The Relationship Between Microplastics and Nanoplastics with Cancer: An Emerging Health Concern

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ABSTRACT

There is an increasing apprehension surrounding the potential health implications associated with prolonged exposure to environmental micro- and nano-plastics (MNPLs) on the human population. Microplastics pose significant threats to both aquatic and terrestrial ecosystems, entering water bodies through various pathways and accumulating in sediments. Additionally, they infiltrate terrestrial environments, spreading contamination through air, water, and soil, impacting soil health and potentially entering the food chain. Likewise, humans encounter microplastics through diverse exposure routes. Studies have demonstrated that multiple substances involved in oncogenetic pathways can trigger carcinogenesis in the human body, leading to various cancers such a colorectal, liver, lung, skin, breast, biliary tract, leukemia, and pancreatic cancers. In this review, we examine the literature highlighting this emerging health issue.

Keywords: Microplastics, Nanoplastics, Oncogenesis, Cancers

INTRODUCTION

In recent years, the insidious infiltration of microplastics (MPs) into our environment has emerged as a critical concern. Now, unsettling research suggests a potential link between these pervasive particles and cancer, shaking the very foundation of our understanding of health risks associated with plastic pollution. The studies delve into the profound implications of microplastics on human health, particularly their role in the development and progression of cancer. Drawing upon extensive data analysis and laboratory experiments, the researchers uncovered a disturbing correlation between exposure to microplastics and increased cancer incidence. [1,2]

One of the most alarming findings of the studies is the ability of microplastics to act as carriers of carcinogenic compounds.[3] These miniature plastic particles, often invisible to the naked eye, have a remarkable capacity to absorb and accumulate toxic chemicals from the surrounding environment. When ingested or inhaled, these microplastics can release these harmful substances directly into the body, potentially triggering cancerous transformations in cells.[4,5]

Furthermore, the ubiquitous presence of microplastics in various ecosystems poses a ubiquitous threat to human health.[6] From the depths of the oceans to the air we breathe, these minuscule fragments have permeated every corner of our planet, leaving no escape from their potential carcinogenic effects. Even more concerning is the ability of microplastics to bioaccumulate in the food chain, amplifying the risk of cancer with each successive trophic level.[7]

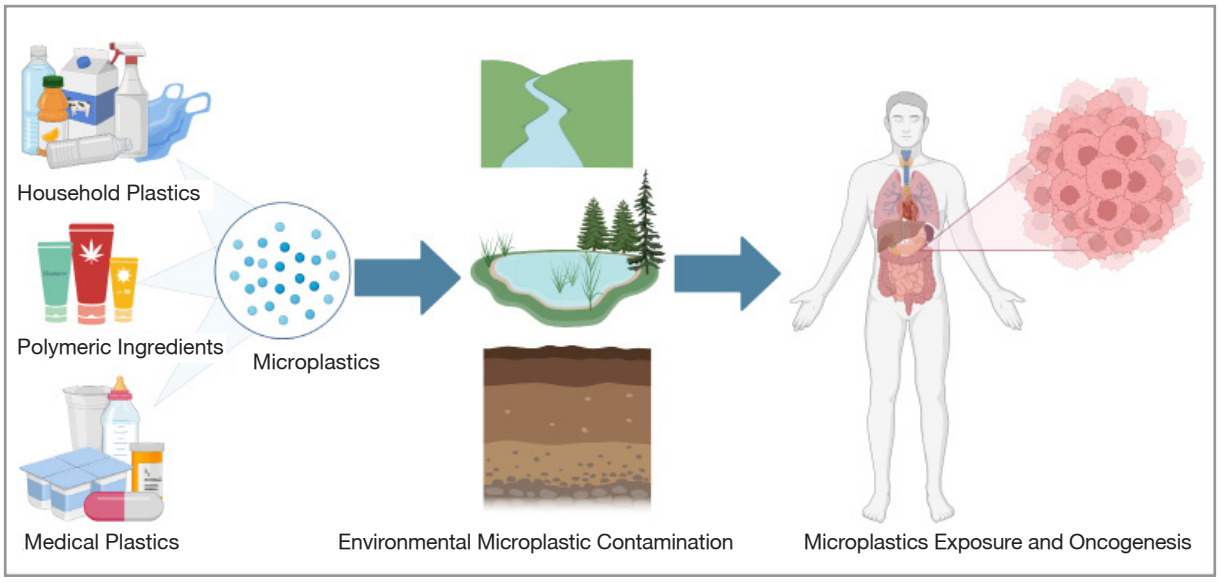

Figure 1. Types of plastics, Environmental Microplastic Contamination, Microplastics Exposure and Oncogenesis

Additionally, the research highlights the necessity for more investigation to clarify the exact mechanisms by which microplastics influence the development of cancer.[8] Unraveling these intricate pathways is essential for devising effective strategies to mitigate the health risks posed by microplastic pollution and safeguarding the well-being of current and future generations (Figure 1).

In this review, we attempted to highlight various aspects of the association between microplastics and different types of cancers.

Definition and Types of Microplastics and Nanoplastics

Plastics are organic polymers derived from finite sources like natural gas, crude oil, and coal. When the size of plastic particles measures less than 5 mm in diameter, they are classified as microplastics.[9] In a more recent definition, adhering to the standard international unit nomenclature (SI units), the lower threshold is established at 1 μm.[10,11] The heightened focus on microplastics entering the environment has prompted many researchers to investigate the fragmentation of plastics to extremely small scales, including dimensions below 1 μm. Furthermore, particles ranging from 1 to 1000 nm, referred to as Nanoplastics (NPs), result from the breakdown of industrial plastic items or manufacturing processes, potentially displaying colloidal behavior.[12]

In 2011, Cole et al. delineated microplastics by their source as either primary or secondary.[13] Primary microplastics are produced by industries or in household applications and are extremely small in size. These plastics are commonly utilized in facial cleansers, cosmetics, and as air-blasting media. Moreover, there is a growing trend of their use in medicine, where they serve as carriers for drugs, a practice that is increasingly documented.[14-16] Secondary microplastics are characterized as minuscule fragments of plastic that arise from the deterioration of larger plastic waste, discovered in oceanic environments as well as land-based surroundings. As plastic waste undergoes various physical, biological, and chemical processes over time, its structural integrity degrades, resulting in the formation of these fragmented particles.[17,18] Microplastics are categorized based on their polymer composition into several types, including polyethylene (PE), polystyrene (PS), polylactic acid (PLA) which are biodegradable, poly (methyl methacrylate) (PMMA), polypropylene (PP), polyvinyl chloride (PVC), polyamide (PA), polyesters (PES), and polyurethane (PUR).[19]

Global Distribution of Microplastics and Nanoplastics

Aquatic ecosystems, including oceans, rivers, lakes, and estuaries, serve as major reservoirs for microplastics.[20] These particles enter water bodies through various pathways, including the fragmentation of larger plastic debris, wastewater discharges, and runoff from land-based sources. Microplastics are ingested by marine organisms across all trophic levels, posing risks to aquatic biodiversity and ecosystem health. Additionally, microplastics accumulate in sediments, potentially acting as vectors for pollutant transport and impacting benthic habitats.[21]

Microplastics have infiltrated terrestrial environments worldwide, from urban areas to remote wilderness regions. Sources of terrestrial microplastic pollution include plastic debris, synthetic textiles, and agricultural activities.[22] Microplastics are transported through air, water, and soil, leading to widespread contamination of terrestrial ecosystems. These particles can accumulate in soils, affecting soil health and potentially entering the food chain through plants and terrestrial organisms.[23]

Recent studies have highlighted the atmospheric transport of microplastics as a global phenomenon.[24] Microplastics are carried by wind currents over long distances, resulting in their deposition in remote regions far from their original sources.[25] Atmospheric microplastics have been detected in urban air, rural areas, and even pristine natural environments, raising concerns about their impacts on air quality, human health, and ecological integrity.[26-29]

Microplastics are omnipresent in anthropogenic environments, including urban areas, industrial sites, and indoor settings. Plastic debris litters urban landscapes, while microplastics are generated from various human activities, such as plastic production, manufacturing, and waste management.[30] Indoor environments, such as homes and workplaces, harbor microplastics from consumer products, furniture, and synthetic textiles. Furthermore, microplastics have been detected in food, beverages, and even the air within indoor spaces, highlighting the pervasiveness of human exposure to these particles.[31]

When a single microplastic particle breaks down, it can generate billions of nanoplastic particles, highlighting the extensive presence of nanoplastic pollution worldwide.[32] Nanoplastics used in various industries such as pharmaceuticals and cosmetics may present environmental challenges either directly or through indirect routes, such as wastewater. Although many of these particles are removed during wastewater treatment, a portion may persist and enter the soil, potentially serving as a significant source of nanoplastic pollution for plant species. These nanoscale plastics, mainly originating from land-based sources, build up in sewage and discharge, ultimately making their way into aquatic environments. It is estimated that approximately 80% of marine plastic pollution comes from land-based sources, which include landfills, nanoplastics carried by waterways, bio-solids and compost, and insufficient management and disposal of untreated waste materials.[33-35]

Routes of Exposure

Humans are increasingly exposed to microplastics through multiple routes, including ingestion, inhalation, and dermal contact.[36] With the ocean hosting a dense concentration of microplastics, reaching up to 102,000 particles per cubic meter, seafood has emerged as a significant contributor to microplastic intake through ingestion.[3] Also, the widespread presence of microplastics across surface water, groundwater, and wastewater prompts concerns regarding the potential contamination of drinking water.[37]

Despite a recent report by the World Health Organization indicating no evidence of detrimental effects from microplastics in drinking water, the persistent exposure to tap water containing an average of 4.23 items per liter underscores the need for further scrutiny of its long-term impacts on human health.[38] In a recent pilot study samples of drinking water sourced from different sources were subjected to analysis using Raman microspectroscopy to identify and characterize microplastic presence in terms of their shape, size, abundance, and polymer composition. Notably, not all samples tested positive for microplastic contamination; in fact, some, particularly those obtained from water

kiosks, were found to be devoid of such pollutants. Across the various water sources analyzed, microplastic levels varied, ranging from less than 2 particles per liter to a maximum of 5 plus or minus 1.5 particles per liter. These microplastics exhibited sizes spanning from 30 to 100 micrometers and primarily comprised common polymers like polyethylene, polypropylene, or polyethylene terephthalate.[39] Another factor contributing to microplastic exposure is the regular use of plastic packaging materials.[40] Besides microplastics being directly released from food packaging, the transfer of chemical plasticizers from food packaging to the food itself also increases human exposure to these chemical additives.[41]

Synthetic textiles and urban dust were identified as the primary sources of microplastic pollution, with plastic particles shedding from clothing, furniture, textiles, and construction materials contributing to secondary exposure through inhalation for humans.[42] The human respiratory system serves as a significant target for inhaled microplastics, as evidenced by the presence of plastic fibers derived from petrochemicals in 87% of lung samples.[43]

Dermal uptake of microplastics can occur through multiple pathways, including direct contact with contaminated surfaces, absorption through hair follicles, and penetration through the skin barrier. Studies have demonstrated that microplastics can adhere to the skin upon contact with contaminated materials or environments, leading to potential uptake through physical contact. Furthermore, smaller microplastic particles may penetrate the skin barrier or be absorbed through hair follicles, gaining access to deeper tissue layers and systemic circulation. Dermal absorption predominantly occurs when individuals utilize personal care products such as hand cleansers, facial/body scrubs, face masks, and toothpaste. This usage pattern may lead to localized toxicity and potential absorption.[32] Because of the size constraints limiting microplastics' ability to penetrate the skin, dermal absorption is more closely linked with the uptake of released monomers or organic plasticizers like phthalates and bisphenols, known for their endocrine-disrupting properties.[44]

Oncogenesis

Recent studies underscore the significant carcinogenic potential of microplastics and nanoplastics due to their pervasive environmental presence and physical and chemical properties. These particles facilitate the bioaccumulation and systemic distribution of various carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs), through food chains, increasing exposure in human tissues. Microplastics and nanoplastics promote carcinogenesis by inducing chronic inflammation and immune dysregulation, mechanisms well-established in cancer development. Additionally, these plastics cause direct and indirect DNA damage through oxidative stress, a result of reactive oxygen species (ROS) generated upon exposure to environmental microplastics and nanoplastics. This oxidative stress leads to mutations and genomic instability, accelerating carcinogenesis. Furthermore, the endocrine-disrupting chemicals associated with microplastics and nanoplastics can interfere with hormone signaling pathways, enhancing the proliferation of hormone-sensitive cancers. Collectively, these mechanisms highlight the [intricate and multifaceted] pathways through which microplastics and nanoplastics contribute to the increasing incidence of cancer, necessitating urgent investigations into their long-term effects on human health.[8]

Microplastics and nanoplastics contribute to systemic toxicity by disrupting cellular and systemic homeostasis by generating ROS. These particles can accumulate within mitochondria, perturbing the mitochondrial electron transport chain, leading to mitochondrial membrane damage and potential depolarization. This mitochondrial dysfunction produces various ROS, which induce DNA damage, protein oxidation, and lipid peroxidation, compromising the cellular antioxidant defense systems. Furthermore, MPs and NPs trigger a plethora of signaling cascades, including the p53 signaling pathway, mitogen-activated protein kinases (MAPKs), and pathways involving nuclear factor erythroid 2-related factor 2 (Nrf2), phosphatidylinositol-3-kinases (PI3Ks)/Akt, and Transforming growth factor-beta (TGF-β). These activated pathways contribute to various forms of cellular damage and can lead to organ-specific toxicities such

as pulmonary, cardiotoxicity, neurotoxicity, nephrotoxicity, immunotoxicity, reproductive toxicity, and hepatotoxicity. The article highlights the extensive impact of MP/NP-induced ROS on both cellular and organismal health, emphasizing the need for further research to mitigate these effects.[45]

The study conducted by Ding et al. explores the size-dependent toxicity of polystyrene microplastics (PS-MPs) on the gastrointestinal tract, focusing on oxidative stress-related DNA damage and potential carcinogenic effects. The research reveals that PS-MPs are ingested and highly concentrated in the stomach, causing significant oxidative stress and genotoxicity, particularly when compared to larger PS-MPs. These microplastics induce more severe oxidative stress and DNA damage due to their smaller size, which enhances their interaction with cellular components. The study also demonstrates that PS-MPs upregulate β-catenin/YAP expression in a redox-dependent manner, suggesting a novel toxic mechanism and potential carcinogenic effects.[46]

The study by Yuchen Wang et al. examines the effects of microplastics on skin cells, revealing that while microplastics promote proliferation in skin cancer cells, they detrimentally impact normal skin cells. Using methods like MTT assays, flow cytometry, and Western blotting, the research demonstrates that microplastics enhance cancer cell growth by altering cell cycle dynamics and activating inflammatory pathways via the NLRP3 inflammasome. This is driven by increased mitochondrial reactive oxygen species and subsequent mitochondrial DNA release into the cytoplasm.[47]

The study by Sharma et al. focuses on the cancer risks associated with microplastics enriched with PAHs, originating from electronic waste. The research highlights how microplastics act as vectors for transferring toxic pollutants, particularly PAHs, into human food chains through seafood and water. Using adsorption experiments, the study quantified the capacity of microplastics to adsorb carcinogenic PAHs, which ranged from 46 to 236 μg/g, with maximum binding occurring within 45 minutes in water. These microplastics, saturated with PAHs, can leach these compounds back into the environment, posing a substantial risk when ingested over a lifetime. The researchers estimated the cancer risk for both children and adults, noting that the potential risk levels exceeded the recommended values, emphasizing a significant public health concern regarding the ubiquity and impact of microplastics in aquatic and marine ecosystems.[48]

Bruna et al.'s study focuses on the environmental and health impacts of microplastics, particularly their role in cancer cell division and migration. The research highlights that microplastics smaller than 1 μm are found within the lysosomes of human gastrointestinal cancer cells and accumulate in non-proliferating areas of tumor spheroids. These microplastics can transfer between cells during division, and 0.25 μm particles significantly increase cell migration potential, suggesting a role in promoting metastatic behaviors. The study investigated the interaction between polystyrene micro- and nanoplastics and human colorectal cancer cell lines, finding size and concentration-dependent uptake across all cell lines, with particles distributed between mother and daughter cells during cell division. Short-term exposure to 0.25 μm particles notably amplified cell migration, potentially leading to pro-metastatic effects, while larger particles demonstrated high persistence in 2D and 3D cultures without interfering with cell proliferation.[49]

The study by Alijagic et al. investigates the toxicity of polyamide-12 microplastics used in additive manufacturing, focusing on their impacts on inflammation, immunometabolism, genotoxicity, endocrine disruption, and cell morphology. The microplastics, particularly those reused in production, showed potential health risks due to their chemical composition and physical properties. The researchers found that these microplastics did not cause an acute inflammatory response in macrophages but did induce a steady increase in pro-inflammatory chemokine IL-8 over time. Genotoxicity was evidenced by the activation of the p53 pathway, indicating stress responses that could lead to DNA damage. Endocrine disruption was also noted, with the microplastics affecting androgenic and aryl hydrocarbon receptor (AhR) pathways, suggesting potential interference with hormone functions.[50]

The study by Poma et al. investigates the cytotoxic and genotoxic effects of polystyrene nanoparticles (PNPs) on human fibroblast cells (Hs27). The study utilized the cytokinesis-block micronucleus

(CBMN) assay to assess DNA damage and observed increased formation of micronuclei and nuclear buds, indicators of genotoxicity. ROS analysis further revealed that PNPs induce significant oxidative stress in cells, particularly at short treatment times. Interestingly, when PNPs were combined with an antioxidant extract from Crocus sativus L., there was a notable reduction in ROS production, suggesting protective effects against PNP-induced oxidative stress. Additionally, scanning electron microscopy (SEM) coupled with energy-dispersive X-ray (EDX) analysis confirmed the presence of carbon and oxygen in the nanoparticles, indicating their polystyrene composition.[51]

The study by Xiaojie Hu et al. explores the bioaccessibility and cancer risks associated with microplastics-sorbed phenanthrene (PHE) and its derivatives in the human gastrointestinal system. This research delves into how microplastics serve as vectors for carcinogenic PAHs and their derivatives, emphasizing the heightened human health risks when these contaminants are ingested. They found that polyethylene PE microplastics had the highest sorption capacity for these compounds, followed by PP and PS. The bioaccessibility of these compounds was significantly high, particularly in gastrointestinal fluids, with the addition of Tenax, suggesting a closer approximation to their bioavailability. Notably, the study highlighted that the incremental lifetime cancer risk (ILCR) values for several conditions were significantly higher than the safety limits suggested by the United States Environmental Protection Agency (USEPA), indicating serious cancer risks. This comprehensive analysis underscores the severe implications of microplastic pollution, mainly through the lens of human exposure to PAHs and their derivatives sorbed onto microplastics.[52]

In a recent study, Rosellini et al. explored the interactions between cytochrome P450 enzymes and microplastics. They identified three plastic-related with high binding affinity to CYP3A4 using virtual screening and molecular docking. These compounds exhibited cytotoxic effects in hepatic cells overexpressing CYP3A4. RNA-sequencing revealed significant alterations in gene expression, particularly the suppression of mitosis and DNA-templated DNA replication pathways. Cell cycle analysis and single-cell gel electrophoresis corroborated these findings. Additionally, the study identified disruptions in several metabolic and inflammation-related pathways, suggesting hepatotoxicity.[53] In a comparable study, human pluripotent stem cell-derived liver organoids (LOs) were employed to examine the biological impacts of 1 μm polystyrene microplastic (PS-MP) microbeads. Increased hepatic expression of HNF4A and CYP2E1 was noted, implying potential molecular pathways involved in PS-MP toxicity.[54]

Microplastics in Different Types of Cancer: Emerging Concerns

While the impact of microplastics on marine ecosystems and wildlife has been extensively studied, their association with cancer remains an emerging area of research (Figure 2).[1,2] Microplastics enter the environment through various sources, including plastic waste, microbeads in personal care products, and synthetic fibers from textiles.[40,41] The ability of microplastics to adsorb and transport environmental contaminants raises concerns about their potential to act as carriers of carcinogenic compounds.[3] Additionally, the small size and surface properties of microplastics may enhance their uptake by cells and tissues, further exacerbating their potential carcinogenicity.[55,56]

Colorectal Cancer: Microplastics infiltrate the gastrointestinal tract through multiple pathways, such as ingestion of contaminated food and water, inhalation of airborne particles, and direct exposure to personal care products and household items. After ingestion, microplastics have the potential to accumulate in the gastrointestinal tract, which could result in adverse health consequences.[57] The long-term consequences of being exposed to elevated levels of microplastics at a young age have not been fully established yet. A recent investigation reveals the presence of microplastics in colectomy samples from colorectal cancer patients.[58] Microplastics could serve as a means for transporting carcinogenic bacterial toxins to the colonic epithelium. For instance, Escherichia coli, associated with an increased risk of colorectal cancer due to its genotoxin expression, may bind to MPs in the

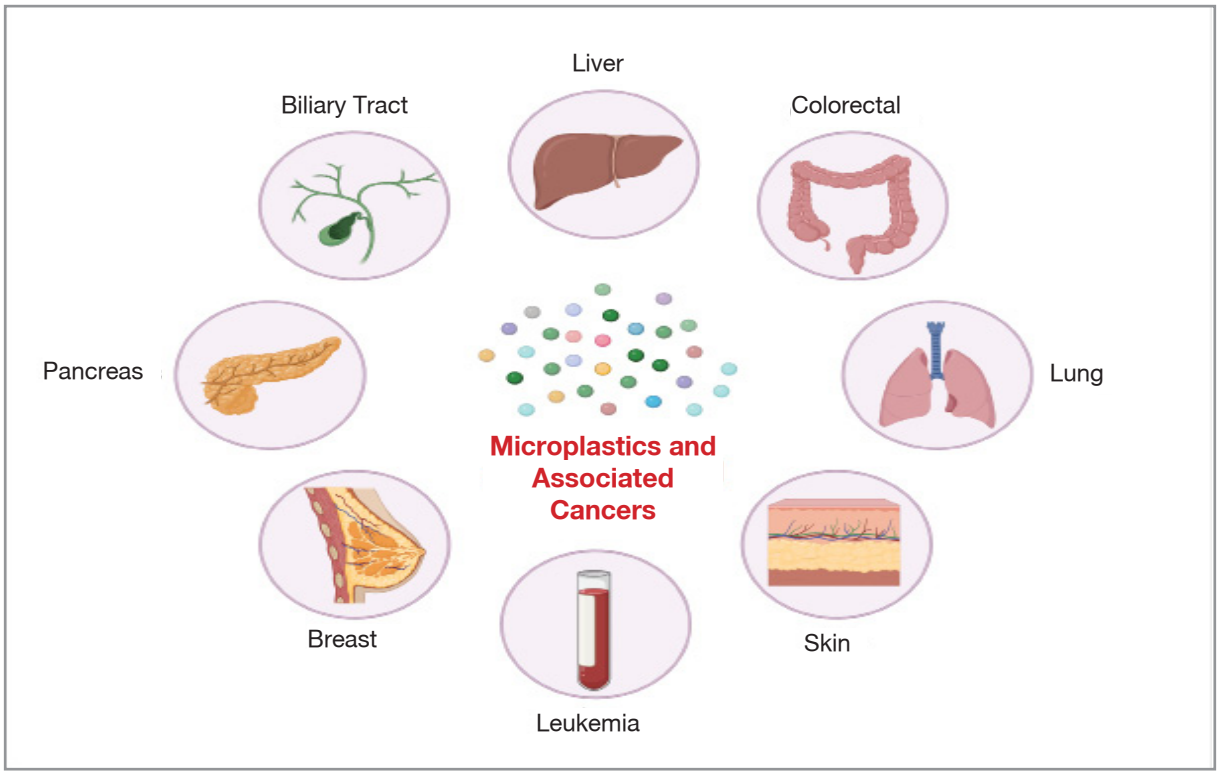

Figure 2. Microplastics and Associated Cancers

colon.[59] If so, MPs carrying adherent pks+ E. coli could potentially deliver these genotoxic bacteria to the colonic epithelium surface. However, this process may be contingent upon the disruption of the intact inner mucus layer.[60] In a study, research findings indicate that the internalization of microplastics leads to metabolic alterations under both short-term and long-term exposure in intestinal cell lines. These changes involve the induction of oxidative stress, elevation of glycolysis through lactate production to support energy metabolism, and enhancement of glutamine metabolism to sustain anabolic processes.[61]

Liver Cancer: Vinyl chloride, which is utilized in the manufacturing of PVC, is widely recognized as a carcinogenic substance, has been shown to cause rare liver angiosarcoma and hepatocellular carcinoma.[62,63] Research on the hepatic effects of polystyrene and styrene in humans primarily concentrated on assessing liver dysfunction through the measurement of enzyme levels in the bloodstream rather than the impact on liver cancer.[64]

Lung Cancer: The potential health effects of microplastics in relation to lung cancer are a topic of ongoing research. With the use of μ-FTIR, Chen, Qiqing, et al. detected a total of 65 microfibers, out of which 24 were classified as microplastics with a size greater than 20 μm, within 100 human lung tissue samples. The occurrence of microfibers in tumor tissue was observed to be 58%, which is higher compared to normal tissue, where it was 46%. Additionally, two-thirds of the identified microplastics were found in tumor tissue.[65]

Skin Cancer :The increasing prevalence of microplastics in cosmetic products and the environment has raised significant concerns within the field of dermatology.[66] Studies have revealed that personal care and cosmetic products can contain significant levels of microplastics reaching up to 50,391 particles per gram.[67] In a recent investigation, two skin squamous cell carcinoma cell lines, SCL-1 and A431, were utilized to assess the influence of microplastics on skin cancer. Through cell behavior experiments, it was observed that microplastics

were absorbed into the skin squamous cell carcinoma cell line in a manner contingent upon both time and dosage. Further analyses unveiled that microplastics promoted the proliferation of skin cancer cells.[47] Several studies have indicated that exposure to microplastics whether in single doses or over the long term, can induce oxidative stress, leading to cell growth restriction and the formation of autophagic structures, ultimately resulting in premature aging.[68]

Breast Cancer: Plastic products are widely acknowledged as sources of estrogenic compounds or endocrine-disrupting chemicals (EDCs). Exposure to these agents may elevate the risk of cancer or metabolic syndrome.[69] The investigation carried out by Park, Jun Hyung, and colleagues focused on examining the influence of polypropylene on human breast cancer cells. The study found that moderate concentrations of polypropylene microplastics (PPMPs) notably quickened the cell cycle of cancer cells and heightened the secretion of interleukin 6 (IL-6) in the MDA-MB-231 and MCF-7 human breast cancer cell lines. Nevertheless, cellular movement and motility were not impacted. Additionally, an analysis of RNA sequencing indicated changes in cancer cell-matrix adhesion and cell cycle-related signaling in human breast cancer cells when exposed to PPMPs. Consequently, prolonged exposure to PPMPs could potentially raise the likelihood of cancer advancement and spread.[1]

Biliary Tract Cancer: Ahrens and colleagues carried out an extensive multi-center study across six European nations. Their findings suggest a possible connection between occupational exposure to endocrine-disrupting substances and the incidence of extrahepatic biliary tract cancer in men, with a particular impact on the extrahepatic bile duct and ampulla of Vater. The study highlights polychlorinated biphenyls as significant contributors to this increased risk.[70]

Leukemia: A recent investigation demonstrated that plastic particles, predominantly composed of polyethylene terephthalate, polyethylene, and polymers styrene have the potential to accumulate within the human bloodstream.[71] Sun and colleagues investigated the effects of polystyrene microplastics on mice, discovering that these particles can cause hematotoxic effects and disrupt metabolic, Jak/Stat, and T cell homeostasis pathways.[72] They noted a drop in white blood cell counts in peripheral blood and a decreased colony-forming capacity in bone marrow cells. These findings suggest that plastic particles in the human circulatory system might similarly lead to hematotoxicity.[73]

Pancreatic Cancer: A multi-center research study looked at how occupational background relates to levels of organochlorines in people with exocrine pancreatic cancer.[74] The study introduced a model to better understand these relationships. It found that individuals working in the metal industry had higher serum levels of polychlorinated biphenyls, whereas those employed in agriculture showed significantly lower levels of organochlorines in their serum.[75] Further research is advised to identify the primary sources of occupational origin of organic compound pollution in electronic waste processing centers and to elucidate the importance of organic compounds in establishing associations between specific industries and the illness.

Conclusion

The widespread presence of micro and nanoplastics in the environment is a growing concern for public health, particularly in relation to cancer. Evidence indicates a potential connection between these small plastic particles and cancer development, as shown in experimental studies. Micro and nanoplastics have been found to cause oxidative stress, inflammation, and cellular damage, all of which can lead to cancer. Public awareness and scientific progress are crucial to address this emerging threat and ensure a safer future for upcoming generations.

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