectal cancer, and to use the power of our knowledge to defeat this silent disease...”.

With these auspices, and this high patronage, the forthcoming century appears more than promising in this field of research.

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