**Short Communication**

Frequency and Type of Colorectal Tumors in Asymptomatic High-Risk Individuals in Families with Hereditary Nonpolyposis Colorectal Cancer

Maurizio Ponz de Leon, Giovanni Della Casa, Piero Benatti, Antonio Percesepe, Carmela di Gregorio, Rossella Fante, and Luca Roncucci

Abstract

In hereditary nonpolyposis colorectal cancer (HNPPC, or Lynch syndrome) a close surveillance is usually proposed to high-risk family members with the ultimate goal of reducing cancer incidence and mortality. Through a specialized registry, between 1984 and 1996, we identified 31 families with clinical features of HNPPC. A total of 390 first-degree relatives of affected patients were considered at high risk for colorectal cancer. The main purposes of this study were: (a) to assess overall compliance; and (b) to evaluate the frequency and morphological features of tumors detected at endoscopy. Two hundred twenty-three subjects could be directly interviewed and colonoscopy strongly recommended. Each of the 86 individuals who underwent colonoscopy was matched to a control of the same age (±3 years) and sex (control subjects were seeking endoscopy for constipation, rectal bleeding or abdominal discomfort). Of the 390 individuals traced as "at risk," 223 (57.2%) could be contacted, and, of these, 86 (38.6%, or 22.0% of the total) underwent colonoscopy. One or more colorectal lesions were found in 35 of 86 (40.7%) HNPPC asymptomatic family members and in 15 (17.4%; \( P < 0.001 \)) controls. In the former group, 29 adenomas were detected in 20 individuals as opposed to 11 adenomas in 9 subjects among controls (\( P < 0.03 \)). Moreover, adenomas in family members were significantly larger \( [9.1 \pm 5.9 \text{ mm (mean \pm SD)} \text{ versus } 5.8 \pm 3.7 \text{ mm; } P < 0.02] \) and more frequently showed a tubulovillous histological type and a high degree of dysplasia. Five colorectal carcinomas (in four patients) were detected among cases (four of which were located between the cecum and the hepatic flexure); only one was detected among controls. Surveillance of high-risk subjects in HNPPC families can be carried out only in a fraction of them, because the majority cannot be reached or refuse to collaborate. On the other hand, the frequency of newly detected lesions among family members and the possible aggressive behavior of the lesions render pan-colonoscopy necessary at regular intervals of time.

Introduction

HNPPC, or Lynch syndrome, is characterized by a striking aggregation of cancer in each sibship, vertical transmission of tumors, early age of onset, frequent localization of tumors in the proximal large bowel, and the occurrence of other types of carcinoma (tumors of the stomach, endometrium, ovaries, and urothelium; Ref. 1). Lynch syndrome is associated with constitutional mutations in one of a series of genes \((hMSH2, hMLH1, hPMS1, hPMS2, \text{ and } MSH6)\) that are closely involved in repairing DNA mismatches (2), and whose malfunctioning is associated with diffuse alterations at various microsatellite loci (3). Despite the availability of biomolecular tests, the identification of HNPPC in the general population remains difficult (4). Nonetheless, recognition of Lynch syndrome is extremely important in clinical practice, inasmuch as it may influence surgical choices (in affected patients) and the follow-up of individuals susceptible to cancer development. Individuals at risk are usually contacted for genetic counseling, during which a screening program is proposed (5, 6). Indeed, there is evidence that a close endoscopic surveillance reduces the colorectal cancer rate (and probably prevents cancer-related death) within these families (7). Between 1984 and 1995, 31 HNPPC families were identified and approximately 400 unaffected individuals were considered at high-risk for colorectal cancer. The main purposes of this prospective investigation were: (a) to assess overall compliance of this large series to the screening program; and (b) to establish the frequency of, and to evaluate the main histological features of, colorectal lesions detected at endoscopy in asymptomatic high-risk individuals.

Materials and Methods

The Registry and the Families. Since 1984, 26 of 31 families were identified through a specialized colorectal cancer Registry instituted in the Health Care District of Modena (Northern Italy) (8, 9). Five families were referred to us from other provinces. Nuclear pedigrees could be traced in 92% of incident cases. Those suspected of being HNPPC were extended to...
second- and third-degree relatives (10). Twenty-four families met the "Amsterdam Criteria" for the clinical definition of Lynch syndrome (11). Seven families did not meet the criteria because early onset endometrial or gastric carcinoma were diagnosed together with colorectal cancer. In five families, constitutional mutations of "mutator genes" were detected (12). Diagnosed together with colorectal cancer. In five families, because early onset endometrial or gastric carcinoma were diagnosed, genetic testing was pursued with complete visualization of all tracts of the large bowel (i.e., "pancolonoscopy") as opposed to "short" colonoscopy. This excess of tumors was observed in families with known mutations of the mismatch repair genes as well as in the others. Finally, among HNPCC family members, 48.3% of the adenomas (14 of 29) were localized in the right colon (the cecum, ascending colon, transverse colon, and flexures) as opposed to 27.3% (3 of 11) among controls. Even more striking was the fact that in the case group, four of five carcinomas developed between the cecum and the hepatic flexure.

**Discussion**

Are we doing our best to prevent cancer development in unaffected HNPCC family members? The results of the present study emphasize the objective difficulties that can be encountered in the surveillance of high-risk individuals in HNPCC families. Of the 390 subjects who were traced as at risk, only 223 (57.2%) could be contacted, and of these, only 86 (38.6%, or 22.0% of the total) underwent colonoscopy. On the other hand, our findings underline the clinical relevance of an accurate follow-up in high-risk individuals: among case-relatives, the frequency of neoplastic lesions was significantly higher than in controls. Moreover, the histological examination of the resected polyps reinforces the common observation that adenomas frequently seem "aggressive" in HNPCC families (14–16).

The low compliance of high-risk individuals was an unexpected (and unexplained) finding; perhaps during the interviews, we only proposed endoscopic investigation but made no arrangement to perform the examination. In a similar study, Järvinen et al. (7) reported a compliance of 63%. Better results were obtained by Vase et al. (17), with a compliance of 80%,

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Case-relatives (n = 86)</th>
<th>Controls (n = 86)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive colonoscopy</td>
<td>35 (56)</td>
<td>15 (20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>4 (5)</td>
<td>1 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>Adenomas</td>
<td>20 (29)</td>
<td>9 (11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Adenomas + carcinomas</td>
<td>24 (34)</td>
<td>10 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperplastic polyps</td>
<td>12 (19)</td>
<td>7 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Polyps</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

The statistical significance was assessed with Mann-Whitney U tests; the number of lesions was considered for comparison between cases and controls.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Case-relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern*</td>
<td>T = 18</td>
<td>T = 10</td>
</tr>
<tr>
<td>Dysplasia*</td>
<td>LD = 16</td>
<td>LD = 8</td>
</tr>
<tr>
<td>Main diameter, mean ± SD (range, mm)</td>
<td>9.1 ± 5.9 (4–25)*</td>
<td>5.8 ± 3.7 (3–15)*</td>
</tr>
</tbody>
</table>

* HD, high degree (severe); LD, low degree (mild).
* P < 0.02 by two-tailed t test.
attributed to the “personal approach” adopted in the genealogical investigations. Because the Italian National Health system covers most of the expenses, it is unlikely that the cost of colonoscopy could have represented a reason for low compliance. Moreover, endoscopy is easily accessible in the whole Health Care District of Modena.

In a recent editorial with the provocative title of “Screening Colonoscopy: the Cost of Common Sense”, Bhattacharya and Sack (18) proposed the widespread use of colonoscopy as the only effective measure for colorectal cancer prevention. The results of the present study cast some doubts on this contention: if in a highly predisposed population—with a 50% risk of developing colorectal cancer—compliance was as low as 38.6%, what response can be expected in the general population, in which the cumulative risk is on the order of only 5%? This negative or “fatalistic” attitude may be less evident in other populations; as a matter of fact, in high-risk individuals of the Finnish (7) and Dutch (17) series the compliance was much higher than in our subjects. However, our 15-year experience clearly indicates that the general population—at least in our country—is not yet ready to accept colonoscopy as the ideal procedure to prevent colorectal cancer.

To our knowledge, this is the first investigation in which the frequency of colorectal lesions in HNPCC family members was compared to that of a control group. The choice of suitable controls is always problematic. For this type of investigation, the main requisite of a control group is to be representative of the general population; ideally, controls should be taken randomly. This goal, however, is more difficult to reach when controls must undergo a colonoscopic investigation. Among the various possibilities, choosing individuals who were undergoing endoscopy for mild symptoms was the most acceptable. Because a symptomatic group (controls) was compared with an entirely asymptomatic population (HNPCC family members), the fact that carcinomas, adenomas, and hyperplastic polyps were found significantly more often in asymptomatic, high-risk individuals suggests that the higher prevalence of these lesions is an intrinsic feature of Lynch syndrome. Jass et al. (14, 16) found that adenomas did not seem to occur more frequently in HNPCC than in the general population, although in HNPCC they were more likely to be large and of a villous histological type. Similar observations were reported by Järvinen et al. (7) and by Vasen et al. (17) but without a suitable control group.

Kinzler and Vogelstein (19) recently suggested that the development of adenomas in HNPCC is due to an accelerated progression of a few lesions more frequently localized in the proximal large bowel. Indeed, in the present series, four of five malignant tumors detected in the follow-up of high-risk individuals were localized between the cecum and the hepatic flexure. However, no excess of adenomas in the proximal colon was observed in previous investigations (7, 17, 20); the reasons for these differences remain unclear.

The main practical implications of the present study can be summarized as follows: (a) surveillance of high-risk individuals in HNPCC families can be carried out effectively in only a few subjects because many of them cannot be easily reached or else refuse the proposed screening program. It is likely that the availability of biomolecular tests will allow a further selection of individuals to be screened; and (b) the high incidence of neoplastic lesions in HNPCC family members, their distribution throughout the large bowel, and their possible aggressive behavior suggest that high-risk individuals should be screened by pancolonscopy only and at intervals of 1–2 years.

References

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