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CLINICAL—ALIMENTARY TRACT

A Prospective Cohort Study Shows Unique Epigenetic, Genetic, and Prognostic Features of Synchronous Colorectal Cancers

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BACKGROUND & AIMS: Synchronous colorectal neoplasias (2 or more primary carcinomas identified in the same patient) are caused by common genetic and environmental factors and can be used to study the field effect. Synchronous colon cancers have not been compared with control solitary cancers in a prospective study. **METHODS:** We analyzed data collected from 47 patients with synchronous colorectal cancers and 2021 solitary colorectal cancers (controls) in 2 prospective cohort studies. Tumors samples were analyzed for methylation in LINE-1 and 16 CpG islands (*CACNA1G*, *CDKN2A* [p16], *CRABP1*, *IGF2*, *MLH1*, *NEUROG1*, *RUNX3*, *SOCS1*, *CHFR*, *HIC1*, *IGFBP3*, *MGMT*, MINT1, MINT31, p14 [ARF], and *WRN*); microsatellite instability (MSI); the CpG island methylator phenotype (CIMP); 18q loss of heterozygosity; *KRAS*, *BRAF*, and *PIK3CA* mutations; and expression of β-catenin, p53, p21, p27, cyclin D1, fatty acid synthase, and cyclooxygenase-2. **RESULTS:** Compared with patients with solitary colorectal cancer, synchronous colorectal cancer patients had reduced overall survival time (log-rank, $P = .0048$; hazard ratio [HR], 1.71; 95% confidence interval [CI]: 1.17–2.50; $P = .0053$; multivariate HR, 1.47; 95% CI: 1.00–2.17; $P = .049$). Compared with solitary tumors, synchronous tumors more frequently contained *BRAF* mutations ($P = .0041$), CIMP-high ($P = .013$), and MSI-high ($P = .037$). Methylation levels of LINE-1 (Spearman $r = 0.82$; $P = .0072$) and CpG island methylation ($P < .0001$) correlated between synchronous cancer pairs from the same individuals. **CONCLUSIONS: Synchronous colorectal cancers had more frequent mutations in *BRAF*, were more frequently CIMP- and MSI-high, and had a worse prognosis than solitary colorectal cancers. Similar epigenomic and epigenetic events were frequently observed within a synchronous cancer pair, suggesting the presence of a field defect.**

Synchronous colorectal cancers refer to 2 or more primary colorectal carcinomas detected in a single individual at the time of the first diagnosis of colorectal cancer. Synchronous neoplasias, which arise in a background of common etiologic (genetic or environmental) factors, can provide a unique model to examine molecular aberrations and field effect.[1] Random molecular aberrations within synchronous tumor pairs may support a stochastic process in carcinogenesis, whereas nonrandom molecular aberrations may support a specific etiology or cause in carcinogenic process,[1] or the hypothesis of field effect in apparently normal colonic mucosa.[2–4] Previous studies have analyzed several molecular markers (p53,[5] microsatellite instability [MSI],[6–10] *MLH1*,[6,7,9–11] *MSH2*,[6,7,9,11] *MSH6*,[7] or CpG island methylation[1]) within synchronous colorectal cancer pairs, suggesting both concordant[1,8–10] and discordant[1,5,7,10,11] alteration patterns. However, no previous study has examined global DNA methylation levels in synchronous colorectal cancer pairs. Global DNA hypomethylation has been linked to genomic instability and carcinogenesis,[12,13] and hypomethylation in LINE-1 repetitive sequence has been associated with poor prognosis in colon cancer.[14]

Previous studies have examined clinical features of synchronous colorectal cancer patients (Table 1; individual studies are listed in Supplementary Table 1).[5–11,15–26] However, the prognostic significance of cancer synchronicity remains inconclusive.[17–24] Whereas synchronous cancer patients and solitary cancer patients showed similar survival in most studies,[17,19–24] 1 study showed worse survival in synchronous cases.[18] However, in all of these studies,[17–24] "control" solitary cancers were retrospec-

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; CIMP, CpG island methylator phenotype; FASN, fatty acid synthase; HR, hazard ratio; LOH, loss of heterozygosity; MSI, microsatellite instability; MSS, microsatellite stable.

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Table 1. Comparison of Study Designs to Examine Synchronous and Solitary Colorectal Cancers

	Retrospective case-control study		
	Based on a single to several hospitals	Based on population-based cancer registry	Prospective cohort study
Study example	Ref.[5,6,9–11,15–22,24,26]	Ref.[23]	Current study
Background populations that have given rise to synchronous and solitary cancers	Largely unknown (D)	Less well-known (A or D)	Well known (A)
Source of bias			
1. Selection bias because of a limited number of hospitals	Yes (D)	Small (A)	Small (A)
2. Selection bias because of different background populations that have given rise to synchronous and solitary cancers	Yes (D)	Small (A or D)	No (A)
3. Referral bias	Yes (D)	Small (A or D)	No (A)
4. Recall bias	Yes (D)	Yes (D)	No (A)
Generalizability	Low (D)	Intermediate (A or D)	High (A)
Ease to conduct a study	Very easy (A)	Easy (A or D)	Difficult (D)
Cost to conduct a study	Inexpensive (A)	Inexpensive (A)	Expensive (D)
Number of synchronous cases	Can be large (A or D)	Can be very large (A)	Confined by cohort size (D)
Follow-up for synchronous and solitary cancers to occur	Not necessary (A)	Not necessary (A)	Necessary (D)
Follow-up of cancer patients	Can be thorough (A)	Registry or questionnaire based (D)	Registry or questionnaire based (D)
Evaluation and confirmation of cancer by study pathologist	Easy (A)	Possible (D)	Possible (D)
Tumor molecular analyses	Easy (A)	Possible (D)	Possible (D)
Criteria for synchronous cancers	Can be strict (A)	Maybe variable (D)	Maybe variable (D)

NOTE. Individual studies are listed in Supplementary Table 1.
A, advantage; D, disadvantage; Ref, reference.

tively selected, thereby subject to potential selection bias. An optimal control group would be solitary colorectal cancers in a population that has given rise to synchronous colorectal cancers. It is possible to secure such a control group in a prospective cohort setting.

In this study, during follow-up of 2 well-characterized, prospective cohort studies, we identified 47 cases of synchronous colorectal cancers and 2021 control solitary colorectal cancers that had arisen in the same background population as synchronous cases. We examined patient survival and various molecular changes in synchronous and solitary colorectal cancers in our prospective cohort studies.

Materials and Methods

Study Population

We utilized 2 prospective cohort studies: the Nurses' Health Study (121,701 women followed since 1976)[27] and the Health Professionals Follow-up Study (51,529 men followed since 1986).[27] Every 2 years, participants have been sent follow-up questionnaires to identify newly diagnosed cancer and other diseases in themselves and their first-degree relatives. For nonresponders, we searched the National Death Index to discover deaths and ascertain any diagnosis of colorectal cancer that contributed to death or was a secondary diagnosis. Study physicians and pathologists reviewed medical and pathology records and recorded tumor stage, location, and synchronicity status.

During prospective follow-up of the cohort participants up to 2004, there were 2068 incident colorectal cancer patients with available pathology reports and follow-up data, which constituted the base of this study (Figure 1). Among them, we identified 47 patients who had synchronous colorectal cancers, which were strictly defined as the presence of 2 or more colorectal cancers (with at least submucosal invasion, stage pT1) that were grossly, unequivocally separated by normal colorectal mucosa at the first diagnosis of colorectal cancer. In addition, metastasis mimicking synchronous tumors were excluded. Two of the 47 synchronous cases had 3 synchronous cancers, and all of the other cases had 2 synchronous cancers: cancer tissues of the patients with 3 tumors were unavailable. The remaining 2021 patients had solitary colorectal cancers at the first diagnosis, which constituted a control group in this study. These solitary colorectal cancers had arisen in the population that had given rise to synchronous colorectal cancer cases and thus constituted an optimal comparison (control) group (Table 1). Patients were observed until death or June 2008, whichever came first. We collected paraffin-embedded tissue blocks from hospitals at which patients underwent tumor resections,[27] and pathologic features were examined by a pathologist (S.O.) who was unaware of other data. Tumor grade was classified as low or high ($<$50% or $\geq$50% solid areas, respectively). Based on tissue specimen availability, we performed pathologic and molecular analysis on a total of 29 cases of synchronous

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