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SHORT COMMUNICATION

Alcohol consumption and early-onset risk of colorectal cancer in Japanese patients with Lynch syndrome: a cross-sectional study conducted by the Japanese Society for Cancer of the Colon and Rectum

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Abstract
We conducted this study to establish whether drinking alcohol alters the risk of early-onset colorectal cancer (CRC) in Japanese patients with Lynch syndrome (LS). The subjects were 66 LS patients with pathogenic mutation of mismatch repair genes (*MLH1, MSH2*, and *MSH6*) from the nationwide Japanese retrospective multicenter study. Cox proportional hazards modeling was used to investigate the factors correlating with early-onset CRC diagnosis, using clinical data such as gender, tobacco use, alcohol consumption, body mass index, gene mutation (*MLH1, MSH2* vs *MSH6*), and family cancer history. Alcohol was significantly correlated with an increased risk of early-onset CRC [HR 2.44, 95% CI 1.13–5.16 ($p = 0.02$)], but tobacco use was not [HR 0.8, 95%CI 0.38–1.62 ($p = 0.53$)]. These findings suggest that alcohol consumption is correlated with an earlier onset of CRC in Japanese patients with LS

Key words Lynch syndrome · Alcohol · Colorectal cancer

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Introduction

Lynch syndrome (LS) is thought to account for 1–5% of all colorectal cancer (CRC) cases [1]. It is caused by a germline mutation in one of the mismatch repair (MMR) genes, including *MLH1, MSH2, MSH6*, or *PMS2*. The pathogenic mutation carriers of the MMR gene have a lifetime risk of CRC development of 60–80% [2]. Understanding the determinants of this phenotypic heterogeneity is critical in the development of cancer prevention strategies for individual high-risk patients. The organ of tumor development in LS patients may be influenced by the environmental or lifestyle factors that have changed over the last century [3]. Therefore, it is possible that there are environmental and/or other genetic factors that influence carcinogenesis and modify penetrance. Studies targeting the Colon Cancer Family Registry Cohort found that the risk of CRC is associated with environmental factors in LS patients [4, 5]. It is acknowledged that high body mass index (BMI), smoking, and the regular consumption of alcohol, red meat, and processed meats interact with a host's genetic factors, and may increase the risk of sporadic CRC [6, 7]. On the other hand, there are limited data linking these factors with increased CRC risk in patients with LS.

Previous cohort studies on LS patients living in western countries demonstrated that current smokers had a significantly higher CRC risk than never smokers [8]. Moreover, colorectal adenoma was found to develop more frequently in current smokers than never smokers, with a higher Brinkman Index among the former also being associated with an increased risk for colorectal adenoma [9]. In Japan, a report analyzing these data also revealed that smoking might be a risk factor for the occurrence of multiple CRCs in men with LS [10]. However, to date there has been no report on the correlation between alcohol consumption and CRC risk in patients with LS. The aim of this study was to evaluate whether certain factors, including alcohol consumption, can predict the early onset of CRC in ethnically homogeneous Japanese patients with LS.

Methods

CRC patients with clinically suspected LS were registered retrospectively in a nationwide Japanese multicenter study conducted by the Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Registry and Genetic Testing Project of the Japanese Society for Cancer of the Colon and Rectum, as previously reported [10–12]. Patient background data, such as gender, BMI, gene mutation, personal and family cancer history, and tobacco and alcohol use, were collected either from medical records or directly from patients who were provided genetic counseling. A person was classified as a tobacco user if they had ever smoked any tobacco product regularly, and as an alcohol consumer if they reported past or current regular consumption of greater than one alcoholic beverage per week. A person was classified as obese if their BMI was over 25. The research was approved by the ethics committee of the authors' affiliated institutions after written informed consent was obtained from all participants.

Statistical analysis

A proportional Cox regression model with age as the time-scale was used to estimate hazard ratios (HR) relating patient background data to CRC risk for LS patients, by univariate and multivariate analysis. Time at risk started at birth and ended at the age of diagnosis of first CRC. Probability values for statistical tests were two tailed and a p value of <0.05 was considered significant. All statistical analyses were performed using JMP® 10 software (SAS Institute Inc.).

Results

Among 69 LS patients with pathogenic mutations of the MMR gene, 66 were eligible for inclusion in this study, after the exclusion of 3 for whom there was no information about tobacco and alcohol use. Table 1 summarizes the clinical characteristics of these 66 patients. The median age at diagnosis of CRC was 44 years (range 24–70 years). The patients included 30 (45.5%) men, 27 (40.9%) tobacco users, 28 (42.4%) alcohol consumers, and 10 (16.4%) who were obese. *MLH1, MSH2*, or *MSH6* mutation was detected in 36 (54.5%) patients, 28 (43.8%) patients, and 2 (3%) patients, respectively. CRC or extracolonic LS-associated cancer had been diagnosed in at least first-degree relative (FDR) of 60 (90.9%) and 51 (77.3%) patients, respectively.

Table 2 summarizes the results of the Cox proportional hazard modeling. Alcohol consumers had a significantly earlier onset of CRC than those who did not drink alcohol. Therefore, alcohol consumption as a significant factor in the univariate analysis remained as a significant factor in the multivariate analysis. This was reflected in the HR of 1.81 (univariate analysis, $p=0.03$) and 2.44 (multivariate analysis, $p=0.02$).

Discussion

Our findings demonstrate clearly that alcohol consumption was associated with an earlier onset of CRC in Japanese LS patients with a pathogenic mutation, but the same

Table 1 Clinical characteristics of the 66 Lynch syndrome patients with colorectal cancer

Characteristics		Value
Age at diagnosis of initial CRC, median (range)		45 (24–70)
Gender	Male/female	30 (45.5%)/36 (54.5%)
Tobacco	User/nonuser	27 (40.9%)/39 (59.1%)
Alcohol	User/nonuser	28 (42.4%)/38 (57.6%)
BMI (kg/m^2)	≥ 25.0/< 25.0	10 (16.4%)/51 (83.6%)
Gene mutation	*MLH1/MSH2/MSH6*	36 (54.5%)/28 (42.4%)/2 (3%)
Extracolonic LS-associated cancer	Yes/no	30 (45.5%)/36 (54.5%)
CRC occurrence in FDR	Yes/no	60 (90.9%)/6 (9.1%)
Extracolonic LS-associated cancer occurrence in FDR	Yes/no	51 (77.3%)/15 (22.7%)

Tobacco user: known to ever use any tobacco product regularly

Alcohol consumer: drank more than one alcoholic beverage per week now or in the past

Extracolonic LS-associated cancer: cancer of the endometrium, small bowel, stomach, ureter or renal pelvis

CRC colorectal cancer, *LS* Lynch syndrome, *FDR* first-degree relative, *BMI* body mass index

Table 2 Hazard ratio of early-onset colorectal cancer in Japanese patients with Lynch syndrome

Variable		Reference	Univariate analysis		Multivariate analysis	
			HR (95%CI)	*p* value	HR (95%CI)	*p* value
Gender	Male	Female	1.29 (0.77–2.15)	0.33	1.18 (0.57–2.42)	0.65
Tobacco	User	Nonuser	1.03 (0.6–1.72)	0.91	0.8 (0.38–1.62)	0.53
Alcohol	User	Nonuser	1.81 (1.06–3.03)	0.03	2.44 (1.13–5.16)	0.02
BMI (kg/m^2)	≥ 25.0	< 25.0	0.9 (0.41–1.76)	0.77	0.53 (0.2–1.28)	0.16
Gene mutation	*MSH2*	*MLH1*	1.1 (0.64–1.87)	0.72	0.9 (0.45–1.76)	0.76
	MSH6	*MLH1*	0.58 (0.09–1.93)	0.42	0.69 (0.04–3.99)	0.73
	MSH6	*MSH2*	0.52 (0.08–1.77)	0.34	0.77 (0.04–4.7)	0.81
CRC occurrence in FDR	Yes	No	0.92 (0.4–2.65)	0.85	0.81 (0.27–2.86)	0.73
Extracolonic LS-associated cancer occurrence in FDR	Yes	No	1.24 (0.69–2.36)	0.49	1.25 (0.65–2.53)	0.51

Tobacco user: known to ever use any tobacco product regularly

Alcohol consumer: drank more than one alcoholic beverage per week now or in the past

Extracolonic LS-associated cancer: cancer of the endometrium, small bowel, stomach, ureter or renal pelvis

p value was calculated from Cox proportional hazards modeling

CRC colorectal cancer, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *FDR* first-degree relative

correlation was not found with either smoking or a high BMI. A previous study using an in vivo model also validated the correlation between alcohol consumption and CRC, by showing that alcohol use was associated with a significant increase in tumor number and size in Min mice [13, 14]. Furthermore, prospective studies on the CRC incidence in the general western populations have consistently supported the positive correlation between alcohol consumption and CRC [15–17]. Similarly, a meta-analysis and a large cohort study also demonstrated a positive correlation between alcohol consumption and rectal cancer [18, 19]. However, the influence of alcohol consumption on CRC risk in patients with LS remains controversial. A prospective analysis of 386 LS patients also demonstrated that alcohol consumption tended to increase the risk of colorectal adenomas, which are assumed to be precancerous lesions [9]. Conversely, a case–control study of 145 patients with colorectal tumors and 103 tumor-free controls did not find any significant association between alcohol intake and colorectal tumors [20]. Another retrospective cohort of 596 MMR gene mutation carriers also reported that alcohol use was not significantly associated with increased CRC risk [21]. However, it is essential to note that most of these studies were based on western populations. In the general Japanese population, a Japan Public Health Center-based Prospective Study revealed that men who drank alcohol regularly showed a significantly increased risk of CRC than those who did not [7]. Therefore, we would expect to find a stronger correlation

between alcohol consumption and CRC in a nationwide Japanese population study than in studies on Western populations.

In regard to smoking, the CRC risk for MMR gene mutation carriers was positively associated with current smoking [8, 20]. Only one study analyzing the association between CRC development and lifestyle habits in Japanese LS patients suggested that long-term smoking significantly increased the risk of multiple CRCs in men [10]. The association between BMI and colorectal adenoma risk for MMR gene mutation carriers was observed only in men [8]. A greater BMI at age 20 years was associated with a higher risk of CRC later in life for MMR gene mutation carriers [4]. Environmental exposures of the MMR gene mutation carriers could also modify their risks of CRC development, as suggested by the findings of our study. Identifying modifiers of CRC risk for carriers of MMR gene mutations is important for understanding carcinogenesis. Identifying potentially harmful and avoidable risk factors creates opportunities for mutation carriers to reduce their risks of a life-threatening disease. The results of this study indicate that LS patients, including those with MMR gene mutations, in whom CRC has not yet developed, should probably abstain from excessive alcohol consumption. Interestingly, participants completing 2 years of aspirin treatment in the CAPP2 trial experienced over a 50% reduction in CRC and other cancers associated with the LS syndrome incidence [22]. More trials are required to further validate the effect of aspirin administration to the high-risk patients such as those with MMR gene mutations who also have a history of excessive alcohol intake.

This study had some limitations. First, it was a retrospective study design with a small sample size. Second, LS patients with *PMS2* pathogenic mutations were not included in this analysis. Third, LS patients in this study were limited to those who had a documented onset of CRC, as it was an enrollment criterion. Fourth, we lacked sufficient data on the patients' alcohol consumption habits. Generally, the amount (grams) of alcohol consumption per week was used for estimations of alcohol use. However, because such data were not collected, alcohol users were defined using their frequency of alcohol intake per week in this study. Therefore, further studies with detailed observations of alcohol consumption, preferably using prospective designs targeting a larger sample size in Japanese LS patients, including those without CRC, are warranted.

Conclusion

The findings of this study indicate that alcohol consumption is associated with an earlier onset of CRC in Japanese LS patients with a pathogenic mutation. Since there has been only one other nationwide study analyzing the association between CRC development and lifestyle habits in Japan [10], we believe that our findings are potentially significant and will help researchers and physicians to identify factors that may predict the earlier onset of CRC in LS patients.

Conflict of interest We have no conflicts of interest to declare.

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