Appropriate Surveillance Interval after Colonoscopic Polypectomy in Patients Younger than 50 Years

Yoon Suk Jung,1 Nam Hee Kim,2 Jung Ho Park,1 Dong Il Park,1 and Chong Il Sohn1

1Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
2Preventive Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

ABSTRACT

Background: Current postpolypectomy surveillance guidelines are based on studies in patients aged ≥50 years. Equal application of the guidelines in patients aged < 50 years may be unreasonable. We aimed to determine an appropriate surveillance interval after adenoma removal in patients aged < 50 years.

Methods: We studied 10,013 patients who underwent ≥ 1 adenoma removal and follow-up colonoscopy. The cumulative risk of metachronous advanced colorectal neoplasia (ACRN) was compared among the eight groups based on age (30–39, 40–44, 45–49 and ≥ 50 years) and baseline adenoma characteristics (low- [LRA] and high-risk adenoma [HRA]).

Results: The risk of metachronous ACRN in patients aged 30–39 and 40–44 years with HRA was comparable to that in those aged ≥ 50 years with LRA (P = 0.839 and P = 0.381, respectively). However, the risk in those aged 45–49 years with HRA was higher than in those aged ≥ 50 years with LRA (P = 0.003), and the risk was not significantly different from that in those aged ≥ 50 years with HRA (P = 0.092). Additionally, the 5-year cumulative risk in those aged 45–49 years with LRA was not significantly different from that in those aged ≥ 50 years with LRA.

Conclusion: The postpolypectomy surveillance interval can be extended up to 5 years in patients aged 30–44 years with HRA, similar to those aged ≥ 50 years with LRA. However, the interval in patients aged 45–49 years with HRA and LRA should be 3 and 5 years, respectively, similar to those aged ≥ 50 years.

Keywords: Metachronous Advanced Colorectal Neoplasia; Surveillance Colonoscopy Interval; Young

INTRODUCTION

The current guidelines recommend that screening of persons with an average risk for colorectal cancer (CRC) starts at the age of 50 years, resulting in the decreased incidence and mortality rate of CRC in adults older than 50 years over the past few decades.1-4 By contrast, the incidence in adults younger than 50 years is increasing.3 Bailey et al.5 predicted that the incidences of colon and rectal cancer among patients aged 35 to 49 years will increase by...
28% and 46%, respectively, in the United States by 2030. Korean population-based data also showed that the incidence of CRC increased by 56%, 41%, 39%, and 30% in persons aged 30–34, 35–39, 40–44, and 45–49 years, respectively, between 1999 and 2015. Considering this trend, young-onset colorectal neoplasia (CRN), including CRC and colorectal adenoma, is currently an important issue. In keeping with this trend, several recent studies have reported the prevalence and risk factors for CRN in the population younger than 50 years. Additionally, some researchers have suggested that the age for commencing screening colonoscopy should be lowered for persons with risk factors for CRN. However, most previous studies have focused on CRC screening in the young population. Relatively, studies on postpolypectomy surveillance in persons aged < 50 years is extremely limited. Current guidelines stratify adenomas into two risk groups, depending upon the probability of developing advanced colorectal neoplasia (ACRN) during surveillance and recommend repeat colonoscopy every 5 years and every 3 years in individuals with low-risk adenoma (LRA) and high-risk adenoma (HRA), respectively. However, these guidelines are based on the results of studies in patients older than 50 years; hence, equal application of these guidelines in patients younger than 50 years may be unreasonable. Indeed, our preceding study and some studies showed that the risk of metachronous ACRN was lower in patients aged < 50 years than in those ≥ 50 years. Another recent study reported that the incidence of multiple (≥ 3) adenomas at 3 years after colonoscopic polypectomy was higher in patients aged < 50 years than in those ≥ 50 years. These results suggest that the postpolypectomy surveillance interval in those aged < 50 years may be longer than that in those aged ≥ 50 years. However, previous studies did not suggest how long the surveillance interval for young patients can be extended. Therefore, we conducted a further study to determine the proper surveillance interval after adenoma removal in patients younger than 50 years. We hypothesized that the risk of metachronous ACRN in patients younger than 50 years with HRA will be comparable to that in those older than 50 years with LRA up to a certain age. If our hypothesis is correct, those younger than 50 years with HRA may be able to undergo follow-up surveillance colonoscopy 5 years later up to a certain age, similar to those older than 50 years with LRA. To confirm our hypothesis, we compared the risk of metachronous ACRN according to age and adenoma characteristics (LRA and HRA).

**METHODS**

**Study population**
The Kangbuk Samsung Health Study is a cohort study comprising South Korean men and women aged ≥18 years who underwent a comprehensive annual or biennial health examination at clinics associated with the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea. The study population comprised a subset of the Kangbuk Samsung Health Study subjects who underwent a screening colonoscopic examination as a component of a comprehensive health examination between 2010 and 2017. We retrospectively analyzed data obtained from a prospectively established cohort.

Inclusion criteria for the study were patients who had ≥ 1 adenoma detected on an index colonoscopy performed between January 2010 and December 2014, and those who underwent another follow-up surveillance colonoscopy at an interval of > 6 months until December 2017.
2017. All polyps were removed endoscopically at the index colonoscopy. Exclusion criteria include patients with a history of CRC or colorectal surgery, those diagnosed with CRC during index colonoscopy, those with a history of inflammatory bowel disease (IBD), poor bowel preparation, and those aged < 30 years. Poor bowel preparation was defined as “large amounts of solid fecal matter observed in the bowel precluding a satisfactory study, unacceptable preparation, or a condition in which < 90% of the mucosa could be adequately visualized.”

In South Korea, the Industrial Safety and Health Law mandates free annual or biennial health screening examinations of all employees. Most individuals in our study were employees of various companies and local governmental organizations, or their spouses. As part of their welfare policy, companies often subsidize comprehensive health examinations, including colonoscopy, regardless of the current guidelines. Such programs are popular in Korea. Colonoscopy is not mandatory by law but an optional test that participants can choose among several tests. Although Korean guidelines recommend that persons with an average risk for CRC begin screening colonoscopy at the age of 50 years, some participants chose colonoscopy among optional tests despite their young age. The selection of a screening test, such as colonoscopy, was decided, based solely on the screenee’s preference.

The setting of the study was a medical examination center rather than a clinic. Before colonoscopy, interviews by general practitioners were conducted to ensure that all participants were asymptomatic (i.e., no abdominal pain, diarrhea, or hematochezia). Symptomatic participants were urged to seek medical care.

Data collection and definitions
Data on medical history and health-related behaviors were obtained through a self-administered questionnaire. The family history of CRC was defined as CRC in at least one first-degree relative(s) of any age. Self-reported regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) during the previous month was assessed. Obesity was defined as body mass index ≥ 25 kg/m², which is the proposed cutoff for the diagnosis of obesity in Asians.

Colonoscopic and histological examinations
All colonoscopic examinations were performed using the EVIS LUCERA CV-260 colonoscope (Olympus Medical Systems, Tokyo, Japan) by board-certified endoscopists. Bowel cleansing was performed with 4 L of polyethylene glycol solution. Suspicious neoplastic lesions were examined or removed via biopsy, polypectomy, or endoscopic mucosal resection.

Overall CRN was defined as cancer or adenoma, and ACRN was defined as cancer or advanced adenoma. Advanced adenoma was defined as the presence of one of the following features: a lesion measuring ≥ 10 mm in diameter, showing a tubulovillous or villous structure, and high-grade dysplasia. LRA was defined as 1-2 adenomas measuring < 10 mm in size, and HRA was defined as advanced adenomas or ≥ 3 adenomas. Sessile serrated polyps or traditional serrated adenomas were included in the definition of CRN. However, hyperplastic polyps were not considered as neoplastic lesions.

Statistical analysis
Data were stratified into eight groups based on age (30–39, 40–44, 45–49, and ≥ 50 years) and adenoma characteristic at index colonoscopy (LRA and HRA). Baseline characteristics between the LRA and HRA groups were compared using the chi-square test. The cumulative incidence of metachronous ACRN was calculated using the Kaplan–Meier method, and the
differences between groups was determined using the log-rank test. To compare the risk for development of metachronous ACRN between groups, we also performed multivariable analysis using the Cox proportional hazards regression model after adjusting for potential confounders, including sex, family history of CRC, NSAID use, obesity, hypertension, and diabetes mellitus. All reported $P$ values were two tailed, and a $P < 0.05$ was considered statistically significant. SPSS software version 21 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses.

**Ethics statement**

This study was approved by the Institutional Review Board (IRB) of Kangbuk Samsung Hospital (IRB No. KBSMC 2017-11-011) with waiver of informed consent. The requirement for informed consent was waived because only de-identified data were retrospectively accessed.

**RESULTS**

**Baseline patient characteristics**

In this study, 12,458 patients with ≥ 1 adenoma at the time of index colonoscopy who underwent follow-up surveillance colonoscopy were eligible for inclusion. Among these, 2,445 were excluded based on the following: history of CRC or colorectal surgery ($n = 97$), diagnosis of CRC at the time of index colonoscopy ($n = 9$), history of IBD ($n = 35$), poor bowel preparation ($n = 2,172$), and age < 30 years ($n = 131$), and those who underwent follow-up surveillance colonoscopy within 6 months ($n = 1$). Ultimately, 10,013 patients were included. Their mean age was 43.9 ± 8.1 years, and the proportion of men was 82.9%. The mean interval between index and follow-up colonoscopy was 3.4 ± 1.4 years (range, 0.5–7.5 years).

The patients were divided into eight groups based on age and adenoma characteristic at index colonoscopy: patients 30–39 years old with LRA (group 1A) and HRA (group 1B); patients 40–44 year old with LRA (group 2A) and HRA (group 2B); patients 45–49 years with LRA (group 3A) and HRA (group 3B); and patients ≥ 50 years with LRA (group 4A) and HRA (group 4B). Table 1 shows the patient baseline characteristics of the eight groups. Groups 1A, 1B, 2A, 2B, 3A, 3B, 4A, and 4B were composed of 2,837, 405, 2,292, 317, 1,606, 336, 1,607, and 558 patients, respectively. Among the 30–39 years age group, the proportion of men and patients with a family history of CRC in the LRA group was higher than that in the HRA group, whereas among the 40–44 years age group, the proportion of smokers and those with obesity in the HRA group was higher than that in the LRA group. Among the 45–49 years age group, the proportion of smokers and those with diabetes in the HRA group was higher than that in the HRA group, whereas among the ≥ 50 years age group, the proportion of men and those with obesity and hypertension in the HRA group was higher than that in the LRA group.

**Risk of metachronous colorectal neoplasia based on age and baseline adenoma characteristics**

The comparison of the risk of development of metachronous ACRN on surveillance colonoscopy between the eight groups is shown in Tables 2 and 3. The cumulative risk of metachronous ACRN in groups 1B and 2B was lower than that in group 4B ($P < 0.001$ and $P = 0.001$, respectively). However, the risk was not significantly different from that in group 4A ($P = 0.839$ and $P = 0.381$, Fig. 1A and B, respectively). Likewise, the 5-year cumulative incidence rate of metachronous ACRN in groups 1B and 2B was not significantly different than that in group 4A (4.6% and 7.7% vs. 5.6%; $P = 0.601$ and $P = 0.405$, respectively) (Tables 2 and 3).
In contrast, the cumulative risk of metachronous ACRN in group 3B was higher than that in group 4A \( (P = 0.003, \text{Fig. 1C}) \), and the risk was not significantly different from that in group 4B \( (P = 0.092, \text{Fig. 1D}) \). Likewise, the 3-year cumulative incidence rate of metachronous ACRN in group 3B was higher than that in group 4A \( (5.6\% \text{ vs. } 1.5\%; P = 0.006) \), and the rate was not significantly different than that in group 4B \( (5.6\% \text{ vs. } 7.4\%; P = 0.336) \). Although the overall cumulative incidence rate of metachronous ACRN in group 3A was lower than that
in group 4A \((P = 0.018)\), the cumulative rate at 3 and 5 years was not significantly different between groups 3A and 4A \((1.0\% \text{ vs. } 1.5\% \text{ at } 3 \text{ years}; \ P = 0.289 \text{ and } 3.5\% \text{ vs. } 5.6\% \text{ at } 5 \text{ years}; \ P = 0.100)\) (Tables 2 and 3).

Similar results for metachronous ACRN were obtained after adjusting the confounding factors (Table 4). Using group 4A as a reference group, the risk for metachronous ACRN in groups 1B (adjusted hazard ratio \([HR]\), 0.995; 95% CI, 0.52–1.90) and 2B (adjusted HR, 1.25; 95% CI, 0.69–2.27) was not different, but the risk in group 3B was higher (adjusted HR, 2.06; 95% CI, 1.20–3.51).
Three patients developed metachronous CRC. One patient in group 1A had metachronous CRC after 4.3 years, one patient in group 1B after 4.0 years, and one patient in group 4A after 2.1 years from the index colonoscopy.

**DISCUSSION**

In this large-scale longitudinal study (n = 10,013), we compared the risk for metachronous ACRN among the eight groups based on age and adenoma characteristics. We found that the cumulative risk for metachronous ACRN in HRA groups aged 30–39 years and 40–44 years was lower than that in the HRA group aged ≥ 50 years, but the risk was not significantly different from that in the LRA group aged ≥ 50 years. However, the cumulative risk of metachronous ACRN in the HRA group aged 45–49 years was higher than that in the LRA group aged ≥ 50 years and the risk was not significantly different from that in the HRA group aged ≥ 50 years. Current guidelines recommend that patients older than 50 years should undergo follow-up surveillance colonoscopy 3 and 5 years after HRA and LRA removal, respectively.\(^\text{12,13}\) Based on the current guidelines, our results suggest that the postpolypectomy surveillance interval can be extended up to 5 years in patients younger than 45 years with HRA, similar to those older than 50 years with LRA, whereas the interval should be 3 years in those aged 45–49 years with HRA, similar to those aged ≥ 50 years with HRA.

Meanwhile, our study showed that the 3- and 5-year cumulative incidence rates of metachronous ACRN were not significantly different between the LRA groups aged 45–49 years and ≥ 50 years. Therefore, surveillance at 5 years can be recommended in patients aged 45–49 years with LRA, similar to those aged ≥ 50 years with LRA. However, the cumulative incidence rate of metachronous ACRN in the LRA groups aged 30–39 and 40–44 years was lower than that in the LRA group aged ≥ 50 years. Thus, the postpolypectomy surveillance interval in patients younger than 45 years with LRA can be extended up to > 5 years. Our findings suggest that an extended postpolypectomy surveillance interval may need to be proposed in patients < 45 years. Surveillance colonoscopy at 10 years may be appropriate for patients younger than 45 years with LRA, similar to those older than 50 years without adenomas. However, we could not confirm this because we did not include persons without baseline adenoma and did not assess the long-term risk of metachronous ACRN, such as the 10-year risk. Further long-term studies are needed to determine how long the surveillance interval can be extended in those aged < 45 years with LRA.

Another issue to consider is surveillance for patients younger than 50 years with multiple adenomas. The guideline by the US Multi-Society Task Force on CRC recommends that patients with > 10 adenomas should undergo colonoscopy with a follow-up interval of < 3 years, and

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**Table 4. Multivariable analysis for risk of metachronous colorectal neoplasia**

| Groups                      | ACRN          | Adjusted HR (95% CI) | P value |
|-----------------------------|---------------|----------------------|---------|
| Group 4A: ≥ 50 years, LRA   | 1 (Reference) |                      |         |
| Group 1B: 30–39 years, HRA  | 0.985 (0.52–1.90) | 0.987               |         |
| Group 2B: 40–44 years, HRA  | 1.25 (0.69–2.27) | 0.463               |         |
| Group 3B: 45–49 years, HRA  | 2.06 (1.20–3.51) | 0.008               |         |

Values were adjusted for sex, smoking status, family history of colorectal cancer, nonsteroidal anti-inflammatory drug use, obesity, hypertension, and diabetes mellitus.

LRA = low-risk adenoma, HRA = high-risk adenoma, ACRN = advanced colorectal neoplasia, HR = hazard ratio, CI = confidence interval.
these patients should be considered for hereditary syndromes. In our study, only one patient had >10 adenomas in those with adenoma before 50 years. This 47-year-old patient had 11 adenomas and had no family history of CRC. Metachronous ACRN was not observed on colonoscopy after 1.1 years in this patient. Meanwhile, the National Cancer Institute Pooling Project notes a marked increased risk of ACRN among patients with ≥5 adenomas at baseline. The UK guideline also recommends a 1-year surveillance interval in patients with ≥5 adenomas. As mentioned earlier, current postpolypectomy surveillance guidelines focused on patients older than 50 years can be equally applied to patients aged 45–49 years, whereas an extended postpolypectomy surveillance interval can be applied to patients aged <45 years. However, it is questionable whether the surveillance interval can also be extended in patients <45 years with multiple adenomas. Therefore, we performed additional analysis on patients aged 30–44 years with ≥5 adenomas. The 3-year cumulative incidence rate of metachronous ACRN in patients aged 30–44 years with ≥5 adenomas was similar to that in those aged ≥50 years with HRA (9.0% vs. 7.4%; \(P = 0.803\)). However, it was higher than that in those aged ≥50 years with LRA, although the difference was not statistically significant (9.0% vs. 1.5%; \(P = 0.221\)). This result might be underpowered to detect statistical differences because the number of patients aged 30–44 years with ≥5 adenomas was very small (only 30 patients). Although the proportion of patients aged 30–44 years with multiple adenomas (for example, ≥5 adenomas) is extremely rare, the surveillance interval may not be extended in these patients.

This is the first study to determine the appropriate surveillance colonoscopy interval after adenoma removal in patients younger than 50 years by comparing the risk of metachronous ACRN among eight groups based on age and baseline adenoma characteristic. Nevertheless, the present study has some limitations. First, this was a retrospective study; thus, follow-up colonoscopy was not performed uniformly, and patients who did not undergo follow-up colonoscopy were excluded. Second, the surveillance interval (the interval between the index and follow-up colonoscopy) was short (mean, 3.4 years; range, 0.5–7.5 years). Indeed, a recent nationwide survey demonstrated that most Korean practitioners tend to recommend shorter intervals for follow-up colonoscopy after polypectomy than recommended in current guidelines. Accordingly, the long-term risk of metachronous ACRN was not evaluated, and recommending how long the surveillance interval for patients aged <45 years with LRA can be extended was difficult. However, HRAs are clinically of more concern than LRAs, and our study was sufficient to evaluate and compare the cumulative incidence of metachronous ACRN at 3-year follow-up, which is recommended following HRA removal. Third, this was a hospital-based and not a population-based study; thus, some degree of selection bias may be likely. Finally, although patients with poor bowel preparation at index or follow-up colonoscopy were excluded, validated scales for bowel preparation were not used in our study. Therefore, some patients with fair bowel preparation may have been included in our study. However, we identified that adenoma detection rate in persons aged ≥50 years exceeded recommended thresholds for colonoscopy quality (32% at index colonoscopy between 2010 and 2014).

Despite these limitations, our data provided a better understanding of the need for differentiated postpolypectomy surveillance strategies that consider not only baseline adenoma characteristics but also age among patients younger than 50 years. The postpolypectomy surveillance interval can be extended up to 5 years and >5 years in patients aged 30–44 years with HRA and LRA, respectively. However, the surveillance interval in patients aged 45–49 years with HRA and LRA should be recommended at 3 and 5 years, respectively, similar to those aged ≥50 years.
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