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Increased Risk of Acute Myelogenous Leukemia After Early Onset but Not Late-Onset Colorectal Cancer

Steven Lehrer, MD^{*}, Peter H. Rheinstein, MD, JD, MS[†]

^{*}Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY;

[†]Severn Health Solutions, Severna Park, MD.

Abstract

Background: Early onset colorectal cancer in persons younger than 50 years is increasingly common. Clinical and molecular characterizations reveal a distinctive disease. Thirty percent of patients have mutations of hereditary cancer syndromes, especially Lynch syndrome. A recent analysis, testing germline DNA for mutations in 25 cancer susceptibility genes, showed that some patients younger than 50 years had mutations of high-penetrance colorectal cancer genes such as *APC* (adenomatous polyposis coli). Others had mutations in high-penetrance or moderate-penetrance genes not traditionally associated with colorectal cancer, such as *ATM* (ataxia telangiectasia mutated), whereas still others had low penetrance colorectal cancer genes. In the current study, we examined the incidence of second cancers following early onset (age less than 50 y) colorectal cancer.

Methods: The initial study population was assembled using records from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The SEER*Stat MP-SIR (multiple primary-standardized incidence ratio) tool was used to calculate SIRs and excess risk for second primary malignancies. The SIR is expressed as the ratio of observed-to-expected (O/E) cases. We used The Cancer Genome Atlas (TCGA) and AACR Project Genie for genetic analysis. The data were accessed with the online Xena Browser and cBioportal.

Results: Acute myelogenous leukemia (AML) O/E ratios were significantly > 1 in patients aged less than 50 years, at 12 to 59 months after colorectal cancer. In patients aged 50 years and older, O/E ratios were equal to 1 or quite close at 12 to 59 months after colorectal cancer. Alterations in 3 AML genes, *CEBPA-AS1*, *MLLT1*, and *MLLT6*, affected the prognosis of colorectal cancer patients less than 50 years but not older than 50 years. One AML gene, *FLT3*, had the highest copy number alteration frequency of any gene in 1438 colorectal patients 18 to 48 years of age. Genetic alterations of *FLT3/TP53* were mutually exclusive. Genetic alterations of *FLT3/JAK2* and *JAK2/CTNNB1* were co-occurrent.

Conclusion: These observations suggest that early onset colorectal cancer and AML may be related diseases.

Reprints: Steven Lehrer, MD, Box 1236 Radiation Oncology, Mount Sinai Medical Center, 1 Gustave L. Levy Place, New York, NY 10029. steven.lehrer@mssm.edu.

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Keywords

SEER; TCGA; leukemia; gastroenterology; genetics

Colorectal cancer is the third most common cancer world-wide and the fourth most common cancer in the United States. Worldwide, 774,000 deaths each year are because of colorectal cancer. Early onset colorectal cancer in persons younger than 50 years is increasingly common.¹ Clinical and molecular characterizations reveal a distinctive disease.² Thirty percent of patients have mutations of hereditary cancer syndromes, especially Lynch syndrome.³

Lieu et al⁴ reported that TP53 and *CTNNB1* alterations were more common in younger patients (age less than 40 y) with colorectal cancer. Another recent analysis, testing germline DNA for mutations in 25 cancer susceptibility genes, showed that some patients less than 50 years of age had mutations of high penetrance colorectal cancer genes such as *APC* (adenomatous polyposis coli). Others had mutations in high-penetrance or moderate-penetrance genes not traditionally associated with colorectal cancer, such as *ATM* (ataxia telangiectasia mutated), whereas still others had low penetrance colorectal cancer genes.⁵

Early onset colorectal cancer has a lower prevalence of *BRAF*V600E mutations (range, 0% to 8%) and *NRAS* mutations (7%) than onset after 50 years of age. About KRAS mutations there is disagreement.²

In the current study, we examined the incidence of second cancers following early onset (age less than 50 y) colorectal cancer. The initial study population was assembled using records from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. We used The Cancer Genome Atlas (TCGA) and AACR Project Genie for genetic analysis.

METHODS

We examined SEER program database records from patients starting in 1992. A 98% case ascertainment is mandated from 14 population-based registries and 3 supplemental registries representing ~26% of the US population.⁶ The SEER registries contain information on patient demographics, tumor site, histology, date and source of diagnosis, date of death, and treatment. Each year quality and completeness studies are conducted in SEER areas to ensure high-quality data.

The SEER program statistical analysis software package (SEER*Stat, version 8.3.5) was used to identify patients diagnosed with primary colorectal cancer from 1992 to 2016 (the histologic subtypes included in the analysis were International Classification of Diseases codes 0 to 3/World Health Organization 2008, colon and rectum). Patients with other cancer histologies or whose colorectal malignancy was not their first primary cancer were excluded from the analysis. The second primary cancers diagnosed within 2 months of the colorectal cancer diagnosis were also excluded. The time of the development of second primary malignancies was calculated from the date of diagnosis of colorectal cancer.

The SEER*Stat MP-SIR (multiple primary-standardized incidence ratio) tool was used to calculate SIRs and excess risk for second primary malignancies by comparing patients' subsequent cancer profile with the number of cancers that would be expected on the basis of incidence rates for the general US population.

Statistics

SEER*Stat estimates the risk of second primary cancers by compiling person-years (PY) of observation according to age and calendar-year periods from 2 months after the date of colorectal cancer diagnosis to the date of death, date of last follow-up evaluation, date of diagnosis of second primary cancer, or the end of the study, whichever occurred first. Cancer incidence rates specifically for 5-year age groups and calendar-year intervals are multiplied by the accumulated PY at risk to estimate the number of cancer cases expected. The observed and expected numbers of second cancers are then summed, with the SIR expressed as the ratio of observed-to-expected (O/E) cases. The absolute excess risk per 10,000 PY is determined by subtracting the expected number from the observed number of second cancers and then dividing the difference by the number of PY at risk. The number of excess second cancers is expressed per 10,000 PY. The statistical analyses, including the tests for heterogeneity and linear trend as well as the regression modeling, are conducted using the Poisson modeling method of Breslow.⁷ This approach is on the basis of the fact that for grouped data, proportional hazards modeling with known baseline hazard is formally equivalent to Poisson regression.

Genomics

We examined the association between colorectal cancer and overall survival in the GDC TCGA Colon Cancer (COAD) dataset. TCGA contains the analysis of over 11,000 tumors from 33 of the most prevalent forms of cancer.⁸ To access and analyze the data we used:

- UCSC Xena Browser, a web-based visual integration and exploration tool for TCGA data, including clinical and phenotypic annotations.⁹
- cBioportal, a web-based interface that enables an integrative analysis of complex cancer genomics and clinical profiles.¹⁰

Survival data of the colon cancer subgroup were extracted for analysis and generation of Kaplan-Meier curves for overall survival. Survival time was defined as the period from the date of surgery to the date of death. If unavailable, then the date of the last follow-up was used for KM right censoring. Differences between Kaplan-Meier survival curves were calculated by the log-rank (Mantel-Cox) test.

Simple statistics were calculated to identify patterns of mutual exclusivity or co-occurrence. For a pair of query genes, an odds ratio (OR) is calculated (Equation 1) that indicates the likelihood that the events in the 2 genes are mutually exclusive or co-occurrent across the selected cases.

$$OR=(A \times D)/(B \times C), \quad (1)$$

where A is the number of cases altered in both genes; B is the number of cases altered in gene A but not gene B; C is the number of cases altered in gene B but not gene A; and D is the number of cases altered in neither gene. Each pair was then assigned to one of 3 categories indicative of a tendency toward mutual exclusivity, of a tendency toward co-occurrence, or of no association. To determine whether the identified relationship is significant for a gene pair, Fisher exact test was performed.¹⁰

RESULTS

SEER data revealed that of 37,705 patients who had colorectal cancer aged less than 50 years, 20,102 were male individuals, and 17,603 were female individuals. A total of 290,702 patients had colorectal cancer aged 50 years and older, 148,136 were male individuals, 142,566 female individuals.

Second cancers after colorectal cancer are common; they include second colorectal cancer (this is different from first cancer recurring), gastric cancer, small bowel cancer, anal cancer, bile duct cancer, uterine cancer, renal cancer, cancer of the ureter, lung cancer, and vaginal cancer.¹¹ Familial adenomatous polyposis is associated with both colorectal cancer and papillary thyroid cancer.¹² In our SEER*Stat MP-SIR analysis, all of these cancers had O/E ratio significantly > 1 in patients aged less than 50 years and in patients aged 50 years and older.

An exception to this pattern was noted in nonlymphocytic leukemia, acute nonlymphocytic leukemia (ANLL), myeloid and monocytic leukemia, and acute myelogenous leukemia (AML). Figure 1 shows the leukemia O/E ratios, which were significantly > 1 in patients aged less than 50 years at 12 to 59 months after colorectal cancer. In patients aged 50 years and older O/E ratios were equal to 1 or quite close at 12 to 59 months after colorectal cancer. The time to leukemia occurrence after primary colorectal cancer, the observed number of leukemia cases and age group distribution are presented in Table 1.

The increased leukemia O/E ratio is not simply because of the usual age at onset of leukemia. For example, AML is generally a disease of older people and is uncommon before the age of 45 years.¹³ The average age of people when they are first diagnosed with AML is about 68 years. Yet AML has the highest O/E ratio of nonlymphocytic and myeloid leukemias 12 to 59 months after colorectal cancer in patients less than 50 years (Fig. 1).

Because of the apparent relationship of colorectal cancer at age less than 50 years with AML, we examined genes associated with AML in the GDC TCGA Colon Cancer (COAD) dataset. We found that:

1. *CEBPA-AS1* RNA expression has a significant effect on early colorectal cancer survival (Fig. 2A). Increased expression was associated with increased survival in 48 patients less than 50 years ($P=0.01433$). There was no significant effect in 451 patients 50 years and older ($P=0.69$).
2. *MLLT1* RNA expression had a significant effect on early colorectal cancer survival (Fig. 2B). Increased expression was associated with increased survival ($P=0.03669$). There was no significant effect in 451 patients 50 years and older

($P = 0.33$). *MLLT1* masked copy number segments have a significant effect on early colorectal cancer survival (Fig. 2C). Increased masked copy number segments were associated with increased survival ($P = 0.04$). There was no significant effect in 251 patients 50 years and older ($P = 0.52$).

3. Five *MLLT6* mutations reduced survival in 48 patients less than 50 years ($P = 0.048$, Fig. 2D). There was no significant effect of 22 mutations in 383 patients 50 years and older ($P = 0.18$). Of 5 *MLLT6* mutations in 48 patients, age less than 50 years, 4 were in exons, 1 in an intron (Fig. 3). Two were missense/inframe, 1 was deleterious, 1 silent.
4. Two mutations in *NPM1* were not significantly related to reduced survival in 48 patients with early colorectal cancer ($P = 0.11$). Three mutations in *IDH1* were not significantly associated with reduced survival ($P = 0.2$). One mutation in *CEBPA* was unrelated to survival ($P = 0.9$). There were no mutations in *IDH-AS1*. One mutation in *IDH2* was unrelated to survival ($P = 0.5$).

To examine other AML genes in a larger sample, we used cBioportal to access the AACR Project Genie Consortium dataset. Genie has already shown novel recurrent variants that affect the molecular diagnosis of sizable numbers of patients with cancer.¹⁴ We utilized the Group Comparison feature of cBioportal to compare clinical and genomic features of 5961 colorectal cancer patients and found 1 AML gene, *FLT3*, which had the highest copy number alteration frequency of any gene in 1438 colorectal patients 18 to 48 years of age (Fig. 4). In addition, genetic alterations in *FLT3* were significantly co-occurrent with alterations in another AML gene, *JAK2*. Alterations of *JAK2/CTNNB1* were also co-occurrent. Genetic alterations of *FLT3/TP53* were mutually exclusive (Fig. 5 and Table 2).

We used the Xena Browser to identify *BRAF*, *NRAS*, *KRAS*, and *APC* mutations by age at initial pathologic diagnosis in the COAD dataset. Age at initial pathologic diagnosis ranged from 31 to 90 years in 385 patients with primary tumors. We found only 2 *BRAF* V600E mutations in 48 patients aged less than 50 and only 1 *NRAS* mutation in 48 patients aged younger than 50 years, whereas *KRAS* and *APC* mutations were common at all ages (Fig. 6).

DISCUSSION

Acute leukemias following a diagnosis of colorectal cancer have been reported. Whether they were therapy-related or not is uncertain.¹⁵

The *NCI Dictionary of Cancer Terms* defines ANLL as an aggressive disease in which too many myeloblasts are found in the bone marrow and blood. ANLL is also called acute myeloblastic leukemia, AML, and ANLL (<https://www.cancer.gov/publications/dictionaries/cancer-terms>). SEER uses both *ANLL* and *AML*, apparently interchangeably, and we have carried over their usage for the current study.

The incidence of AML is rising in developed countries such as Australia and Canada. The incidence in the UK has increased by 73% in the last 40 years.¹⁶

AML genes are well characterized. AML is most likely the result of an interaction of alterations in at least 2 broad genetic classes, class I and class II. A separate group of mutations promotes epigenetic modification.¹⁷

Class I genes affect AML proliferation and survival. *FLT3* (Fms-like tyrosine kinase 3) mutations are a poor prognostic factor. Fms, first discovered as the oncogene responsible for Feline McDonough Sarcoma, is a type III receptor tyrosine kinase that binds to the macrophage or monocyte colony-stimulating factor (M-CSF or CSF-1).¹⁸ In 2018, the US Food and Drug Administration and the European Medicines Agency approved the protein kinase inhibitor midostaurin for both newly diagnosed *FLT3*-mutated AML and advanced systemic mastocytosis.¹⁹ But *FLT3* inhibitors may not be of value in solid tumors such as colorectal cancer.²⁰

Class II genes and their mutations influence AML cell differentiation and apoptosis. Cell differentiation genes could be responsible for the appearance of AML in a patient after early onset colorectal cancer. We found, as noted previously, that 3 class II genes, *CEBPA-AS1*, *MLLT1*, and *MLLT6*, were involved in colorectal cancer in patients aged less than 50 years but not colorectal cancer in patients aged 50 years and older.

- *CEBPA-AS1* is a member of the basic region leucine zipper family of transcription factors. This protein is essential for cell cycle arrest and the inhibition of self-renewal and myeloid differentiation throughout the process of hematopoiesis. It is upregulated in AML.²¹ *CEBPA-AS1* expression correlates with poor prognosis and promotes tumorigenesis in oral squamous cell carcinoma. *CEBPA-AS1* targets *CEBPA* in oral cancer.²²
- *MLLT1* is a transcriptional regulator that can activate transcription from synthetic reporter genes in both lymphoid and myeloid cells. A chromosomal aberration involving *MLLT1* is associated with acute leukemias.²³
- *MLLT6* (myeloid/lymphoid or mixed-lineage leukemia translocated to 6), located on chromosome 17q21, was originally isolated as an MLL partner gene in leukemia.²⁴ *MLLT6* synergistically promotes the development of AML (AML) as an oncogene or a gene fusion.

TP53 is the most frequently mutated gene in human tumors. The reported *TP53* mutation rate in AML is low (2.1%). But the incidence of *TP53* mutations in AML with a complex aberrant karyotype is higher (69% to 78%) and predicts a poor outcome.²⁵ In AML, alterations in *JAK2*, another class I gene, and *FLT3* play key roles in hematopoietic stem cell proliferation, differentiation, and survival.²⁶

BRAF mutations, especially V600E, are present in 10% of colorectal cancer cases.²⁷ Although malignant melanoma is a disease more commonly associated with *BRAF*V600E mutation, colorectal cancer is a much more prevalent disease and deaths from *BRAF*-mutant colorectal cancer exceed those from *BRAF*-mutant melanoma. As others have reported, *BRAF* mutations are uncommon in early onset colorectal cancer.

Biological processes or pathways in cancer are often deregulated through different genes or by multiple different mechanisms. But cancer gene alterations usually do not occur at random.

Some alterations are mutually exclusive. The concept of mutual exclusivity can be exploited to identify previously unknown mechanisms that contribute to oncogenesis and cancer progression. In mutual exclusivity, events in genes associated with specific cancer tend to be mutually exclusive across a set of tumors; that is, each tumor is likely to have only one of the genetic events. This may be the case with *FLT3* and *TP53* in early onset colorectal cancer (Table 2).

The opposite situation (co-occurrence) is when genetic alterations occur in multiple genes in the same cancer sample, as seen in the cases of *FLT3/JAK2* and *JAK2/CTNNB1* in early onset colorectal cancer (Table 2). Co-occurrence indicates that genes may work in tandem to drive tumor formation and development.¹⁰

In conclusion, early onset colorectal cancer and AML may be related diseases. More knowledge of the relationship may lead to new means to prevent and treat both conditions.

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FIGURE 1.

Leukemia O/E ratios were significantly ($P < 0.05^*$) > 1 in patients age less than 50 years at 12 to 59 months after colorectal cancer. In patients aged 50 years and older, O/E ratios were equal to 1 or quite close. **** $P < 0.05$ for all four leukemia groups. O/E indicates observed-to-expected.

FIGURE 2.

A, *CEBPA-AS1* RNA expression has a significant effect on early colorectal cancer survival. Increased expression was associated with increased survival in 48 patients less than 50 years ($P = 0.01433$). The median survival of the reduced expression (blue) group was 1100 days. The survival curve does not drop to 0.5 in the increased expression (red) group and the median time cannot be computed. There was no significant effect in 451 patients 50 years and older ($P = 0.69$). B, *MLLT1* RNA expression had a significant effect on early colorectal cancer survival. The median survival of the reduced expression (blue) group was 1910 days. Increased expression was associated with increased survival ($P = 0.03669$). There was no significant effect in 451 patients 50 years and older ($P = 0.33$). C, *MLLT1* masked copy number segments have a significant effect on early colorectal cancer survival. Increased masked copy number segments are associated with increased survival ($P = 0.04$). The median survival of the reduced expression (blue) group was 1900 days. There was no significant effect in 251 patients aged 50 years and older ($P = 0.52$). D, *MLLT6* mutations reduced survival in colorectal cancer patients less than 50 years of age ($P = 0.048$). There was no significant effect of 22 mutations in 383 patients aged 50 years and older ($P = 0.18$).

The survival curves do not drop to 0.5 in either group and the median times cannot be computed.

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FIGURE 3. MLLT6 mutations in 48 colorectal cancer patients aged less than 50 years. Four of the mutations are in exons, 1 is in an intron. Two are missense/inframe, 1 is deleterious, 1 silent.

FIGURE 4.

The Group Comparison feature of cBioportal was used to compare clinical and genomic features of 5961 patients with colorectal cancer in 4 age groups. One acute myelocytic leukemia gene, *FLT3*, had the highest copy number alteration frequency in 1438 patients with 18 to 48 years of age ($P = 0.01$) (copy number alterations: AMP = amplification, HOMDEL = deep deletions).

FIGURE 5. Oncoprint diagram showing significantly co-occurring and mutually exclusive genetic alterations in *FLT3*, *JAK2*, *TP53*, and *CTNNB1* in 717 colorectal cancer patients aged less than 40 years (cBioportal.org).

FIGURE 6.

A, number of samples. Each horizontal block represents 50 samples. The part of a block at the bottom represents 35 samples. Total 385 samples ($7 \times 50 + 35$). *BRAF*, *NRAS*, *KRAS*, and *APC* mutations by age at initial pathologic diagnosis of colorectal cancer in 385 patients. The youngest patient was 34 years, the oldest 90 years (B). Mutations in patients aged less than 50 years are below the solid black horizontal line in boxes D, E, F, and G. Note that there are only 2 *BRAF* V600E mutations (blue dots) in 48 patients aged less than 50 years and only 1 *NRAS* mutation (blue dot) in 48 patients aged less than 50 years, whereas *KRAS* and *APC* mutations are common at all ages. Each row contains data from a single sample. Row order is determined by sorting the rows by their column values. Column C value (age at initial pathologic diagnosis) is used to sort the rows. In the case of a tie, the next columns to the right are used to break the tie (xenabrowser.net).

TABLE 1.

Leukemia Occurring After Primary Colorectal Cancer: Observed Number of Cases by Age Group (Age Less Than 50 or 50 y and Older), and Time to Occurrence (12 to 59 or 60 to 119 mo)

	Age <50 y		Age 50 y	
	12–59 mo	60–119 mo	12–59 mo	60–119 mo
Nonlymphocytic leukemia	13	10	183	174
Acute nonlymphocytic leukemia	11	6	122	117
Myeloid and monocytic leukemia	13	8	164	157
Acute myelogenous leukemia	11	4	106	98

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TABLE 2.
Significantly Co-occurring and Mutually Exclusive Alterations in 717 Colorectal Cancer Patients Aged Less Than 40 Years

A	B	Neither	A Not B	B Not A	Both	Log2 Odds Ratio	P	q-Value	Tendency
FLT3	JAK2	435	38	6	6	> 3	< 0.001	0.001	Co-occurrence
FLT3	TP53	119	20	322	24	-1.173	0.01	0.029	Mutual exclusivity
JAK2	CTNNB1	433	8	40	4	2.436	0.017	0.034	Co-occurrence