

A Review: Malignant Diseases and Pesticide Exposure

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ABSTRACT

Pesticides are widely used for crop protection, increasing agricultural product yield, and public health programs. Traditional pesticides include insecticides, herbicides, rodenticides, miticides, fungicides, nematocides, fumigants, and antimicrobial agents. However, these pesticides can negatively affect public health, the ecosystem, and biodiversity. We conducted a review of 162 studies and found that occupational exposure to pesticides was a major trigger for cancer development in 22 papers. Studies have shown that pesticides can cause immunostimulation or immunosuppression, leading to diseases like cancer.

Industrialized nations have seen an increase in these disorders in recent decades due to immune system changes. Tumor patterns are shifting, with an increase in prostate cancer, melanoma, non-Hodgkin lymphoma, and multiple myeloma. Despite limited human studies, many pesticides, such as organophosphate, organochlorine pesticides (OCPs), neonicotinoid insecticides (NEOs), and polychlorinated biphenyls (PCBs), are positively connected with the likelihood of developing cancer, and some are thought to contribute to cancer promotion. The study highlights the importance of increasing education on pesticide exposure to prevent malignancies and emphasizes the need for workers to be trained on safety procedures and hazardous substances. As such, public health programs should prioritize this.

Keywords: Pesticide Exposure, Malignant Diseases, Tumors, cancer development.

INTRODUCTION

Pesticides are applied in many households, companies, and agriculture to manage fungi, insects, weeds, rodents, and even microbiological organisms (Mostafalou and Abdollahi 2017). As the number of chemical pesticides used to battle pests increased, investigations of nonoccupational people revealed more significant impacts on the endocrine system at modest doses (Hardell *et al.*, 2007; Santiago *et al.*, 2021). Over the last decade, there has been exponential growth in the number of articles published on the relationship between pesticides and cancer with the majority of the studies undertaken in the USA, the United States, India, France, and Brazil, with participation from an additional seventeen different countries. Insecticides, fungicides, and herbicides were the three main types of pesticides studied for their role in intoxication and cancer.

Pesticide-associated illnesses include numerous forms of cancer (Calaf, 2021). Multiple myeloma, non-Hodgkin lymphoma, bladder cancer, leukemia, breast cancer, and prostate cancer were the most often reported cancers. And debate still surrounds the pesticides covered by the International Agency for Research on Cancer (Pearce *et al.*, 2015) and Trasande (2017). Most evidence in the IARC report and elsewhere suggests pesticide carcinogenicity, which has resulted from

animal and mechanistic investigations. Since then, epidemiologic evidence has expanded to include pesticides not reviewed by IARC or other organizations (FAO, 2017).

IARC concluded in 2017 that tetrachlorvinphos, malathion, parathion, glyphosate, and diazinon were among the five main organophosphate pesticides, in addition to one herbicide and a few insecticides have been linked to human exposure that was either "probably carcinogenic to humans" (group 2A) or "possibly carcinogenic to humans" (2B), The most likely mechanisms of action, according to the report, are oxidative stress and genotoxicity (Guyton *et al.*, 2015). Even though there is a proven link between pesticides and cancer, research on the subject is still sparse when compared to the amount of xenobiotics used worldwide. This is a result of rising global demand for agricultural products (Pedroso *et al.*, 2022).

The current review focuses on epidemiological research on pesticide exposure and the hazard of cancer in humans, published during the previous five years. We connect this newly acquired data with the most relevant previous reviews and discuss methodological methods and gaps in the existing research. Our work aims to properly review and assess various results on pesticides and cancer, as well as to offer new avenues for improving potentially valuable information.

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METHODS

A systematic review of the literature was performed by searching the National Library of Medicine and National Institutes of Health PubMed, Web of Science (open access), and Scopus databases for the last five years using the following keywords: Pesticide exposure, malignant diseases, and cancer risk. Out of 162 studies, occupational pesticide exposure has been identified as a major cause of cancer development in 22 papers. Pesticides, including insecticides, herbicides, and fungicides, are used to determine the association between cancer and pesticides in some countries based on their chemical makeup and consist of a wide range of traditional chemicals such as insecticides, herbicides, rodenticides, plant growth regulators, nematicides, miticides, fumigants, fungicides, and antimicrobial agents. These items are classified by the Environmental Protection Agency (EPA) for 2020.

RESULTS AND DISCUSSION

RESULTS

Globally, about three billion tons of insecticides are applied annually, costing about \$40 billion (Sharma *et al.*, 2020). Several pesticides include organophosphorous pesticides (OPs) such as malathion, parathion, tetrachlorvinphos, glyphosate, and diazinon. Are widely used for crop protection, increasing agricultural product yield, and in public health programs in the home and gardens, industry, commerce, and government worldwide. They presently account for around 35% of pesticides (Calaf, 2021). Pesticides, while necessary for agricultural production, can have serious negative effects on biodiversity, the environment, and, in particular, public health (Vale *et al.*, 2019; Sharma *et al.*, 2020; Ramos *et al.*, 2021). Also, several studies have shown that pesticides' harmful effects can cause immunostimulation or immunosuppression. Pesticide-related illnesses include cancer (Barnett and Brundager, 2010; Corsini *et al.*, 2013; Mostafalou and Abdollahi, 2017; Calaf, 2021; and Ramos *et al.*, 2021), table 1.

Industrialized nations have seen a considerable increase in such disorders in recent decades, which can be related to changes in immune system function (Burr *et al.*, 1989; Cooper *et al.*, 2002; Selgrade *et al.*, 2006; Jacobson *et al.*, 2020). In addition, epidemiological statistics show that tumor patterns are shifting over time, with rising cases of prostate cancer, non-Hodgkin lymphoma, melanoma, and multiple myeloma in this world.

Despite the limited number of human studies, Yang *et al.* (2020) discovered that chlorpyrifos, malathion, and terbufos were all linked to an increased risk of human breast cancer, and some laboratory investigations revealed that chlorpyrifos and malathion have estrogenic effects and other cancer-causing qualities. The study encompassed agricultural settings in a variety of geographical areas across the United States. However, it did not look at cumulative exposure.

In Iowa and North Carolina, Lerro *et al.* (2021) found that using lindane and metalaxyl raised the chance of thyroid cancer, but carbaryl had the opposite effect. They indicated that more research is needed to determine the possible relevance of these substances in thyroid carcinogenesis. (Karavasiloglou *et al.*, 2022) discovered that the outcomes of eight prospective cohort studies were done in Europe and the USA among over 500 publications, indicating a slight inverse correlation between increased adherence to sustainable diets and cancer incidence or death.

Thyroid cancer incidence has risen dramatically in recent decades, with environmental risk factors suspected to play a role. Organochlorine pesticides (OCP) and polychlorinated biphenyls (PCB) are recognized thyroid hormone disruptors, but their association with thyroid cancer is unknown. On the contrary, the data from Connecticut, U.S.A., do not usually show a relationship between PCB/OCP exposure and thyroid cancer risk, although certain correlations in the younger birth cohort indicate that more research into early-life exposures is necessary (Deziel *et al.*, 2021).

Some studies have linked organophosphate pesticides (especially the organodithioate family) and organochlorine to an elevated risk of clinically significant prostate cancer subtypes and discovered a negative link between advanced prostate tumors and the herbicide triclopyr, particularly among individuals who used it for more than four years. After analyzing the full data from this large cohort of private pesticide applicators in North Carolina and Iowa, a few more chemicals were linked to prostate cancer risk (Pardo *et al.*, 2020).

Vasan *et al.* (2023) discussed the possible effects of endosulfan exposure, citing the persistent and semi-volatile, biomagnifying, and bioaccumulative features of endosulfan metabolites in especially. Despite limits on endosulfan use, studies on the association between thyroid cancer incidence rates and endosulfan exposure in the U.S. have shown that it is effective.

Table 1. classification of Studies according to Type of Cancer, Country, and Pesticide Use

Studies (first author and year)	Types of cancer	country	Chemicals use
Yang <i>et al.</i> (2020)	prostate cancer, melanoma, non-Hodgkin lymphoma, and multiple myeloma	United States	Chlorpyrifos, malathion, and terbufos
Lerro <i>et al.</i> (2021)	Thyroid cancer	U.S.A. (Iowa and North Carolina)	Lindane and metalaxyl
Karavasiloglou <i>et al.</i> (2022)	cancer incidence	Europe and the USA	Pesticide exposure
Deziel <i>et al.</i> (2021).	Thyroid cancer	U.S.A. (Connecticut)	Organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs)
Pardo <i>et al.</i> (2020)	Prostate cancer	U.S.A. (North Carolina and Iowa)	Organophosphate pesticides and organochlorine
Vasan <i>et al.</i> (2023)	Thyroid cancer	United States	Endosulfan
Kim <i>et al.</i> (2023)	Hodgkin lymphoma (HL)	French, United States, and Norwegian	Pyrethroids, deltamethrin and esfenvalerate
Aguayo <i>et al.</i> (2021)	Tumor development and may be implicated in Epstein-Barr virus (EBV)-associated malignancies.	France	Pesticide exposure
Van Gerwen <i>et al.</i> (2023)	Thyroid cancer	Italy (Seveso)	TCDD exposure
Peñalver-Piñol <i>et al.</i> (2023)	Endometrial cancer	Spain	Pesticides, fungicides, and herbicides.
Norouzi <i>et al.</i> (2023)	Thyroid cancer	Spain	Insecticide exposure
Abhishek <i>et al.</i> (2020)	Prostate cancer (PCa)	India	β-HCH, Malathion, Fenvalerate, and Chlorpyrifos
Varghese <i>et al.</i> (2021)	Lung cancer, prostate cancer, multiple myeloma, and colon cancer	India	Organophosphate and organochlorine
Garg <i>et al.</i> (2021)	Breast cancer	India	Organochlorine pesticides (OCPs)
Thakur <i>et al.</i> (2021)	Cancer risk	India	Organophosphate pesticides
Shah <i>et al.</i> (2020)	Ovarian cancer (EOC).	India	Pesticide exposure
Bonan <i>et al.</i> (2021)	Head and neck cancer sites (pharynx, larynx, and nasal cavity)	Brazil	Pesticide exposure
Da Silva Leonel <i>et al.</i> (2021)	Head and neck cancer	Brazil	Insecticide exposure
Zhang <i>et al.</i> (2022)	Liver cancer	China (Guangzhou)	Neonicotinoid insecticides (NEOs)

Kim *et al.* (2022) reported 91 cases of Hodgkin lymphoma (HL) among data from three agricultural cohorts in the AGRICOH consortium: the French agriculture and cancer cohort from 2005 to 2009, the United States agricultural health study from 1993 to 2011, and Cancer in the Norwegian Agricultural Population from 1993 to 2011. The pyrethroids deltamethrin and esfenvalerate were shown to have the highest overall risk of HL, while parathion and glyphosate had comparable inverse relationships. The risk of Hodgkin lymphoma (HL) at age forty and above

was highest for dicamba usage and lowest for glyphosate.

According to a review in France conducted by Aguayo *et al.* (2021), it has been postulated that, because cancer affects only a small proportion of the human population, pesticide exposure is an element essential for tumor development and may be implicated in the Epstein-Barr virus (EBV)-associated malignancies that lead to cancer. In Seveso, Italy, Van Gerwen *et al.* (2023) review the limited evidence on the potential link between thyroid cancer and TCDD exposure from three studies that assessed acute

exposure to a chemical plant accident. They found a non-significant increase in the hazard of thyroid cancer. However, no correlation was identified in one investigation that assessed exposure to TCDD compounds by herbicides.

In Spain, Peñalver-Piñol *et al.* (2023) indicated that endometrial cancer was linked to occupational exposure to pesticides, fungicides, and herbicides.

Norouzi *et al.* (2023) found contradictory results between thyroid cancer and pesticide exposure in the surveyed papers on OCPs. The causes of inconsistencies in results are attributed to (a) the limited number of studies, (b) the various ways to assess exposure, some of these include the use of questionnaires, interviews, blood or serum collection, and (c) the study's various designs.

In India, Abhishek *et al.* (2020) observed higher amounts of pesticides such as β -HCH, Malathion, Fenvalerate, and Chlorpyrifos in prostate cancer (PCa) group patients. The Kruskal-Wallis H test revealed a significant correlation between β -HCH and Malathion levels and higher grades of infection PCa. Also, Varghese *et al.* (2021) found that pesticide applicators are at a higher risk of developing cancer. Pesticides classified as organophosphate and organochlorine were the most commonly linked to cancer. Pesticide applicators had the highest rates of lung cancer, followed by prostate, multiple myeloma, and colon cancer. Garg *et al.* (2021) explained Exposure to organochlorine pesticides (OCPs) may be particularly significant in developing nations like India, where these compounds are widely used in agriculture and may be a hazardous agent for breast cancer. 18 different types of OPCs and six OCs (γ -hexachlorocyclohexane (HCH), δ -HCH, endosulfan, endrin, dichlorodiphenyldichloroethane (DDD), and dichlorodiphenyltrichloroethane (DDT)) were found in the tissues of breast cancer patients (BC). Endosulfan, DDT, and DDD tissue levels are considerably greater in breast cancer patients. Thakur *et al.*'s (2021) epidemiological and molecular research found that exposure to organophosphate pesticides is connected with elevated cancer risk. Shah *et al.*'s 2020 epidemiological investigation verified that pesticide exposure increased the incidence of epithelial ovarian cancer (EOC).

In this regard, according to Boman *et al.* (2021) and Da Silva Leonel *et al.* (2021), certain high-quality studies have revealed a positive correlation between pesticide exposure and many head and neck cancer sites, including the pharynx, larynx, and nasal cavity, especially when exposure frequency was considered.

In Guangzhou, South China. Zhang *et al.* (2022) provide new insight into the toxicity to the liver of

neonicotinoid insecticides (NEOs) and their metabolites, suggesting that human exposure to neonicotinoid insecticides and their metabolites may raise the risk of liver cancer.

DISCUSSION

Pesticides are poisonous and biological agents used to control dangerous pests. Their use in agricultural areas and households exacerbated environmental contamination. Studies have shown that they are hazardous to human health, particularly in youngsters, who are more sensitive than adults. The IARC (International Agency for Research on Cancer) has designated numerous chemicals as carcinogenic. Pesticide manufacturing, transport, and usage can cause acute or chronic cytotoxic illnesses, genotoxic processes with immunotoxicity, hormonal abnormalities, or carcinogenesis (Kapeleka *et al.*, 2019 and Saad-Hussein *et al.*, 2019). pesticides can create free radicals, which causes oxidative stress, as well as changes in the enzymatic system that eliminate and deplete the antioxidant reservoir in the cell, resulting in DNA damage, mutations, double-stranded DNA, chromosomal breaks, and the formation of DNA adducts (Cuenca *et al.*, 2019 and Marcelino *et al.*, 2019).

According to epidemiological research, pesticides are a big worry for human health, particularly the development of cancer. After examining multiple studies, we discovered that most showed a strong link between an elevated cancer incidence rate and pesticide exposure. Mechanistic research found that pesticides may raise the risk of several cancers through genetic factors such as increased expression of genes such as p21 and p53, as well as epigenetic defects. Cell cycle disruptions, such as increasing the G1 to S phase transition, are another pathway of cancer formation. DNA methylation and histone alterations raise the hazard of many malignancies (Ataei and Abdollahi, 2022).

Organochlorine (OC) pesticides are one of the most extensively researched pesticide categories. OC insecticides and their residues have the potential to greatly promote cancer in humans. Many investigations have linked pancreatic cancer to organochlorine chemicals, perhaps by modification of K-ras activity (Porta *et al.*, 1999; Hoppin *et al.*, 2000; Hardell *et al.*, 2007; Ataei and Abdollahi, 2022). Also, Organophosphorus toxicants impede thyroid hormone activity by affecting many components of the hypothalamus-pituitary-thyroid axis (Rashidi *et al.*, 2020).

DDT and hexachlorobenzene were shown to be substantially related to colorectal cancer. The Cyclodienes family had comparable findings.

Polychlorinated biphenyls at low doses have also been linked to colorectal cancer. In this regard, Zárata *et al.* (2023). explained that exposure to hexachlorobenzene (HCB) at relevant concentrations activates the kynurenine pathway and disrupts ER β and GPER levels, contributing to the advancement of HER2-positive breast cancer. Thakur *et al.* (2021) found that rising cancer rates are connected to organophosphate pesticide-induced oxidative stress. Organophosphates, carbamates, and triazines yielded equivocal results (Cavalier *et al.*, 2023). Da Silva Leonel *et al.* (2021) stated that there was widespread agreement on the favorable association between pesticides and HNCs such as laryngeal, pharyngeal, and nasal malignancies, particularly when exposure frequency was considered.

Finally, increasing the educational level of people who have been exposed to pesticides can help them avoid malignancies (like HNCs). So we are emphasizing the need to educate and train workers on proper safety procedures and make them aware of dangerous substances. As such, public health programs should prioritize this.

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الملخص العربي

مراجعة : الأمراض الخبيثة والتعرض للمبيدات الحشرية

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الأورام، مع زيادة في سرطان البروستاتا، والورم الميلانيني، وسرطان الغدد الليمفاوية اللاهودجكين (HL)، والورم النقوي المتعدد. وعلى الرغم من الدراسات البشرية المحدودة، فإن العديد من المبيدات الحشرية، مثل مركبات الفوسفات العضوي، والمبيدات الحشرية الكلورية العضوية (OCPs)، والمبيدات الحشرية النيونيكوتينويد (NEOs)، وثنائي الفينيل متعدد الكلور (PCBs)، ترتبط بشكل إيجابي باحتمالية الإصابة بالسرطان، ويعتقد أن بعضها يساهم في تعزيز السرطان.

تسلط الدراسة الضوء على أهمية زيادة الوعي الصحي حول التعرض للمبيدات الحشرية للوقاية من الأورام الخبيثة وتؤكد على ضرورة تدريب العمال على إجراءات السلامة والمواد الخطرة. وعلى هذا النحو، ينبغي لبرامج الصحة العامة أن تعطي الأولوية لهذا الأمر.

تستخدم مبيدات الآفات على نطاق واسع لحماية المحاصيل الزراعية وزيادة إنتاجيتها ، وفي برامج الصحة العامة. وتشمل مبيدات الآفات التقليدية : المبيدات الحشرية، ومبيدات الأعشاب، ومبيدات القوارض، ومبيدات العناكب، ومبيدات الفطريات، ومبيدات النيماطودا، ومواد التبخير، والعوامل المضادة للميكروبات. ومع ذلك، يمكن أن تؤثر هذه المبيدات سلباً على الصحة العامة والنظام البيئي والتنوع البيولوجي. لقد أجرينا مراجعة لـ ١٦٢ دراسة ووجدنا أن التعرض المهني للمبيدات الحشرية كان سبباً رئيسياً لتطور السرطان في ٢٢ ورقة بحثية. أظهرت الدراسات أن المبيدات الحشرية يمكن أن تسبب تحفيز المناعة أو كبتها، مما يؤدي إلى أمراض مثل السرطان.

وقد شهدت الدول الصناعية زيادة هذه الاضطرابات في العقود الأخيرة بسبب التغيرات في جهاز المناعة. تتغير أنماط