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Pesticides and Gastrointestinal Cancers

Short Communication

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Introduction

Living organisms such as insects, weeds, mites, mollusks and fungi that have harmful effects on humans, animals and agricultural products are called pests. Pesticides are substances that are used to kill these harmful creatures or change their behavior and can remain intact in nature for a long time. Pesticides include insecticides against insects, fungicides against fungi and molds, herbicides against weeds, rodenticides against rodents, molluscicides against mollusks and chemicals affecting plant growth. Pesticides are commonly used to destroy pests that damage the food substances during their production, preparation and storage [1].

Since 2000 BC humans have utilized pesticides to protect their crops and the first known pesticide was sulphur used in ancient Sumer about 4,500 years ago in Mesopotamia. Until the 1950s, the use of arsenic-based pesticides was widespread but after the discovery of dichlorodiphenyltrichloroethane (DDT) as a very effective insecticide, they were replaced by organochlorines until 1975 [2].

A portion of the pesticides applied against pests that may potentially cause product loss are effective for the target pest, while the remaining majority reach non-target organisms and soil, drifting to the surrounding natural ecosystems. Since pesticides remain active and intact in nature for long periods of time, they cause soil, water and air pollution, disrupting the balance of the ecological system [3,4]. In addition to causing acute or chronic toxicity in humans and animals, food and environmental pollution and disruption of the biological balance, pesticides are also known to have teratogenic, mutagenic and carcinogenic effects. A key mechanism associated with DNA damage in the cells is the formation of reactive oxygen species (ROS). Most pesticides cause oxidative stress by inducing the production of ROS and the resulting damage to cell membrane lipids, proteins and DNA leads to the destruction of pests. Pesticides enter the food chain of humans as a result of plant uptake of pesticide directly or through residues in soil, followed by the use of these plants as human food or animal feed. After ingestion of foods contaminated by pesticides, these substances are not converted into more harmless metabolites through metabolic processes and because they are not water soluble, they cannot be eliminated and gradually accumulate in body fat [5,6]. Potential accumulation of pesticides in the adipose tissue of humans and animals, their toxic effects on non-target species and adverse effects on ecology and human health were first stated by biologist Rachel Carson in 1962 in her work titled “Silent Spring” [7].

Pesticides destroy all forms of life in the soil, be it useful or useless, and eventually resistance develops in the pests that are exposed to pesticides. With progressive loss of soil fertility, farmers use more effective pesticides more intensively every year to increase the yield. However, excessive use of pesticides poses several problems. Fruits and vegetables that are considered healthy are actually

the foods that contain the highest amounts of pesticide residues. Animal products also contain pesticide residues from animal feed or exposure to protective processes against parasites or resulting from bioaccumulation in aquatic food chains as in seafood. The pesticide residues that we are exposed to accumulate in our body, potentially affecting our DNA. It may be too late when we notice the symptoms caused by these substances that poison us insidiously. Exposure to pesticides should not be regarded as a problem that is limited to consumers only. Potential risks associated with inhalation, skin contact and possible exposure of pesticide applicators during the manufacture, transfer and storage of pesticides are also of concern in terms of occupational safety.

Tumor formation in the liver and thyroid tissue induced by some pesticides, mainly organochlorines, has been demonstrated in experimental animals in a dose dependent manner. Epidemiological studies have shown that there is a relationship between pesticide exposure and many types of cancer [8-11]. Prolonged exposure to pesticides results in genotoxicity with a subsequent increase in the risk for carcinogenicity. Thus, detrimental effects of extensive use of pesticides on public health are a source of widespread concern. In this review, the role of pesticides in the etiology of gastrointestinal cancers will be discusses in the light of current literature.

Pesticides and esophageal cancer

Many pesticides including carbamates, organophosphates, thiamethoxam, nitenpyram, chlothianidin, thiachloprid and chlorinated hydrocarbons have genotoxic effects. A pesticide that causes mutation can affect DNA at the gene or chromosome level. For example, mutations causing a single nucleotide change in DNA, addition or removal of base pairs to the DNA sequence lead to changes in the base sequence or composition of DNA. Depending on the alteration, proteins and enzymes with completely different functions or reduced activity may be produced. The resulting structural and numerical chromosomal aberrations vary according to the type of pesticide use, duration of exposure and dose. Hexachlorobenzene and organochlorine pesticides used as fungicides produce carcinogenic effects through their direct action on DNA by alkylating the DNA molecule without entering the biotransformation pathway [12,13].

High levels of basal cell hyperplasia leading to esophageal squamous cell carcinoma were observed in rats exposed to nitenpyram, an insecticide used to destroy leafhoppers. Compared to control group, lower survival rates were found in rats exposed to nitenpyram for two years, and esophageal tumor was identified as the most likely cause of premature death in the group exposed to nitenpyram [14].

Pesticides and gastric cancer

In a case-control study investigating gastric cancer mortality rate in agricultural workers in Brazil where pesticides are extensively used, the risk of death from gastric cancer was shown to be significantly higher among agricultural workers compared to non-agricultural workers. Additionally, the magnitude of the risk of death from gastric cancer increased with the increase in pesticide exposure per agricultural worker. The authors of the study concluded that gastric cancer risk is associated with pesticide exposure in agricultural workers [15].

In a study prompted by heightened concern for cancer risk associated with pesticide residues in food, two pesticides widely used in agriculture, dichlorvos and dimethoate, were found to induce gastric cancer by upregulating the expression of p16, Bcl-2 and c-myc genes in mouse gastric tissue. The study demonstrated gastric tissue cancer in mice exposed to dichlorvos and dimethoate both at a high dose and low doses over a long term [16].

In one study investigating cancer risk among agricultural workers exposed to methyl bromide, a soil fumigant known to produce high acute toxicity with unclear carcinogenicity in humans, increased risk for gastric cancer was observed with increased use of methyl bromide [17]. A recent study examining the link between occupational exposures to pesticides and gastric cancer risk in a total of 5279 cases of gastric cancer reported 1.5 to 2-fold increased odds of developing diffuse type gastric cancer with exposure to pesticides [18].

Increased risk of gastric cancer was observed among agricultural workers from California exposed to high levels of pesticides (2,4-dichlorophenoxyacetic acid, triflurane, malathion, organochlorine insecticides). These findings are consistent with those reported by studies from Europe and suggest that elevated gastric cancer risk among agricultural workers may be attributed to specific and preventable occupational exposure [19].

In a study from Hungary, higher gastric cancer rates were found in the first village with significantly greater pesticide

exposure compared to the second village where alcohol consumption was much higher and pesticide exposure was lower. The authors of the study concluded that pesticides and primarily those containing nitrosamines may have an etiological role in gastric cancer [20].

Pesticides and colorectal cancer

There are epidemiological studies showing a link between exposure to pesticides and the risk of colorectal cancer [9,21,22].

Increased risk for rectal cancer has been reported among farmers in mortality studies from Italy and Iceland [9]. Similarly, increased mortality from rectal cancer was found among workers employed at organochlorine pesticide manufacturing plants in the United States [21]. A high incidence of colorectal cancer was shown in a cohort study of manufacturing workers with exposure to alachlor, a herbicide [22].

In a case-control study involving populations residing in two districts with high and low environmental pesticide exposure in Southern Spain, significantly higher prevalence rates of gastric cancer, colorectal cancer, liver cancer, skin cancer, bladder cancer and brain cancer were observed in the districts with greater pesticide use. A 67% higher risk of colorectal cancer was found in the population living in the areas with greater pesticide use than in the areas with lower pesticide exposure [8].

A study from Egypt reported higher serum organochlorine levels in patients with colorectal cancer compared to healthy individuals [23]. In a study investigating the effects of chronic oral exposure to endosulfan, an insecticide, on histological changes in the colon as well as on in situ expression of β-catenin, P-selectin, IL-6 and TNF-alpha in mice, severe colonic inflammation and preneoplastic lesions were seen starting at six weeks in mice exposed to oral endosulfan at a dose of 2 mg/kg weekly. Moreover, β-catenin and P-selectin levels increased with length of exposure as did serum pro-inflammatory cytokines IL-6 and TNF-alpha [24].

In Brazil which has recently become the largest pesticide consumer across the world, 10-year colorectal cancer mortality rates retrieved from the database of the Ministry of Health were examined in relation to the geographical distribution of the pesticide sales data from the Brazilian Institute of Environment and Renewable Natural Sources and both parameters were found to be concentrated in the Southern and the Southeast regions of Brazil [25]. This confirmed the belief that pesticide use is associated with increased colorectal cancer mortality rates. Likewise, in a study investigating the incidence of cancer among pesticide applicators exposed to Imazethapyr in the US, significantly elevated risk of proximal colon cancer was reported due to altered DNA methylation mechanisms, with no increase in the risk for distal colon cancer or rectal cancer [26].

Pesticides and liver cancer

Neonicotinoids, a broad spectrum insecticide that is highly effective in many crops worldwide have occupied about one-quarter of the global insecticide market until 2010. Formerly considered to have low toxicity, neonicotinoids were subsequently shown to pose potential risk to mammals and even humans. Green et al. demonstrated that thiamethoxam from the neonicotinoid class induces liver tumors in mice and this was the first study to suggest that neonicotinoid insecticides can cause cancer in animals [27]. In an in vivo study attempting to elucidate the mechanisms for liver cancer associated with exposure to nitenpyram and thiamethoxam, the metabolites of these substances were identified to induce carcinoma formation mechanistically [28].

It has been shown in a study that the exo-8,9-epokside metabolite of aflatoxin B1 produced by *Aspergillus flavus* causes the formation of DNA adducts which then interact with the guanine base of the DNA, leading to mutations in the p53 tumor suppressor gene. p53 mutations have been identified in patients with hepatocellular carcinoma with high aflatoxin B1 exposure [29].

In a separate study in patients developing liver cancer caused by chronic exposure to Aflatoxin B1, genetic polymorphisms in DNA repair genes XRCC4 and XRCC5 were examined and the genetic polymorphisms at XRCC4 codon were found to increase liver cancer risk in chronic exposure to aflatoxin [30].

The incidence of liver cancer in relation to pesticide exposure was examined in a review of 14 studies (2 prospective and 12 retrospective) and among these, six studies (40%) reported statistically significant associations (increased risk) between pesticide exposure and hepatocellular carcinoma (HCC). The authors of the review concluded that, given the extensive exposure to pesticides in geographic areas with a high incidence of HCC, future research should focus on improving assessment of pesticide exposure taking into account past exposures,

multiple exposures to pesticides, exposure pathways and the impact of specific organochlorine, organophosphate and carbamate pesticides [31].

A study from China, a country with a high HCC prevalence, reported synergistic interactions of DDT with diabetes mellitus (DM) and aflatoxin B1 which are risk factors for HCC although a clear correlation could not be shown between HCC incidence and DDT, an organochlorine pesticide [32]. A significant increase in the formation of hepatocyte adenocarcinoma was observed in mice exposed to nitenpyram compared to control group. Although there is sufficient data to show that nitenpyram is carcinogenic, further studies are clearly needed to reveal its carcinogenic mechanism [14].

Hepatitis B and hepatitis C are known primary risk factors for HCC. A study was conducted in Egypt where the majority of the population is employed in agriculture to investigate whether exposure to the two most widely used pesticides, carbamates and organophosphates, is a risk factor for HCC cases in rural areas in addition to HCV and HBV infections. No significant association was observed between HCC and pesticides in females and males living in urban areas. However, in that case-control study involving 236 HCC patients, pesticide exposures were shown to be additional risk factors to HCV and HBV infections among rural males [33].

In another study, although it was concluded that exposure to organochlorine pesticides is an independent risk factor for HCC, the role of pesticides in hepatocarcinogenesis has not been established yet [34]. There is limited evidence from human and animal studies and few epidemiological studies exist in literature to draw definitive conclusions about the aforementioned association.

Pesticides and pancreatic cancer

Pancreatic cancer is an infrequent disease but it is associated with a very high mortality rate. Diabetes, pancreatitis, smoking, obesity, family history and pesticide exposure are known risk factors for pancreatic cancer. Several epidemiological studies have reported increased risk of pancreatic cancer in relation to agricultural occupations [35-37].

Increased mortality rates due to pancreatic cancer were shown in a case-control study of 5,886 workers employed at a DDT manufacturing plant. In that study, a 7.4-fold higher risk of pancreatic cancer was reported in workers exposed to DDT for an average of 47 months compared to workers without DDT exposure. The authors suggested that the risk of pancreatic cancer is associated with total duration of exposure and time elapsed since first exposure to the chemical [38]. In a hospital-based case-control study from Spain that observed an exposure-response relationship between serum DDT concentrations and the risk of pancreatic cancer, increased risk was statistically significant only in patients with a K- *ras* mutation [39]. These studies suggest that organochlorines might be associated with pancreatic cancer but only among certain populations or conditions.

Organochlorine compounds may play a role in the pathogenesis of exocrine pancreatic cancer via modulation of K-ras activation. Occupational exposure to DDT increases the risk of pancreatic cancer. The reason for the high frequency of K-ras mutations in pancreatic cancer has yet to be explained. In a study analyzing the association between serum concentrations of selected organochlorine compounds and mutations in the codon 12 of the K-ras gene in patients with exocrine pancreatic cancer, significantly higher serum DDT concentrations were found in pancreatic cancer cases with a K-ras mutation than in cases without a mutation [40].

In a case-control study of 108 cases of pancreatic cancer in which serum organochlorine levels were measured, higher organochlorine levels were detected in cases in comparison to controls [41]. Exposure to organochlorine chemicals occurs in some environmental conditions and occupational settings as well as from the intake of these long-lived compounds and their metabolites with food. Organochlorine compounds such as DDE, the primary metabolite of DDT, are lipophilic, resistant to metabolism and have long term storage in the fat tissue. Since the amount of serum lipids varies among individuals, organochlorine values were adjusted for serum lipid content to estimate the chemical concentration in the lipid fraction of the body in that study. Pancreas cancer is characterized by cachexia; therefore, a sensitivity analysis was conducted assuming a 10 to 40% bioconcentration of organochlorines in case samples, taking into account the bioconcentration of organochlorines in the diminished lipid pool. Organochlorine levels remained elevated in cases compared to controls even at these conditions.

In another study analyzing pesticide concentrations in the adipose tissue samples from the abdominal wall

in patients with pancreatic cancer, increased amounts of pesticides were detected in these tissues. However, it is not clear whether the increased pesticide concentration in the adipose tissue should be attributed to a significant association between pesticides and pancreatic cancer or to an uneven distribution of pesticides in the abdominal wall fat tissue as a result of weight loss in pancreatic cancer [42].

Previous studies have reported an increased risk of pancreatic cancer with organochlorines such as DDT but many other commonly used pesticides have not been studied. A case-control analysis was conducted to further examine potential associations between the use of a number of pesticides and pancreatic cancer in pesticide applicators and their spouses. Among 13 pesticides studied, exposure to two herbicides (EPTC and pendimethalin) was found to be significantly associated with the prevalence of pancreatic cancer. Compared to never users, pendimethalin applicators had a 3.0-fold (95% CI 1.3-7.2, p-trend=0.01) higher risk and the risk increased 2.5-fold with EPTC use (43). Among these herbicides, pendimethalin (*N*-[1-ethylpropil]-2,6-dinitro-3,4-xylidine) is a commonly used dinitroaniline herbicide classified as a Group C possible human carcinogen by the US Environmental Protection Agency. The risk of pancreatic cancer was shown in relation to both of these herbicides but the underlying biological mechanisms have not been described. However, it was highlighted that these herbicides contain nitrosamines and can produce N-nitroso compounds in reaction with nitrite. Being potent animal carcinogens and implicated in many cancers including pancreatic cancer, the involvement of nitrosamines may explain this link.

In another study investigating the level of occupational exposure to pesticides and its association with pancreatic cancer, a significant increase in the risk was observed with increased level of exposure to pesticides. Excess risks were found for occupational exposure to fungicides and herbicides at moderate-to-high level but increased risk of pancreatic cancer was not observed for exposure to insecticides [37]. While carbamate insecticides are considered safe due to their low toxicity and rapid degradation in the environment, it has been recently shown that they may be converted to strong mutagenic and carcinogenic N-nitroso derivatives by interacting with nitrites under weakly acidic conditions. Currently, carbamate insecticides are known to produce carcinogenic N-nitroso compounds in the acidic pH of the stomach and are no longer considered safe.

Previous studies in the literature on pesticide exposure and its association with cancer have mostly focused on breast, prostate and hematologic cancers and few studies exist for gastrointestinal cancers. The mechanisms by which pesticides can trigger the formation of carcinogens have not been elucidated yet. Thus, further studies are warranted to identify the proteins, pathways and pesticide exposure patterns involved in the onset and progression of neoplasia.

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