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Environmental and Ingestible Toxins: A Review of their Role in the Development of Colon and Rectal Cancer

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Abstract

Objective: In this paper, we review the epidemiological evidence on the relationship between environmental and ingestible toxins and colorectal cancer.

Data sources and date extraction: We searched PubMed, Embase, and Web of Science for epidemiological studies on environmental and ingestible toxins and colorectal cancer published before June 1, 2022.

Results: Studies have reported positive associations between colorectal cancer and different persistent organic pollutants, non-persistent organic pollutants, polycyclic aromatic hydrocarbons, volatile organic compounds, and metals.

Conclusion: While the pathogenesis of CRC is likely multifactorial including both modifiable lifestyle factors (e.g., dietary, smoking, physical activity) and nonmodifiable (genetic, colitis-associated) risk factors, the role of the environment may be an additional and frequently forgotten contributor.

Introduction

Colorectal Cancer (CRC) is the third most common cancer among both men and women (excluding non-melanoma skin cancer) and is also the third most deadly cancer in the United States [1]. In 2020, worldwide, there were 1.9 million new cases and 0.9 million deaths, and cases are projected to escalate further, especially in developed countries [2]. The risk of developing colorectal cancer increases with age. Other known risk factors include presence of inflammatory bowel disease, a family history of colorectal cancer or polyps, and genetic syndromes including Familial Adenomatous Polyposis (FAP), and hereditary non-polyposis colorectal cancer (Lynch syndrome). Additionally, studies have shown that lifestyle factors are well-established risk factors for developing colorectal cancer. For example, alcohol consumers have 1.79-times higher odds of developing colorectal cancer versus non-alcohol users (95% Confidence Interval [CI]: 1.23-2.61) and increased tobacco use showed a 13.18% increased attributable risk (95% CI: 6.80-19.58) [3,4]. Furthermore, people with high levels of regular physical activity showed a 19% decreased risk of developing CRC, while another study showed fiber intake of greater than 20 g a day decreased risk of developing CRC by 25% [5,6]. As such, it is estimated that approximately half of colorectal cancers in the US are attributed to all known modifiable risk factors [7].

There have been marked improvements in CRC screening rates. As colonoscopy may be preventative in that polypectomy removes polyps before they evolve into cancer, this has contributed to the overall decline in CRC incidence rates in patients aged 65 years and older. More concerning, however, is the dramatic increase in the incidence of colorectal cancer in young patients, (<50 years

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old), also referred to as Early Onset Colorectal Cancer (EOCRC). Over the past several years, this age group has experienced a 63% increase in CRC rates in the US and projected to double by 2030 [8]. This rapid rise in EOCRC incidence cannot only be attributed to hereditary factors that do not change dramatically in such a short time period; hence, other factors must be considered when such drastic changes are seen within one generation.

One possible factor is environmental changes regarding pollution and toxin exposures that have not been thoroughly evaluated as carcinogens for CRC or EOCRC in humans. It is hypothesized that certain environmental factors can be linked with mutations directly in the colon and rectum [9,10].

This review will discuss evidence behind several different toxins commonly found in the environment or are more prevalent in industrialized regions that have been shown an association with CRC. Individual toxins are discussed under their respective larger chemical groups, such as: Persistent Organic Pollutants (POPs), Non-Persistent Organic Pollutants (non-POPs), Polycyclic Aromatic Hydrocarbons (PAH), Non-Halogenated Phenolic Chemicals (Non-HPCs), Volatile Organic Compounds (VOCs), and metals.

Methods

We aimed to identify epidemiological studies assessing the association between environmental toxins and colorectal cancer. PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Embase (http://www.embase.com/home), and Web of Science (https://www.webofscience.com/wos/woscc/basic-search) databases were searched using free text and Medical Subject Heading (MeSH) terms: colorectal cancer, colon cancer, and rectal cancer AND a) Metals (arsenic, cadmium, chromium, copper, manganese, mercury, nickel, lead, zinc, organotin compounds, tributyltin and compounds, triphenyl tin, thallium, antimony, cobalt, manganese, and vanadium); b) Pesticides (alachlor, aldrin, atrazine, chlordane, clofenvinphos, chlorpyrifos, DDT, dieldrin, diuron, endosulfan, endrin, heptachlor, lindane, mirex, pentachlorobenzene, pentachlorophenol, simazine, tetrachloromethane, isoproturon, organotin compounds, trifluralin, and isodrin); c) PACs: polycyclic aromatic chemicals (anthracene, ethylene oxide, naphthalene, PAHs, fluoranthene, benzo (g,h,i) perylene, benzo (a) pyrene, benzo (b) fluoranthene, benzo (k) fluoranthene, and indeno(1,2,3-cd)pyrene); d) Non-HPCs: non-halogenated phenolic chemicals (nonylphenol and nonylphenol ethoxylates, and octylphenols and octylphenol ethoxylates); e) Plasticizers (di-(2-ethyl hexyl) phthalate, and C10-13-chloroalkanes); f) POPs (aldrin, chlordane, DDT, dieldrin, endosulfan, endrin, heptachlor, hexachlorobenzene, 1-6-hexachlorocyclohexane, lindane, mirex, dioxins + furans, pentachlorobenzene, polychlorinated biphenyls, brominated diphenylethers, organotin compounds, PAHs, hexabromobiphenyl, benzo(a)pyrene, benzo (b) fluoranthene, and benzo (k) fluoranthene); g) VOCs: volatile organic compounds (non-methane volatile organic compounds, 1,2-dichloroethane, dichloromethane, hexachlorobutadiene, tetrachloroethylene, trichlorobenzenes, 1,1,1-trichloroethane, trichloroethylene, trichloromethane, vinyl chloride, benzene, ethyl benzene, ethylene oxide, naphthalene, and toluene). The search was limited to articles published in English and before June 1, 2022. 3808 total articles were identified from the three databases.

To assess exposure, studies that had biomarkers (serum toxin levels or other specimens), environmental measures (air, water, ground), or indirect measures (occupational exposures and contaminated residential areas) were obtained. When studies had appropriate effect estimates (percentage difference, regression coefficient, hazard ratios, rate ratios, odds ratios, standardized mortality ratio, or standardized incidence ratio), they were reported. Titles and abstracts were screened for relevance, and full texts were assessed further if criteria were met.

Specific classes of toxins

Persistent Organic Pollutants (POPs)

Persistent Organic Pollutants (POPs) are organic chemicals that contaminate the environment and subsequently, agriculture, due to their persistent nature and ability to bioaccumulate [11]. The accumulation of POPs in the environment is mainly from the use of pesticides along with industrial chemicals and byproducts. Most of the human exposure to POPs is from the consumption of contaminated food, particularly animal products [12-14]. Even though certain regulations have been implemented to safeguard against consuming contaminated foods, POPs still pose some risk to population health. The role of particular POPs such as pesticides, insectides and fungicides, and CRC are discussed below.

Organochlorine Pesticides (OCP)

Pesticides pose a risk as possible human carcinogens, as well as neurotoxins and neuroendocrine modulators, and are commonly used in agriculture all over the world. Organochlorine Pesticides (OCPs) are a major group of pesticides that are particularly stable in the environment and can therefore accumulate in human tissue, leading to toxicity with increasing levels over time. They are classified as Persistent Organic Pollutants (POPs) because of their constant presence in the environment years after their application. Their utilization is primary due to their effectiveness in maximizing the production of food by controlling the spread of typhus and malaria (via elimination of pests and mosquitos, respectively). However, many countries (including the US) have banned the use of OCPs due to the aforementioned negative environmental consequences [15]. Positive associations between organochlorine pesticides and colorectal cancer were observed in a case control study of 42 individuals with CRC and 38 healthy controls [16]. They found significantly elevated levels of the oxidative stress marker serum malondialdehyde in cases vs controls ($p<0.001$), which is an end product of lipid peroxidation caused by free radicals. Also, decreased activity of erythrocyte acetylcholinesterase ($p<0.001$) was seen, which has downstream effects leading to increased levels of cAMP response element binding protein, crucial to cell proliferation. Similarly, a Korean case control study with 99 CRC patients, 102 polyp patients, and 76 controls measured serum levels of multiple OCPs, and showed an increased risk of developing colonic polyps (OR=2.3 95% CI 0.9-5.7, ptrend=0.05) and CRC (OR=3.6, 95% CI 1.1-11.8, p=0.05) in 6 of 11 OCPs measured [14]. Mean ages for control, polyp, and cancer patients were 52.1, 55.6, and 65.9 years respectively. Men comprised 46.1%, 70.6%, and 55. 6% of control, polyp, and cancer patients. Confounding variables of physical activity, red meat consumption, fiber intake, and family history of CRC were considered and not significantly different across the groups, though comorbidities were not adjusted for.

Aldrin and dieldrin

In the United States, Aldrin and dieldrin were commonly used insecticides on crops between 1950-1970 and to eliminate termites from homes until 1989 [17]. The CDC's Agency for Toxic Substances and Disease Registry indicates that aldrin and dieldrin can be found on contaminated food and soil as well as homes that were previously treated for termites. Aldrin and dieldrin have been shown to cause liver metastases in a mouse model as a potential carcinogen [18]. In a study measuring levels of aldrin epoxidase (the aldrin metabolizing enzyme), its activity in colonic tumor cells was decreased compared to non-cancerous tissues, showing a possible loss of regulation and decreased metabolism of aldrin in cancerous tissues [19]. However, this effect has not necessarily been linear in humans. An occupational cohort study of 570 workers exposed to aldrin and dieldrin showed an increased mortality from rectal cancer compared to the general population [20,21]. However, an inverse relationship was found between levels of exposure and colon cancer, which may indicate other confounding factors or selection bias (ex. the healthy worker and the healthy worker survivor effect) may explain the observed findings in these occupationally exposed populations. There are no known studies on the exposure of aldrin and dieldrin and CRC in non-occupationally exposed populations to date.

P,p'-dichlorodiphenyltrichloroethane

Dichlorodiphenyltrichloroethane (DDT) was one of the most common pesticides in the world but became banned in most Western countries in 1972 due to the discovery of adverse effects on wildlife and humans. Many metabolites of DDT are still present in the environment and accumulate at high levels in humans, including P,p'dichlorodiphenyltrichloroethane (DDE). DDE has been shown to increase proliferation in human colorectal adenocarcinoma DLD1 cells through disruption of the Wnt/β-catenin pathway by increasing the production of reaction oxidative species and inhibiting superoxide dismutase, known to help protect against damage from free radicals [22]. The Wnt/β-catenin pathway has been implicated as being a central pathway for colorectal carcinogenesis [23-25]. In mouse models, DDE was shown to increase the tumor size through Wnt/β-catenin and Hedgehog/Gli1 signaling mediated by oxidative stress [26]. DDE promotes aerobic glycolysis, a common attribute of proliferating cancer cells.

These biochemical findings have clinical correlation in CRC patients. Elevated serum levels of organochlorine pesticides (including DDT and DDE) have been found in CRC patients compared to controls without cancer [27]. It was shown that people living in rural areas had higher serum levels of organochlorine pesticides and attributed this to higher levels of exposure in agricultural areas that utilized organochlorine pesticides. Older adults also had higher serum levels because of lifetime cumulative exposure to these chemicals. In 11 towns in Zhejiang province, China, similar associations were seen in a random sampling of DDT and DDE levels in rice paddy fields; rectal cancer was correlated with total DDT ($r=.691$, $p<0.05$) and DDE ($r=.716$, $p<0.05$) [28].

Pentachlorophenol (PCP)

PCP is a commonly used substance, mostly used in wood preserving as a fungicide, that has had a lasting negative effect on the environment and has been shown to cause DNA damage in humans through formation of oxygen radicals [29]. In case control studies, pentachlorophenol has been shown to be associated with higher odds of non-Hodgkin and soft-tissue sarcomas [30,31]. A meta-analysis evaluating the association between PCP and colorectal cancer risk showed a 16.4 times increased risk for people with occupational exposure than people who were exposed via food and drink [32].

Lindane, chlordane, heptachlor, and nonachlor

Lindane, an insecticide that is no longer produced in the United States, has shown a marginally significant association with colorectal cancer risk [33]. Registered pesticide applicators in the United States responded to extensive take-home surveys evaluating pesticide exposure as well as protection equipment, application methods, and lifestyle habits. These respondents numbered 56,813 and CRC cases and deaths of these participants were tracked between 1993-2002 [34]. In this study, Chlordane (which was banned in 1988 by the EPA) was shown to have a significantly positive association with rectal cancer risk (Rate Ratio 1.7, 95% CI 1.0-2.8) [35]. Similar findings were reported in a case-control study in Korea with 104 CRC patients vs. 235 controls. Nonachlor (a metabolite of chlordane) was positively associated with colorectal cancer (2nd tercile, Hazard Ratio (HR)=3.90, 95%, CI: 1.56-9.75) [36]. They also found heptachlor (another chlordane metabolite) had a positive association with colorectal cancer (3rd tercile, HR=2.76, 95%, CI: 1.25-6.07).

Polychlorinated biphenyls

Polychlorinated Biphenyls (PCBs) are a group of 209 chlorinated compounds used in rubber, inks, hydraulic fluid, copy paper, resin, etc. before it was banned due to its highly carcinogenic nature and its extreme persistence and subsequent negative effects on the environment. It is also considered a POP and is like OCPs in its environmental accumulation in the form of its metabolites which, especially in adipocytes due to their lipophilic properties, accumulates in humans [37,38].

An Italian study followed workers in a trichlorophenol production plant after an industrial accident, exposing them to high levels of 2,3,7,8- tetrachlorodibenzo-p-dioxin (TCDD, or "dioxin"), a PCB, and showed a significant increase in rectal cancer mortality of men in high exposure zones (Rate Ratio=2.4, 95% CI 1.2-4.6) [39]. Furthermore, this finding was corroborated by a study in Germany following workers in a dioxin plant, also showing an increased mortality rate from rectal cancer (Standardized Mortality Ratio, SMR=1.96, 95% CI 0.98 3.51) [40]. A case-control study in 132 patients with newly diagnosed colorectal adenocarcinoma and 76 controls showed that elevated levels of mono-ortho PCBs, which have a similar chemical structure to dioxin, is associated with an increased CRC risk (OR=2.94, 95% CI 1.39 6.20; p=0.004) [41]. TCDD acts as a synthetic ligand binding aryl-hydrocarbon receptors (AhR), a target gene to CYP1A1 and CYP1B1, catalyzing the conversion of polycyclic aromatic hydrocarbons into toxic metabolites that alter DNA [42,43]. AhR also interacts with several growth factor mediated signaling pathways resulting in the ability to cause cell proliferation or apoptosis, depending on the cell type. Specifically, the effects of TCDD on human colorectal cancer cells showed proliferative interaction between AhR and EGFR [44].

Organotin compounds

Organotin compounds were initially used to stabilize chlorinated hydrocarbons from thermal degradation, but the applications are increasing and it is now utilized in agriculture, industrial water systems, and wood preserving [45]. However, several organotin compounds have been found to be toxic and have a variety of negative health consequences ranging from neurotoxicity to reproductive and immunologic disturbances [46]. An observational study with multiple control groups adjusted for geographic location of 557 CRC patients and 2948 controls across 11 sites showed that residential proximity within three kilometers of the production of organotin compounds increased the risk of developing colorectal cancer (OR=2.03, 95% CI 1.44-2.87, OR=1.26, 95% CI 1.00-1.59, respectively) [47].

Nonylphenols

Nonylphenols are the final product in the degradation of alkylphenol ethoxylates that are commonly used in cleaners and detergents; they are especially present in wastewater [48]. Nonylphenol has also been shown to have estrogenic activity in breast cancer cells and have an impact in a handful of different cancers such as breast, ovarian, and uteruses [49]. Nonylphenol has both increased the rate of proliferation and inhibited the apoptosis of COLON205 CRC cells through multiple different pathways involving protein kinase C ζ , ERK/TGF β pathway, and the GPR-30 mediated activation of ERK1/2 signaling [50,51]. Furthermore, nonylphenols upregulate the expression of cell cycle regulators, promoting the epithelial-mesenchymal transition; thus enabling the cancer cells to invade and migrate [52]. To date, no epidemiological studies have evaluated the relationship of individual-level nonylphenols and colorectal cancer incidence.

Non-persistent organic pollutants

Organophosphate Pesticides (OPPs)

Organophosphate Pesticides (OPPs) do not share the persistent nature of OCPs and are considered safer because they do not accumulate in the environment. However, they still have negative consequences for human health and disease which is particularly concerning because they are being continually used today. Below, we highlight chlorpyrifos and alachor in relation to CRC because of their wide indications and ongoing use by some countries, including the US.

Chlorpyrifos

Chlorpyrifos is one of the most applied broad-spectrum pesticides in the world. It was shown to have a positive association with rectal cancer in the large cohort study of 56,813 pesticide applicators mentioned above (RR=2.7, 95%, CI=1.2-6.4) [53]. Suriyo et al. illustrated its carcinogenic effect by promoting cell growth in the human colorectal adenocarcinoma H508 cell line through increased phosphorylation of epidermal growth factor receptor and its downstream effector, extracellular signal regulated kinase [54].

Alachlor

Alachlor is an herbicide that was used for a wide range of crops around the world but was banned in the European Union in 2006 [55]. The United States Environmental Protection Agency has not banned it but has issued guidelines in 1996 to prevent environmental contamination and the protection of humans from pesticides including alachlor [56]. A cohort study in the United States followed 943 manufacturing workers in an alachlor plant and showed elevated rates compared of colorectal cancer compared to the general population (Standardized Incidence Ratio=5.2, 95% CI 1.1-15.1), especially in those with elevated levels of exposure [57]. Interestingly, workers were exposed via contaminated drinking water at the plant, so exposure levels were higher than what farmers utilizing alachlor on crops would likely experience, but certainly lends the question as to if the end of the line consumer would be ingesting similar amounts as the manufacturers.

Polycyclic Aromatic Hydrocarbons (PAHs)

Polycyclic Aromatic Hydrocarbons (PAHs) are known to be both persistent and toxic to the environment. PAHs are released into the environment during volcanic eruptions, forest fires, fossil fuel combustion, industrial processes, and common cooking techniques like barbequing, smoking, baking, etc [58]. Naphthalene is in this category and has shown an association with CRC, as discussed below.

Naphthalene

Naphthalene is released into the air mostly from industrial processes, tail emissions, open burning, and smoking. It is also used as a deodorizer, fumigant, and repellent. A popular use of naphthalene, creating a large amount of indoor exposure, is in mothballs [59]. A case control study in Spain with 557 CRC cases and 2948 controls in 11 provinces that were matched by age, sex, and region found associations between developing CRC and living proximity to industrial factories. It showed that living less than 3 kilometers away from industries releasing naphthalene increases the risk of developing colorectal cancer (OR=3.11; 2.16-4.49) [25]. Limitations of this study included the inability to determine how geographical features impacted real exposure along with recall bias.

Volatile Organic Compounds (VOCs)

Volatile Organic Compounds (VOCs) are usually manmade industrial solvents that have a high vapor pressure and low water solubility and are used in the manufacturing of paints, pharmaceuticals, and refrigerants [60]. Exposure to VOCs can cause acute symptoms like headaches, dizziness, nausea/vomiting, and ear, nose, & throat irritation. Longer chronic exposure from inside the home can cause cancer, liver & kidney damage, and central nervous system damage [61].

1,2-dichloroethane

1,2-dichloroethane is used in the production of vinyl chloride and other chemicals; it is also used as a lead scavenger in gasoline [62]. A study in the United States from 1969-1981 investigated towns with a single ground water source and looked for associations between CRC incidence and different VOCs and heavy metals. Municipalities were grouped according to each detectable VOC, and incidence rates were calculated correcting for age and sex. Male colon cancer incidence rate was significantly greater (p=0.009) at 222.8 per 100,000 in municipalities with concentrations of 1,2-dichloroethane greater than 0.10 µg/l compared to 170.3 per 100,000 in municipalities with less than 0.10 µg/l of 1,2-dichloromethane. Male rectal cancer incidence rate was also

significantly greater (p=0.02) at 126.5 per 100,000 in municipalities with concentrations of 1,2-dichloroethane greater than 0.10 µg/l compared to 92.5 per 100,000 in municipalities with less than 0.10 µg/l of 1,2-dichloromethane [63].

Dichloromethane

Dichloromethane is used as an industrial solvent and paint stripper; it can also be found in pesticides and aerosol products. An important route of entry into the body for dichloromethane was shown to be bathing and showering as opposed to drinking contaminated water [64]. A case control study in Spain (mentioned earlier of 557 CRC cases vs 2948 controls) in living proximity to industrial factories showed that those industries releasing dichloromethane had higher odds of developing colorectal cancer (OR=2.52, 95% CI 1.74-3.66) [47].

Tetrachloroethylene

Exposure to tetrachloroethylene is mostly occupational, especially in the dry-cleaning industry and the production of other chemicals [65]. However, a tetrachloroethylene leak from vinyl pipes into public drinking water occurred in Massachusetts, and a population-based case-control study evaluating the associations of tetrachloroethylene-contaminated drinking water and cancer was performed. It reported higher risk of colon cancer at 11 years of latency (OR=1.3, 95% CI 0.5-3.5) and was slightly higher at 13 years (OR=1.5, 95% CI 0.3-5.8), but the 95% CIs were also consistent with no association. Latency was defined as the time between exposure and a clinical diagnosis. Similar findings were reported for rectal cancer for 11 and 13 years of latency (OR=2.6, 95% CI0.8-6.7 and OR=3.1 95% CI 0.7-10.9, respectively] [66].

Trichloroethylene

Trichloroethylene is used in the manufacturing of refrigerants, as a metal degreaser, and is found in a variety of aerosols. It has been shown to be associated with kidney cancer and non-Hodgkin lymphoma [67]. A case-cohort study of 3464 participants evaluating occupational exposure to 17 different endocrine disrupters, in Ontario, showed an elevated risk of developing colorectal cancer when exposed to trichloroethylene (OR=1.43, 95% CI 1.08-1.88) [68].

Benzene, toluene, xylene

Benzene, toluene, and xylene are widely known carcinogens commonly found in gasoline. They are all water soluble, making them prime candidates for contaminating water, though they are biodegradable in certain conditions [69]. In a study evaluating workers with excess exposure to benzene, 181,709 colon cancer cases and 109,227 rectal cancer cases between years 1961-2005 were identified in the countries of Sweden, Norway, Iceland, and Finland. Each case was matched with five case controls from the same cohort matching age, country, and sex. Lifestyle factors based on occupation, specifically smoking, drinking, exercise, BMI, and diet were also taken into consideration for Finland only due to available information. Workplace exposure to benzene was estimated from exposure matrices that were specific for each specific country. An increased risk of colorectal cancer was shown, especially in the ascending colon (OR=1.27, 95% CI 1.13-1.43) and transverse colon (OR=1.21, 95% CI 1.01-1.41) [70]. Other confounders considered and corrected for were physical strain at work, formaldehyde, ionizing radiation, and wood dust. Another population-based case-control study evaluated nineteen sites of cancer in patients between the ages of 35-70 living in the metropolitan Montreal area. 4576 cases were identified between the years 1979-1986 in which 3730 patients consented to participate in the study. There were 497 colon cancer patients with 2050 controls and 257 rectal cancer patients with 1295 controls. Each cancer type was compared against three groups of controls: a group with other cancers, population controls, and a mixed subset of other cancers and population controls. Population controls were age-matched to cancer patients. A professional team of chemists and hygienists determined level of exposure to benzene, toluene, styrene, and xylene based on 300 occupational agents regarding frequency and amount of exposure. Continuous variables of age, family income, and cumulative smoking index were considered, and ethnicity, smoking status, and respondent status (either self or next of kin) were considered as categorical variables. High exposure levels of xylene showed an increased rates of colon cancer (OR=5.8, 95% CI 1.5-22.0), and high exposure levels of toluene had an increased rates of colon cancer (OR=1.8, 95% CI 0.7-4.4). High exposure levels of toluene also showed increased rates of rectal cancer (OR=3.2, 95% CI 1.3-8.0), high exposure levels of xylene showed increased rates of rectal cancer (OR=2.7, 95% CI 0.9-8.3), and medium/high exposure levels of styrene showed increased rates of rectal cancer (OR=5.1, 95% CI 1.4-19.4). There was a high correlation between exposure to benzene, toluene, and xylene, as 58, 74, and 88% of patients exposed to benzene, toluene, and xylene respectively were exposed to all three.

Metals

Some metals are individually listed on the International Agency for Research on Cancer (IARC) list of "Group I: Known Human Carcinogens [72]". The specific metals and their associations with CRC are discussed below. No epidemiologic studies at the individual-level have studied metal exposures and CRC incidence. CRC cancer patients living in the rural United States were analyzed for trace element analysis were shown to have increased concentrations of trace elements as byproducts of coal production, showing higher levels of arsenic, nickel, and chromium were higher compared to controls from nearby urban cities [73]. Significant differences in serum levels of Nickel (2.721 µg/g), Cadmium (0.563 µg/g), Arsenic (0.539 µg/g), and Lead (1.273 µg/g) have been demonstrated in a study of 165 Colorectal Cancer (CRC) patients when compared to 151 matched healthy controls. Most of the elemental differences could be explained when taking into consideration dietary habits, gender, and smoking. However, further study is needed to investigate each element's influence on the etiopathology of CRC [74].

Arsenic

Arsenic is on the IARC Class 1 carcinogen list, and the U.S. Environmental Protection Agency classifies it as a group A human carcinogen (Carcinogenic to Humans: Agents with adequate human data to demonstrate the causal association of the agent with human cancer) [75]. Human exposure to arsenic occurs in both occupational and environmental settings, including the occupational industries of nonferrous smelting, wood preservation, glass manufacturing, and arsenical pesticide production and application. The main source of environmental arsenic exposure to the gene-

ral population is contaminated drinking water, often via soil in the form of pesticides or solid wastes [76,77]. A study conducted in Turkey demonstrated higher rates of cancer-related death in villages with high levels of arsenic contamination in their drinking supply when compared to villages without high levels of contamination; however, they were unable to determine if a direct correlation exists between arsenic exposure and cancer-related deaths [78]. A case cohort study of 3,464 participants in Canada measured colorectal cancer risk in relation to occupational exposures via CANJEM, a job-exposure matrix accounting for most occupations and numerous agents. Concerning Arsenic, they found an association between occupational arsenic exposure and increased risk of colorectal cancer (OR=2.86, 95% CI: 1.06-7.63) [68].

Cadmium

As with arsenic, the IARC classifies cadmium as a class I carcinogen [79]. Multiple in vitro cell culture and in vivo animal experimental studies have demonstrated cell transformation and induction of cancer as a result of exposure to cadmium [80,81]. One such study investigating underlying mechanisms of carcinogenesis of cadmium showed that within colorectal cancer cells, cadmium stimulated phosphorylation of Smad2/3, suggesting that cadmium induces the activity of participants in the TGF-β signaling pathway involved in colorectal cancer development [82]. It is known that exposure of human cells to cadmium suppresses Mismatch Repair (MMR) activity, an important process for repairing errors in DNA, which plays an important role in colon cancer by altering gene expression and inducing inflammation. A study examining the effect of environmental exposure to cadmium on MMR-proficient human cells revealed that environmentally relevant concentrations of cadmium suppressed the ability of the MMR system to evade the G2 cell cycle checkpoint and continue to proliferate, another hallmark of cancer cells. Healthy colonocytes damaged by DNA alkylating agents are expected to arrest at the G2 checkpoint, and either initiate DNA repair or undergo apoptosis [83].

Chromium

Chromium is also classified by the IARC as a class I carcinogen, and there is growing concern about the effects of ingesting chromium via contaminated drinking water [84,85]. A study investigating the tumorigenesis of orally administered hexavalent chromium (Cr (VI)) in drinking water in mouse colitis-associated colorectal cancer models revealed that all treatments who were administered Cr (VI) in combination with Azoxymethane/Dextran Sodium Sulfate (AOM/DSS) developed colorectal cancer [85]. However, given that association of CRC with colitis is a significant cofounder, it is important to investigate the relationship between chromium and CRC in colitis-free models. Promotion of tumor formation has been recorded in mouse CRC models induced by 1, 2-Dimethylhydrazine (DMH) that were given drinking water containing Cr (VI). In this colitis-free model, tumor incidence in the DMH + Cr group was 100%, with 5/5 mice developing colonic tumors [86].

Copper

Alteration of copper metabolism has been demonstrated during inflammation, infection, and cancer, and serum copper levels rise during these events [87]. When evaluating the association between trace elements and the risk of developing colorectal cancer, a cohort of 27,548 people were recruited, and high copper serum concentrations were associated with a higher risk of developing CRC (HR per SD, 95% CI 1.29, 1.05-1.59) [88]. Additionally, results of a retrospective study of 187 CRC patients and 187 controls showed a statistically significant strong, positive correlation (OR=12.7, 95% CI: 4.98-32.3; p<0.001) between blood copper level and occurrence of colorectal cancer, and a strong association was present for both early and late-stage CRC [89].

Magnesium

Magnesium, in clinical prescribed doses, has a wide range of indications, and is necessary for normal cellular metabolism. Most available data suggests that magnesium is a chemo-preventive agent given the known roles it plays in cell cycle regulation and DNA damage repair [90]. Magnesium deficient mouse models have demonstrated that low magnesium promotes tumorigenesis. However, there are similar effects at supratherapeutic ranges. A case-control study of 76 CRC patients and 28 healthy controls comparing levels of magnesium in tumor tissue vs healthy tissues showed a statistically significant higher concentrations of Magnesium in tumor tissue with median concentrations being 147.0 and 114.6 μg/g respectively (p=0.0008) [91]. Additionally, a study comparing malignant vs. normal tissue in human colon cancer patients revealed that concentrations of magnesium were significantly higher (170%) in the malignant tissue [92].

Manganese

Manganese is a transition metal that is required in trace amounts to maintain one's health but is toxic in large amounts. Specifically, manganese divalent cations are necessary for colorectal cancer cells to bind to the extracellular matrix during migration and invasion [93]. Excess exposure to manganese from groundwater was positively associated with increased rates of colorectal cancer, with 2.84 deaths/100,000 increase over unexposed areas [94]. Garcia-Perez et al. demonstrated that living proximity to industrial plants releasing manganese also increases the risk (OR=2.53, 95% CI 1.63-3.93) of developing colorectal cancer [47]. Furthermore, a significant difference in levels of serum manganese (16.3±4.5 μg/L) between CRC patients and age-matched healthy controls was found [95].

Lead

Exposure to lead leads to accumulation throughout the body having a negative impact on the reproductive, hepatic, endocrine, immune, and gastrointestinal systems [96]. Lead has been suggested to prevent the cell from repairing damage to DNA as well as causing direct damage to DNA by generating reactive oxygen species [98]. A study in Southeast China of 167 gastrointestinal cancer patients including 46 CRC patients and 112 controls showed a significantly higher level of lead in patients with cancer; 60.03 μg/L vs 53.84 μg/L, respectively (p=0.027) [98]. Canada showing an increased risk of colorectal cancer (OR=1.29, 95% CI: 1.03-1.60) with occupation exposure to lead [68].

Antimony

Antimony is used in the production of textiles, plastics, glass, and metals, and antimony toxicity is most often seen from occupational exposure [99,100]. A study of CRC incidence in 888 art glass

industry workers between 1950-1982 showed an increased risk (OR=5.0, 95% CI: 2.6-9.6) in developing colorectal cancer due to increased exposure to antimony [101]. on Swedish workers in the glass industry showed an excess risk of colorectal cancer but was unable to separate the effects of concomitant metals exposures and the confounding variables precluded definitive results [102]. Another multi-control case study in Spain showed an increased risk (OR=5.30, 95% CI: 3.45-8.15) of colorectal cancer when living near industries releasing antimony.

Conclusion

Toxins commonly utilized in industrialized or agricultural realms, have a lasting impact on the environment, and in many cases accumulate over long periods of time. The downstream effects of this can impact human health via proven cellular mechanisms described above and have clinical implications in the development of CRC. While the pathogenesis of CRC is likely multifactorial including both modifiable (dietary, smoking, physical activity) and nonmodifiable (genetic, colitis-associated) risk factors, the role of the environment may be an additional and frequently forgotten contributor.

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