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Maternal stress and early-onset colorectal cancer

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A B S T R A C T

Early-onset colorectal cancer (EOCRC) is defined as colorectal cancer (CRC) diagnosed before the age of 50. Alarmingly, there has been a significant increase in EOCRC diagnoses' worldwide over the past several decades. Emerging data suggest EOCRCs have distinguishing clinical, pathological, biological and molecular features; and thus, are a fundamentally different subtype of CRCs. Unfortunately, there is no simple explanation for the causes of EOCRC. Scientifically rigorous studies are needed to determine what may be driving the challenging epidemiology of EOCRC. We contend here that a reasonable hypothesis is that prenatal risk factors such as maternal stress and associated sleeping disorders influence offspring epigenetic make-up, and shape immune system and gut health contributing to an increased risk for EOCRC.

Introduction/background

EOCRC is the second most common cancer and the third leading cause of cancer mortality in people under 50 years old in the USA [1,2]. It has been on the rise for the past few decades [1,3], and is expected to increase by over 140% by 2030 [4]. Mortality from EOCRC during 2000 to 2014 has increased by 13% [compared to a 34% decline in Late-Onset Colorectal Cancer (LOCRC)] [1]. The National Cancer Institute State Cancer Profiles (SEER + NPCR databases) show the average annual count of EOCRC in the USA (2010–2014) is over 14,000 people/year. These numbers exceed that of non-Hodgkin's lymphoma, acute lymphocytic leukemia, chronic myeloid leukemia, and cervical cancer in the young (< 50 years old). Although the standard cancer-driving offenders have been linked to EOCRC (e.g., diet, sedentary lifestyle, alcohol) [2,5,6], there is also a general understanding that EOCRC is an epidemiologically, pathologically, anatomically, logically, and biologically different diseases than LOCRC. EOCRC, therefore, has to be investigated, evaluated, and managed differently than LOCRC. We suggest that several known and unknown factors may explain this alarming trend in the young. Specifically, here, we address the putative role of maternal stress in the rise in EOCRC incidence.

EOCRC is a global phenomenon [4,7–29], and therefore has to be studied in both a local context and in a global context. In this light, many studies have linked obesity to EOCRC [1,29–31]; and therefore there is a suspicion the increased incidence of EOCRC may be due to the generational shift toward a higher BMI [32]. However, although there has been a global shift in BMI, and EOCRC has been correlated with obesity, many thin people get EOCRC; indicating multiple mutually exclusive, or overlapping mechanisms are at play. EOCRC rates are increasing most prominently in The Americas (USA, Canada, Brazil, Columbia) [2,5,6,33–38], Oceana (Australia, New Zealand, New South Wales) [18,27,39], Northern/Western Europe (Austria, France, Finland, Greece, Germany) [23,40–46], Far East (China, Japan, Singapore, Korea) [47–52], India [53,54], Iran [55], Ethiopia [56], Pakistan [57], Egypt [8,58], and Saudi Arabia [59]. Unfortunately, data from other countries have yet to be reported in the literature, so data are incomplete when trying to link EOCRC to the exposome and global generational shifts in biobehavioral health.

In the USA, EOCRC accounts for 11% of all CRCs in men and 10% of all CRCs among women [1,2]. Although many USA studies have shown rates of EOCRC increasing mostly in Caucasian males [2,5,6,34–36], we know it occurs across sexes and races. EOCRC is most frequently seen in American Indian/Alaskan Natives (annual % change: 5.3%), then Hispanics (2.4%), Caucasians (2%), and Asian/Pacific Islanders (1%). Although EOCRC does not appear to be increasing in African Americans [60,61], the proportion of EOCRC remains nearly double among African Americans compared to Caucasians [62]; so disparities remain in EOCRC [3,5,6,13,18,36,61,63–73]. Finally, although there is a tendency toward the increasing rates of EOCRC occurring in males [2,5,6,34–36], the disease affects both males and females [1,3].

Although genetics plays a significant role in about 30% of cases, the jury is still out for the causes of the remaining 70% of cases. We are just

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beginning to understand the factors driving EOCRC in this latter cohort. The exposome encompasses the totality of human environmental (i.e., non-genetic) exposures from conception onwards [74–78]. Many of the exposome culprits appearing to be associated with EOCRC are dietary [79–98]. Arguing against a specific diet (but not ruling out specific ingredients such as additives or emulsifiers [99–101]) is the observation that the increase in EOCRC is a global phenomenon [4,7–28,53,54,102–104], and that both thin and obese people acquire EOCRC [2,6].

Until we delineate the exposome culprits, our science will be driven by evidence-based hypotheses'. There is clear evidence that a mother's stress, anxiety, and depression during pregnancy can alter the development of her fetus and her child, with an increased risk for later psychopathology [105]. Indeed, maternal stress can also drive hypertension, and cause immune dysfunction [106–108]. Since (1) perceived stress has also been linked to both CRC itself [109]; (2) perceived stress is associated with other factors that have been linked to EOCRC including physical activity and higher sedentary behavior [110]; and (3) both stress and EOCRC have been on the rise over the past few decades [2,5,6,34–36,106,111]; then it is not unreasonable to suspect that maternal stress can contribute to EOCRC in her offspring.

Hypothesis

Maternal stress and associated sleeping disorders can be transmitted to offspring through epigenetic mechanisms which shape immune system and gut health and contributes to an increased the risk for EOCRC.

Evaluation of hypothesis

Although the crude birth rate has been decreasing worldwide by 1–2% every five years [112], both pre-term incidence [113], and low birth at term (indicating fetal distress) are on the rise [114]. One cited a reason for birth weight declining (and a sign of an adverse uterine environment) in the U.S. is the mothers' psychosocial stress [115,116], which is on the rise due to career demands and social factors [106,111]. To this end, although it is not known whether there is a direct link between maternal stress and EOCRC in her offspring, there is circumstantial evidence that is consistent with this hypothesis.

Stress targets the GI tract

The global point prevalence rate for anxiety disorders is 7.3% [117]. Females experience 65% of severe cases, with most of these during a period of reproductive age (15–34 yrs) [118]. It has long been understood that perceived stress can drive the formation of ulcers [119] and can trigger irritable bowel syndrome [120]. This fact indicates two things: (1) stress affects the GI tract; and (2) stress drives inflammation and ulceration; both of which increase the risk for EOCRC [121–123].

Stress targets microbiota

The gut microbiota plays a crucial role in CRC development [124]. It also plays a fundamental role in postnatal development and maturation of immune and endocrine systems that influence central nervous system (CNS) programming and signaling. Regulation of the bi-directional microbiome-brain-gut axis is essential for maintaining homeostasis.

There is expanding evidence that commensal organisms within the gut play a role in early programming and maturation of the stress machinery. An increasing body of research indicates that intestinal microbes affect brain function and neurogenesis, including sensitivity to stress [125]. Alternatively, perceived stress modulates the microbiota with racial differences in the response [126]. In animal models, stress can cause the gut microbiota of lean mice to more closely resemble that of obese mice [127]. Maternal separation can cause intestinal inflammation, hypercorticosteronemia, enhanced intestinal permeability and dysbiosis; and excitingly is prevented by a probiotic [105,128]. Supporting this anxiety-microbiome link, diets containing probiotics and prebiotics attenuate anxiety-like behavior and hippocampal-dependent stress-circuitry and learning [129–131]. Similarly, maternal periconceptional exposure to antibiotics provokes alterations in offspring behavior in the absence of maternal infection [132]. In women, probiotics prevent post-partum depression [133]; and we are only beginning to understand the ability of dysbiosis to transfer from mother to child. Indeed, antibiotic exposure shaping the maternal gut microbiota has effects that extend to the offspring, with consequences of inflammatory bowel disease (IBD) [134]. Similarly, neomycin treatment of pregnant mice leads to generation of immune-tolerogenic antigen-presenting cells (APCs) in the offspring and these APCs had reduced specific autoantigen-presenting function and protects from the development of diabetes [134]. Results suggest that prenatal exposure to antibiotic influenced gut bacterial composition at the earliest time point in life and is critical for consequent education of the immune system and prevention of diseases, including cancer.

Likewise, obesity (a risk factor for EOCRC) during pregnancy influences the compositional structure of gut microbiota in infants through vertical transfer of microbiota and/or their metabolites during pregnancy, delivery and breastfeeding [135,136]. Although much is to be learned on the influence of the mother's microbiota on the developing GI tract of her fetus and the long-term consequences on gut health, data so-far are consistent with the hypothesis that the microbiota can shape gut health and possibly shape the risk for EOCRC.

Sleep disruption and associated stress is associated with CRC

We know from animal and epidemiological studies that perceived stress increases CRC risk [137]. We also know that the less sleep, the higher the risk for metabolic syndrome [138,139]; and that obesity is linked to EOCRC [1,2]. Finally, we know that stress disrupts sleep and vice-versa [140–142]. Although we currently do not know whether disrupted sleep and associated stress in the mother (maternal) causes an increased risk for CRC in their offspring, we do know that disrupted sleep patterns and stress in the mother are associated with many ailments in the fetus, including gut health, and increases the risk of CRC in the mother [134,143–155].

Another observation is that maternal stress causes sleep disruption in offspring [156] and can predict low birth weight and intrauterine growth restriction [115]. Since EOCRC is considered a disease of the young, it makes sense to examine timing and the link between maternal stress and EOCRC. Although direct studies have not been done in this respect, we can glean information from similar studies looking at endpoints other than CRC but associated with a high risk of CRC. For example, perceived stress increases the risk of diabetes [157], and diabetes not only increases the risk of late(r) onset CRC [158,159], but may also be linked to EOCRC [72,160].

Although we do not know whether the offspring of diabetic mothers have an increased risk of CRC at a young age, animal studies suggest offspring of diabetic mothers (ODM) have increased fetal adiposity and disrupted sleep patterns [161]. Animal studies suggest that the offspring of diabetic mothers (ODM) have increased fetal adiposity and disrupted sleep patterns [161]. Maternal psychological stress is associated with low birth weight and intrauterine growth restriction [115], which underscores the vulnerability of the fetus while in utero. Stress experienced during pregnancy not only leads to pregnancy complications (e.g., miscarriage, pre-eclampsia, low birth weight), but also increases the risk of the child to develop diseases in the subsequent periods of life (termed "fetal programming of adult disease"). Programming agents include growth factors, cytokines and hormones; all of which can be altered by stress. As a consequence, such 'stress-modified' systems of the offspring are more susceptible to environmental