

## CLINICAL VIGNETTE

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# Concerning Trend: Rising Incidence of Early-Onset Colon Cancer in “Average-Risk” Patients

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A 44-year-old Southeast Asian female with no significant past medical history presented for her annual well women exam. She had no complaints, exercises regularly and consumed a vegetarian diet. Her BMI was 23 and she took no medications. Exam was normal. Counseling was given on a well-balanced vegetarian diet, including adequate B12 and protein intake. Screening labs were drawn. The patient followed up a month later to discuss her abnormal lab results. She remained asymptomatic. Labs were remarkable for: HgA1c at 5.9% (nl: less than 5.7%), vitamin D level at 19 ng/ml (nl: 20-50 ng/ml), hemoglobin at 9.4 g/dl (nl: 11.2-15.7 g/dl) and hematocrit 30.5% (nl: 34.1-44.9%), mean corpuscular volume 78 fL (nl: 79-94.8 fL), platelet 492  $10^3/uL$  (nl: 163-369  $10^3/uL$ ), iron 27 mcg/dL (nl: 41-179 mcg/dL), iron binding capacity 446 mcg/dL (262-502 mcg/dL), percent iron saturation 6%, ferritin 5 ng/ml (nl: 8-180 ng/ml), Vitamin B 12 281 pg/ml. Counseling was given on iron rich diet. Prediabetic education also given for lifestyle modifications. She was asked to start vitamin B 12 and iron supplementation and to recheck these labs in three months.

Three months later, having not completed her labs, the patient was reminded to follow up. She reported that she did not take the iron supplements as prescribed and did not want to come for an office visit yet. After several additional attempts to have the patient return for reexamination, one year later she presents to follow up on her anemia. She states she supplemented with iron twice daily with only occasionally missed pills. She intentionally lost 20 pounds from reduced carbohydrate intake in her diet and hired a personal trainer for better fitness. Review of symptoms remained negative, except for “darker” stool since starting iron. She specifically denied blood in stool. Patient also reported her mother had partial colectomy for an unknown reason in her mid-50s and she denied family history of cancer. Point of care testing in the clinic showed no significant improvement in her hemoglobin level. The patient was counseled that further investigation was warranted given her persistent anemia, including stool fecal immunochemical test (FIT), that returned positive.

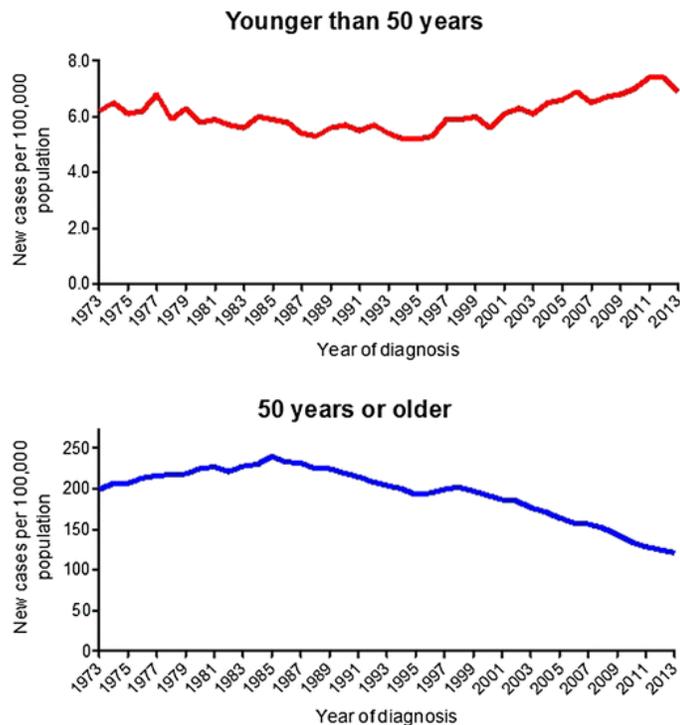
She was referred to gastroenterology for persistent anemia with positive FIT test. Limited colonoscopy revealed a partially obstructing fungating mass in sigmoid colon 10cm in length. The obstruction precluded complete colonoscopy. The biopsy showed moderately differentiated invasive adenocarcinoma. CEA was 3.9. The patient was diagnosed with Stage III colon cancer and underwent segmental resection and adjuvant chemotherapy.

Although this patient’s mother had a hemicolectomy in her 50’s which raised questions of post family history of colon cancer, her persistent anemia and positive FIT test prompted a diagnostic evaluation which led to her diagnosis of colorectal cancer. Deficiency anemia is among an increasing trend of “average risk” patients with colorectal cancer diagnosed before the age of 50. In fact, the incidence rate of colorectal cancer for adults less than age 50 increased by 22% from year 2000 to 2013.<sup>1</sup> Furthermore, the death rate from colorectal cancer for those less than 50 increased by 13% from 2000 to 2014, whereas the death rate among individuals greater than age 50 decreased by 34%. Overall though, the highest rate of new cases of colorectal cancer is in age 65 to 74, with age 67 being the median age at diagnosis.<sup>2</sup> The current USPSTF colorectal screening guideline is based on this older population.<sup>3</sup> Given the rising incidence of colorectal cancer in those younger than age 50, this guideline may need revision in the future.

Obviously, it is concerning that the colorectal cancer incidence rate is increasing in younger adults. Currently, one in seven of colorectal cancers are diagnosed in adults less than the age of 50.<sup>5</sup> Younger adults are more likely to have advanced stage disease at diagnosis because “average-risk” individuals age less than 50 are not being screened. African Americans have a higher incidence and mortality rate from colorectal cancer.<sup>6</sup> Consensus has been reached among the American College of Gastroenterology and American College of Gastrointestinal Endoscopy to start screening African-Americans at age 45.<sup>4</sup>

Similarly, there are earlier colorectal screening guidelines for “higher risk” individuals with either a known family history of early colon cancer or adenomatous polyps, personal history of inflammatory bowel disease or hereditary colorectal cancer syndrome (i.e. Familial Adenomatous Polyposis or Lynch syndrome). Again, however, no recommendations are made for colorectal screening for an “average risk” population less than 50 years old. The concern for screening earlier than current guidelines boils down to the basic principle of benefit of early detection versus risk of invasive procedure.

Clearly, more research needs to be done to further identify the risk factors for these sporadic early-onset colorectal cancers. Making this challenging is that the molecular profile for these sporadic early-onset colorectal cancers tend to be more heterogeneous and different from the late-onset colorectal cancers. Further research may help with strategies for prevention, detection and treatment of early onset colorectal cancers.



**Figure 1:** The incidence of colorectal cancer in the population younger and older than 50 years of age according to the Surveillance, Epidemiology, and End Results Program (SEER) database from 1973 to 2013.<sup>4</sup>

Research thus far, has shown more “modern” lifestyle changes associated with increased incidence of early-onset of colorectal cancer. A review article<sup>4</sup> evaluating meta-analysis studies reports lack of exercise, excessive caloric intake, excessive alcohol intake, tobacco smoking, a diet high in red or processed meat, and cooking meats at very high temperatures (e.g. frying/grilling) have been associated with an increased risk of colorectal cancer. Relatedly, some scientists hypothesized mechanisms of carcinogenesis from obesity from various effects of increased insulin, insulin-like growth factor-1, sex hormones, and pro-inflammatory mediators. Patients with type 2 diabetes mellitus have an increased risk of colorectal cancer, even after adjusting for the above mentioned “modern” lifestyle changes.<sup>7,8</sup>

Different hypothesis have been proposed for the carcinogenicity of high-heat cooking methods for red and processed meat.<sup>9,10</sup> Several molecules of interest have been identified, including the heterocyclic amines, polycyclic aromatic hydrocarbons, N-nitroso-compounds and N-glycolyneruamic acid (Neu5Gc). These molecules, in combination of other lifestyle factors such as obesity, high fat and/or high protein intake, as well as genetics may lead to the damage of colonic mucosa and epithelium and genes, triggering hyperproliferation and finally cancer.

Interestingly, other investigators are exploring the relationship between night shift work and colorectal cancer.<sup>11</sup> It is hypothesized that the disruption of the circadian rhythm leads to decreased melatonin levels, and melatonin is thought to have a

protective effect against cellular damage. This theory suggests that people with lower levels of melatonin of any cause, have an increased risk for colorectal cancer.

Although, recent opinions<sup>4</sup> are now shifting to starting earlier screening for non-Hispanic African-Americans starting at age 45, until there is more conclusive evidence to support early screening in the current “average risk” adult, we must allow the screening for colorectal cancer to begin at age 50. In the meantime, more awareness on modifiable risk factors may motivate more patients to change lifestyle. Also, physicians may consider being more aggressive in pursuing diagnostic colonoscopy in patients who would have been otherwise managed conservatively. Perhaps in the near future, similar consensus can be reached for earlier colon cancer screening, for diabetics who have had the disease for more than “x” years; or, for people with BMI greater than “x” with intake of red meat or average alcohol intake of “x” times per week. One week after this manuscript was submitted, The American Cancer Society up-dated their colorectal cancer screening guidelines. They recommend initiation of screening at age 45 for adults at average risk.<sup>12</sup>

## REFERENCES

1. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A. Colorectal cancer statistics, 2017. *CA Cancer J Clin*. 2017 May 6;67(3):177-193. doi: 10.3322/caac.21395. Epub 2017 Mar 1. PubMed PMID: 28248415.
2. Cancer Stat Facts: Colorectal Cancer. Surveillance, Epidemiology and End Results program. <https://seer.cancer.gov/statfacts/html/colorect.html>.
3. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FAR, Gillman MW, Harper DM, Kemper AR, Krist AH, Kurth AE, Landefeld CS, Mangione CM, Owens DK, Phillips WR, Phipps MG, Pignone MP, Siu AL. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016 Jun 21;315(23):2564-2575. doi: 10.1001/jama.2016.5989. Erratum in: *JAMA*. 2016 Aug 2;316(5):545. Erratum in: *JAMA*. 2017 Jun 6;317(21):2239. PubMed PMID: 27304597.
4. Connell LC, Mota JM, Braghiroli MI, Hoff PM. The Rising Incidence of Younger Patients With Colorectal Cancer: Questions About Screening, Biology, and Treatment. *Curr Treat Options Oncol*. 2017 Apr;18(4):23. doi: 10.1007/s11864-017-0463-3. Review. PubMed PMID: 28391421.
5. Abdelsattar ZM, Wong SL, Regenbogen SE, Jomaa DM, Hardiman KM, Hendren S. Colorectal cancer outcomes and treatment patterns in patients too young for average-risk screening. *Cancer*. 2016 Mar 15;122(6):929-34. doi: 10.1002/ncr.29716. Epub 2016 Jan 25. PubMed PMID: 26808454; PubMed Central PMCID: PMC4777631.
6. Williams R, White P, Nieto J, Vieira D, Francois F, Hamilton F. Colorectal Cancer in African Americans: An Update. *Clin Transl Gastroenterol*. 2016 Jul 28;7(7):e185. doi: 10.1038/ctg.2016.36. Review. PubMed PMID: 27467183; PubMed Central PMCID: PMC4977418.

7. **Handelsman Y, Leroith D, Bloomgarden ZT, Dagogo-Jack S, Einhorn D, Garber AJ, Grunberger G, Harrell RM, Gagel RF, Lebovitz HE, McGill JB, Hennekens CH.** Diabetes and cancer--an AACE/ACE consensus statement. *Endocr Pract.* 2013 Jul-Aug;19(4):675-93. doi: 10.4158/EP13248.CS. Erratum in: *Endocr Pract.* 2013 Sep-Oct;19(5):899. PubMed PMID: 23978590.
8. **Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA.** Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? *Am J Gastroenterol.* 2011 Nov;106(11):1911-21; quiz 1922. doi: 10.1038/ajg.2011.301. Epub 2011 Sep 13. Review. PubMed PMID: 21912438; PubMed Central PMCID: PMC 3741453.
9. **Demeyer D, Mertens B, De Smet S, Ulens M.** Mechanisms Linking Colorectal Cancer to the Consumption of (Processed) Red Meat: A Review. *Crit Rev Food Sci Nutr.* 2016 Dec 9;56(16):2747-66. doi: 10.1080/10408398.2013.873886. Review. PubMed PMID: 25975275.
10. **Casella M, Bimonte S, Barbieri A, Del Vecchio V, Caliendo D, Schiavone V, Fusco R, Granata V, Arra C, Cuomo A.** Dissecting the mechanisms and molecules underlying the potential carcinogenicity of red and processed meat in colorectal cancer (CRC): an overview on the current state of knowledge. *Infect Agent Cancer.* 2018 Jan 15;13:3. doi: 10.1186/s13027-018-0174-9. eCollection 2018. Review. PubMed PMID: 29371880; PubMed Central PMCID: PMC5769331.
11. **Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, Fuchs CS, Colditz GA.** Night-shift work and risk of colorectal cancer in the nurses' health study. *J Natl Cancer Inst.* 2003 Jun 4;95(11):825-8. PubMed PMID: 12783938.
12. **Simon, Stacy.** "American Cancer Society Updates Colorectal Cancer Screening Guidelines." May 30, 2018; <https://www.cancer.org/latest-news/american-cancer-society-updates-colorectal-cancer-screening-guideline.html>.

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