BACKGROUND
- Proportion of colorectal cancer cases diagnosed before age 50, known as young-onset colorectal cancer (YCRC), has increased over time.1
- Individuals with YCRC tend to be diagnosed at later stages, requiring more intensive treatments.2
- 70% of YCRC cases detected due to signs/symptoms signaling presence of YCRC, such as iron deficiency anemia (IDA) or hematocrit (in blood in stool).3
- The risks for YCRC after diagnosis of IDA or hematocrit have not been well established.

OBJECTIVES
- Examine association between iron deficiency anemia (IDA) and YCRC risk
- Examine association between hematocrit and YCRC risk

METHODS
Design:
- Cohort study of US Veterans ages 18-49 receiving care in the Veterans Health Administration (VHA) between 1999-2016.
- Matched cohorts with replacement used to perform analyses, matching on sex, birth year, first VHA visit date (±180 days), and date of IDA/Hematocrit diagnosis date of exposed individual (start of follow-up).
- Excluded individuals with YCRC or inflammatory bowel disease prior to start of follow-up.

Analytic Samples:
1) 4:1 matching individuals without incident IDA to those with IDA (n = 239,000)
2) 4:1 matching individuals without incident hematocrit to those with hematocrit (n = 653,740)

Measures:
- IDA: Defined using WHO criteria as: (hemoglobin <13.0 mg/dL in males, <12.0 mg/dL in females), AND
- Follow-up iron test within 3 months indicating iron deficiency (ferritin levels ≤515 ng/mL, or transferrin saturation levels ≤15%)
- Hematocrit: Identified by ICD-9 and ICD-10 diagnosis codes.
- Outcome: YCRC diagnosed within five years of start of follow-up defined by:
  - Primary or secondary diagnosis identified in VA Central Cancer Registry or Oncology Raw database, OR
  - National Death Index-identified YCRC
- Covariates: Race/ethnicity, body mass index (BMI), smoking status (current, former, never), diabetes prevalence, aspirin use.

Statistical Analysis:
- Five-year cumulative YCRC risk estimates accounting for censoring (turning 50, non-YCRC-related death, five years of follow-up, December 31, 2016)
- Used to calculate risk differences and number needed to scope to detect 1 YCRC (NNC).
- 95% confidence intervals derived by boot-strapping with 1000 replications
- Cox proportional hazards models to estimate hazard ratio of YCRC and corresponding 95% confidence intervals.
- Accounted for matching using cluster-specific random intercepts.

RESULTS
IDA Analytic Cohort:
- Cohort population was predominantly female (53%), ages 40-49 and overweight or obese (Table 1).
- Individuals with IDA were more likely to be Black (43% vs. 27%), never smokers (32% vs. 40%), have prevalent diabetes (13% vs. 7%), and be aspirin users (13% vs. 6%) compared to individuals without IDA.

Hematocrit Analytic Cohort:
- Cohort population was mostly male (87%), ages 40-49, non-Hispanic White, and overweight or obese (Table 1).
- Individuals with hematocrit were more likely to be current smokers (33% vs. 26%), overweight or obese (72% vs. 49%) and aspirin users (10% vs. 6%) compared to individuals without hematocrit.

Summary of Findings:
- YCRC five-year cumulative incidence markedly higher among individuals diagnosed with IDA or hematocrit (Figure 1).
- YCRC risk elevated among men with IDA diagnosis and individuals ages ≥30 with IDA or hematocrit diagnosis (Figure 2).
- NNS is at below 33 cut-off for IDA and hematocrit diagnosis overall, and for men diagnosed with IDA or hematocrit and individuals ages ≥40 diagnosed with IDA or hematocrit (Figure 3).

Figure 1. Cumulative incidence curves for YCRC risk by IDA and hematocrit exposure.

Figure 2. Risk difference and hazard ratio findings, main effect and stratified, for IDA and hematocrit analytic cohorts.

CONCLUSIONS
- Individuals between ages 18-49 diagnosed with IDA or hematocrit of undetermined origin are at increased YCRC risk.
- YCRC risk associated with IDA is highest among men.
- YCRC risk associated with hematocrit or IDA is highest among individuals ages ≥30.
- Colonoscopy should be strongly considered in adults <50 with IDA or hematocrit without a clinically confirmed source.

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