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REVIEW

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Hereditary non-polyposis colorectal cancer

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Abstract Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant condition in which affected individuals develop colorectal cancer or extracolonic cancers, most commonly endometrial, at an early age. Recent advances in molecular genetics have led to the identification and sequencing of four genes thought to be responsible for the majority of cases of hereditary non-polyposis colorectal cancer. A description of the disease along with details of the underlying genetics and pathological features are presented. Current management and screening policies in these pedigrees are not clearly established. This article discusses some of the controversies in the light of predictive testing.

Key words HNPCC · Colorectal cancer · RER status · Lynch syndrome

Résumé Le cancer colo-rectal héréditaire non polypoïde (HNPCC) est une pathologie autosomique dominante dans laquelle les individus atteints développent des cancers colo-rectaux et des cancers extra-coliques, le plus souvent de l'endomètre, à un âge précoce. Des progrès récents dans la génétique moléculaire ont permis d'identifier et de préciser la séquence de quatre gênes dont on pense qu'ils sont responsables, pour la plupart des cas, des HNPCC. Nous rapportons une description détaillée de cette affection et des troubles génétiques sous-jacents ainsi que des constatations pathologiques. Le traitement courant et les règles de dépistage ne sont pas encore clairement établis. Cet article discute quelques-unes des controverses à la lumière des tests prédictifs.

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Introduction

Genetic factors have long been recognised to be important in the development of colorectal cancer. Aldred Warthin in the late 1800s first documented the 'family cancer syndrome' with his description of "Warthin's family G" [1]. This pedigree demonstrated a marked aggregation of bowel, endometrial and ovarian cancers. The significance of this description was not fully realised until the description of two large pedigrees by Lynch et al. in 1966 [2]. The syndrome was later called the hereditary non-polyposis colorectal cancer syndrome (HNPCC), or Lynch syndrome.

HNPCC is an autosomal dominant condition which is clinically characterised by the development of colorectal cancer at an early age (mean age 44 years), an excess of synchronous and metachronous tumours and a preponderance of right-sided tumours (70%) [3].

Associated tumours

Another feature seen in many of these families is the occurrence of adenocarcinomas at other sites, in particular the endometrium, ovary, stomach, pancreas, ureter, renal pelvis and skin [3–5].

Mecklin and Jarvinen [6] looked at the tumour spectrum in 40 HNPCC families and found colorectal (64%), endometrial (8%), gastric (6%), biliary/pancreatic (4%) and uroepithelial carcinomas (2%) to be the most frequent. Vasen et al. [7], in 24 kindreds in the Netherlands, and Watson and Lynch [8], from a study of 23 HNPCC families, likewise found carcinoma of the endometrium to be the second commonest malignancy in HNPCC. They also reported an excess of gastric, urinary tract, small bowel, ovarian and hepatobiliary cancers. An increased incidence of breast cancer and lung cancer have been reported in female family members [9], but others workers have found no excess of these cancers in HNPCC [8, 10, 11]. Indeed Lynch et al. [10, 11] found significantly fewer lung cancers oc-

curring in HNPCC families than in control groups. It is obviously more difficult to demonstrate a positive link between these two cancers and HNPCC because of the relatively high incidence of breast and bronchogenic carcinoma in the general population. Risenger et al. [12], however, described widespread microsatellite instability in several breast carcinomas from known HNPCC kindreds. Furthermore, one family member had a germline hMLH1 mutation along with the wild-type allele in her normal tissues but was homozygous for the mutant allele in the breast cancer tissue, suggesting that breast cancer may occur as an integral tumour in HNPCC. Beck et al. [13] also found germline HNPCC mutations in individuals from HNPCC kindreds with breast cancer but felt this may simply be the result of chance. Other studies have reported an increased incidence of lymphatic/haemopoietic cancers and sarcomas in HNPCC [14–16] but this has not been substantiated.

Clinical characteristics

Lynch's early description subdivided HNPCC into two clinical variants: Lynch syndrome I, which is the predisposition to site specific colorectal cancer, and Lynch syndrome II, which is characterised by the development of extracolonic malignancies. Many authorities now believe that there is no clear distinction between these two variants, and that they are merely manifestations of a single syndrome. This is supported by recent data showing families with extra-colonic cancers and those with 'site-specific HNPCC' to be linked to the same chromosomes [17, 18].

Unlike familial adenomatous polyposis (FAP), in which colorectal cancer is preceded by the development of hundreds to thousands of adenomatous polyps, HNPCC has no such phenotypic features. Evidence suggests colorectal carcinomas in HNPCC do develop from adenomatous polyps, but that adenomas do not occur in large numbers. Jass [19] reviewed 131 cancers from 117 HNPCC family members. None of the cancers was of the small, superficial, de novo type, but residual adenoma (contiguous with cancer) was present in 100% in situ cancers, 89% of cancers involving only the submucosa, 29% of cancers limited to the muscle coat and 12% of cancers extending beyond muscle, suggesting that the majority had arisen from adenomatous polyps. In an earlier study Jass and Stewart [20] compared the prevalence of colorectal adenomas in 23 patients with HNPCC to that in an age-matched forensic autopsy population. Although the incidence of adenomas was greater in the HNPCC patients than in the autopsy group (particularly those under 50 years of age; 30% and 5%, respectively) all the adenomas were solitary, apart from that in one patient who had two synchronous adenomas. Mecklin et al. [21] evaluated the histopathology of colorectal cancers and adenomas in 75 HNPCC patients with colorectal cancer compared to control patients with sporadic colorectal cancer. They found a similar incidence of synchronous adenomas in the two groups, 19% in HNPCC patients compared to 16% in controls. In a colonoscopic screening program Love and Morrissey [22] found adenomas in 7/42 (17%) asymptomatic HNPCC family members, the majority solitary.

Extra-colonic phenotypic markers such as congenital hypertrophy of the retinal pigment epithelium (CHRPE) and osteomas have been reported in some presumed HNPCC pedigrees [23, 24], but these may well represent attenuated forms of FAP [25–28].

Diagnostic criteria

In view of the absence of phenotypic markers in HNPCC the identification of probands to date has relied on the accurate documentation of family histories. Difficulties arose in distinguishing familial clusterings of colorectal cancer due to shared environmental influences from those with a true genetic predisposition. This led the International Collaborative Group on HNPCC to put forward a set of minimum criteria to define HNPCC, the Amsterdam criteria [29]. These state that: (a) At least three relatives should have histologically verified colorectal cancer; one of them should be a first-degree relative of the other two. Familial polyposis should be excluded. (b) At least two generations should be affected. (c) In one of the relatives colorectal cancer should be diagnosed under 50 years of age.

It should be noted that these criteria were designed to focus research resources effectively and are often too stringent for use with small families. Percesepe et al. [30] found that family size plays an important role in determining the outcome of pedigree assessment; the relative risk of reaching a positive diagnosis of HNPCC according to the Amsterdam criteria increases by 24% with each additional first-degree relative. There is also the possibility of false-positive diagnosis in large pedigrees that may contain chance clusters of tumours. These criteria also ignore extra-colonic malignancies as a clinical manifestation of HNPCC, which may lead to under diagnosis of the syndrome. Beck et al. [13] looked at ten families with pedigrees suggestive of HNPCC but in which the Amsterdam criteria were not fulfilled. DNA was screened for germline mutations in the *hMLH1* and *hMSH2* genes. Mutations were identified in six of the ten families. They concluded that the Amsterdam criteria are inappropriate for use in a clinical setting.

Incidence

The true incidence of HNPCC is not yet known. It has been reported to be responsible for from less than 1% to up to 13% of all colorectal carcinomas [31–34]. Ponz de Leon et al. [35] estimated the frequency of HNPCC from their regional registry, using the Amsterdam criteria, to be between 3.4–4.5%. Ghadirian et al. [36] in Montreal found 5.1% of colorectal cancers in a case control study to have a family history compatible with HNPCC compared with 0.6% of controls. Hall et al. [37] examining all individuals under 45 years of age presenting with colorectal cancer, found that 8% of those family histories which could

be obtained fulfilled the Amsterdam criteria, and that a further 12% satisfied less strict criteria.

Genetics

Most colorectal cancers develop from benign adenomatous polyps, via the so-called adenoma-carcinoma sequence proposed by Morson [38]. It is thought that carcinomas develop by a stepwise progression from normal mucosa through an adenoma to invasive cancer [39]. Fearon and Vogelstein [39] described a sequence of genetic changes that accompany these histological events. Sequential and cumulative genetic damage leads first to a hyperprofilerative state, thence to adenomas and subsequently to an invasive carcinoma. This involves mutational activation of several known oncogenes, in particular K-*ras*, coupled with the mutational deactivation of several known tumour suppressor genes: *APC* (chromosome 5), p53 (chromosome 17) and *DCC* (chromosome 18). Although Fearon and Vogelstein [39] described a preferred sequence of mutations, this is a simplified model, and it appears to be the total accumulation of changes that is important rather than their order. Nevertheless, loss of *APC* is probably an initiating event while *p53* loss appears to occur late in most tumours.

Tumour suppressor genes behave in a recessive manner, so that both alleles must be inactivated in order for the growth suppressive function to be eliminated (Knudson hypothesis), i. e. two hits must occur [40]. Clonal expansion then occurs if the mutation conveys a survival advantage to the cell. If a germline mutation in one allele of a tumour suppressor gene is inherited, only one "hit" is required. Individuals with FAP have a germline mutation in the *APC* gene together with mutation of the wild type allele at the somatic level.

Chromosome localisation

In the search for the HNPCC gene(s) it seemed likely that the culprit would be a tumour suppressor gene. However, it became apparent from studying the molecular genetics of tumours in HNPCC that a different mechanism of tumourigenesis exists in these individuals. Peltomaki et al. [41] were the first to show close linkage of HNPCC to anonymous microsatellite markers on chromosome 2, suggesting that this is the most likely physical location of the HNPCC gene. Microsatellite markers are short nucleotide sequences which are repeated within the DNA strand. Subsequent work demonstrated a rather unexpected finding in that there are differences in these microsatellite markers between tumour DNA and normal DNA, the tumour DNA showing very variable increases in the length of these sequences, probably the result of repeat expansion or deletion. These microsatellites are normally scattered throughout the human genome, and many normally exhibit variations in the number of repeat sequences between individuals (length polymorphisms), thus explaining their use in linkage analysis. In general, however, alleles at these sites are inherently stable, and this variability in tumour tissue was therefore unexpected. It was consequently postulated that replication errors, uncorrected by repair mechanisms, had occurred in these sequences during tumour development.

Several DNA editing and repair systems exist in all cells to ensure accurate replication of genetic material, thus preventing propagation of somatic mutations. The DNA lesions that lead to mutations are most frequently modified, missing or mismatched nucleotides. The best defined 'mismatch' repair pathway is the so-called MutHLS pathway in *Escherichia coli*. Subsequent work has identified human homologues of two bacterial mismatch repair proteins, MutS [42, 43] and MutL [44, 45], which have been called hMSH2 and hMLH1. hMSH2 maps to human chromosome 2p22-21, very close to the locus described by Peltomaki et al. [41]. hMLH1, on the other hand, is located on chromosome 3p21-23. More recently two further homologues of the prokaryotic mutL gene, hPMS1 and hPMS2, have been identified and sequenced [46]. They have been localised to chromosomes 2q31-33 and 7p22, respectively.

Gene interaction

Germline mutations in all four of these genes have been identified in affected individuals from different HNPCC families [42, 46, 47]. In order for tumourigenesis to occur in these individuals a second mutation is probably required to inactivate the normal wild-type allele since it appears that adequate amounts of the gene product are produced to be functional in the heterozygous state. Parsons et al. [48] have shown that lymphoblastoid cells from an HNPCC patient, whose colorectal cancer revealed multiple replication errors, were repair proficient. Casares et al. [49], using somatic cell hybrids between a tumour cell line without genomic instability at simple repeated sequences and colon carcinomas cell lines with somatic genomic instability, demonstrated that restoration of defective mismatch repair and microsatellite stability is achieved by transfer of a wild-type chromosome, i. e. confirming the recessive nature of the mutator phenotype. Further evidence that a second, somatic mutation is required comes from Williams et al. [50]. They showed, using the mPAS histochemical technique to identify a polymorphism for *O*-acetyltransferase activity, loss of which is due to a somatic mutation, that the somatic mutation frequency in the normal mucosa of patients with HNPCC is no greater than that in patients with sporadic colorectal cancer. They therefore concluded that germline defects in HNPCC do not result in a generalised increase in liability to mutation in normal colonic mucosa but that a second, somatic event is required.

It seems likely that mutation of a second allele must occur at an initial or very early stage in tumour development, inactivating repair enzymes and thus allowing mutations to accumulate rapidly, leading to the accelerated develop-

ment of cancer in these families. This hypothesis is supported by experimental data in which Lazar et al. [51] demonstrated the presence of somatic mutations in the *APC* and *p53* genes in RER^+ tumours from two HNPCC families. Only three tumours were analysed (one polyp and two carcinomas). All the mutations detected were absent from patient lymphocyte-extracted DNA and could therefore be considered as somatic mutations. The mutational pattern, however, was interesting. In the polyp one mutation was found in the *APC* gene and no mutations in the *p53* gene, but in the carcinomas six mutations were found in the *APC* gene and four in the *p53* gene in one and four mutations in the *APC* gene and none in the *p53* gene in the other. This mutational pattern is strikingly different from that observed in sporadic colorectal tumours, which are characterised by single or, at most, two different mutations in each gene. This supports the hypothesis that in HNPCC inactivation of a DNA repair gene results in the progressive accumulation of mutations in critical genes known to be involved in colorectal tumourigenesis.

More recently, however, Parsons et al. [52] have looked again at the non-neoplastic cells of HNPCC patients for mismatch repair defects using more sensitive methods. They found evidence of microsatellite instability in non-neoplastic cells in a subset of HNPCC patients. They postulated that this is due to inherited mutations of other genes that participate in mismatch repair, with multiple germline mutations leading to a reduction of mismatch repair activity. An alternative hypothesis is that mismatch repair gene mutations are acting in a 'dominant-negative' fashion; the product of the abnormal allele interferes with the function of the normal protein.

HNPCC is thus an end result of defects in one or more of several mismatch repair genes. hMSH2 and hMLH1 are thought to account for 70–90% of all cases of HNPCC. hPMS1 and hPMS2, along with possibly other as yet unidentified DNA mismatch repair genes, account for the remainder.

Pathology

Despite the name "non-polyposis colorectal cancer" evidence to date suggests that the carcinomas in HNPCC, as discussed above, arise from benign adenomatous polyps [20, 53, 54]. Although adenomatous polyps are no more prevalent in individuals from HNPCC pedigrees than in the general population [20, 22, 53, 55], they do appear to show a greater propensity for malignant transformation [20]. In keeping with this they are also more likely to have a villous component and to show moderate or severe dysplasia.

Comparison with 'sporadic' colorectal carcinoma

Colorectal carcinomas in HNPCC are more often found in the proximal colon than sporadic carcinomas, and there is a higher incidence of synchronous and metachronous tumours. They usually have a normal diploid constitution rather than being aneuploid, are frequently mucinous and poorly differentiated, with areas of necrosis [3, 55–58]. It has been suggested that, paradoxically, stage for stage the prognosis of HNPCC tumours is relatively good [20, 59, 60], though this may in part be a selection bias by focusing on large pedigrees with surviving gene carriers. One theory suggested to account for a good prognosis in the presence of pathologically poor prognostic features is that the relatively high mutational load that occurs in tumours with defective DNA repair systems is detrimental to tumour survival [60]. Another possibility is that tumours carrying a large number of mutations stimulate a stronger immune response [31].

The majority of colorectal cancers in HNPCC [>80%) manifest replication errors and are thus termed replication error positive (RER^+) tumours. Some 10–16% of sporadic colorectal cancers have also been found to be RER^+ [54, 62–63]. Interestingly, RER^+ sporadic cancers exhibit many of the features of colorectal tumours in HNPCC mentioned above, when compared to RER^- sporadic tumours [62, 63]. In one study 80% of sporadic RER^+ tumours were proximal to the splenic flexure [54]. Some of these tumours may represent unrecognised HNPCC or may be due to a de novo rather than inherited germline mutation. Alternatively somatic mutations in HNPCC genes may have occurred during tumourigenesis.

Cancers at other sites

The RER phenotype is not limited to colon cancers. Peltomaki et al. [64] studied the incidence of microsatellite instability in more than 500 sporadic tumours, representing six different types of cancer. They found that 18% of gastric cancers and 22% of endometrial cancers were RER^+ whereas all of the lung, breast and testicular cancers examined were RER^-. Importantly, the first two cancers, as opposed to the latter three, are part of the HNPCC tumour spectrum. Risenger et al. [12] found microsatellite instability in both sporadic and HNPCC endometrial cancers. Microsatellite instability has also been observed in keratoacanthomas [65], a distinctive skin tumour frequently seen in Muir Torre syndrome, which is now known to be part of the HNPCC syndrome.

The reason for the observed site specificity of tumours in HNPCC is still unclear. It may simply be a reflection of the frequent exposure of these tissues to specific mutagens. The colorectal, gastric, small bowel and urothelial mucosas are often in contact with potential carcinogens, for example heterocylic amines, unlike breast and testicular cancers. If this were the case, however, it is somewhat surprising lung cancer is not part of the HNPCC tumour spectrum. Alternatively, Peltomaki et al. [64] suggested that the site specificity is due to differences in the vulnerability of various genes to replication errors. If target genes contain mutation prone sequences at critical sites in their structure, tumourigenesis is more likely to occur.

Replication errors have also commonly been found in adenomas derived from patients with HNPCC. Around 60% of such adenomas have been found to be RER^+ compared to only 3% of "sporadic adenomas" [54]. These findings provide further strong evidence that adenomatous polyps are precursors of colorectal cancer in HNPCC. Studying adenomas for RER^+ has been suggested as a tool to help in the diagnosis of HNPCC, especially in families in whom a mutation has not been identified.

Management

Identification of HNPCC

Family history

Probably the most difficult hurdle in the management of HNPCC is the identification of gene carriers. This is due partly to the absence of a recognisable phenotype. The clinician must therefore always be alert to the possibility of an inherited predisposition. The initial step in identification should be a routine family history of all malignancy. One major problem with reliance on family history is the accuracy of patient recall. Studies have shown inaccuracies in patient recollections of relatives' illnesses, both over- and underreporting pathology. Other factors which should alert the clinican are multiple colonic tumours, extra-colonic cancers, particularly those recognised as part of the HNPCC tumour spectrum and tumours occurring at an early age. As discussed above, strict adherence to the Amsterdam criteria is not appropriate as they are too stringent. All families with a pedigree suggestive of HNPCC should be identified and referred to a geneticist.

Experience with FAP [66] suggests that the tracing of pedigrees, counselling and recruitment of individuals for screening is best performed by a trained genetics nurse, along with a clinical geneticist. These pedigrees are often complex and extensive. Contacting a healthy individual to inform them of a potential health risk must be carried out with tact and without the time restriction of a busy clinic. The management of HNPCC is still not uniform, and pedigree tracing is not yet a routine concept as it is with FAP. It has been adequately demonstrated with FAP that a regional register identifies more individuals at risk [66] and leads to a more uniform approach to management. Most FAP registries are now documenting cases of HNPCC, but the increased workload (four to five times the incidence of FAP) suggests that establishing regional registers for HNPCC should be a goal in the near future.

Predictive testing

The recent identification and cloning of four genes, *hMSH2*, *hMLH1*, *hPMS1* and *hPMS2*, provides the basis for direct mutation analysis. It is therefore now possible to offer predictive testing to some families, but at present the search for mutations in the mismatch repair genes is time consuming and expensive.

Predictive testing cannot be established without adequate back-up. Pre- and post-testing counselling must be available. The counselling sessions should educate the family about the clinical and management aspects of HNPCC, the risks of cancer and the consequences of receiving a gene positive test result with the broader implications, for close relatives and insurance prospects, for example [67]. Likewise the consequences of a gene negative test result must be discussed. Family members who do not carry the gene can be reassured and discharged from further follow-up but may find it hard to stop regular screening if they have already been enrolled into a screening program. It is also important to emphasise that they still have the same risk as the general population of developing colorectal cancer. Those who are gene carriers should be enrolled into a screening program, as outlined below, screening for extra-colonic as well as colonic malignancies. The decision to proceed with any gene test should be freely made by the at-risk person after having had time to carefully consider the consequences of genetic testing. Those deemed to have a significant risk from pedigree analysis who decline predictive testing should also probably be maintained on a regular screening program.

RER status

Several workers have looked at using RER status of tumours combined with family history to refine the clinical diagnosis of HNPCC and hence to select patients for mutation analysis. The reported incidence of RER^+ tumours in HNPCC varies from 77% [68] to 95% [69] but also occurs in 13–20% of sporadic colorectal cancers. Jass et al. [70] suggested that reliance on the clinical criteria alone results in overdiagnosis of HNPCC. They examined 50 families, 19 in whom the Amsterdam criteria were totally fulfilled (group A) and 31 in whom the criteria were partially fulfilled (group B). A family was designated RER^+ if at least half the tumours tested showed microsatellite instability. In group A 12 families were RER^+ and 7 RER^-; in group B 9 families were RER^+ and 22 RER^-. The accepted clinical and pathological characteristics of HNPCC were found to cluster within the 12 group A RER^+ families, suggesting that the Amsterdam criteria for HNPCC could be refined by inclusion of RER status. Muta et al. [71], however, suggested the Amsterdam criteria under diagnose HNPCC. They studied 56 patients with colorectal cancer, 8 of whom fulfilled the Amsterdam criteria and 23 of whom fulfilled modified clinical criteria, which included extra-colonic cancers, multiple and proximal cancers. They found 86% of those fulfilling the Amsterdam criteria were RER^+ but 62% of those fulfilling the modified clinical criteria were also RER^+. They concluded that the presence of microsatellite instability, in concert with modified clinical criteria, identifies legitimate cases of HNPCC that might otherwise be excluded by the Amsterdam criteria.

Samowitz and Slattery [72], on the other hand, looked at RER status as a marker of HNPCC in a general population study. In this context they found that RER status was not a useful marker of family history and concluded that it should not be considered as evidence for an inherited syndrome. Both Dunlop et al. [73] and Liu et al. [74] in general population studies likewise found RER analysis of tumours not sufficiently discriminatory in identifying those with a family history, unless stratifying age groups. Dunlop et al. [73], extrapolating from their data, indicated that 58% of patients under 35 years of age with colorectal cancer have RER^+ tumours, 24% of which have a germline mismatch repair gene mutation. This compares with the non-age-stratified group where 15% have RER^+ tumours and only 1% have germline mutations. Liu et al. [74] found 18 out of 31 (58%) patients aged under 35 years with colorectal cancer to be RER^+, compared to 12% of those aged over 35 years. Twelve of those below 35 years of age were evaluated for mutations in the mismatch repair genes, and five (42%) were found to harbour a germline mutation.

Screening gene carriers and individuals with a significant clinical risk of HNPCC

Screening should be performed in as streamlined a fashion as possible to minimise impact on "normal" life. It is essential to minimise anxiety if compliance is to be optimised, and counselling is very important from an early stage. This is probably best provided in the setting of a family cancer clinic, with a specialist nurse dedicated to working with these families. Collaboration between the surgeon or physician and the geneticist is crucial to good management. Data from the United States have highlighted problems due to both patient compliance and physician delay [75]. Education of both parties is essential and a registry should have a central role in such activities.

Screening should not be directed merely to colon cancer but also to other tumours that commonly occur in HNPCC in order to be effective, for example, uterus and possibly stomach and ovarian tumours in families where there is a preponderance of these malignancies.

Colon

Flexible sigmoidoscopy is not appropriate in these patients because of the preponderance of right-sided lesions. Double-contrast barium enema has a similar error rate in the detection of small polyps (<10 mm) as colonoscopy (11.7% compared to up to 10% for colonoscopy) but gives no opportunity to biopsy or remove polyps [76–78]. Screening for faecal occult blood is mentioned merely to be dismissed as a sole technique for such high-risk cases because of its low sensitivity [79–81]. About 40% of cancers and 80% of adenomas are missed by a single screen with standard guaiac slide tests.

It is difficult to specify a precise age at which to initiate screening, but it is logical to recommend starting at 25 years of age or 5 years earlier than the earliest onset of colon cancer in the family [10, 29]. Likewise the age at which to discontinue colonoscopy is not certain. Gene carriers generally develop colorectal cancer at ages 15–20 years younger than the general population, but some do present with tumours in their 7th or 8th decade [82]. Indeed a study of 41 families with HNPCC showed that 8% of affected individuals presented with symptomatic cancers at greater than 60 years of age [83]. Thus, although discontinuance of screening has been recommended by some at 60 years of age [29], colonoscopic screening should probably continue for life, unless comorbidity dictates otherwise.

The optimal screening interval is not known. Unlike 'sporadic' adenomas, which take around 5 years to reach 1 cm in diameter and 8–10 years to become malignant, adenomas in HNPCC have a greater potential for growth [20]. Indeed interval cancers have been reported in several screened groups at 3 years [29] although these may represent missed lesions rather than de novo growths.

The range of recommendations varies from yearly colonoscopy to an interval of 2–3 years [10, 22, 29, 55, 84]. Lynch et al. [11] have recommended biannual screening from 25 to 35 and annual screening from 35 onwards. Patient acceptance of the screening protocol is vitally important for their own further compliance and that of relatives. If colon preparation is good and the whole colon right round to caecum is well visualised, 2-yearly colonoscopy is probably adequate, but in those proven by molecular genetic analysis to carry the gene defect it may be more prudent to offer annual examination until the natural history of HNPCC is more clearly defined.

Endometrium

Endometrial carcinoma is the most commonly observed extra-colonic cancer in HNPCC [6–8, 16]. The lifetime risk for female members of an HNPCC family of developing endometrial cancer has been calculated to be as high as 20–40%, compared to 3% in the general population, and the period of highest risk occurs 15 years earlier than in the general population [70, 74]. Effective treatment is available if endometrial cancer is detected early, and therefore it is reasonable to include this as part of a screening program. Lynch et al. [85] have recommended yearly uterine washings for endometrial cytology and transvaginal ultrasound, but it is not possible to say yet whether the costs of screening outweigh the benefits.

Ovary

Ovarian carcinoma is one of the less common cancers associated with HNPCC, occurring in 3% of female cases compared to a population incidence of 1 in 5000 (0.02%) [6]. Transvaginal ultrasound is the mainstay of ovarian screening, performed at yearly intervals. Lynch et al. [55]

recommended yearly colour flow Doppler transvaginal ultrasound and CA-125 tumour markers. However, women must appreciate the limitations of ovarian cancer screening.

Other cancers

In total, gastric, pancreatico-biliary and urothelial cancers arise in less than 10% of affected individuals [6]. Therefore it is questionable whether gastroscopy, abdominal ultrasound and urine cytology should be included routinely in the screening protocol. Perhaps in families in whom other cancers have been recorded it may be appropriate to screen for these specifically.

Surgery

Although Lynch and coworkers [85, 86] have recommended prophylactic subtotal colectomy, total abdominal hysterectomy and bilateral salpino-oophorectomy in identified gene carries, we do not know enough at present on the disease penetrance and expression to confidently offer such advice. Not all gene carriers eventually develop colorectal cancer or extra-colonic malignancy. Unlike FAP, where the penetrance is approximately 100%, the penetrance in HNPCC has been estimated to be approximately 80%, and thus 20% of individuals carrying the mutation do not develop colorectal cancer [87]. Vasen and Wijnen [88] reported a lifetime risk of colorectal cancer greater than 80%, but this was in well-defined HNPCC families. Dunlop et al. [73], on the hand, used a population-based strategy to calculate lifetime cancer risk associated with germline DNA mismatch repair gene mutations, irrespective of family history. Index patients were identified from the Scottish National Cancer Registry and were diagnosed with colorectal cancer aged 35 years or less. Those with a family history fulfilling the Amsterdam criteria were excluded. Of 27 patients 13 were RER^+ (56%) and underwent mutation analysis for germline mutations in the *hMLH1* and *hMSH2* genes. A germline mutation was found in 6 (46%). From these probands 156 relatives aged over 18 years were traced. Of these, 67 (43%) carried a germline mismatch repair gene mutation. The lifetime risk of developing cancer was calculated from these individuals. For all cancers this was 91% in men and 69% in women. This difference was due largely to the significantly increased risk of colorectal cancer in men, 74% compared to 30% in women, by 70 years of age. In women the risk of endometrial cancer was greater than colorectal cancer, 42% by age 70. Cancer incidence increased rapidly from age 40, but many patients destined to develop cancer did not do so until a relatively elderly age.

Considering the high incidence of colorectal cancer in males reported by Dunlop et al. [73] (74%) and the incidence of interval cancers reported on screening programs, prophylactic colectomy should probably be offered to male gene carriers.

One of the cardinal features of HNPCC is the occurrence of synchronous and metachronous colorectal tumours, and therefore segmental resection is not appropriate in gene carriers. The risk of metachronous cancers is 40% at 10 years if segmental resection is performed [89]. The procedure of choice then is total colectomy with ileorectal anastomosis (IRA), which removes the maximal area at risk, consistent with avoidance of a stoma, yet has low morbidity and mortality [3, 10, 90]. The rectum must be screened sigmoidoscopically following this, and for those individuals for whom this is unacceptable a restorative proctocolectomy is an appropriate choice.

Several important factors must be addressed when offering a prophylactic total colectomy, including whether or not the procedure eliminates the cancer risk, its morbidity and its timing [87]. The cancer risk, although less, still exists in that the rectum remains in situ. The risk of developing rectal cancer is in the region of 12% 12 years following total colectomy and IRA, and regular surveillance is therefore mandatory [87]. There is also still the risk of extra-colonic malignancies developing. Lynch et al. [85] suggest that female gene carriers should be encouraged to have their families early so that they can consider the option of hysterectomy and bilateral salpingo-oophorectomy between the ages of 35 and 40 years, but they must be aware of the possibility of developing peritoneal cystadenocarcinoma, ovarian in origin, despite having their ovaries removed. The patient must understand that total colectomy and IRA is a major procedure with significant morbidity, reported to be in the region of 7.8–10% in FAP [91, 92]. The optimal timing of surgery is not known, and advice can only be based on the available data. The mean age at presentation with colorectal cancer is the middle 40s [3, 83], but the range is wide (14–82 years), [85]. The risks of elective surgery increase with increasing age, but early surgery inflicts a not insignificiant operative procedure on individuals who may not develop cancer until their 60s or 70s, if at all.

It has taken a long time from Warthin's first observations on 'family G' to the establishment of the genetic basis of HNPCC. Recent developments have contributed greatly to our understanding of HNPCC, but if we are to reduce morbidity and mortality rates, medical practitioners must become more aware of the syndrome, and we must look towards the establishment of regional registers and management protocols for such families. Wider availability of mutation analysis, as techniques improve, will help clarify the natural history of the disease and greatly assist in the management of these families in the future.

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