Proportion of De Novo Cancers Among Colorectal Cancers in Japan

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Background & Aims: Adenomatous polyps are main precursors of colorectal cancers (CRCs). In Japan, de novo cancers, which do not arise from preexisting adenomas, are considered to account for a substantial number of CRCs, but the relative importance of de novo carcinogenesis remains controversial. This study estimated the proportion of de novo cancers among CRCs in Japan.

Methods: The subjects were persons 40–79 years of age who were relatively similar to those in the general population. The subjects underwent colonoscopy between 1997 and 2001. Early cancers among CRCs detected in this study were classified as de novo cancers or polyp cancers derived from adenomas. The age-specific incidence of the early CRCs was calculated, and the proportion of de novo cancers was estimated. The lifetime risk of early CRCs was estimated. Results: The study group comprised 14,817 persons. CRCs were diagnosed in 189 subjects, including 83 early cancers. There were no differences with regard to size and location between de novo cancers and polyp cancers, but morphology differed. Eighty-four percent (16/19) of de novo cancers were flat elevated or depressed. The expected lifetime risk of early CRCs was 5.27% for men and 3.21% for women. Among persons with early cancers, the expected probabilities of developing de novo cancer were 18.6% for men, 27.4% for women. Conclusions: De novo cancers account for a considerable proportion in Japan. This information suggests that the recommended interval for colonoscopic examination in Japan should be shorter than that in the United States.

The incidence of colorectal cancer (CRC) has rapidly increased in Japan. At present, CRC is the fourth leading cause of death in males and the third in females. Recent studies in the United States and Europe have shown that most CRCs develop from adenomatous polyps via the adenoma-carcinoma sequence; this theory is now widely accepted. In 1977 in Japan, Kariya et al described a case of depressed cancer that did not arise from an adenomatous polyp. Subsequently, Ishii et al and Shamsuddin et al reported depressed cancers associated with invasion or metastasis, including some lesions less than 1 cm in diameter. These findings led to the theory that some CRCs develop by de novo carcinogenesis, rather than from adenomatous polyps. In Europe, the existence of small de novo cancers less than 1 cm in diameter with invasive properties was reported. Several authors showed that de novo cancers lacked K-ras mutations on gene analysis. Kaneko et al suggested that some small invasive cancers less than 2 cm in diameter and characterized by a nonpolypoid growth pattern and no K-ras mutations are due to de novo carcinogenesis. These findings led to the hypothesis that de novo cancer may develop independently of the adenoma-carcinoma sequence. CRCs developing from adenomatous polyps can be prevented by colonoscopic surveillance and treatment. Estimation of the impact of colonoscopic screening on public health requires an accurate estimate of the proportions of CRCs developing from adenomatous polyps and CRCs developing from de novo carcinogenesis. Several studies have attempted to quantify the proportion of de novo cancers among all CRCs, but estimates have ranged from as low as 3.8% to as high as 80%. This wide discrepancy is attributed to differences in factors such as sample size, the definition of de novo cancer, and the criteria for the selection of subjects or study design. We estimated the proportion of de novo cancers among CRCs based on well-defined criteria in a large number of subjects with characteristics relatively similar to those of the general population.

Abbreviation used in this paper: CRC, colorectal cancers.
Materials and Methods

Subjects

The subjects were persons who attended a gastroenterology clinic in Kumamoto, Japan, from 1997 through 2001. We excluded persons who had a history of polypectomy, mucosal resection, or surgery for advanced neoplasms (adenomas more than 10 mm in diameter, severe dysplasia, or cancer) within the previous 5 years; those who were referred for treatment by other clinics; and those with symptoms of bowel stenosis suspected to be caused by CRC. The study group finally comprised 14,817 persons 40 to 79 years of age who underwent total colonoscopy. When we found the area with a different color from surrounding mucosa, or slight deformity on the folds, we used chromoendoscopy or magnifying endoscopy technique during colonoscopy procedures to make the existence of a lesion or its appearance clear. The subjects had no gastrointestinal symptoms and underwent colonoscopy for screening or had a slight transient abdominal discomfort or a positive fecal occult blood test. All patients gave oral informed consent for this study, which was approved by the Ethics Committee of Hattori GI Endoscopy and Oncology Clinic.

Procedures

It is difficult to distinguish de novo cancers among advanced cancers when they are in the advanced stage of carcinogenesis because their shape has changed completely from early stage, all adenomatous components have been replaced by cancerous components, and they have accumulated genetic changes during their progression. Even Dukes A, stage I or early cancers cannot be classified as de novo or polyp cancer with morphologic appearance only because some de novo cancers become flat elevated or polypoid as they begin to invade. De novo cancers can be distinguished among early CRCs on the basis of growth pattern, existence of adenomatous components, and genetic changes. De novo cancers among early cancers were diagnosed according to both of the following histologic criteria: (1) the absence of adenomatous components in the tumor and (2) all lateral margins of the tumor covered with normal mucosa and nonpolypoid growth pattern (Figure 1). All other cancers in this study were diagnosed as polyp cancers arising via the adenoma-carcinoma sequence because there remained some possibility of including unusual polyp cancers as de novo cancers if the only diagnostic criterion used were the absence of adenomatous components.

In accordance with Japanese guidelines, we defined early CRCs as cancer with mucosal or submucosal involvement and advanced CRCs as cancer with deeper involvement regardless of the presence or absence of lymph node metastases. Early CRCs were classified as either de novo cancer or polyp cancer, and the proportions of these lesions were calculated. The age distribution, size, location, and morphologic appearance of these lesions were also examined.

Figure 1. The histologic features of de novo and polyp cancer. (A) De novo cancer. The morphology is depressed type. Lateral margins are covered with normal mucosa. (B) Polyp cancer. Polyp includes adenomatous components.

Under the assumption that survival declines exponentially, we can convert a cumulative incidence to an incidence rate. This approximation, called the declining exponential approximation of life expectancy (DEALE) method, was applied to estimate age and gender-specific incidence rates of early CRCs. The calculated incidence rates were compared with those of all stages of CRCs from the Surveillance, Epidemiology, and End Results (SEER) study in the United States.

Method for Calculating Lifetime Risk

As only limited information is available for estimating the lifetime risk of early CRCs, we used a simplified approach to calculate the expected number of early CRCs and their subtypes (polyp cancer/de novo cancer) developing in persons 40 to 79 years of age. The following formula was used to calculate the expected number of early CRCs in age category x.
To estimate the expected number of early CRCs developing from 40 to 79 years of age, we set \( l_x \) as 100,000 and calculated \( a_x \) for each age group (ages 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and 75–79 years). The sum of the number for each age group was calculated to derive the total expected number of early CRCs. We also calculated the expected number of early CRCs from 40 to 79 years of age according to subtype (polyp cancer and de novo cancer). We used these data to estimate the age-specific rate of early CRCs and the proportion of de novo cancers. We also estimated the lifetime risk of all stage CRCs including early and advanced CRCs. Age-specific mortality rates excluding CRC-related deaths in category \( x \) were derived from the Vital Statistics of Japan.1

### Results

The characteristics of the subjects are shown in Table 1. The total number of subjects was 14,817 (men, 6660; women, 8157). There was no difference in age distribution between men and women. CRC was detected in 189 subjects (early cancer, 83; advanced cancer, 106); the incidence proportion was 1.74% (116/6660) in men, 0.89% (73/8157) in women, and 1.28% (189/14,817) overall. Of the 189 patients in whom CRCs were detected, 83 (44%) had early CRCs.

The characteristics of polyp cancers and de novo cancers detected among early CRCs are shown in Table 2. The crude incidence proportion was 0.56% (men, 0.74%; women, 0.42%). The incidence proportions of polyp cancers and de novo cancers increased with age. In contrast to polyp cancers, de novo cancer was not found in the age 40–49-years group. The proportion of de novo cancers among all early CRCs was 22.9% (men, 18.4%; women, 29.4%).

The expected number of persons with early CRCs, ie, so-called lifetime risk, per 100,000 inhabitants 40 to 79 years of age in Japan and the estimated prevalence of de novo cancer are shown in Table 4. The expected lifetime risk of developing early CRC was 5.27% for men and 3.21% for women. Among persons with early CRC, the expected probabilities of developing de novo cancer were 18.6% (0.98/5.27) for men, 27.4% (0.88/3.21) for women, and 22.0% for the whole population.

The estimated incidence rates of early CRCs are compared with those of all stages of CRCs in the United States in Figure 2. Our data showed a higher incidence rate in the 40–55 year olds, followed by a gradual increase in the older age groups. This pattern differed from that in the United States, characterized by an exponential increase in the incidence rate of CRC with age.

### Discussion

Estimation of de novo cancer is very important for setting the strategies for CRCs prevention and treatment and, simultaneously, is an issue very difficult to address correctly. To our knowledge, there have been few studies...
that estimated the incidence proportion of early CRC in the general population based on the results of colonoscopy in a representative number of subjects. Because the colonoscopic examination fee in Japan is considered reasonable (approximately 136 US dollars), this is often included in medical checkups and screening of the general population.

Given that repeated colonoscopic examinations at appropriate intervals allow us to detect most CRCs at a very early stage, we have estimated the age-specific incidence proportion of early CRCs in Kumamoto by the DEALE method, and those rates of all stages of CRCs in the United States (white) were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.

Table 3. Age-Specific Incidence Proportion of Early Cancer and Their Subtype

<table>
<thead>
<tr>
<th>Age category, y</th>
<th>Number of subjects</th>
<th>Polyp cancer</th>
<th>De novo cancer</th>
<th>Proportion of De novo cancer in the total cases (%)</th>
<th>Incidence proportions of cancer (%)</th>
<th>Polyp cancer</th>
<th>De novo cancer</th>
<th>All</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men 40–49</td>
<td>1578</td>
<td>5</td>
<td>0</td>
<td>0.0</td>
<td>0.32</td>
<td>0.00</td>
<td>0.32</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>2152</td>
<td>14</td>
<td>1</td>
<td>6.7</td>
<td>0.65</td>
<td>0.05</td>
<td>0.70</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>1901</td>
<td>12</td>
<td>5</td>
<td>29.4</td>
<td>0.63</td>
<td>0.26</td>
<td>0.89</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>1029</td>
<td>9</td>
<td>3</td>
<td>25.0</td>
<td>0.87</td>
<td>0.29</td>
<td>1.17</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6660</td>
<td>40</td>
<td>9</td>
<td>18.4</td>
<td>0.60</td>
<td>0.14</td>
<td>0.74</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Women 40–49</td>
<td>1636</td>
<td>5</td>
<td>0</td>
<td>0.0</td>
<td>0.31</td>
<td>0.00</td>
<td>0.31</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>2547</td>
<td>6</td>
<td>4</td>
<td>42.9</td>
<td>0.16</td>
<td>0.12</td>
<td>0.28</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>2410</td>
<td>8</td>
<td>4</td>
<td>33.3</td>
<td>0.33</td>
<td>0.17</td>
<td>0.50</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>1564</td>
<td>7</td>
<td>3</td>
<td>30.0</td>
<td>0.45</td>
<td>0.19</td>
<td>0.64</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8157</td>
<td>24</td>
<td>10</td>
<td>29.4</td>
<td>0.29</td>
<td>0.12</td>
<td>0.42</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40–49</td>
<td>3214</td>
<td>10</td>
<td>0.0</td>
<td>0.31</td>
<td>0.00</td>
<td>0.31</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>4699</td>
<td>18</td>
<td>4</td>
<td>18.2</td>
<td>0.38</td>
<td>0.09</td>
<td>0.46</td>
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<tr>
<td>60–69</td>
<td>4311</td>
<td>20</td>
<td>9</td>
<td>31.0</td>
<td>0.46</td>
<td>0.21</td>
<td>0.67</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>2593</td>
<td>16</td>
<td>6</td>
<td>27.3</td>
<td>0.62</td>
<td>0.23</td>
<td>0.85</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14,817</td>
<td>64</td>
<td>19</td>
<td>22.9</td>
<td>0.43</td>
<td>0.13</td>
<td>0.56</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

SE, Standard error.

Table 4. Expected Number and Probability of Persons With Early Colorectal Cancer From 40 to 79 Years of Age in Japan

<table>
<thead>
<tr>
<th>Age category, y</th>
<th>Expected number of persons developing early colorectal cancer in 100,000 people</th>
<th>Total</th>
<th>De novo type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>40–49</td>
<td>316.9</td>
<td>305.6</td>
<td>0.0</td>
</tr>
<tr>
<td>45–49</td>
<td>313.7</td>
<td>303.8</td>
<td>0.0</td>
</tr>
<tr>
<td>50–54</td>
<td>679.4</td>
<td>270.9</td>
<td>45.3</td>
</tr>
<tr>
<td>55–59</td>
<td>661.8</td>
<td>267.7</td>
<td>44.1</td>
</tr>
<tr>
<td>60–64</td>
<td>816.4</td>
<td>477.2</td>
<td>240.1</td>
</tr>
<tr>
<td>65–69</td>
<td>771.7</td>
<td>466.2</td>
<td>227.0</td>
</tr>
<tr>
<td>70–74</td>
<td>919.0</td>
<td>576.7</td>
<td>229.7</td>
</tr>
<tr>
<td>75–79</td>
<td>790.6</td>
<td>541.8</td>
<td>197.6</td>
</tr>
<tr>
<td>Total</td>
<td>5269.4</td>
<td>3210.0</td>
<td>983.9</td>
</tr>
</tbody>
</table>

Expected probability of developing early colorectal cancer (%)

Figure 2. Age-specific incidence rates of early CRCs in Kumamoto were estimated by the DEALE method, and those rates of all stages of CRCs in the United States (white) were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.
early stage, the data can be used to predict the lifetime risk of CRC. In this study, we excluded the detection rate of advanced CRCs from the estimated lifetime risk of CRC because such cancers would probably have been detected at an earlier stage if colonoscopy had been done at appropriate intervals. In our model, such advanced cancers are included in the incidence of early CRC several years before their detection as advanced CRCs. The lifetime risk of CRC was 11.4% for men and 6.29% for women when advanced CRCs were taken into account. That was much higher than the SEER data of 6.31% for men and 5.94% for women and supports the usefulness of our model.

At present, colonoscopy is the best means to detect early CRCs. However, de novo early cancers are considered difficult to detect even by colonoscopy because the protrusion is inconspicuous.19,20 One study has described an early cancer initially detected while it still was 6 mm in diameter that was not reconfirmed on several subsequent colonoscopic examinations, only to be detected after progression to an advanced cancer (18 mm in diameter) 3 years 4 months later.21 On the other hand, colonoscopy has enabled the detection of some small advanced cancers 2 cm or less in diameter that were difficult to detect by barium enema because they were flat or flat elevated or depressed.

In this study, the majority of de novo cancers were flat elevated or depressed, whereas all polyp cancers were literally polypoid. At the same time, small advanced CRCs 2 cm or less in diameter accounted for 14% (15/106) of advanced CRCs. According to our criteria of de novo cancer, 80% (12/15) of small advanced CRCs were de novo. Thus, the proportion of de novo cancers might be underestimated in our study because it is difficult to detect most of them in the stage of early CRCs, even if colonoscopy is carried out at appropriate intervals.

The characteristics of our subjects were assumed to be relatively similar to those of the general population. The important risk factors for CRC such as family history were not considered because such risk factors among the general population are unknown in Japan. Instead of risk factors, the reason for a colonoscopic examination was considered. The most common reason was screening with no symptoms, slight transient abdominal discomfort, or anxiety about cancer. The medical conditions in Japan are such that people can easily undergo colonoscopic examinations at a reasonable cost. In addition, our target in this study was early asymptomatic CRC. Persons with positive fecal occult blood tests, who accounted for approximately 10% of our subjects, were included because the fecal occult blood test is a screening technique with a high sensitivity but a low specificity for CRCs, especially advanced CRCs. The inclusion of persons with positive fecal occult blood tests was therefore considered not to influence the detection of early cancers.22 Patients who had received treatment for advanced neoplasms during the past 5 years were excluded from the study because such patients are at a decreased short-term risk and at an increased long-term risk for developing CRC.23 The extrapolation of our data to the general population has some limitations.

The natural history of tumors cannot be followed in humans for ethical reasons. There is no way to know whether small early cancer stays small, resolves spontaneously, or goes on to become symptomatic. The origin of tumors can only be inferred on the basis of indirect methods. Most early CRCs are thought to retain their initial structural features. The origin of such early cancers can therefore be inferred on the basis of histologic appearance. Our criteria of de novo CRC might not be agreed with in Western countries. However, we believe our criteria to be most credible because the changes in the morphology, the replacement of adenomatous components by cancer components, and the genetic changes occur during the progression from an early to an advanced cancer.

Kaneko et al have demonstrated that carcinomas showing the nonpolyloid growth characteristic of small invasive CRCs do not contain K-ras mutations, a characteristic of adenomatous polyps. Such carcinomas therefore probably do not derive from adenomatous polyps and are most likely de novo cancers.12 In accordance with this hypothesis, we considered carcinomas showing nonpolyloid growth pattern with none of the features of carcinomas derived from polyps to be de novo cancers. We believe that it is the most practical method to estimate the proportion of de novo cancers among patients with early CRC.

To estimate the lifetime risk of CRC and proportion of de novo cancer, we used a simplified SEER method to apply our age-specific data. CRC incidence rate, CRC mortality rate, and total mortality rate except CRC mortality rate were collected from the literature. To account for the competing risk, CRC mortality rate and total mortality rate except CRC mortality rate were treated separately in the calculation of lifetime risk of CRC. The lifetime risk of CRC was calculated by summing up age-specific incidence of CRC until the age of 80 years. Although the resulting method was not exactly the same as the SEER technique, there was no major problem in practical use.

The SEER data showed that the lifetime risk of CRC per 100,000 residents in the United States was 6.31% for
men and 5.94% for women. In Japan, the incidence of CRC has increased more than 4 times during the past 20 years. Our estimates of the lifetime risk for developing early CRC from 40 to 79 years of age (5.27% for men and 3.21% for women) were similar to the SEER estimates, especially in men. Similar risk levels might reflect the increasing Westernization of lifestyle in Japan or might support that some of the early cancers do not grow and do not become symptomatic or fatal. Our data showed higher incidence rates in middle age and lower incidence rates in advanced age as compared with the SEER data. The SEER data may reflect mainly the incidence of advanced CRCs. The differences in age-related incidence rates between our results and the SEER data, despite similar lifetime risks, might be associated with the time interval required for progression from early to advanced CRCs. Verification of this assumption would provide evidence that repeated colonoscopy at appropriate intervals is useful for the detection of most CRCs at an earlier stage, which can be cured by appropriate intervention.

Our results showed that de novo cancers account for approximately 22% of early CRCs. The estimation of our results is limited for the reasons described above. Estimation of de novo cancer is very important for setting the strategies to prevent and treat CRCs, and, simultaneously, it is a very difficult issue.

Our risk estimate was lower compared with that obtained in a simulation study carried out in Taiwan (30%). When analyzing early CRCs and small advanced CRCs ≤ 2 cm, 30% of these cancers were de novo. This high prevalence of de novo cancer among small advanced CRCs might be attributed to the difficulty in identifying de novo cancer as early CRC because of morphologic reasons or rapid growth. In this study, we used chromoendoscopy or magnifying endoscopy technique when the existence of a lesion is suspected. Repeated colonoscopy at appropriate intervals or another new technique, such as fluoroscopy or narrow-band images, might be needed to detect most de novo cancers in the stage of early CRCs.

The National Polyp Study conducted in the United States proposed that follow-up examinations after colonoscopic removal of newly diagnosed adenomas should be done every 3 years. If only 1 or 2 small (<1 cm) tubular adenomas are detected, follow-up examinations should be done every 5 years. These proposals are evidence based as well as practical. However, the results of our study suggest that de novo cancers account for 22% of early CRCs, even after resection of all adenomatous polyps. Available evidence suggests that the recommended interval for colonoscopic examination in Japan should be shorter than that in the United States. The Japan Polyp Study, a large, multicenter, randomized, controlled study organized by investigators at the National Cancer Center that includes our hospital has been initiated to determine the characteristics of CRC and the most cost-effective surveillance intervals for colonoscopy in Japan. That will show another aspect of the magnitude of the risk and incidence proportion of de novo cancer in Japan. Information on de novo cancer will contribute to the determination of the appropriate interval for colonoscopy and to establish the strategies for the prevention and treatment of CRCs.

References


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