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Assessment of the Risk of Colorectal Cancer Survivors Developing a Second Primary Pancreatic Cancer

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Background/Aims: We aimed to investigate the incidence of second primary pancreatic cancer (PC) after colorectal cancer (CRC) and to identify risk factors associated with subsequent PC. **Methods:** The observed incidence of a subsequent PC in patients with CRC was standardized using a population with CRC from the Korean Central Cancer Registry (KCCR). The expected incidence rate of PC was obtained by assuming that the select group experienced the same cancer incidence as the corresponding general population in the KCCR. **Results:** The registry included 4,822 patients with CRC aged 45 to 74 years, representing 16,725.1 person-years of follow-up. Thirteen patients (0.3%) were diagnosed with a subsequent PC, and the overall age-adjusted incidence of second primary PC was 269.6 per 100,000 cases. In contrast, the overall incidence of primary PC in the general population was 18.68 per 100,000 individuals. The standardized incidence ratio of subsequent PC was 14.44, which was significantly higher in patients with CRC than in the general population. Sex, diabetes mellitus, smoking, body mass index, and a history of receiving chemotherapy as a treatment for CRC did not increase the risk of subsequent development of PC. **Conclusions:** The risk of a second primary PC was higher in patients with CRC. Further studies are needed to identify the risk factors and generate a screening strategy for cancer survivors. **(Gut Liver 2017;11:728-732)**

Key Words: Pancreatic neoplasms; Colorectal neoplasms; Second primary neoplasm

INTRODUCTION

Due to advances in diagnostic and therapeutic techniques, life expectancies for most cancers have increased over the past decades. However, despite medical progress, the prognosis of pancreatic cancer (PC) is still not favorable, and the 5-year survival rate has only shown a small increase.[1] Merely 10% of PC patients are candidates for curative resection at the time of initial diagnosis, without any effective screening method available for early diagnosis of PC. Although intensive surveillance with endoscopic ultrasound for high-risk patients with familial PC could detect PC at an early stage, the cost-effectiveness of such screening method is questionable.[2] To make matters worse, there are only a few chemotherapy options available for locally advanced, metastatic, or recurred PC. Despite recent positive results with combination chemotherapies, such as FOLFIRINOX[3] and nab-paclitaxel/gemcitabine,[4] very few patients get these benefits due to poor Eastern Cooperative Oncology Group (ECOG) performance status and chemo-toxicities. In this regard, early diagnosis of PC and selection of high-risk patients are extremely important.

In general, it is assumed that a patient who previously had cancer (a cancer survivor) is at risk of developing new cancer in another organ.[5] In particular, cancer survivors for certain gastrointestinal malignancies with long overall survival time such as gastric cancer or colorectal cancer (CRC) may be at a higher risk of a second primary cancer. Investigation of second primary PC can provide clues to etiologic factors, and also identify patients who need more intensive medical surveillance. In this study, we assessed the incidence of second primary PC in patients with CRC compared to the incidence of PC in the general population, and investigated the risk factors for second primary PC.

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MATERIALS AND METHODS

1. Patients

From January 2001 to July 2009, we identified consecutive patients with diagnosis of CRC who were prospectively enrolled in the cancer registry database at Severance Hospital in Seoul, Korea. Clinical data were collected for the patients' age, sex, comorbidities (diabetes mellitus [DM], body mass index [BMI] for obesity), and smoking history at the time of initial CRC diagnosis, as well as their chemotherapy history of CRC and the occurrence of second primary cancer during follow-up period. The diagnosis of malignancy in this registry was confirmed histologically. Follow-up data of these patients were collected until August 2011. We selected patients of ages between 45 and 74 years. Follow-up duration was expressed as person-years of observation, and the risk of second primary PC was stratified by 10-year age groups and sex. The Institutional Review Board of Severance Hospital at Yonsei University approved this retrospective study.

2. Statistics

The observed incidence rate of second primary PC in CRC patients was standardized using a CRC population in the Korean Central Cancer Registry (KCCR) of the National Cancer Center.[6] The expected incidence rate of PC was obtained by assuming that these persons experienced the same cancer incidence as prevailed in the corresponding general population in the KCCR. The standardized incidence ratio (SIR) was calculated as the ratio of the observed number to the expected number of PC cases within the age and sex groups. Statistical significance was assessed under the assumption that the observed number of PC followed a Poisson distribution, as the occurrence of second primary PC was relatively rare.[7]

A 95% confidence interval (CI) was calculated for each SIR using the Fisher exact test. To identify risk factors of PC, potential association of clinical factors with PC was evaluated using either the Pearson chi-square test or the Fisher exact test. To identify independent factors associated with development of a second primary PC, multivariate logistic regression analysis was performed. Adjusted odds ratios were calculated to measure the degree of association, while the Hosmer-Lemeshow test for goodness of fit was used to ensure that the calibration of multivariate analysis was significant for the development of PC. A p-value less than 0.05 was considered significant, and statistical tests were two-sided. All statistical analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 5,988 CRC patients were identified in the registry at our hospital, out of which 4,822 patients were eligible for this study. We excluded two patients who were diagnosed with PC, in concurrence with the initial diagnostic work up for CRC. The median age at initial diagnosis of CRC was 61.0 years (range, 45.0 to 74.0 years), and 61.8% of patients were men. The median follow-up duration from CRC diagnosis was 40.1 months (range, 0 to 384.3 months). About one-fifth of CRC patients (19.1%) had a history of smoking, while three-fourths of them (73.5%) had received one or more chemotherapies. Patient characteristics of this study are summarized in Table 1.

Table 1. Demographic Characteristics of Patients with Colorectal Cancer

Variable	Value
Total patients	4,822
Male:female	2,981 (61.8):1,841 (38.2)
Age at initial diagnosis, yr	61.0 (45.0–74.0)
Age group, yr*	
45–54	1,153 (23.9)
55–64	1,962 (40.7)
65–74	1,707 (35.4)
Follow-up duration, mo	40.1 (0–384.3)
Total follow-up duration, person-year	16,725.09
Body mass index ≥25 kg/m^2	1,289 (26.7)
Diabetes mellitus	670 (13.9)
Smoking history	
Smoker or ex-smoker	922 (19.1)
Never smoker	3,813 (79.1)
Unknown	87 (1.8)
Chemotherapy for colorectal cancer	3,543 (73.5)

Data are presented as number (%) or median (range).
*The age at the diagnosis of colorectal cancer was divided into 10-year groups.

Over a period of 16,725.09 person-years of observation, 13 cases of PC (0.3%) developed in 4,822 CRC patients. The median age reported at initial CRC diagnosis was higher in patients with subsequent PC than those without PC (p=0.128). The median time interval between diagnosis of CRC and development of PC was 45.57 months (range, 9.46 to 119.50 months). There were one stage I PC, six stage II, one stage III, and five stage IV. The distribution of subsequent PC, by sex and age at initial CRC diagnosis is displayed in Table 2.

Table 3 shows the SIR of second primary PC following CRC, according to sex and age groups. Overall SIR was significantly higher in CRC patients compared to the general population (SIR, 14.44; 95% CI, 12.71 to 16.16). An increased risk of subsequent PC was noted for both sexes: SIR 10.07 (95% CI, 8.78 to 11.36) in men and 22.87 (95% CI, 20.39 to 25.35) in women. However, the SIR of PC after CRC did not tend to increase linearly with aging.

To explore the risk factors in more detail, we performed additional analysis by stratifying by the following factors: age at

Table 2. Clinical Features of Patients with Colorectal Cancer Who Did or Did Not Subsequently Develop Pancreatic Cancer

Variable	CRC patients with subsequent PC	CRC patients without PC	p-value
No. of patients	13	4,809	
Male sex	7 (53.8)	2,974 (61.8)	0.576
Age, yr	65.0 (48.0–72.0)	61.0 (45.0–74.0)	0.128
Age group, yr*			
45–54	1 (7.7)	1,152 (24.0)	
55–64	4 (30.8)	1,958 (40.7)	
65–74	8 (61.5)	1,699 (35.3)	
BMI ≥25 kg/m^2	3 (23.1)	1,286/4,649 (27.7)†	>0.999
Diabetes mellitus	4 (30.8)	666/4,754 (14.0)‡	0.098
Smoking history			0.296
Smoker or ex-smoker	4 (30.8)	918/4,722 (19.4)	
Never smoker	9 (69.2)	3,804/4,722 (80.6)§	
Chemotherapy for CRC	10 (76.9)	3,533/4,598 (76.8)‖	>0.999
Time to diagnosis of PC, mo	45.57 (9.46–119.50)	-	

Data are presented as number (%) or median (range).
CRC, colorectal cancer; PC, pancreatic cancer; BMI, body mass index.
*The age at the diagnosis of colorectal cancer was divided into 10-year groups; †We excluded 160 patients whose BMI was not identified in this analysis; ‡We excluded 55 patients whose DM history was not identified in this analysis; §We excluded 87 patients who did not answer the smoking history in this analysis; ‖We excluded 211 patients whose chemotherapy history was not identified in this analysis.

Table 3. SIR of Second Primary Pancreatic Cancer after Colorectal Cancer, Stratified by Age

Age at initial diagnosis	Observed no.*	Expected no.†	SIR	95% CI
Male sex, yr				
45–54	152.21	8.70	17.50	14.72–20.27
55–64	163.00	26.54	6.14	5.20–7.08
65–74	364.63	58.49	6.23	5.59–6.87
Total	234.82	23.32	10.07	8.78–11.36
Female sex, yr				
45–54	0	4.18	0	-
55–64	272.11	13.44	20.25	17.84–22.65
65–74	655.74	36.4	18.01	16.64–19.39
Total	325.91	14.25	22.87	20.39–25.35
All patients, yr				
45–54	86.73	6.47	13.40	10.58–16.23
55–64	203.87	19.87	10.26	8.85–11.67
65–74	468.66	46.12	10.16	9.24–11.08
Total	269.60	18.68	14.44	12.71–16.16

SIR, standardized incidence ratio; CI, confidence interval.
*The observed incidence of second primary pancreatic cancer (PC) in patients with colorectal cancer (CRC) was standardized using a population with CRC from the Korean Central Cancer Registry (KCCR) of the National Cancer Center; †The expected incidence rate of PC was obtained from the KCCR.

initial diagnosis of CRC, sex, DM, smoking, BMI, and history of chemotherapy for CRC (Table 4). We found no significant factor for increasing the risk of subsequent PC.

DISCUSSION

With the general adoption of screening colonoscopy and the progress in chemotherapy and surgical techniques, the 5-year survival rate of CRC has increased to 65%.[8] As a result,

Table 4. Relative Risks of Subsequently Developing Pancreatic Cancer According to Age, Sex, Smoking, DM, BMI, and Prior Chemotherapy

	Adjusted OR	95% CI	p-value
DM	2.647	0.799–8.777	0.111
Age at diagnosis of CRC	1.058	0.979–1.144	0.156
Smoking	2.724	0.687–10.801	0.154
BMI ≥25 kg/m^2	0.729	0.199–2.671	0.634
Chemotherapy for CRC	1.063	0.290–3.902	0.926
Female sex	2.265	0.630–8.146	0.211

DM, diabetes mellitus; BMI, body mass index; OR, odds ratio; CI, confidence interval; CRC, colorectal cancer.

CRC survivors have a higher chance of developing a second primary malignancy, especially cancers that have similar carcinogenic mechanisms as those of CRC. Additionally, there has been an increase in the number of reported incidences of other solid organ malignancies after CRC, such as prostate cancer in men; breast, uterus, and ovarian cancers in women; and small intestine cancers in both sexes.[9] In this regard, we supposed that PC would likely develop in patients with CRC due to the overlapping genetic predisposition. However, since patients with PC represent only a minority of the total cancer population, there are discrepant reports of the risk of second primary PC after CRC, depending on the type of research. Data from the Surveillance, Epidemiology, and End Results registries showed that CRC survivors had a higher risk of subsequent pancreatic adenocarcinoma (SIR, 1.22; 95% CI, 1.09 to 1.35).[10] A nationwide epidemiologic study from Sweden reported that the risk of second primary PC in colon cancer patients increased, by 1.77-fold in men (95% CI, 1.42 to 2.19) and 1.34-fold in women (95% CI, 1.02 to 1.72).[11] However, the risk was not significant for rectal cancer (SIR, 0.94; 95% CI, 0.64 to 1.32 in men; SIR, 1.09; 95% CI, 0.70 to 1.62 in women) in the same study. On the other hand, a 50-year observational study conducted in Connecticut, United States showed that patients with rectal cancer had a reduced risk of PC.[12] In an international multicenter study, Shen *et al*.[13] reported that the risk of PC following CRC was as low as 0.9-fold (SIR, 0.88; 95% CI, 0.82 to 0.94).

Results from our current study showed that patients with CRC had a very high risk of developing PC compared to the general population. The overall incidence of PC in CRC patients aged 45 to 74 years was 269.60 per 100,000 patients, which was significantly higher than the 18.68 per 100,000 people reported in the general population of the same age (SIR, 14.44; 95% CI, 12.71 to 16.16). The incidence of PC in our study might be high compared to other studies, since we monitored our patients very closely and thoroughly conducted diagnosis of PC. In addition, our results reflect the current trend of growing incidences of PC in the Korean population.[14] It is also possible that PC and CRC share a more common etiology in Korea compared to other countries. Although we tried to rule out the possibility of metastasis and recurrence of CRC at the pancreas by imaging and pathologic evaluation, metastases might not have been differentiated from primary PC in some cases. Further studies are needed to validate and explain the high risk of subsequent PC in Korea.

In spite of high incidence of subsequent PC in CRC patients, PC tended to be diagnosed at the early stage. There is no statistics of PC stage at diagnosis in Korean general population, but in the United States, about 37% of PC was either resectable or locally advanced.[15] In this study about 62% of patients had resectable or locally advanced PC. Awareness of cancer risk and regular follow up could play a role in this trend. Also, there also could be difference in cancer behavior between first and second PC. This result suggests that well planned surveillance would be beneficial for early detection and treatment of subsequent PC in CRC survivors, which would ultimately bring survival gain. More studies are needed to understand the characteristics of subsequent PC.

Risk factors for subsequent PC were analyzed by DM, sex, aging, smoking, obesity, and chemotherapy history for CRC. However, we could not identify any significant risk factor for increasing subsequent PC. DM has previously been suggested to be a risk factor for PC in other studies.[16,17] In our study, CRC patients with DM showed higher adjusted odds ratio (AOR) of 2.647 for subsequent PC, but there was no statistical significance (95% CI, 0.799 to 8.777). As in most adult tumors, the incidence of PC is age-dependent,[18] but increased age showed only a slight increased risk without statistical significance (AOR, 1.058; 95% CI, 0.979 to 1.144). The SIR tended to be higher in women (SIR, 22.87) than in men (SIR, 10.07), but the sexual difference was not significant (p=0.211). Although other factors such as smoking, alcohol drinking, BMI, and previous chemotherapy have been suggested as risk factors for other types of cancer, these variables were not significant in our study. In previous studies, an increased risk of PC was observed in patients with familial adenomatous polyposis syndrome/Gardner's syndrome compared to the general population.[19] Since cancer syndromes and familial PC are very rarely reported in Korea, there was a minimal relationship between familial PC or cancer syndromes and patients with subsequent PC in our registry.

This study has several limitations regarding generalization of the results. First, although the data were obtained prospectively, our analyses were performed retrospectively. Such investigational design may have presented some inherent drawbacks that could affect the results. For example, genetic abnormalities related to CRC and PC could not be identified. This information would have been very useful for determining the effects of genetic factors. Second, since our study was based on a single cancer registry, only a few PCs accumulated and the data was limited for providing reliable and robust results. Third, our inclusion of only histologically confirmed cases of PC in the anal-

ysis may have caused underestimation of the disease. The loss of CRC patients to follow-up is also a point to be considered. For more reliable results, either a nationwide or an international multicenter study from high-quality cancer registries should be organized, and these databases should be combined to investigate relative risks and factors associated with PC.

In conclusion, we found that CRC survivors are relatively at a higher risk for second primary PC compared to the general population in Korea. In order to determine how often the patients should be screened and the optimal modality for screening, we recommend a nationwide CRC cohort study to be initiated and followed for the lifetime of patients, in which researchers collect and analyze detailed data including the patients' genetic abnormalities, family history, and medical history.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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