Risk of Gastric Cancer in Hereditary Nonpolyposis Colorectal Cancer in Korea

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INTRODUCTION

HNPCC is a cancer-susceptible condition in multiple organs caused by a germ-line mutation of HNPCC genes. Colorectal cancer is the most common cancer encountered in HNPCC families, followed by endometrial and gastric cancer; however, cancers of the small bowel, urinary tract, and ovary are also frequent (2–6). Although the cancer-susceptible organs for this disease are well documented and similar worldwide, the frequency of cancer in individual organs can vary substantially depending upon ethnic, racial, and geographic differences (7–9). According to a series of reports on family G, the first HNPCC family described (thus the period of investigation is long and extends for several generations), gastric cancer was the most common cancer at the time of the initial description when the incidence of gastric cancer was extremely high in the background population. Thereafter, the incidence of gastric cancer in family G decreased rapidly in accordance with the decreasing incidence of it in the background population (10, 11). This dramatic change in the extracolonic cancer spectrum observed in family G, particularly the decline in gastric cancer incidence, strongly implies that the phenotype of HNPCC, including the frequently associated extracolonic cancer, may vary according to the cancer spectrum of the background population. Korea is one of the most prevalent areas in the world for gastric cancer, where gastric cancer comprises 25 and 17% of all cancers in males and females, respectively, and the cumulative risk for the age span 0–74 reaches 7.6% in males and 3.1% in females (12, 13). Therefore, it would be natural to expect a different, probably increased, risk of gastric cancer in a Korean HNPCC family than from that derived from a gastric cancer nonendemic area. According to our previous studies, the incidence of gastric cancer was even more frequent than endometrial cancer in a Korean HNPCC family (8), which is very unexpected considering the far higher incidence of endometrial cancer in most series (1, 5–8).

We performed this study to evaluate the gastric cancer risk in HNPCC families in Korea, where the background population has a high incidence of gastric cancer. This study also aimed to evaluate whether the risk of gastric cancer in HNPCC families in Korea is high enough to justify screening for this disease.

PATIENTS AND METHODS

The data on HNPCC families were derived from the Korean Hereditary Tumor Registry, which was established in 1991. The “HNPCC families” in this study include both families fulfilling the Amsterdam criteria as well as the less strict, suspected HNPCC criteria, which was proposed by the Korean
Hereditary Tumor Registry (14, 15). A genealogical tree was made for all HNPCC families included in this study. Overall, 1011 familial members from 28 Amsterdam criteria-fulfilling families and 38 suspected HNPCC criteria-fulfilling families were included.

Twenty-five patients with gastric cancer were detected. Diagnoses of gastric cancer were made after surgery, with the exception of three patients whose diagnoses were dependent upon clinical findings. However, the exact pathological information, including cancer types (intestinal or diffuse type), was unavailable in most cases for the reason that the re-evaluation of specimens or the acquisition of exact information through pathological records was not possible. Only four specimens were exactly re-evaluated (three cases were intestinal type and one case was diffuse type). Mutation analysis of the mismatch repair genes was performed using single-strand conformation polymorphism and followed direct DNA sequencing as described previously (15, 16).

The relative risk of gastric cancer, which is the ratio between the observed and the expected number of gastric cancer cases, was calculated in the familial members of HNPCC patients. The expected number of gastric cancer patients was calculated by multiplying the age- and sex-specific person-years by the corresponding age-specific gastric cancer incidence rate obtained from the Seoul Cancer Registry (17). The data of the Seoul Cancer Registry include the age and sex specific incidence rates for all types of cancers that occurred among the population in Seoul (population more than 10 million) between 1992 and 1995. The cancer spectrum of Seoul is expected to represent well that of the whole Korean population because the cancer spectrum is very similar between rural and urban areas in Korea (12, 13, 17). Person-years were defined as the number of years that family members were observed from birth to age of gastric cancer onset, death, last contact, or closing date of the study. In addition, 95% confidence intervals were calculated under the assumption that the data follow a Poisson distribution.

RESULTS

There were 25 gastric cancer patients among the study population. Nineteen families contained one gastric cancer patient, and the remaining three families contained two patients. The expected number of gastric cancer patients in the study population calculated from the gastric cancer incidence of the general population decreased with age. The risk became equal in the 60s and was lower in the HNPCC families than in the general population thereafter (Figs. 1 and 2; Table 1).

| Table 1 | Prevalence of gastric cancer patients in families suspected of HNPCC |
|---|---|---|---|---|
| Familial members of HNPCC | Gastric cancer patients |
| Number (male:female) | Mean age of population | Expected number | Observed/expected (95% confidence interval) | Mean age at diagnosis |
| Total | 1011 (534:477) | 44.6 | 25 | 11.8 | 2.1 (1.4–3.2) | 47.0 |
| Amsterdam criteria (+) | 515 (279:236) | 43.4 | 10 | 5.4 | 1.9 (1.0–3.5) | 44.8 |
| Amsterdam criteria (−) | 496 (255:241) | 45.9 | 15 | 6.4 | 2.4 (1.4–3.9) | 48.5 |
| Mutation (+) family | 379 (201:178) | 43.1 | 12 | 3.8 | 3.2 (1.8–5.6) | 46.1 |
| Mutation (−) family | 632 (333:299) | 45.3 | 13 | 8.0 | 1.6 (0.9–2.8) | 47.8 |

The risk of gastric cancer was increased when one or more family members possessed the mutated HNPCC gene. The relative risk in these mutation carrier families was 3.2-fold higher than the reference population (Table 1). The relative risk was slightly higher in the families fulfilling the suspected HNPCC criteria (relative risk, 2.4) than in the families fulfilling the Amsterdam criteria (relative risk, 1.9).

The mean age of patients with gastric cancer was 47.1 years (SD, 12.5 years), which was very similar to the mean age of patients with colorectal cancer in this series (45.9 ± 10.8 years). The relative risk of gastric cancer was remarkably higher in younger age groups, particularly in the 30s and 40s. The risk of gastric cancer in members of HNPCC families was increased to 11.3- and 5.5-fold over that of an age-matched general population in their 30s and 40s, respectively. The difference in the gastric cancer risk between HNPCC family members and the general population decreased with age. The risk became equal in the 60s and was lower in the HNPCC families than in the general population thereafter (Figs. 1 and 2).

DISCUSSION

An overall 2.1-fold increased lifetime risk of gastric cancer was observed in Korean HNPCC families when compared with the risk in the general population. The increased risk was particularly remarkable at a younger age; relative risk was increased up to 11.3-fold in the 30s and 5.5-fold in 40s. There have been studies reporting an increased risk of gastric cancer in the familial members of HNPCC patients (3, 4, 18). However, most of these studies were derived from Western countries, where the prevalence of gastric cancer in the general population is relatively low. According to a study by Watson and Lynch that was performed in America, the gastric cancer risk in the familial members of HNPCC was increased 4.1-fold over the general population (4). Aarnio et al. (6) calculated the lifetime risk of gastric cancer in mutation carriers of the HNPCC gene as 19% in the Finish population. The gastric cancer risk in the HNPCC families of this study is lower than that of the Watson and Lynch study in terms of relative risk. However, the relative risk is increased to 3.2-fold when a family harbors an HNPCC gene mutation. The 3.2-fold increased risk represents an approximately 15% lifetime risk of gastric cancer in the Korean population when both male and female populations are taken into account. The risk in mutation carriers, who theoretically account for half of all HNPCC family members, would apparently be >15% and probably approach 30% (doubled risk). Therefore, the absolute risk of gastric cancer in a mutation carrier would be somewhat higher than in Aarnio’s series. This implies a similar or some-
what higher absolute risk of gastric cancer in a HNPCC gene mutation carrier but lowering relative risks according to whether it is compared with the higher incidence of gastric cancer in the general population in Korea or the lower incidence in the West.

The incidence of gastric cancer in HNPCC families was regarded as correlating with that of the background population as shown in family G (10, 11). Considering the extreme high frequency of gastric cancer in family G when gastric cancer was prevalent in the background population of that family, the frequency of gastric cancer in the present study, which is also performed in a gastric cancer prevalent area, seems to be somewhat insufficient. It is known that the mutation carrier of hMLH1 has a lower risk of extracolonic malignancies, including gastric cancer, than that of hMSH2 (18–20), and almost all mutations in Korean HNPCC patients were located in the hMLH1 gene (15, 16). Therefore, this unique mutational spectrum should also be considered in interpreting the lower relative risk.

Various environmental factors are known to be associated with an increased risk of gastric cancer (21). Epidemiological studies have revealed that the high prevalence of Helicobacter pylori infection and dietary factors including a high intake of salt, cooking methods such as broiling, and chewing are the major causative factors of the high prevalence of gastric cancer.

### Table 2

<table>
<thead>
<tr>
<th>No. of family members</th>
<th>No. of stomach cancer patients</th>
<th>Observed/expected (95% confidence interval)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>212</td>
<td>25</td>
<td>2.1 (1.4–3.2)</td>
</tr>
<tr>
<td>31–40</td>
<td>219</td>
<td>6</td>
<td>7.4 (1.0–53.4)</td>
</tr>
<tr>
<td>41–50</td>
<td>234</td>
<td>8</td>
<td>11.3 (5.0–25.7)</td>
</tr>
<tr>
<td>51–60</td>
<td>180</td>
<td>6</td>
<td>5.5 (2.7–11.2)</td>
</tr>
<tr>
<td>61–70</td>
<td>109</td>
<td>6</td>
<td>2.0 (0.9–4.4)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>57</td>
<td>3</td>
<td>0.8 (0.2–2.4)</td>
</tr>
</tbody>
</table>

* $P = 0.032$ at trend test.
in Korea (13, 22, 23). Theoretically, these environmental factors are expected to accelerate the development of gastric cancer in cohorts of mutation carriers who are already in a gastric cancer-susceptible condition. Unfortunately, however, we were unable to clearly demonstrate this genetic and environmental interrelationship in gastric cancer development because we could not calculate the mutation carrier-specific gastric cancer risk from present data.

There is a possibility that the high prevalence of gastric cancer in the general population of this country has resulted in a chance development of gastric cancer in the HNPCC families. However, the gastric cancer development at a significantly lower age in the HNPCC families when compared with the general population and the elevated risk in the mutation carrier families when compared with noncarrier families imply the important role of genetic factors in the development of gastric cancers in the HNPCC families of this study. According to Watson’s series, the age for gastric cancer development was somewhat later than that of colon and endometrium cancer in HNPCC (4); however, the gastric cancers developed at nearly the same age as colon cancer in the present series (±45 years).

Recently, an E-cadherin mutation-induced, cancer-susceptible condition was reported (24). Most of the cancers found in an E-cadherin mutation family are located in the stomach, but cancer of the colon and breast are also known to be frequent (25, 26). Thus, when a family encompasses both patients with colon cancer(s) and gastric cancer(s), it would be difficult to determine whether the defective gene is the MMR gene or the E-cadherin gene. A diffuse-type histology is a characteristic feature of familial gastric cancer associated with the E-cadherin mutation (24), whereas, the intestinal type is far more prominent than the diffuse type in gastric cancers caused by a mutation of the MMR gene (27). Exact information on the histological type of a given gastric cancer would be very helpful in discriminating between gastric cancer caused by the MMR gene mutation and gastric cancers with other etiology. Unfortunately, pathological information in this regard was restricted in our data set, as described previously, and this lack of information on pathological type, along with the unavailability of the mutation carrier-specific gastric cancer risk, constitute the major limitations of this study.

However, the primary aim of this study was to determine the overall and age-specific gastric cancer risk in an HNPCC family to assess whether the risk of gastric cancer is high enough to justify a surveillance program. The absolute risk of gastric cancer would be more important than the relative risk in determining the validity of surveillance.

The present study, probably the first report of an investigation of gastric cancer risk in a gastric cancer endemic area, could provide a reference in designing a cancer surveillance program for HNPCC families in gastric cancer prevalent areas by demonstrating the age-specific gastric cancer risk. When an HNPCC family has a 2- or 3-fold increased risk of gastric cancer versus the background population, the clinical implication of gastric cancer in that family would be greatly different between a gastric cancer endemic area and an area where such cancer is rare. Screening of gastric cancer from age 40 has been recommended in Japan, another endemic area of gastric cancer in Asia, even when one does not have a specific risk factor. This mass screening program has been very effective in the early detection of gastric cancer and the improvement of its surgical outcome (28, 29). Therefore, the higher risk of gastric cancer in members of an HNPCC family, particularly at a younger age, as demonstrated in this series deserves a careful screening from an early age.

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