Some studies have correlated a prior history of malignancy with an increased incidence of CRC. Patients with history of cancer are generally excluded in clinical trials. This practice, not only affects clinical trials accrual, but also limits the potential therapeutic options for this population. The rationale behind this exclusion is that a history of malignancy could potentially interfere with the study outcomes. However, little is known about its real impact on survival of subsequent CRC.

**Methods:** We identified patients with CRC diagnosed between 1973 and 2008 using the National Cancer Institute’s SEER database. Outcomes of interest were overall survival and cause-specific survival of subsequent CRC in general, and specifically stage IV disease. Unadjusted Kaplan-Meier test and multivariable covariate-adjusted Cox models were used to assess the eligibility of enrollment of stage IV CRC patients in clinical trials.

**Results:** Overall, 550,325 patients with CRC were identified, of whom 31,663 patients had a prior malignancy. Both, history of prior non-leukemic malignancy and prior leukemia were associated with a worse overall survival (HR = 1.165 95% CI = 1.148–1.183, P < 0.001) and (HR = 1.825 95% CI = 1.691–1.970, P < 0.001), respectively. However, a history of any prior non-leukemic malignancy showed a favorable colorectal-specific survival (HR = .930 95% CI = .909–.952, P < 0.001). Analysis of stage IV CRC showed that a history of any prior non-leukemic malignancy was not associated with a significant difference in overall survival but having a history of leukemia showed a worse overall survival (HR = 1.535, 95% CI = 1.303–1.809, P < 0.001).

**Conclusion:** Clinical trials should take these results into consideration when including/excluding stage IV CRC patients with prior malignancies.