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Point of View

Inheritance and Susceptibility to Tumours of the Large Bowel: a New Classification of Colorectal Malignancies

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INTRODUCTION

PROBABLY IN no other neoplastic disease have we learnt more over the last 10 years than for colorectal cancer. Thus, we now know that colonic and rectal cancer can be viewed as different diseases, especially from an epidemiological point of view [1, 2]. Moreover, the stepwise nature of these tumours has been well defined, and various authors have been particularly active in identifying changes of oncogenes or tumour suppressor genes which might be implicated in each passage from normal mucosa to adenoma and to cancer [3, 4]. Finally, in hereditary non-polyposis colorectal cancer (HNPCC or Lynch Syndrome), constitutional mutations have been found in one of a group of genes (called *hMSH2*, *hMLH1*, *hPMS1* and *hPMS2*, from the homologous bacterial genes or 'mutator genes') which are closely involved in the DNA mismatch repair system [5,6].

The last observation is particulary attractive, since biochemical tests are now available which can tell us in many cases whether or not close relatives of cancer patients are predisposed to tumour development [7]. Being costly and time-consuming, however, these biomolecular techniques cannot be applied to the whole population of colorectal cancer patients, but only to highly selected groups. It follows that one of the most difficult tasks for clinical oncologists is not only the identification of 'full-blown' HNPCC but—even more important for genetic testing and counselling—the recognition and stratification of patients with colorectal malignancies according to different levels of genetic risk of cancer.

A colorectal cancer registry was instituted in the health care district of Modena in 1984. Among the purposes of the registration were the study of familial occurrence of cancer and the detection of families with Lynch Syndrome. In accordance with other reports [8, 9], we found that the frequency of HNPCC—according to the Amsterdam criteria—was of the order of 2–4% of all colorectal tumours [10–12]; in addition, many other families maintained a strong suspicion of having Lynch syndrome, although they did not meet the standard clinical criteria [13]. The accurate analysis of almost 1200 pedigrees, observed between 1984 and 1992, led us to hypothesise that human colorectal malignancies can be subdivided and classified into five categories. Here, we describe in more detail: (1) the experimental evidence upon which this hypothesis is based; (2) the tentative estimate of the frequency—in the general population—of each class of tumour; and (3) the practical importance of this new classification for surveillance and early detection of colorectal malignancies.

THE COLORECTAL CANCER REGISTRY

The general organisation and main features of the registry have already been described in detail [14–16]. The local health care district includes Modena and 10 smaller communities covering a total of 265 227 residents (men: 128 288; women: 136 939; 1991 census). Modena is 180 km South East of Milan; the area is entirely flat, almost exclusively urban, industrialised and with one of the highest incomes per person in Italy. The population density is 450/km^2. Systematic registration of all colorectal malignancies started in 1984; by the end of 1992, 1337 tumours in 1298 patients were detected, for a crude incidence rate of 61.7 new cases/100 000/year in men and 51.9 in women. The corresponding age-adjusted rates (to the world population) were 35.3 and 23.6, respectively. Tumours of the large bowel were classified according to the International Classification of Disease for Oncology (IDC-O, 9th revision). In the registration form—besides personal data, details of surgery, endoscopy, staging and morphologic diagnosis—an accurate genealogical tree was traced, limited to first-degree relatives, in which the main causes of morbidity and mortality were recorded. During the 9-year period or registration, a total of 1195 'nuclear' (i.e. limited to first-degree relatives) pedigrees out of 1298 patients (92%), were collected and analysed. In 103 of the registered subjects, information on close relatives could not be obtained owing to

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poor documentation; in our final analysis these were considered together with sporadic cases.

ANALYSIS OF PEDIGREES

Having obtained the nuclear pedigree, the next step was the subdivision of these family trees into different subgroups. In previous reports [10–12], we have discussed in greater detail the definition and clinical application of six criteria all indicative of an increased susceptibility to hereditary colorectal cancer. Briefly, these criteria can be described as follows. (1) *Vertical transmission*: one parent and offspring affected by colorectal cancer or other malignancies which characterise HNPCC [17]; (2) *familial aggregation*: in the sibship of the proband, 50% (or more) of siblings affected by cancer of all sites; (3) *early onset*: development of colorectal cancer (or of other tumours featuring Lynch syndrome) before the age of 55; (4) *right localisation*: cancer localised in the caecum, ascending, transverse colon, hepatic or splenic flexures; (5) *multiple carcinoma*: presence of 2 (or more) independent primary malignant tumours; (6) *mucinous histological type*: presence of mucus in 50% or more of the tumour at histology.

Thus, nuclear pedigrees of patients registered between 1984 and 1992 were classified into various strata according to the presence of less than two, two, three or four or more criteria, with the underlying assumption that the more criteria observed in a given family, the higher the probability of genetically determined colorectal cancer. This was actually verified in a previous investigation [10], in which HNPCC or suspected cases of Lynch Syndrome were found—after extension of the family tree—only in nuclear pedigrees with at least two clinical criteria. In the present series (1984–1992), there were 40 nuclear pedigrees with four or more criteria, 101 with three criteria and 187 with two; the remaining families showed one, or more often, no criteria. It should be clear at this point that the subdivision of family trees according to our proposed criteria should only be viewed as an empirical approach with the precise objective of selecting those families with whom to proceed in the analysis by extending the pedigree to second- and third-degree relatives.

The subsequent step was the selective extension—to second- and third-degree relatives—of all nuclear pedigrees showing two or more of the abovementioned criteria. This was usually done by directly contacting and interviewing the proband (when alive and collaborating) and/or other family members. In some cases, little further information was obtained, but in others, pedigrees extending to more than 300 individuals could be traced. Once again, all causes of morbidity and mortality (especially related to cancer) were carefully recorded.

We then ascertained how many of the extended pedigrees met the minimum requisites for HNPCC, the so-called "Amsterdam criteria" proposed by the International Collaborative Group on HNPCC [18], with minor modifications [11]. A second group (of great interest) was represented by families which did not meet the "Amsterdam criteria" [19] but nevertheless maintained a strong suspicion of being HNPCC ('suspected HNPCC'). A tentative definition of those families was the following: (1) at least two consecutive generations affected by colorectal cancer (or tumours of the HNPCC spectrum); (2) at least one case under the age of 55; and (3) in the sibship of the proband, 50% or more of the siblings affected by cancer. A third group was constituted by pedigrees with one or more first-degree relatives affected by cancer of all sites but without any suspicion of being Lynch Syndromes (we defined this series as 'familial tumours'). A fourth group was represented by 'juvenile cases'; these were patients in whom colorectal cancer developed before the age of 50 years, but who were not included in HNPCC or suspected HNPCC because the family history was not consistent with this diagnosis. The last group included patients older than 50 years and without cases of cancer among relatives (apparently sporadic cases). The overall clinical procedure is outlined in Figure 1.

We put all our efforts in trying to verify (by histological records, clinical charts or death certificates) all cases of cancer diagnosed among relatives. Verification was almost complete for cancers which occurred between 1980 and 1992, 50% complete for cases developed between 1970 and 1979, and largely incomplete for the preceding years. Moreover, HNPCC and suspected HNPCC were studied in more detail, with verification rates of 72% and 64%, respectively, whereas in the group defined as 'familial tumours', verified cases of cancer were of the order of 20%.

CLASSIFICATION AND FREQUENCY OF COLORECTAL TUMOURS

Pedigree analysis was consistent with a tentative subdivision of all colorectal tumours developed in the general population into five major classes: HNPCC, suspected HNPCC, juvenile cases, familial tumours and apparently sporadic cases. 36 HNPCC cases (in 25 families) were detected among a total of 1298 registered patients (2.8%, a proportion in agreement with other reports), 63 cases of suspected HNPCC were detected (in 52 families; 4.8% of the total), whereas juvenile cases accounted for 4.9% of all registered malignancies ($n = 64$). Familial tumours (i.e. without clinical features suggestive of HNPCC or suspected HNPCC) could be detected in 489 patients (37.7%); finally, the remaining 646 cases (49.8%) could be interpreted as apparently sporadic (and included 103 pedigrees with poor documentation).

In Figure 2, the proposed new classification of colorectal tumours is compared with the hypothetical subdivision of the colorectal cancer burden proposed by Lynch and associates in 1985 [20]. In our experience, only one case of colorectal cancer developed in a patient with familial polyposis (FAP), a value which is much lower than previous estimates [21], but that can be explained by the more efficient presymptomatic diagnoses of FAP [22, 23]. Although the present observations provide definite percentages and a more detailed subdivision into various groups, the intuitive suggestions of Lynch and associates maintain their validity: a small fraction of all colorectal tumours can be considered to have a genetic origin, a larger proportion can presumably be attributed to multifactorial inheritance, and the remaining cases presumably represent sporadic neoplasms.

This new classification can be applied to routine clinical practice, with the objective of identifying individuals and families at genetic risk of cancer. Moreover, the proposed stratification of all colorectal malignancies appears to be of major importance for selecting those families (i.e. HNPCC,

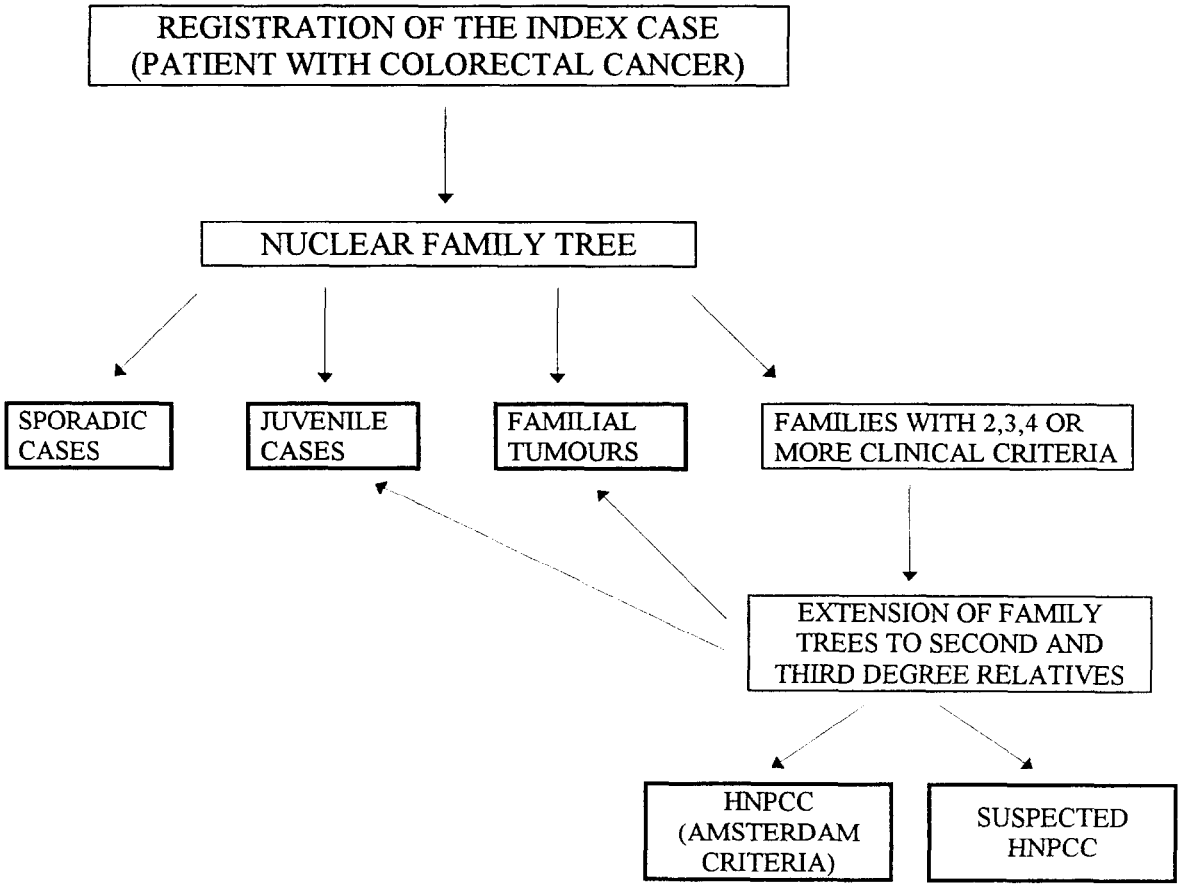

Figure 1. General outline of the clinical procedure followed for this new classification of colorectal malignancies. The first and the second steps were common to all index cases (i.e. registered patients). Subsequent steps concerned only family trees showing 2, 3, 4 or more of our clinical criteria. Whenever possible, the diagnosis of cancer among relatives was verified with histological records or clinical charts. Note that part of familial and juvenile cases was diagnosed from the inspection of nuclear pedigrees, while part of them was defined after extension of the family tree.

suspected HNPCC and juvenile cases) which should be studied for mutations of mismatch repair genes [5–7].

According to the International Classification of Diseases (ICD), tumours of the large bowel are classically classified as colonic or rectal cancer (ICD 153 and 154, respectively). A novel classification was recently suggested by Weinburger and Wynder [1], mainly on the basis of epidemiological observations; the authors proposed that tumours of the right colon were different from carcinomas of the left colon (descending, sigmoid and rectosigmoid junction), the latter being more closely associated with environmental factors, such as diet and style of life. Tumours of the rectum (the last 7 cm of the large bowel) represented a third group, aetiologically distinct from the other two. Lynch and associates [20, 24] repeatedly proposed that colorectal tumours could be subdivided into three broad categories: 'hereditary' tumours (characterised by vertical transmission, early age of onset and preferential—although not obligatory—localisation in the proximal colon), 'familial' tumours (when other cases of cancers were reported among relatives, but without features of Mendelian inheritance) and apparently 'sporadic' neoplasms. More recently, segregation analysis has shown that an autosomal dominant (or codominant) type of transmission could be documented in selected series of families with colorectal tumours [19, 25–28].

Our hypothesis can be viewed as further refinement of the classification proposed by Lynch and coworkers [20, 24]; at variance with these authors, the population-based approach led to the inclusion of two more groups: 'suspected' HNPCC and juvenile cases. Moreover, we provided a tentative estimate of the frequency of each type of colorectal tumour in the general population. A major weakness of the present interpretation is that it refers to a limited period of time, whereas it is rather intuitive that the occurrence of cancer in families is a dynamic (not a static) process. In other words, it is entirely possible that some families initially classified in one group, during the follow-up develop features of a different group, owing to the occurrence of other tumours. This was actually observed in some HNPCC families, whose extended pedigrees were previously interpreted as suspected. The fact, however, should not obscure the main advantage of our approach, which is to provide a logical (and biological) basis for a proper classification of colorectal malignancies according to the presence of a genetic component.

Finally, it should be pointed out that any attempts to classify colorectal (as well as other) tumours does not represent a mere academic exercise, but it bears relevant implications either for affected patients or for their relatives at high risk of cancer. This contention is further supported by

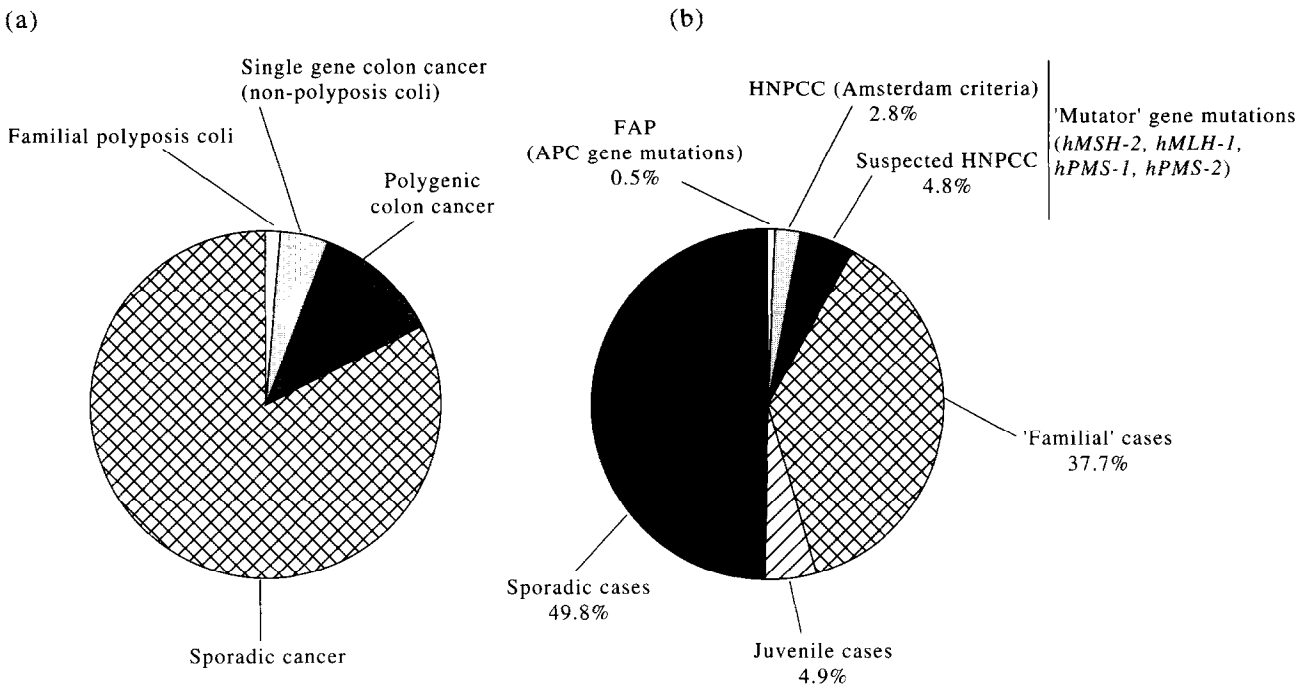

Figure 2. (a) The hypothetical subdivision of colorectal cancer burden in the general population suggested by Lynch and associates [20]. Single gene colonic cancer refers to HNPCC (Lynch syndrome). Polygenic colon cancer refers only to families with other malignancies of the large bowel among close relatives. (b) The new classification of colorectal malignancies proposed in the present article. HNPCC and suspected HNPCC represent subjects (and families) with a high probability of a genetically transmitted disease and, indeed, in many of these families constitutional mutations of the four mismatch repair ('mutator') genes have been detected. Familial cases refer to families with other cases of cancer (of any site) among first-degree relatives, while juvenile cases are individuals in whom cancer develops before the age of 50 years. In sporadic cases, no other malignancies—besides the proband—were observed among relatives. This group included 103 pedigrees in which clinical documentation was extremely poor. The percentages refer to all patients (n = 1298) registered between 1984 and 1992.

the possible integration of clinical observations with biomolecular data.

THE 'NEW' CATEGORIES OF COLORECTAL CANCER

The observed frequency of HNPCC (2.8% of all registered colorectal tumours) is in agreement with most of the previous observations [10, 29–31]. However, other authors have found an appreciably lower frequency (of the order of 1%) [32], while at the other extreme, Houlston and associates [28], on the basis of segregation analysis, suggested that an autosomal dominant transmission could be responsible for approximately 13% of all colorectal carcinomas developed in the general population. Probably, we can reconcile these observations by assuming that between 1% and 5% of all tumours of the large bowel show unequivocal clinical features of HNPCC, but that this proportion can rise to 10–15% if one also considers suspected HNPCC families. The existence of this subgroup was perceived by almost all investigators interested in the clinical aspects of hereditary tumours, but so far no systematic approach has been attempted. In a recent study, Vasen and associates [33] defined as 'late onset' HNPCC a subgroup of families which fulfilled the Amsterdam criteria [18] with the exception of the early age of onset. In our population-based analysis, we reasoned that the presence of at least one colorectal tumour diagnosed before the age of 55 years was a major distinctive feature of those families which should raise the suspicion of being HNPCC, while in the absence of a juvenile case we preferred to classify the family as 'familial tumours'. Thus, the observed frequency of suspected HNPCC (4.8% of all registered tumours) cannot be compared with any other investigations. Although we are aware of the fact that the criteria adopted for the definition of this subgroup are rather arbitrary, it is worth noting that recent studies also showed mutations of the mismatch repair gene in families which might have been classified as suspected HNPCC [34].

Juvenile cases without familiality (4.9% of all registered patients) represent an extremely interesting category. It is well known that in FAP, in approximately 20–40% of the families, the proband is the only affected patient; the most plausible explanation is that these cases represent new mutations [35]. By analogy with FAP, it is entirely possible that some juvenile cases of colorectal cancer are actually due to constitutional mutations of the mismatch repair genes. In accordance with this contention, a recent study [36] showed microsatellite instability in 12 of 35 (34%) patients with colorectal cancer diagnosed before the age of 35; moreover, 5 of these individuals showed germline mutations of either *hMSH2* or *hMLH1* genes. As an alternative explanation, non-penetrance of a major gene should also be taken into consideration, especially for those families in which information on the proband's parents is inadequate or insufficient.

A more or less marked aggregation of cancer (colorectal or of other organs) but without features of hereditary cancer syndromes (in particular, verticality, early age of onset and

multiple primaries) was found in 37.7% of the registered patients. We extended more than 50 of these families to second- and third-degree relatives, but in no case did this expansion of the pedigree lead to the diagnosis, or the suspicion, of HNPCC. These cases, therefore, are presumably explained by multifactorial inheritance, i.e. by the interaction of several environmental factors (diet, lifestyle) with an undefined (in biomolecular terms) genetic background which predisposes to cancer development. Finally, the last group (646 individuals, 49.8% of the total) is constituted by the so-called sporadic cases, whose pathogenesis should almost entirely be attributed to exogenous agents.

PRACTICAL IMPLICATIONS

Our hypothesis further underlines the importance of collecting an adequate cancer family history of all first-degree relatives, aspects which are frequently omitted in the daily medical work-up of patients.

Common recommendations to first-degree relatives of colorectal cancer patients are virtually limited to a sigmoidoscopic examination at age 45–50 years [37]. However, this suggestion seems inadequate for many relatives at major risk of cancer. On the basis of our observations—and in accordance with other recent reports [11, 38]—we recommend starting pancolonscopy at the age of 25 years for all family members of HNPCC patients, and continuing at regular intervals of time (usually every 2 years). For close relatives of patients with suspected HNPCC or with juvenile colorectal carcinoma, we would suggest initiating colonscopy at the age of 35–40 years. In addition, high-risk individuals should receive detailed instructions on how to modify their dietary habits [11, 12] and to adopt a 'healthier' lifestyle, since these factors may influence the penetrance of the gene in carriers. For family members of the two other subgroups ('familial tumours' and 'sporadic colorectal carcinoma'), the common recommendations are probably adequate, although we would favour a more extensive use of colonscopy instead of limiting the examination to the lower segments of the large bowel.

Finally, our findings suggest that HNPCC and suspected HNPCC families—both characterised by a Mendelian pattern of transmission—are the natural candidates for the search of mutations in the DNA mismatch repair genes. However, this analysis might also be proposed for patients with juvenile colorectal carcinoma and to their offspring.

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