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Research Article

Urgency of Regulating Children& Adolescents Diet-Not H2S Producing to Prevent highly vicious Early onset Colorectal Cancer (EOCRC)- A Narrative Review

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Abstract

Earlier we had reviewed the role of LncRNA's in Colorectal Cancer (CRC) besides role of different Gut Microbiota in the generation of escalating Obesity ,insulin resistance and type2Diabetesmellitus(T2DM).Furthermore recently describing how the part of Hydrogen Sulfide (H2S), which has been recently acknowledged to be a gasotransmitter is implicated in various significant physiological and disease situations, inclusive of vasodilation, stimulation of cellular bioenergetics, anti-inflammation, and pro-angiogenesis can be used in resistant Breast Cancer inclusive of Triple-negative breast cancer (TNBC), on reviewing therapy for Breast Cancer. Here we have tried to emphasize on the escalating incidence of Early onset Colorectal Cancer(EOCRC)(≤50yrs);this inimical EOCRC tendency partly gets reasoned out specifically by the robust impact of dietary habits escalated intake of red as well as processed meat andhigh fat high sugardiet .The animal- dependent diet with high fat high sugardiet (alias Western diet) results in switch in dominating Microbiota along with their metabolic action which might aid in the interference of homeostasis of H2S quantities. Bacterial Sulfur metabolism has been acknowledged to be a key mode in the EOCRC pathogenesis. Here we reviewed the pathophysiological mode by where manner by which diet correlated switch in Gut Microbiota alias Microbial Sulfur Diet stimulates damage as well as inflammation of the colonic mucosaalong with aids in generation of CRC .Stress ongreater ingestion of intake of fruits ,yellow vegetables, whole grain ,legumes, cruciferous vegetables were correlated with lesser CRC occurrence which is more to be initiated right from childhood and adolescents would help in decreasing CRC imcidence. Furthermore, we have tried to clarify how H2S action might be via nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain- containing 3 (NLRP3 inflammasome).

Keywords: colorectal cancer (crc); exposomes; western diet; microbial sulfur diet; hydrogen sulfide (h2s)

Introduction

Colorectal Cancer (CRC) is presently the 3rd commonest malignant tumor all over world. Roughly 1.8 million new cases along with approximately 900,000 deaths GET documented worldwide every year, being the 2nd maximum frequent etiology of mortality worldwide[1].The incidence of CRC is directly proportional with the escalation of socioeconmic or the human developmental index(HDI) with time[2]. Earlier studies have pointed that the greater HDI levels are probably correlated with the alterations in prevalence of lifestyle associated with risk factors inclusive of escalated intake of red as well as processed meat in addition to obesity, refined carbohydrates, decreased physical activity, smoking, ingestion of alcohol[3].With the plan to decrease CRC incidence along with mortality numerous countries have decided to conduct routine colonoscopy screening strategies for early pickup as well as avoidance by re-section of precancerous polyps at the time of colonoscopy[4].There has been a total reduction in incidence in numerous countries inclusive of United States of America (USA),Israel, along with Japan, where early estimation strategies have been generated from 1990s[4,5].

Nevertheless, an International evaluation of present tendencies regarding CRC incidence suggested that there has been a significant escalation in case of young adulthood ≤50yrs observed in the past 20yrs[6]. CRC which gets diagnosed in case of subjects≤50yrs old is as known as Early onset Colorectal Cancer (EOCRC). Explaination of drastic enhancement of formation of EOCRC are enigmatic. However a part from traits risk factors aiding in the generation of EOCRC are akin; however are not restricted, to those correlated with the elderly population inclusive of Western diet, in addition to obesity in addition to lifestyle correlated with decreased physical activity[2,6]. In contrast to late onset Colorectal Cancer (LOCRC), the clinical manifestation of EOCRC usually has had greater advancements apart from poor prognosis [7]. Thereby it becomes necessary to have acquisition of insight regarding modes behind and find the risk factors along with inimitable properties of EOCRC regarding early diagnosis along with correct management.

Escalating confirmation has pointed that diet portrays a significant factor correlated with the Gut Microbial actions correlated with escalated EOCRC incidence [8]. The high fat high sugar diet referred to in the form of Western diet, changes the genetic constitution as well as the metabolic actions of the Gut Microbiome, in particular implicated in Sulfur Metabolism[8]. Earlier we had reviewed the role of LncRNA's in CRC besides roles of epigenetics in DKD [9,10]. Here we review the alterations in the epidemiology of CRC associated with worldwide food ingestion. We evaluate the actions of the dietary constituents on inherent alterations in Gut Microbial constitution as well as the metabolic actions . Moreover, here we emphasize the pathophysiology of the way diet correlated switch in Gut Microbiota (GM) stimulates damages as well as inflammation to colonic mucosa in addition to aids in the generation of CRC specifically early in life.

Methods

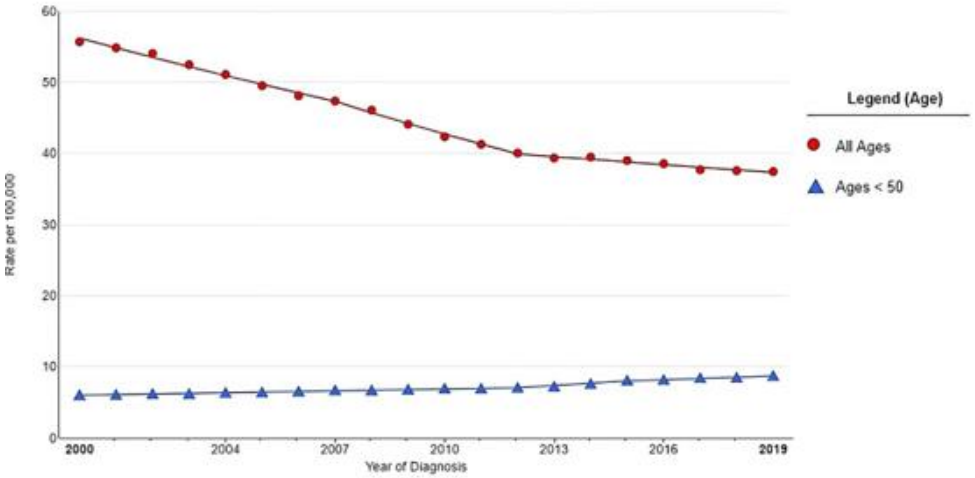
Here we conducted a systematic review utilizing search engine pubmed, google scholar ;web of science ;embase; Cochrane review library utilizing the MeSH terms like Colorectal Cancer; Early onset Colorectal Cancer(EOCRC); late onset Colorectal Cancer(LOCRC), Gut Microbiota(GM) ; Hydrogen Sulfide (H2S); Epigenetics; LncRNA as biomarkers ;as therapeutic targets ;mode of action DNA methylation; Histonealterations ; biomarkers ; epigenetic liquid biopsy; role of tea phenols; curcumin ;nicotine ; phosphatidylinositide 3-kinase(PI3K) /protein kinase B(AKT) ;Wnt. beta catenin signaling pathways from 2000 to 2023 till date.

Results

We found a total of 600 articles out of which we selected 83 articles for this review. No meta-analysis was done.

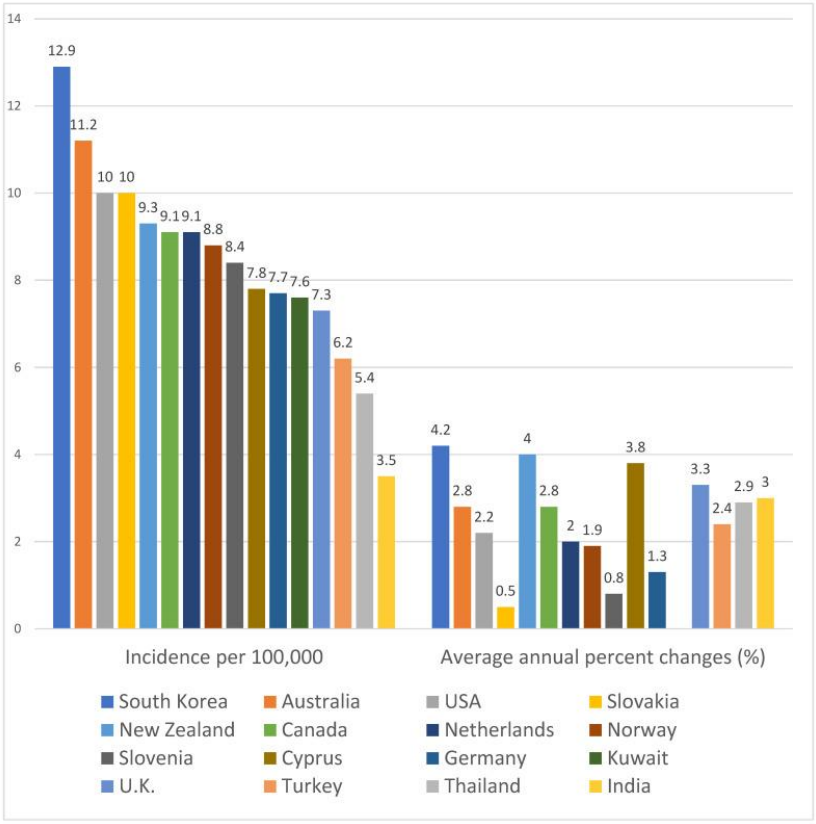
2.The Bothering Trajectory in CRC incidence amongst young adults got

As per the United States Cancer Registries results from 2013-2017,54% of CRC patients get diagnosed in case of subjects >65yrs old along with 34% amongst50-64yrs with a median age at 67yrs[111]. Subsequent to utilization of conducting routine colonoscopy screening strategies in addition to enhancement of recognition of CRC risk factors, the incidence rate have undergone reduction at a fast pace by 3% yearly in US, in case of old subjects[12-14] .In comparison to, that the incidence of CRC in younger adults ≤50yrs illustrated an escalation of 4.3% yearly proportional alteration at the time of 2015-2019(Figure1a)[rev in 12,13].



Legend for Figure 1(a): Courtesy ref no-12(**a**). A recent trend in SEER Age-adjusted colorectal cancer incidence rate from 2000 to 2019. This figure was created by https://seer.cancer.gov/statistics-network/explorer (accessed on 15 February 2023).

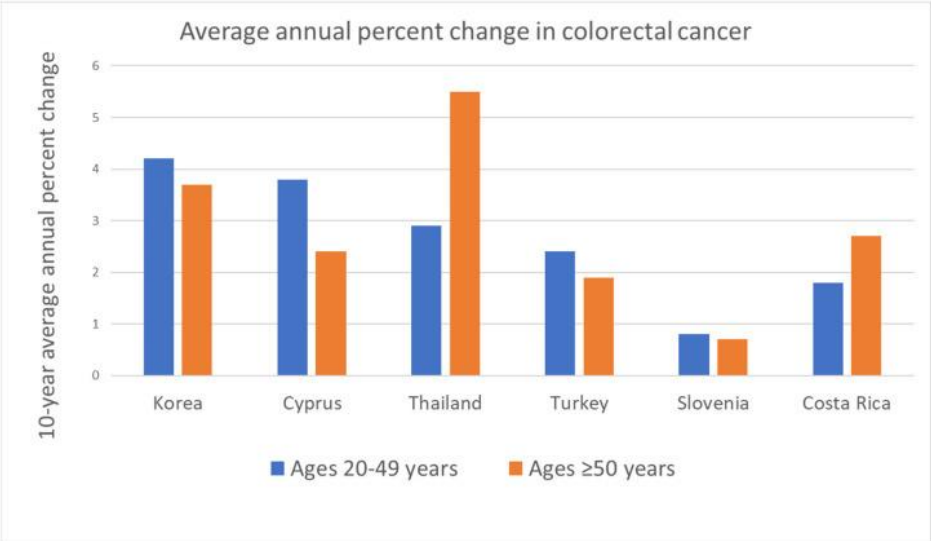
Furthermore, a Global evaluation of CRCv incidence illustrated an escalation of EOCRC in men as well as women in 19 countries across 5 continents [9]. Despite maximum CRC diagnosis continues tobe in the elderly>50yrs CRC mirrors a considerably greater hurdle in younger adults<50 all over world (Figure1b) [1-14].



(**b**)

Legend for Figure 1b: Courtesy ref no-12 (**b**) Increase in early-onset colorectal cancer incidence rate. This graph is created based on the summary of the published articles by Siegel, R.L. et al. [9].

The upward trajectory in incidence of EOCRC was initiated in the 1970's over the continuous cohort born in as well as subsequent to 1960's consecutively [11,15]. Dependent on CRC incidence tendencies in the United States amongst 1975-2010, the yearly proportional alteration- dependent anticipated incidence rates of colon cancer would escalate in 2030 by 27.7% for the age of 35-49 as well as90% for the age of20-34[18]. The incidence rate of rectosigmoid in addition to rectal cancer is anticipated to be further greater- in contrast to colon cancer-46% of the ones amongst35-49 as well as124.2% for the age of20-34[16]. This kind of steep upward trajectory regarding incidence of EOCRC has further been observed in countries which hunderwent or currently are going through fast industrialization for instance Korea, Cyprus, Thailand, Taiwan etc[1-17]. Intriguingly, as illustrated in (Figure2),



Legend for Figure 2: Courtesy ref no-12-The countries demonstrate increasing colorectal cancer incidence rates in both younger and older populations. This graph is created based on the summary of the published articles by Sung, H. et al. [1] and Siegel, R.L. [11].

EOCRC enhancement in these countries takes place concurrently with the escalation of LOCRC at the time of 2008 -2012.This concurrent alteration in the CRC incidence mirrors a fast alteration in lifestyle as well as diet which has impacted elderly in addition to younger population in the last numerous years [11].

Unestimated exposure taking place in early life, or exposure commonly encountered by the younger generations in case of countries possessing considerably greater HDL might enhance the risk of EOCRC along with can be delineated in the form of the birth cohortactions on EOCRC incidence[15]. Furthermore the elevation of CRC can be portrayed for overall ages in countries with rapid switch of generational status pointed that exposure of some risk factors at the time of a time frame in life might have the expression of CRC subsequent to a latent period[15]. The maximum fear is the susceptibility to carcinogens early in life from prenatal to adolescence might influence mutagenic injury at the time of generational period probably leading to a postponed action on EOCRC incidence [18].The cancer trajectory might represent a substantial disease load in the further times if immediate action is not started regarding the younger generations.

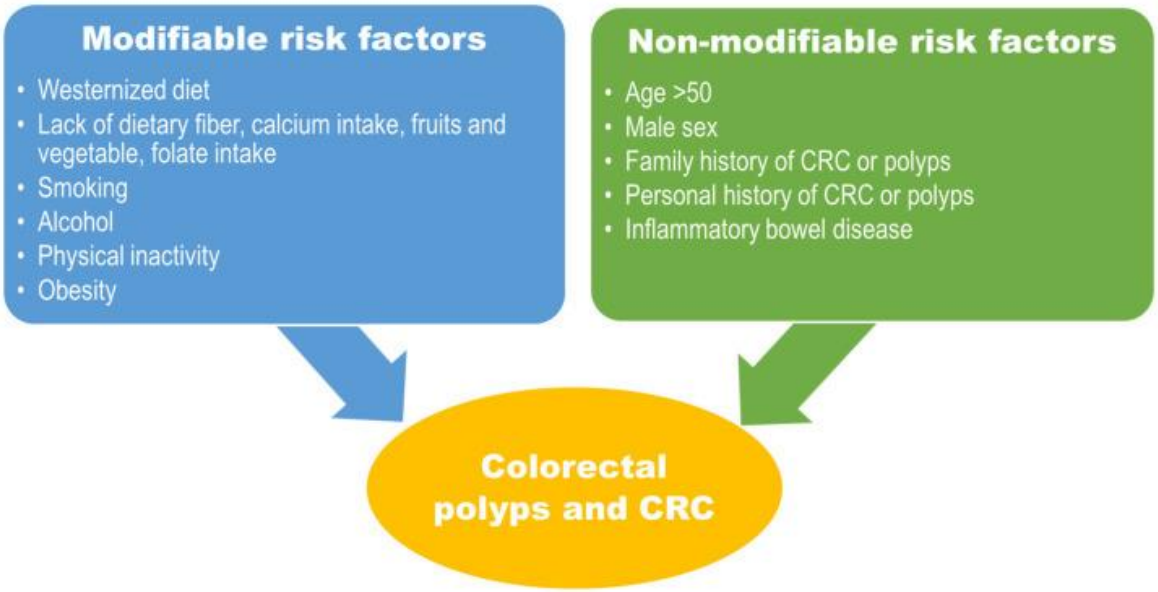
3. Variations in Clinical along with molecular characteristics amongst EOCRC as well as LOCRC

The Clinical characteristics of EOCRC vary amongst older patients regarding in stage, tumor placement along with histology at the time of the diagnosis to start with. In case of young adults diagnosis of CRC is in general done once maximum symptoms like hematochezia/melena are the manifestations[19]. In case of 80.5% patients usually separate symptoms for instance abdominal pain, intestinal obstruction, anaemia as well as alterations in bowel habits took place [20]. Although presentation with symptoms, the degree of suspicion by the primary clinicians is considerably less apart from their reluctance to send young patients for medical consultation that might postpone the diagnosis by a median of6.2mths in young adults under 50yrs in contrast to patients ≥ 50yrs [19,21]. Whereas at the time of diagnosis patients apparently present with advancement of stage, lymph nodes along with distant metastasis as well as possess the greater probability of generation of asynchronous or distant metastasis in time period of disease in contrast to turnover to patients ≥ 50yrs[7, 19-21]. Whereas the anatomical placement of LOCRC is organized across the colon and rectal at equivalent frequencies in case of EOCRC an uneven organization- maximum frequently in rectum, next left sided Colon that is followed by ride sided colon at 42%,31% along with27% , respectively [22]. Moreover, in contrast to LOCRC, the histopathological properties of EOCRC possess the greater probability of manifestation with exacerbated properties, high grade, poor differentiation of tumors possessing signet ring or mucin generating that are usually associated with perineural or lymphovascular invasion of the CRC cells [7,23].

The molecular characteristics of EOCRC are substantially heterogenous composed of hereditary CRC syndromes originating from different germline mutations in addition to non hereditary or sporadic mutations without robust familial clubbing [15,23]. Hereditary CRC gets constituted about 5-16% of EOCRC patients, influencing subjects early in life, basically at age of 20-30 ys[24].The pathogenesis of hereditary EOCRC is correlated with germline genetics mutations resulting in genetics instability, cells proliferation or decontrolled microenvironment[25]. Contrary to hereditary EOCRC molecular properties of sporadic EOCRC are baffling in addition to might illustrate distinct characteristics differentiable from those of hereditary EOCRC[26,27]. Despite hereditary EOCRC takes place at a greater rate in a younger population in contrast to older population sporadic EOCRC is responsible for 80% EOCRC patients being the maximum frequent kind[17]. In contrast to the LOCRC patients, the cancerous properties of sporadic EOCRC most commonly possess microsatellite stability in addition to absence of DNA healing mode aberrations that are variable in gene expression as well as molecular pathogenesis[24,26,].Significant variation of EOCRC which are microsatellite stable(MSS) EOCRC with regards to gene expression along with molecular pathogenesis from LOCRC[26]. MSS EOCRC in stable displays over expression of catenin- β(CTNNB1) gene in addition to correlation with upregulation of Wnt/β-catenin, mitogen activated protein kinase (MAPK), growth factors signaling as well as Tumor necrosis factor receptor 1 (TNFR1) pathways; in all probability impacting metastasis along with chemoradiosensitivity [42]. Other molecular abnormalities, inimitable to EOCRC inclusive of epigenetic change, maximum frequently line interspersed element (LINE-1) hypomethylation, correlated with escalated chromosomal instability[29]. Variations in molecular changed profiles a represent in EOCRC which are being actively assessed. However, in line of evidence that maximum frequent kinds of EOCRC subjects are the with the sporadic once, the repercussion of genetics mutations with regards to pathogenesis can't be explained. crosstalk amongst environmental factors in addition to genetic susceptibility would be necessary regarding tumor expression.

4. Lifestyle associated along with environmental risk factors correlated with EOCRC

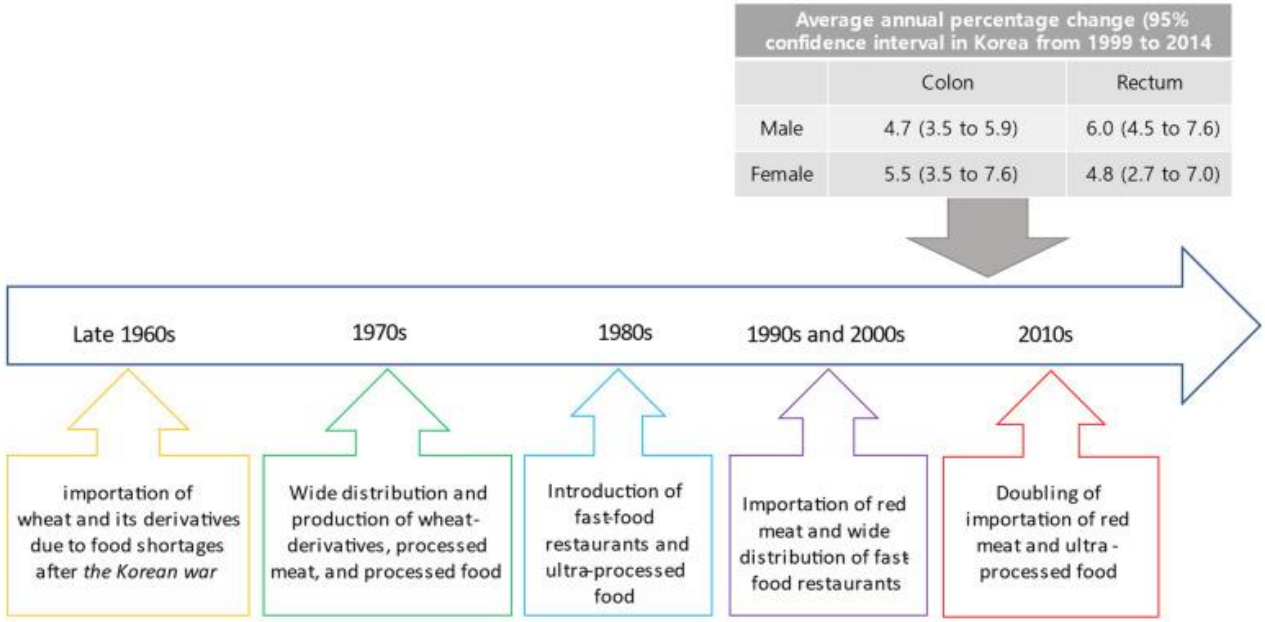
The properties of risk factors regarding CRC have been thoroughly investigated dependent on numerous population dependent cohort as well as case control studies, basically divided into modifiable as well as nonmodifiable as illustrated in Figure3.



Legend for Figure 3: Courtesy ref no-12-Risk factors can be categorized as modifiable and nonmodifiable.

Despite the maximum risk factors have been revealed from older populations, results regarding younger populations, suggest that,like in older populations risk factors correlated with western'' diet along with lifestyle associated with decreased physicalactivity, works in the form of considerably significant escalation of CRCgeneration[30]. Western diet, possessing greater high fat high sugardiet inclusive of escalated intake of red as well as processed meat ingestion in addition tosedentary lifestyle are pointers to human generation generation in addition to fast industrialization that are closely intertwined with Obesity apart from Obesity correlated chr diseases or malignancy[2,,31]. This tendency is well with displayed by CRC in Asia for instance Chinese,Singapore, Taiwan, Japan with 2-4 times enhancement etc[1,32]. Moreover, noticeable discripancies in incidence as well as geography of EOCRC in addition to ethnicity in the United States (US)[33]. greater incidence are found in areas for instance southern states like Mississipi Delta along withAppalachia[15] . In the contextof racial discrepancy, noticeable escalation of EOCRC incidence is observed in Hispanic/Latino men as well as Whites,though CRC incidence has Earlierbeen greater in African Americanmen[33]. These discripancies partially implicate poverty,no employment,inaccessiblity of health care facility in the younger population [33]. However easy acquisition of poor quality diets might be me implicated in the escalating incidence of EOCRC.

Subsequent to substantial socioecomic growth ,a rapid dietary transition to elevated ingestion of remarkably ,refined wheat as well as its products, processed or red meat as well as ultraprocessed food ingestion was initiated in SouthKorea as reported in Figure4[34].



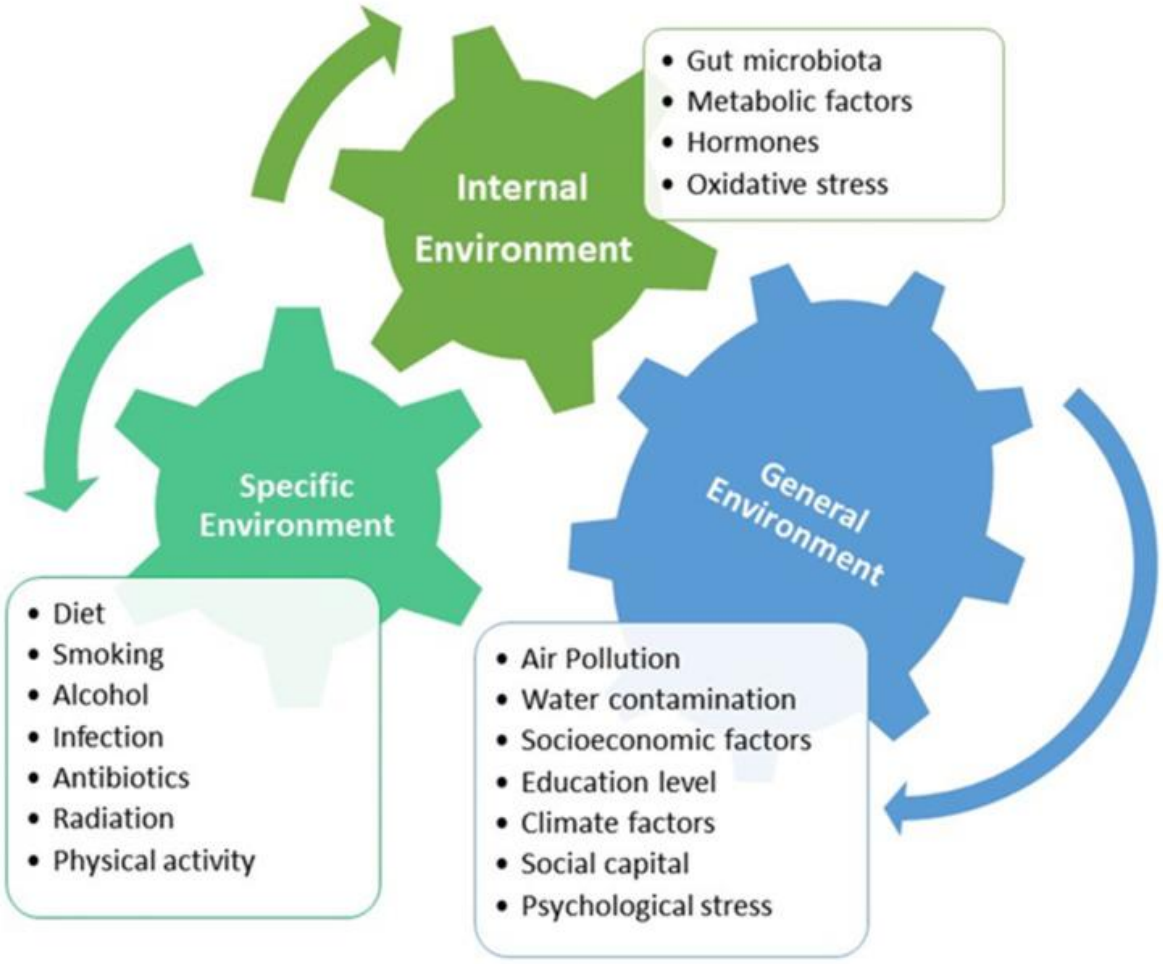
Legend for Figure 4: Courtesy ref no-12-Dietary transition and the incidence of early-onset colorectal cancer.

There by, it is not astonishing that the prevalence escalated from 6.8-10% in Korean childhood in addition to adolescents aged 6-18yrs from 1998-2013[51]. Simultaneously Type2 Diabetes mellitus(T2 DM) amongst children≤18yrs escalated by153.5%/100,000 in 2006-

205.0/100,000,a germane escalation of 33.6%[35]. Moreover, assessment of physical activity , screen time ,sleep period, a crossectional study, with the utilization of national outcomes pointed that just 1.6% of adolescents were as per meeting advocated Canadian 24hour movement guidelines for children and youth,that implicates a minimum of 60' of moderate- robust physical activity,no greater than2 hrs of screen time,8 &11hrs of sleep period in timespan of24 hrs of a canonical day[36].What was greater inimical,a separate study that analyzed the 6year prevalence trajectory which struck to the advocated Canadian Guidelines demonstrated that<1% of adolescents were meeting all these 3advocates consistently[37]. There is clarification with regards to early life exposure to acknowledged risk factors, intake of processed food or inadequate physical activity have taken over in children as well as adolescents from Korea. With the information regarding a long latent period is required for transformation of normal colonic mucosa into cancer is essential, considerable physiological as well as metabolic abnormalities intiated early in life partially reasons out the escalation of incidence of EOCRC[38].

5. Diet in the form of ''exposome'' correlated with EOCRC

With the propagation of genetic research along with molecular epidemiology illustrated that environmental life period exposure to risk factors possessed an elemental part in disease expression[39].In 2005 Wild posited ''exposome''; implying a person's environmental exposure right from the perinatal prenatal period further in view ofit matching the person's genome[40]. Exposome is comprised of 3 overlapping domain;i) the general external environment ii) the particular environment iii) the internal environment as depicted in Figure5 [26,41].



Legend for Figure 5: Courtesy ref no-12-Three components of exposomes for colorectal cancer.

Placement of a specific exposure in a single domain or another is tough in addition to determination of what degree of exposure possess the capacity of resulting in disease in a person taking into account the lifespan as well as variable generation periods[38]. Nevertheless, epidemiologic studies have tried to uravel the risk factors at the populationlevel along with the molecular pathological epidemiology of epigenetics displayed some abnormal epigenetic signatures in isolating disease properties, specifically of malignant neoplasms[39]. Epigenetic changes for instance , LINE-1 hypo methylation or CpG islands methylator phenotype are usually correlated with EOCRC[39]. Despite particular exposomal outcomes associated with EOCRC are restricted ,an enrichment of epidemiologic outcomes in addition to molecular research on CRC suggested that dietary habits , antibiotics utilization, exposure to chemicals, smoking, ingestion of alcohol in the form of exposome possess complicated crosstalk with endogenous Gut Microbiota(GM) as well as host factors, which stimulates inflammation ,cell proliferation as well as genetic mutation [27].

Dietary constituents substantially impact the GM constitution apart from which might transfer dominant bacterial colonies amongst the Gut Microbiome, impacting host metabolism in addition to immunity[42]. Earlier in vitro along with murine studies illustrated that a diet having enrichment of animal protein escalates Bacteroides species(spp), Alistipes spp ,Bilophila spp that portray microorganisms possessing bile tolerance , whereas resulting in reduction of bacterial spp which

metabolize dietary plant polysaccharides for instance *Lactobacillus, Roseburia, Eubacterialis rectales* along with *Bacillus bifidus[[*43]. Furthermore a diet having enrichment of fat apparently escalated *Firmicutes* in addition to *Mollicutes* ; however diminished *Bacteroides***;** escalated metabolites like lipopolysaccharide(LPS), trimethylamine-N-oxide (TMAO),but diminishing favourable short chain fatty acids (SCFA)[44].Such metabolites usually are the metabolic by products of the microorganisms from the Western diet,with high fat, high sugar diet are correlated with chronic low grade Inflammation, as well as metabolic aberrations leading to obesity, insulin resistance along with Diabetes mellitus [43,44].

Akin observations have been demonstrated in human studies.A study that utilized biopsy samples from colonic mucosa as well as faecal samples from African Americans possessing 2wks food exchange from a Western diet with greater fibre diet pointed to a considerable escalation of saccharolytic fermentation along with butyrogenesis whereas repressing secondary Bile Acids(BA's) generation that has an association with conferring protection to the colonic mucosa in addition to diminished CRC risk[45]. David etal. [8], performed a study regarding diet intervention with utilization of human faecal samples revealed that bacterial colonization might be rapidly switched based upon kind of diet; animal dependent or plant dependent along with changed GM might evoke a transcriptional reactions of gene enrichment of dominant bacterial Microbiome[8]. in view of wide accessibility of ultra processed food ,the inimical actions from Microbiota which are dominating along with dhave formed adaptation based upon Western diet might be influencing at the time of generational duration.This dietary exposomal actions might reason out the sporadic EOCRC enhancement,where in terms of long time of carcinogenesis pointed to numerous yrs of exposure in relative terms to bad dietary constituents impacting a pathogenic switch Microbiome of inimical metabolism[46].

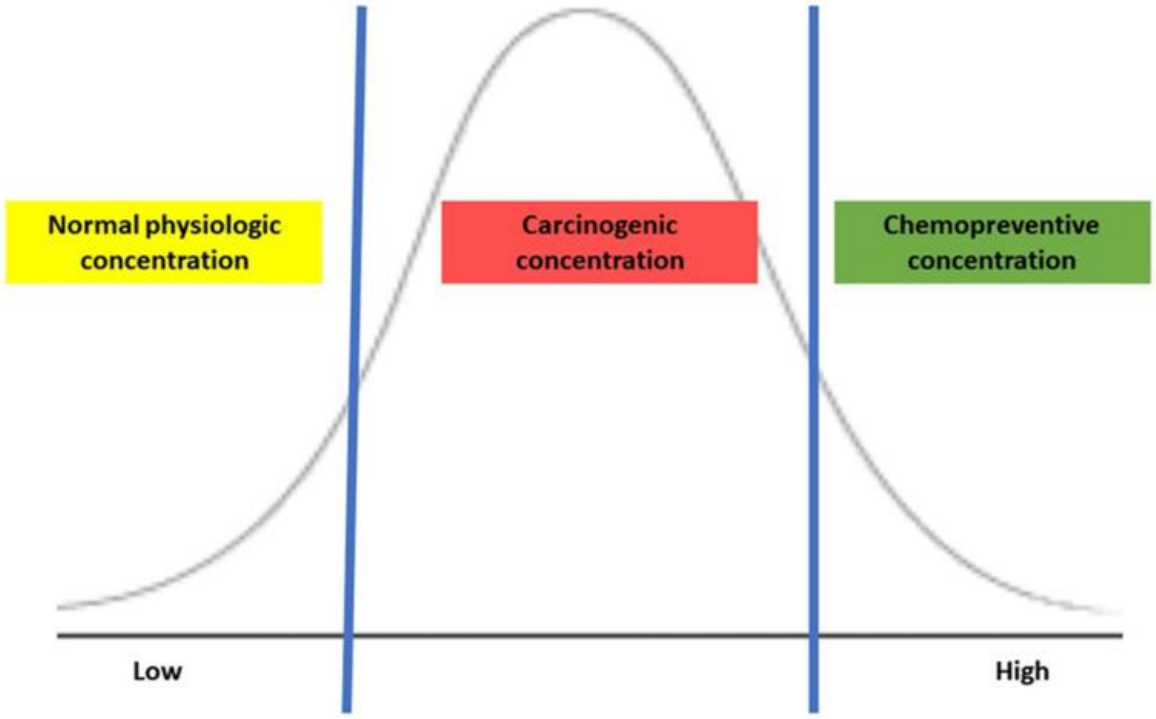
Intestinal dysbiosis might leads to start of chronic low grade Inflammatory situations of the colonic mucosa, generate carcinogenic metabolites or might result in DNA injury as well[42,47]. Earlier studies with utilization of Metagenomic results regarding the Microbiome correlated with a colorectal polyp or CRC illustrated that some strains of bacteria were seen more commonly in patients with precursor adenoma or c ancer like enterotoxigenic Bacteroides fragilis-Fusobacterium nucleatum- as well as polyketide synthase gene complex (pks)+bacteria along with *Escherichia Coli* (E.Coli) [48]. These bacteria might result in direct e DNA injury, modulate cadherin/ β-catenin , facilitate a tumor permissing microenvironment by enrollment of myeloid obtained suppressor cells along with anti tumor immunity of NK/T cells[49]. These bacterial modes behind are usually correlated with sporadic CRC originating from the adenoma- carcinoma sequence [50].

6.Sulfur metabolism of the Gut Microbiota along withits correlation with CRC generation

Hydrogen Sulfide((H2S)has been braoadly believed to be a key signaling molecule in human, that has been isolated in the form of a gastrotransmitter posessing various chemical characteristics,modes behind reactions along with the capacity of changing protein apart from taking part in numerous metal redox events[51]. Endogenously H2S gets basically generated by GM by metabolizing inorganic Sulfur (sulfate along with sulfite) from preservatives present in processed food on as well as organic substances ; basically cysteine along with taurine present in red meat[52]. Sulfate reducing Bacteria for instance *Bilophila*, *Desulfovibrio*, *Desulfo*microbium , *Fusobacterium* possess the capacity of colonization of the Gut in the human Gastrointestinal Tract(GIT), in addition to produce endogenous H2S by metabolizing inorganic or organic Sulfur substances[47,53]. Different microbial enzyme inclusive of cystathione-β- synthase(CBS), cystathione-γ-Layse(CSE), as well as 3-mercapto pyruvate Sulfur transferase(3-MST) are implicated in the generation of endogenous H2S by catabolization of cysteine along with homocysteine[53].

In view of H2S gets generated by microbal metabolic reactions,with ease H2S crosses the biofilms by which colonocytes in addition to epithelial membrane are covered possessing greater permeability[54].On gaining entry into the colonocytes, catabolism of H2S takes place via intracellular Oxidative metabolism in mitochondria as well as cytoplasm[55]. Constitution of various mitochondrial enzyme in the colonocytes inclusive of Sulfide quinone Oxidoreductase(SQR)ethyl malonic encephalopathy protein 1[ETHE1],thiosulfate as well as thiotransferase, the Sulfide oxidation unit is involved in H2S oxidation to form persulfides; substantially reactive molecules whose protein binding takes place[56].This physiological post-translational modifications of protein(S- Sulfuration) is acknowledged to along with influence events like cell survival as well as demise, cell proliferation, cell differentiation in addition to hypertrophy, cellular metabolism, mitochondrial bioenergetics as well as biogenesis,vasorelaxation, inflammation as well as Oxidative stress(OS) [57].It is acknowledged regarding role of S- Sulfuration in controlling DNA injury healing system by activation of the RAS/RAF/MEK/ERK stepwise signaling via Sulfhydration of MEK 1, thereby impacting tumor growth[58]. Furthermore ,persulfidation of the nuclear factor κB(NFκB) triggers metastasis facilitating gene expression apart from activating NFκB/IL-1β that might leads to propagation of cancer as well as metastasis through activation of the vascular endothelial growth factors(VEGF) [59].

The biological actions of H2S are based upon its quantities in the lumen of the colon; these quantities in the lumen get decided by the endogenous generation via bacterial metabolism that impacts H2S modulated tumor development. Various in vitro studies where CRC cell lines on treatment with exogenous H2S displayed a bell shaped quantity reaction in cancer which depicts the double actions of H2S[51]. CRC cells exposure to slowly liberated H2S donors at lesser quantities(0,2-0.3μmol) ; mitochondrial working in addition to glycolysis formation led to escalated cancer cells proliferation by activation of enzymes that form H2S amongst cancer cells; however canonically were not existent in colonic epithelial cells[60]. Furthermore, the expression of H2S generating enzymes were greater in CRC tissue in contrast to normal surrounding tissue probably resulting in sustenance of ideal quantities regarding tumor growth as well as proliferation[85]. On the other hand, CRC cells treatment with greater quantities(1mmol)of an H2Sdonor as isothiocyanates; which mirrors a cruciferous plant product- resulted in apoptosis of CRC cells[61].The way illustrated in Figure6, exogenous H2S illustrates a quantity based actions; sustenance of normal physiology at lower, carcinogenic on reaching the upper



Legend for Figure 6: Courtesy ref no-12-The action of H_2S is based on its concentration. threshold,then probably chemopreventive at greater quantities .Thus sustenance of proper quantities of H2S might be key regarding cell cycle balance in addition to controlling apoptosis as well as tumor development.

H2S along with Sulfidogenic bacteria upregulation possess positive correlation with a diet possessing high fat high protein [47,62]. Greater quantities of Sulfidogenic bacteria in stool is correlated with the risk of distalCRC[63]. Furthermore contrasting the flatus samples from patients with CRC with healthy substances ,quantities of Sulfur substances were significantly greater in the patients with CRC [63].An in vitro study where utilization of colon cancer obtained epithelial cells lines illustrated in selective upregulation of the of H2S generating enzyme that quantities of H2S in contrast to nonmalignant colonic mucosa cells[57].Mice possessing elimination of H2S generating enzyme working ;there was reduction of blood flow hampering tumor growth along with angiogenesis[57].The quantity of CBS in human samples is lesser in healthy colonic mucosa ; however slowly escalates overtime once epithelial cells get converted into polyps, hyperplastic polyps, tubular adenoma- carcinoma[65]. The protein CBS quantities in human colon cancer are intricately associated with disease robustness in addition to tumor staging as well as tumors with greater advancements express greater CBS protein quantities with greater expression of VEGF[66]. Moreover,it has been illustrated that expression of H2S detoxifying enzymes for instance TST with placement in colonocytes lumen is substantially diminished in advancements of colon cancer [67].A meta-analysis flowchart by isolation of differentially expressed genes within normal colonic mucosa, primary tumor sites in addition to metastatic samples in the liver as well as lung illustrated that the mitochondrial oxidation enzymes inclusive of SQR ,ETHE1 along with TST reduced at the time of evolution events from the normal epithelium to the primary tumor in addition to metastatic areas[68].These observations indicated that decontrolled expression along with activity of detoxifying or generating enzymes might aid in the interference of homeostasis of Sulfur possessing substances. Sequentially , escalated H2S quantities might possess a part as a tumor growth factor,triggering tumor growth as well as proliferation apart from facilitating angiogenesis along with vasorelaxation.

Intriguingly, H2S might possess double actions; inimical or of advantages, based on its source along with quantities.In an earlier in vitro study where asssessment of the modes behind the H2S actions resulting in carcinogenesis, Sulfide at quantities equivalent to the ones in normal colonic mucosa(~ mmol) stimulate direct genomic DNA injury in mammalian cells. Moreover, H2S might result in mucosal injury by stimulating degradation of di Sulfide bonds in the mucus layer. Sequentially , luminal bacteria in addition to their metabolites possess the capacity of penetration of the epithelial lining, trigger apoptosis of epithelial cells in addition to stimulating the inflammatory chain of steps[52,70].This proof is in agreement with the observation that Western diet enhances CRC; Specifically in the distal intestine where Sulfur metabolizing bacteria are observed in greater quantities in contrast to proximal colon[90]. Interestingly, certain studies have illustrated that H2S might be conferring protection as well as repairing action on the colonic epithelium . Endogenous H2S in minimal quantities(mmol) might work in the form of a vasorelaxant, decrease endoplasmic reticulum (ER) stress along with result in avoidance of apoptosis[71]. Furthermore, exogenous H2Sis present in garlic ,onions as well as cruciferous vegetables for instance cabbage, cauliflower, kali as well as broccoli that are acknowledged to be advantageous for colonocytes besides enterocytes, which work in the form of a source of energy with regards to microbiial metabolism. Inorganic plant obtained H2S aids in colonocytes respiration as well as stimulation mitochondria for detoxification; thereby recover from epithelial damage [51]. Thereby the oral ingestion of exogenous H2S results in stabilization of GM biofilm intactness as well as avoidance of the pathogenic switch in colonies finally hampering inflammation as well as tumor development[72]. Nevertheless, the particular mode of H2S effects correlated with the crosstalk amongst dietary sources in addition to GM is required for future assessment.The distinct biological characteristics of H2S yield newer avenues for the treatment of CRC, targeting modulation of H2S through administration of H2S exogenously in escalated dosage or hampering endogenous H2S expression[51]. Generation of exogenous H2S substances has already

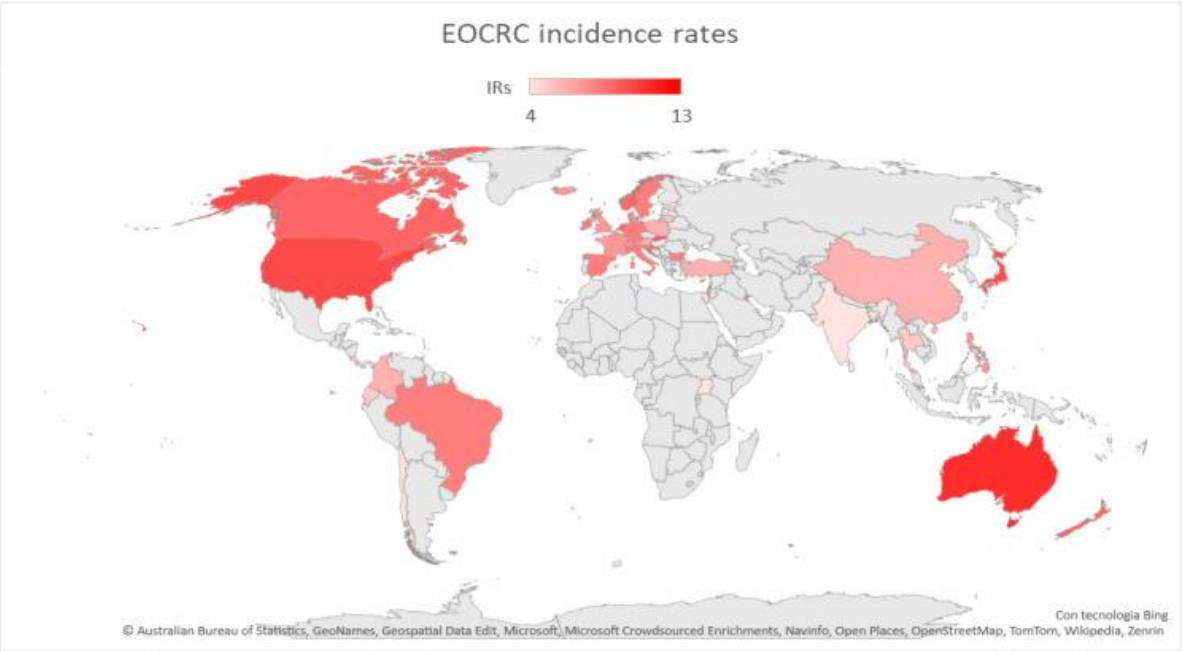
been initiated which possess the capacity of getting liberated in a site particular along with time based – fashion. Different biocompatible polymeric in the form of H2S donors, illustrated their capacity of targeting in particular the tumorous lesions,react to the pathological milieu in addition to monitoring the alteration in the microenvironment subsequent to administration[73]. H2S liberating nonsteroidal anti inflammatory drugs(H2S -NSAIDS) have been formed ; along with posited to work in the form of anti cancer agents [74]. Subsequent to anchoring H2S to NSAIDS, Chattopadhya etal.[74], evaluated the growth characteristics of separate human cell lines from 6 separate tissues.Their observation was that H2S -NSAIDS hampered the growth of all the cell lines evaluated, with robustness of 28 to>3000 times more in contrast to canonical NSAIDS[74]. HS -NSAIDS hampered cells proliferation, stimulated apoptosis along with resulted in G (0) / G (1) cell cycle block[74]. Furthermore, hampering of endogenous H2S formation basically concentrated on targeting enzymes correlated with endogenous H2S formation[75]. Different small molecule hampering models have got fashioned as well as generated for hampering CBS, CSE, along with 3-MST , basically stimulating antiproliferative activity[51]. Aminooxyaceticacid(AOAA) is a well acknowledged CBS hampering agent which reacts with Vitamin B 6 converting Vitamin B 6 into a biologically inert kind [75].Since CBS needs a biologically active co- factor obtained from Vitamin B 6,pyridoxal-5' phosphate(PLP) CBS hampering takes place in case of AOAA'spresence. For instance assessment of hydroxocobalamin(Vitamin B(12a)) has been performed in the form of a plausible forager for H2S overdose[76].At all quantities hydroxocobalamin avoided death of mice treated with Sodium Hydrogen Sulfide. 104]. Despite hampering agents or foragers decrease H2S quantities efficiently ,they might display inimical sequelae at the time of practical utilization in view of omnipotence of enzymes apart from systemic influence obviously resulting in body injury .For the generation of any therapeutic agent it is a must toinvestigate the issue covering all aspects for obviating probable inimical sequelae. Future translational studies regarding getting potential therapeutics which can be practically used clinically that is viable.

7. Present Status Regarding Asssessment of the Sulfur Microbial Diet along with its Correlation with CRC

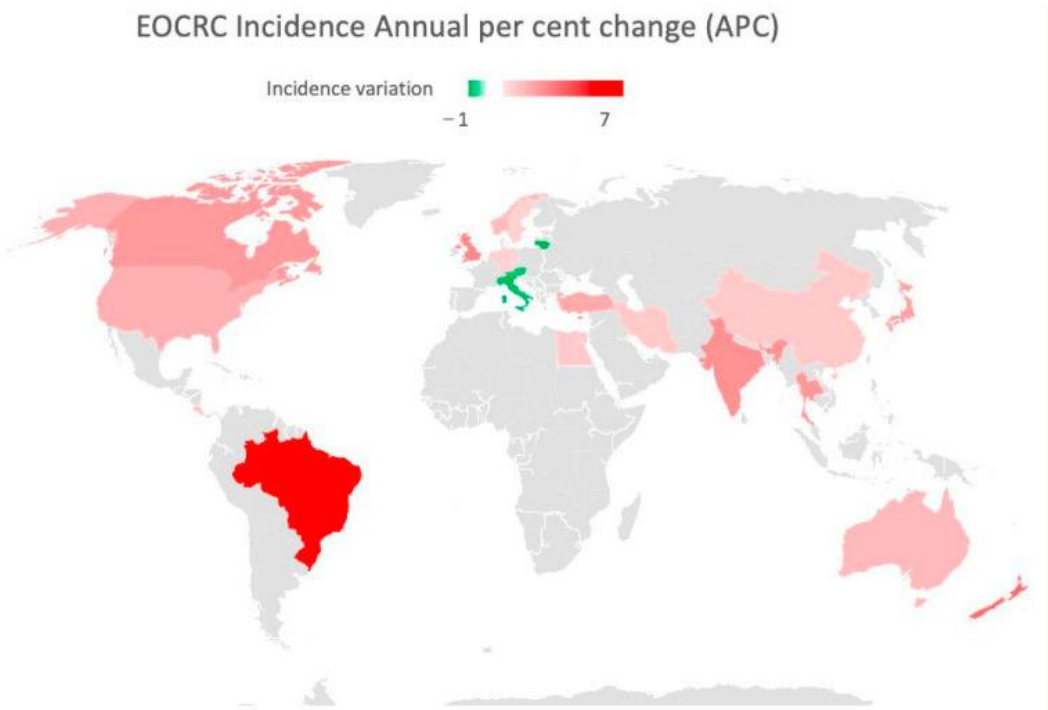
Scarce clinical studies have conducted asssessment of any dietary design correlated with Microbial Sulfur metabolism regarding CRC generation. Nguyen etal.[105], have formed a Sulfur Microbial diet scoring systems dependent on dietary constituents correlated with bacterial spp implicated in Sulfur metabolism. Evaluating the stool Metagenomic as well as Metatranscriptome from CRC patients in correlation with Sulfur Microbial diet score ;they isolated greater ingestion of low -calorie beverages,French fries, red meat, processed meat as well as lesser intake of fruits ,yellow vegetables, whole grain ,legumes, cruciferous vegetables were correlated with CRC [63,77]. Thereby implying that the Sulfur Microbial diet once long term sticking on them was correlated with greater quantities of Sulfur metabolizing bacteria in the faeces of CRC patients in contrast to healthy subjects [90]. Moreover strictly adhering to this Sulfur Microbial diet was correlated with an escalated risk of CRC in particular in the distal part[77]. Akin to that a large prospective cohort study of women with full history of adulthood, as well as adolescents diet was correlated with an escalated risk of generating adenoma possessing malignant probability prior to 50yrs[78]. Nguyen etal.[78], indicated that the escalated risk might get initiated as early as adolescence[78].

However, the earlier studies were dependent on the posit with the presumption regarding greater quantities of Sulfur metabolizing bacteria might be correlated with injury to colonic mucosa that producing to correlated with. the generationof CRC along with CRC precursors like adenoma. In view of the complicated nature of the Gut Microbial metabolism along with it has an intermixing with various exposomal factor ; future Clinical studies need replication in separate areas as well as culture communities with regards to food habits. Moreover a correct strategy for estimating if endogenous H2S quantities generate by GM results in carcinogenesis by direct determination of H2S quantities in the gut. Nevertheless, a direct determination of H2S quantities is inaccessible in addition to possesses technical hurdles [51]. Thereby it becomes necessary with regards to attempting formation of such a diagnotic methodology regarding detection of association of dietary habits with bacterial metabolism .

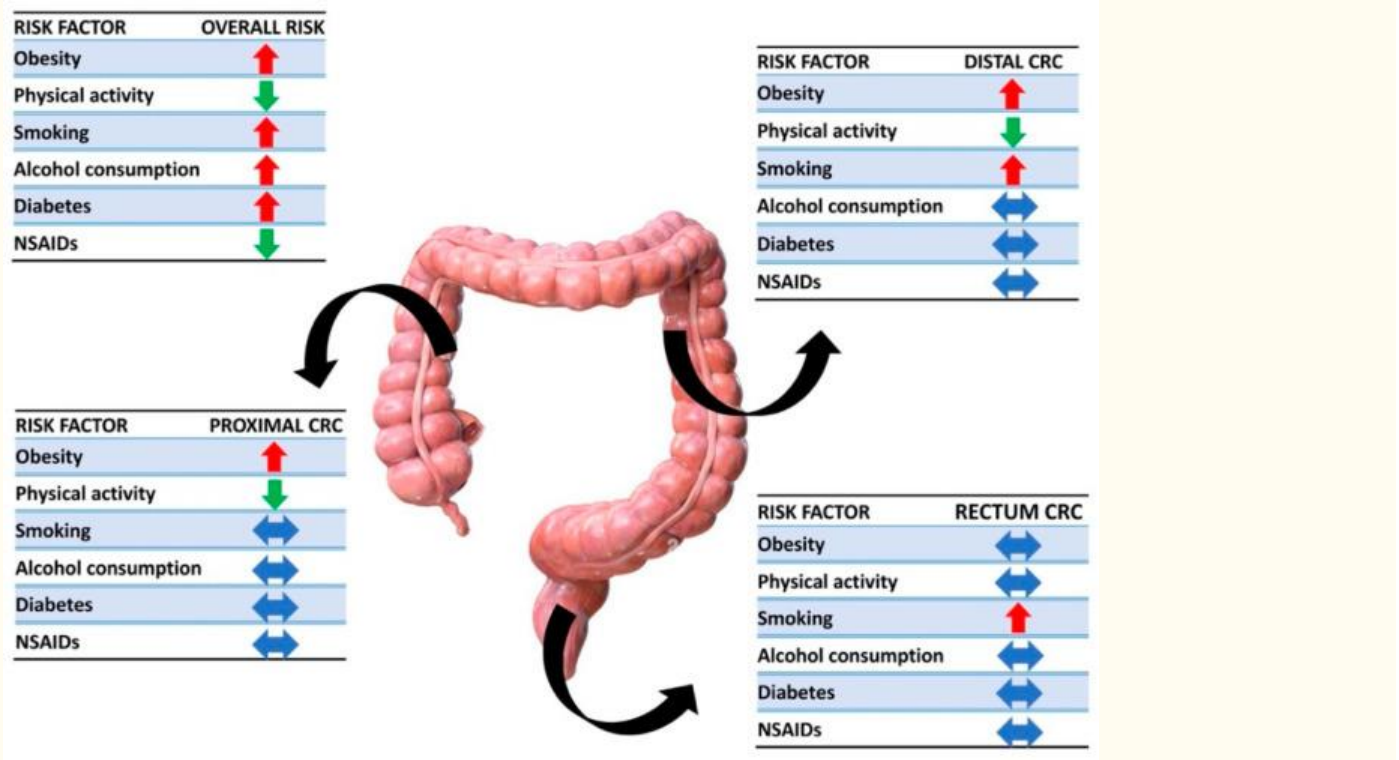
8. Furthermore, Medici etal.[79],very recently have revalidated the escalating incidence of EOCRC with reemphasizing the earlier origination of CRC where they have contrasted with regards to epidemiology; countries where EORCC is still high while reduced in others like (see Fig 7-10]. EOCRC incident rates (IRs) keep varying from 3.5 per 100,000 in residents from India to 12.9 in the Republic of Korea [rev in 75]. In the last10yrs , an IR enhancement revealed was in 19 out of 36 countries, amongst which 9 (e.g., Australia, Germany, along with the US) illustrated reduced orhad stable or diminishing tendencies in older adults. Only three countries (Austria, Italy, and Lithuania) revealed a reduction in EOCRC IRs [rev in 75]. An akin organization was shown in a further recent study [rev in 75], which further illustrated how the escalation is basically correlated with rectal cancer, other than in the United Kingdom as well as Brazil. The maximum incidence of EOCRC was observed in females in Switzerland (4.2/100,000) as well as in males in the Republic of Korea (4.6/100,000), with no variation in tendency trend differences in rectal as well as colon cancer [rev in 75].



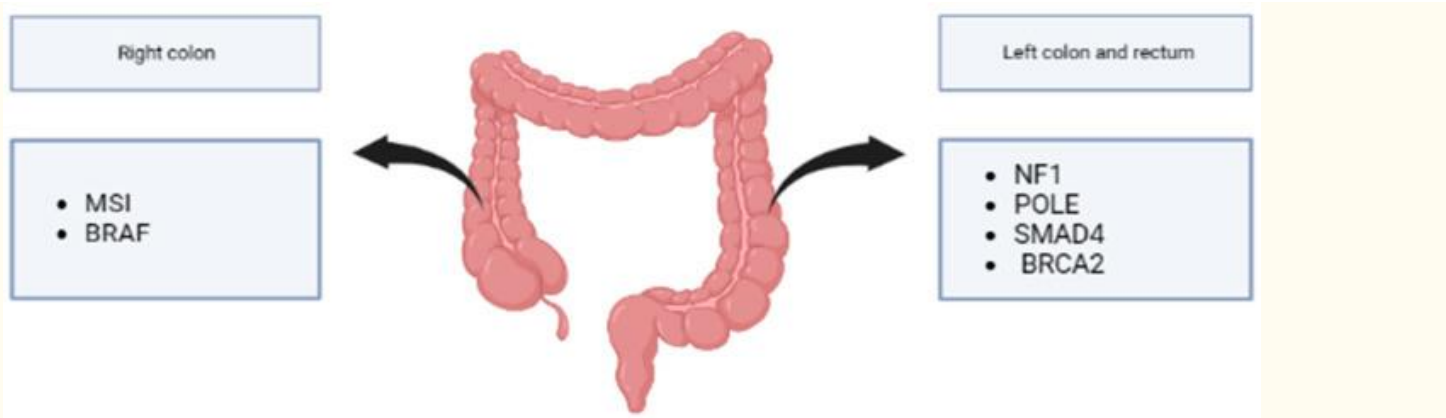
Legend for Figure 7: Courtesy ref no-79-Map showing EOCRC incidence rates worldwide. Red countries are those in which an increased incidence rate of EOCRC has been documented .



Legend for Figure 8: Courtesy ref no-79-Map showing EOCRC incidence annual per cent change (APC) in the last 30 years. Red countries are those in which an increased APC has been documented. Green countries have experienced a decrease in APC .



Legend for Figure 9: Courtesy ref no-79-Associations between risk factors and anatomical sites. Red arrows are placed next to risk factors that have been shown to have a role in cancer promotion, green arrows identify protective elements, and blue arrows represent no correlations.



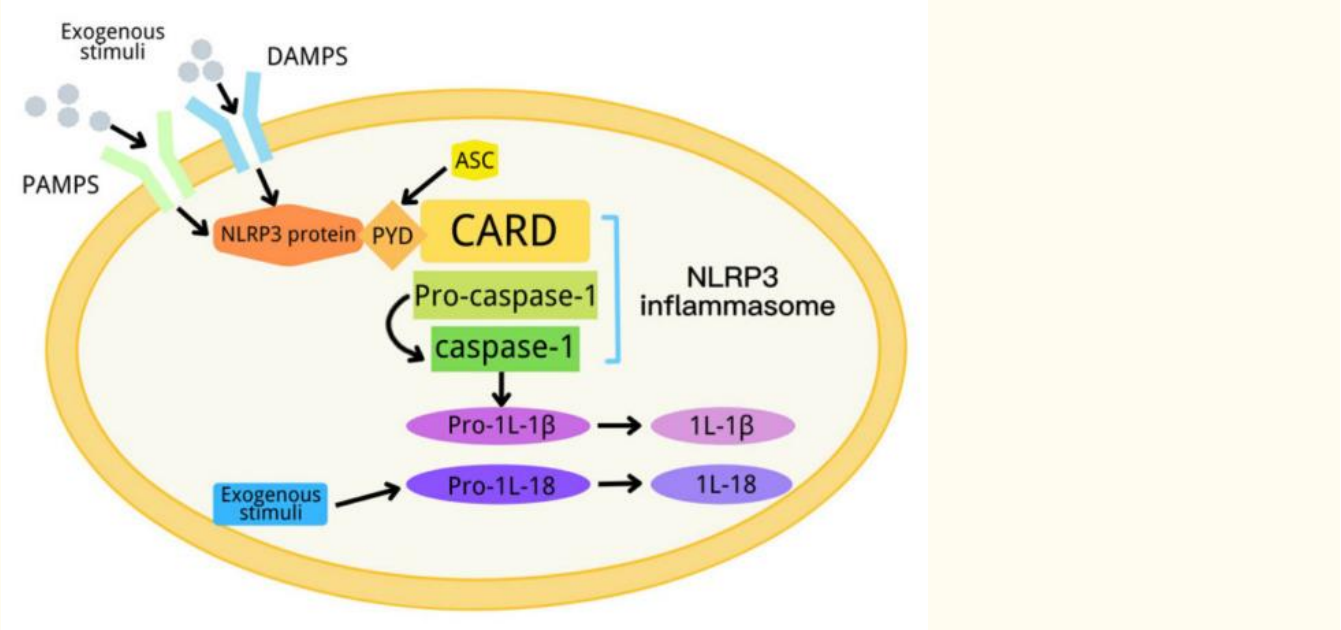
Legend for Figure10: Courtesy ref no-79-Mutation predominance in EOCRC in right vs. left colon. Right colon tumors have a higher rate of BRAF and MSI mutations than left colon, and left-sided and rectal showed higher mutation rates of NF1, POLE, SMAD4, and BRCA2.

Moreover, they have detailed besides part of H2S quantities on other etiologic factors are significant. However it is of utmost significance to pay heed to the importance of earlier CRC possesses greater malignant potential of young generation of CRC. They also described how left colonic tumor were correlated with greater mutation rates of NF1, POLE SMAD4 BRCA2, whereas right sided along with rectum displayed BRAF MS1 mutations[79]..

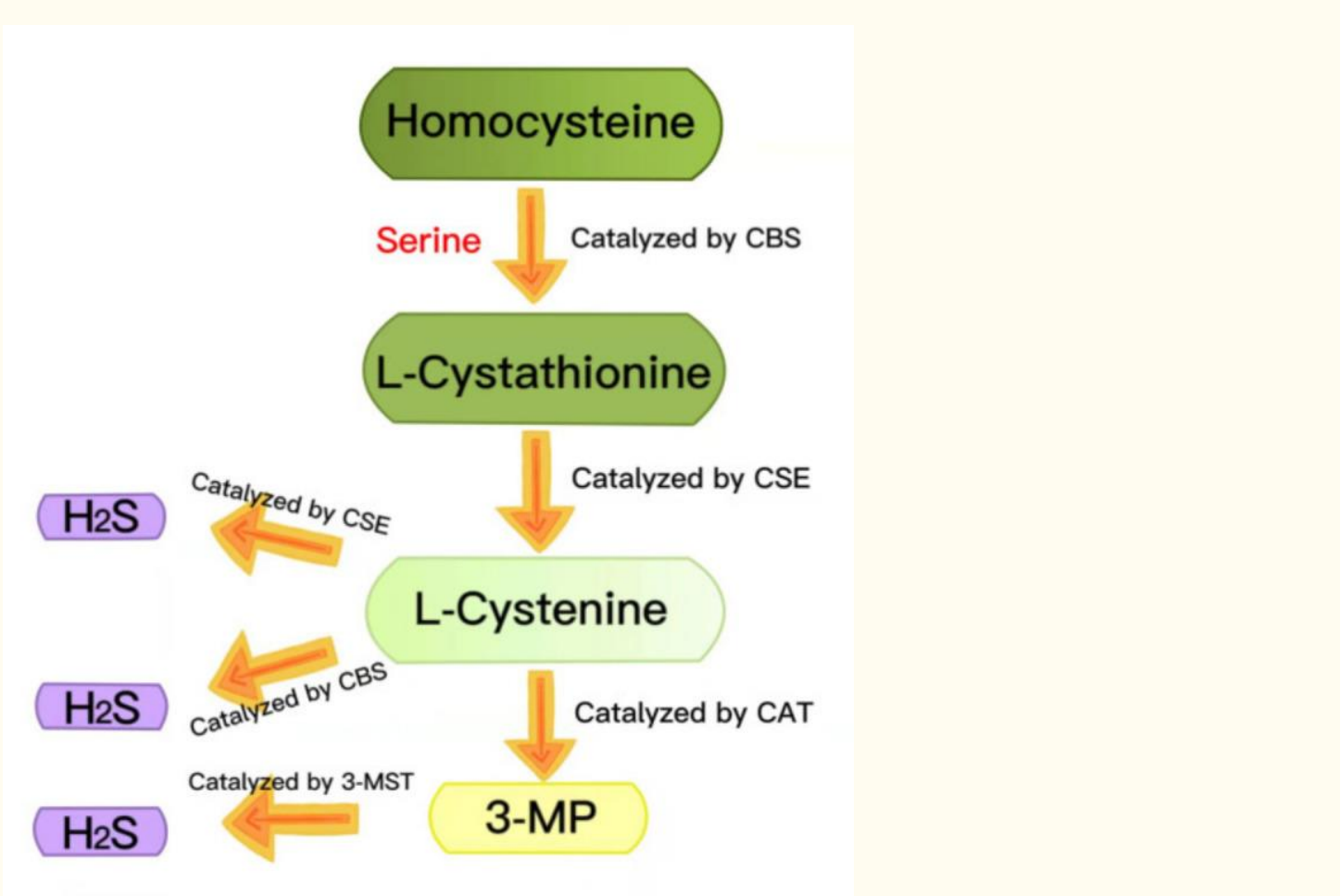
9.Conclusions

The fact of the escalating incidence of EOCRC world over is depressing. Urgent need of tackling this issue is the need of the hour. One has to give significance to ensuring that we escalate public knowledge with regards to inimical influencing of ultraprocessed food or Western diet Specifically in children as well as adolescents. Nevertheless, the part of diet acting in the form of an exosomal factor is just a posit. The modes behind the way dietary constituents have a positive or negative crosstalk with Gut Microbiota portrays a crucial factors in getting insight with regards to tumor generation taking place early in life . Sulfur metabolism that takes place in by microbiota has been pointed to be a key product of the Western diet that is directly associated with carcinogenesis. Based upon its quantities, the close action of H2S yields considerable understanding with regards to avoidance efforts with/day dietary management regarding tumor targeting therapeutic approaches.One probability is H2S works via the nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain- containing 3 (NLRP3 inflammasome). The NLRP3 inflammasome possesses NLRP3 along with apoptosis- correlated speck like protein possessing a caspase enrollment domain (ASC)via its N terminal PYD, as well as precursor caspase 1. NLRP3 inflammasome is implicated in numerous diseases inclusive of DM. Recently we had reviewed howH2S represents an inimical gas possessing rotten egg aroma. Recently itsisolated in the form of a 3rd gas signal subsequent to nitric oxide (NO), as well as carbon monoxide .It possesses numerous biological functions possesses substantially significant part in innumerable

diseases inclusive of DM. Recently it has been illustrated that H2S controls inflammasome which aids in various diseases(seefig 11,12]which might work in regulation of NLRP3 inflammasome&might be the probable pathway needed to act on[80]. Further we had reviewed role of bile acid metabolism in CRC besides role of curcumin in CRC[80-3].Thus inclusion of curcumin in diet might be more beneficial in such patients.



Legend for Figure 11: Courtesy ref no-83-Schematic diagram of the NLRP3 inflammasome activation process.



Legend of Figure 12: Courtesy ref no-83-Summary of the production of endogenous H2S. CBS: cystathionine-beta-synthase; CSE: cystathionine-gamma-lyase; 3-MST: 3-mercaptopyruvate thiotransferase; 3-MP: 3-mercaptopyruvate; CAT: cysteine aminotransferase

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