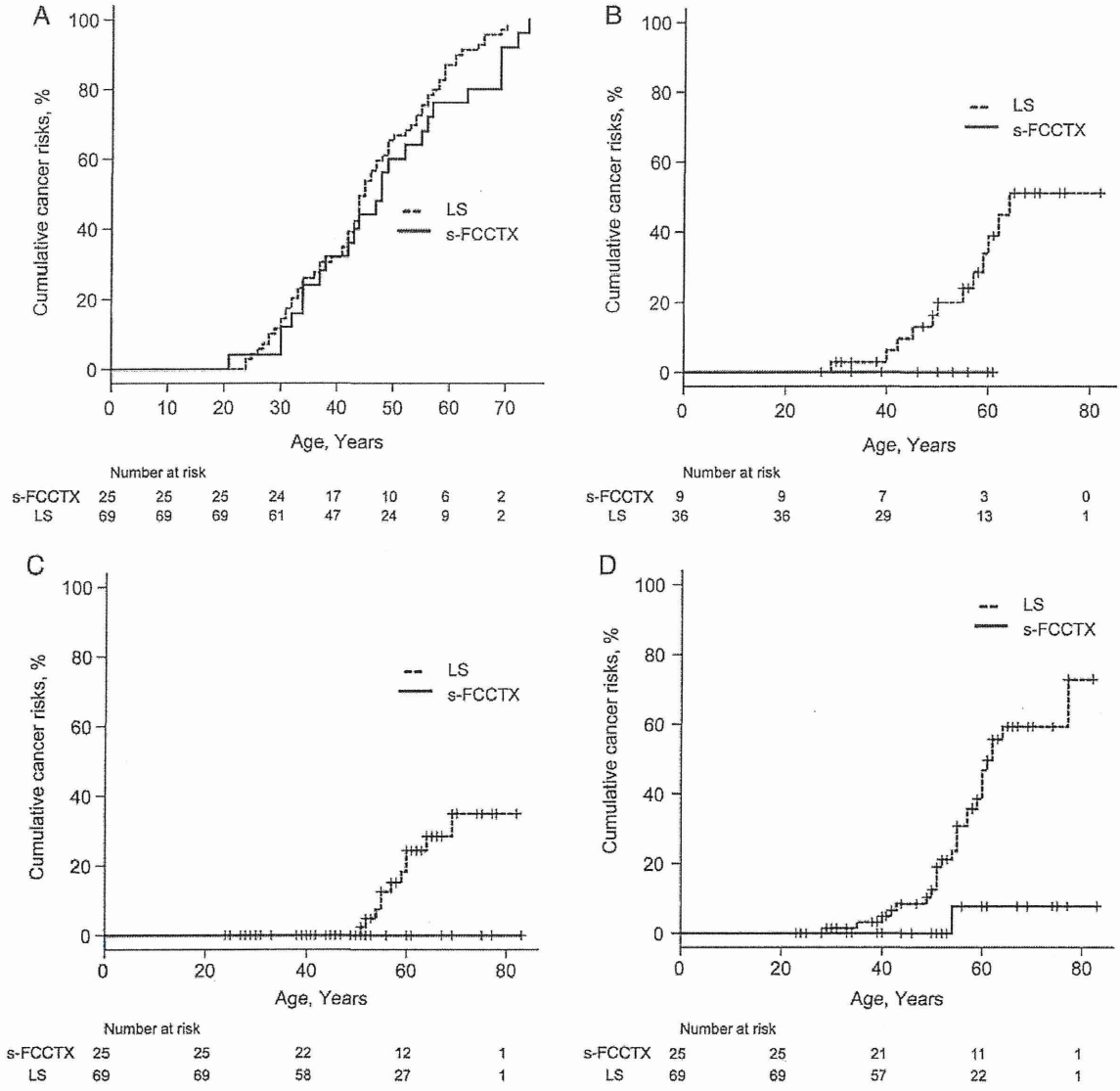

Figure 2. Comparison of the cumulative cancer risk between patients with suspected familial colorectal cancer type X (s-FCCTX) and patients with Lynch syndrome (LS) according to cancer type. (A) colorectal cancer; (B) endometrial cancer; (C) gastric cancer; (D) extracolonic LS-associated cancer.

included in the category of 'FCCTX' because of a lack in examination of the tumor tissues. Therefore, we used 'suspected FCCTX' in this study.

The cancer risk of patients with LS was 40–80% for colorectal cancer, 25–60% for endometrial cancer and 1–4% for urinary tract cancer (20). However, whether gastric cancer is an LS-associated cancer remains controversial. In East Asia, it is believed that gastric cancer is common in patients with LS (10). Reportedly, European patients with LS lack the MMR protein corresponding to the germline mutation, and exhibit microsatellite instability (21). Our data demonstrated that gastric cancer is significantly more frequent with LS than with s-FCCTX. This finding suggests that gastric cancer is an LS-associated cancer.

With respect to cancer incidence, it was reported that only the incidence of colorectal cancer is higher, whereas the incidence of LS-associated cancer is lower, in patients with FCCTX than in patients with LS (8). This study showed that the frequencies of LS-associated cancers, including gastric cancer, were lower in patients with s-FCCTX than in patients with LS. These results are consistent with reports from Western countries. Moreover, the number of organs with LS-associated cancer was lower in patients with s-FCCTX than in patients with LS. These data support the theory that s-FCCTX is a completely different syndrome from LS.

The median age at diagnosis of cancer is reportedly 43–45 years in patients with LS (22). A difference in median age at diagnosis between patients with s-FCCTX and patients with LS is evident for every organ. For example, the median age at diagnosis of colorectal cancer was 47–50 years and that of endometrial cancer was 54 years (23), and the median age at diagnosis of colorectal cancer is lower in men than in women (24). Patients meeting the Amsterdam Criteria I with dMMR tend to develop colorectal cancer at a younger age than those meeting the Amsterdam Criteria I without dMMR (8). In our study, we demonstrated a later onset of LS-associated cancer in patients with s-FCCTX compared with that in patients with LS. However, the median age at diagnosis of cancer remained young with s-FCCTX compared with sporadic cases. These findings suggest that s-FCCTX is a hereditary syndrome. Gene alterations and expressions were different in FCCTX than in LS (13,25). Recently, studies to

identify the causative genes of FCCTX have been conducted, and some candidate genes have been proposed, such as *CENPE*, *CDH18*, *GREM1*, *BCR*, *KIF24*, *GALNT12*, *ZNF367*, *HABP4*, *GABBR2* and *BMP4* (26). However, the causative genes of FCCTX have yet to be identified. In this study, additional investigation to detect causative gene of FCCTX was not performed yet. Further study is warranted.

This is first report of Japanese s-FCCTX patients. It is difficult to compare Japanese s-FCCTX patients to Western FCCTX patients directly. As mentioned above, however, both cancer incidence and median age at diagnosis of colorectal cancer in Japanese s-FCCTX patients were very similar to those in Western FCCTX patients.

The limitations of this study include low statistical power due to the limited number of cases of s-FCCTX ($n = 25$) and LS ($n = 69$), and the lack of data on *PMS2* mutation. In this study, we did not analyze *PMS2* mutation, because of the low frequency of *PMS2* mutation and the number of pseudogenes of *PMS2* (27). However, we consider the influence of this on the overall results to be small. Nonetheless, considering that there are only a few publications on FCCTX and s-FCCTX, and none from Asia, we believe that our findings will help researchers and physicians clarify the nature of s-FCCTX.

In conclusion, our study indicated that, among Japanese patients with colorectal cancer, extracolonic LS-associated cancer occurred less frequently in patients with s-FCCTX than in patients with LS, the median age at diagnosis of extracolonic LS-associated cancer was greater in patients with s-FCCTX than in patients with LS, the number of organs with LS-associated cancer was lower in patients with s-FCCTX than in patients with LS, and the cumulative incidence of extracolonic LS-associated cancer was lower in patients with s-FCCTX than in patients with LS. A significant difference in extracolonic LS-associated cancer was evident between s-FCCTX and LS.

Authors' contributions

The Japanese Society for Cancer of the Colon and Rectum contributed collectively to this study. All authors contributed to this work: Conception and design of this study, Y.M., N.T., K.T., C.I., N.M., T.W., K.S., H.I., M.A., T.Y., H.I. and K.S.; Genetic analysis, Y.F., Y.N., K.T., C.I., N.M. and K.S.; Collection and assembly of data, N.T., K.T., C.I., N.M., K.S. and M.A.; Statistical analysis, T.Y. and H.I.; Drafting of the article, T.Y. and H.I.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

Acknowledgements

The authors would like to acknowledge all the patients and their families as well as all investigators. The authors also would like to acknowledge the significant contribution to this study of Kohji Tanakaya, Department of Surgery, Iwakuni Clinical Center, Iwakuni, Japan, and Keiji Hirata, Department of Surgery 1, University of Occupation and Environmental Health, Kitakyusyu, Japan.

Funding

The present study was supported in part by a grant-in-aid for Cancer Research from the Ministry of Health, Labor and Welfare and by Japanese Society for Cancer of the Colon and Rectum.

Conflict of interest statement

None declared.

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