Letters to the Editor

Am. J. Hum. Genet. 68:1533–1534, 2001

Is Breast Cancer Part of the Tumor Spectrum of Hereditary Nonpolyposis Colorectal Cancer?

To the Editor:

In the January issue of the *Journal,* Scott et al. (2001) reported the incidence of various types of cancer in 95 families with hereditary nonpolyposis colorectal cancer (HNPCC [MIM 120435 and 120436]). The patients in these families were categorized according to their mismatch-repair (MMR) profiles. Of these families, 12 were identified as having an *hMSH2* mutation, 22 families had an *hMLH1* mutation, and, in 61 families, no mutation was identified. To our surprise, a remarkably high incidence of breast cancer was found in the family members with HNPCC, particularly in the *hMLH1* (standardized incidence rate [SIR] 14.77 [95% confidence interval {CI} 6.2–35]) and the mutation-negative (SIR 18.03 [95% CI 12.2–26.7]) groups. No increased incidence was found in the *hMSH2* mutation carriers (SIR 2.02 [95% CI 0.3–12.7]). Previous studies reported much lower incidences of breast cancer in HNPCC. For instance, Watson and Lynch (1993) identified only 19 cases of breast cancer in 23 families with HNPCC, occurring at a median age of 51 years. The observed:expected (O:E) ratio in the Watson and Lynch (1993) study was 0.9. Another recent study of 183 MMR-mutation carriers by Aarnio et al. (1999) reported an incidence (SIR) of 1.4 (95% CI 0.4–3.7). These contradictory data prompted us to evaluate the risk of developing breast cancer in the families registered at the Dutch HNPCC registry.

Almost 200 families suspected of HNPCC are currently known at our registry. A total of 138 families either meet the "Amsterdam criteria" or harbor a germline mutation in one of the MMR genes. In 79 families, a germline mutation has been identified (34 *hMLH1,* 40 *hMSH2,* and 5 *hMSH6*). Only 4 of 187 proven or putative *hMLH1* mutation carriers and 3 of 141 *hMSH2* mutation carriers developed breast cancer. The O:E ratio of breast cancer in *hMLH1* mutation carriers was 0.6 (95% CI 0.2–1.5); in *hMSH2* mutation carriers, the O:E ratio was 0.6 (95% CI 0.2–1.7). The mean age at diagnosis was 46 years (range 32–59 years).

One of these patients, a 32-year-old *hMSH2* mutation carrier, underwent periodic examination of the colon and rectum, endometrium, ovaries, and stomach at the Department of Gastroenterology and Gynaecology, Leiden University Medical Center. Recently, she presented with an enlarged lymph node (5 cm in diameter) in the right axilla. On further analysis, a very small tumor in the upper lateral quadrant of the right breast was discovered. Fine-needle aspiration of the axillary tumor revealed an adenocarcinoma. The patient subsequently underwent a modified radical mastectomy. Histological examination of the surgical specimen demonstrated poorly differentiated adenocarcinoma in the breast and a metastasis in the axilla. Sixteen other lymph nodes were free of cancer. The estrogen and progesterone receptors were negative. The tumor exhibited widespread microsatellite instability (MSI).

In 1996, Risinger et al. performed molecular genetic studies in five patients with breast cancer from families with HNPCC. In three of the five tumors, MSI was observed. In one family with a known mutation, expression of only the mutant allele was identified in the breast cancer tissue. In 1999, Boyd et al. described a male patient, in a large family with HNPCC, affected by breast and colorectal cancer. This patient had an *hMLH1* germline mutation, and the breast tumor exhibited MSI and reduction to homozygosity for the *hMLH1* mutation.

Our study, like most studies reported in the literature, suggests that the relative risk of developing breast cancer is not increased in HNPCC. On the other hand, these studies show that breast tumors in families with HNPCC may present at an unusually early age, as illustrated by our patient. In addition, molecular genetic studies reveal MSI in breast tumors identified in families with HNPCC.

We propose a possible explanation for the contrasting observations of, on one hand, an unusually early age at diagnosis of breast cancer and, on the other hand, a normal (or even decreased) risk of developing breast cancer. It has generally been accepted that the development of breast cancer in the general population takes, on average, ~20 years. This suggests that, like non–mutation carriers in the general population, a carrier of an MMR gene mutation may develop the first stages of a tumor at age 40 years. However, because of the defect in the MMR system, mutations may accumulate in genes involved in the progression of breast cancer. The accu-

mulation of mutations may lead to acceleration of tumor development and to presentation of breast cancer at a much earlier age. The normal lifetime risk of developing breast cancer in HNPCC patients may indicate that the MMR defect is not involved in the initiation of breast cancer.

The answer to the question whether breast cancer is part of the tumor spectrum of HNPCC should be "no" if we consider the absence of an increased lifetime risk. Yet this question should be answered with "yes" if we take into account the possible role of the MMR defect in the progression of a breast tumor. Application of the latter criterion implies that a large variety of tumor types should in fact be regarded as part of the tumor spectrum of HNPCC. We believe that decisions as to whether surveillance should be advised for a specific type of cancer should be based on the age-specific cancer risk and the availability of sensitive and specific screening tools. Many cancers that are currently not included in the surveillance program may develop at an early age in patients with HNPCC. Therefore, we urge clinicians managing HNPCC to be especially alert when the patient presents with unusual symptoms.

H. F. A. VASEN,[1] H. MORREAU,[2] AND J. W. R. NORTIER[1]
Departments of [1]Clinical Oncology and [2]Pathology
Leiden University Medical Center
Leiden, The Netherlands

Electronic-Database Information

The accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for HNPCC [MIM 120435 and 120436])

References

Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, Peltomaki P, Mecklin J-P, Jarvinen HJ (1999) Cancer risk in mutation carriers of DNA–mismatch-repair genes. Int J Cancer 81:214–218

Boyd J, Rhei E, Federici MG, Borgen PI, Watson P, Franklin B, Karr B, Lynch J, Lemon SJ, Lynch HT (1999) Male breast cancer in the hereditary nonpolyposis colorectal cancer syndrome. Breast Cancer Res Treat 53:87–91

Risinger JI, Barrett JC, Watson P, Lynch HT, Boyd J (1996) Molecular genetic evidence of the occurrence of breast cancer as an integral tumor in patients with the hereditary nonpolyposis colorectal carcinoma syndrome. Cancer 77: 1836–1843

Scott RJ, McPhillips M, Meldrum CJ, Fitzgerald PE, Adams K, Spigelman AD, du Sart D, Tucker K, Kirk J, Hunter Family Cancer Service (2001) Hereditary nonpolyposis colorectal cancer in 95 families: differences and similarities between mutation-positive and mutation-negative kindreds. Am J Hum Genet 68:118–127

Watson P, Lynch HT (1993) Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 71:677–685

Address for correspondence and reprints: Dr. H. F. A. Vasen, The Netherlands Foundation for the Detection of Hereditary Tumours, Leiden University Medical Center, Rijnsburgerweg 10, "Poortgebouw Zuid," 2333 AA Leiden, The Netherlands. E-mail: nfdht@xs4all.nl

0002-9297/2001/6806-0027$02.00

Am. J. Hum. Genet. 68:1534–1535, 2001

Reply to Vasen et al.

To the Editor:

Hereditary nonpolyposis colorectal cancer (HNPCC) is associated, at least in part, with germline mutations in genes involved in DNA mismatch repair. Two genes, termed "*hMSH2*" and "*hMLH1,*" account for HNPCC in ~60% of families whose symptoms adhere to the Amsterdam Criteria (Syngal et al. 2000). Three other genes—*hPMS1, hPMS2,* and *hMSH6*—account for an additional 5%–10%, the exact percentage not being known at this time. There remains a significant proportion of families, ~30%, in which HNPCC does not appear to be accounted for by these genes, suggesting that additional genes, which may or may not have anything to do with DNA mismatch repair, are involved. Given that errors in DNA mismatch repair result in the characteristic signature of microsatellite instability (MSI), it should be relatively straightforward to determine whether families whose symptoms adhere to the Amsterdam Criteria but who do not harbor changes in known DNA mismatch-repair genes display MSI. To our knowledge, little information exists that indicates which of these two scenarios is most likely.

The letter by Vasen et al. (2001) questions the association between mutations in the DNA mismatch-repair gene *hMLH1* and breast cancer, which we identified in a report published at the beginning of this year (Scott et al. 2001). In our report, we presented data that indicated a statistically significant difference between the likelihood of developing breast cancer in the *hMLH1* mutation–positive group and the mutation-negative group compared with the likelihood in *hMSH2* mutation–positive families. One of the reasons we focused on breast cancer was precisely because there was little or no agreement as to whether it was part of the disease spectrum of HNPCC. Furthermore, there were sufficient anecdotal reports of breast cancer occurring at an earlier