

Review Article

Organochlorine pesticides application, xenobiotic metabolizing gene polymorphism and incidences of cancers in India: a review

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ABSTRACT

Excessive application of pesticides on crops has been noticed to gain maximum yield. It results in heavy damage to human health as well as environment. Pesticides application beyond permissible limit has detrimental effects on ecosystem. Organochlorine compounds are widely used as pest controller. These are considered as substantial environmental pollutant and carcinogens due to their extensive environmental release. There are sufficient numbers of studies that supports positive co-relation of organochlorine pesticides with cancer. To evaluate these detrimental effects on human health we have reviewed various studies and concluded the positive co-relation of organochloro compounds with cancers. In this study, the altered metabolism effects of organochlorine pesticides on cytochrome P450 enzyme have been observed.

Keywords: Organochlorine pesticides, Cytochrome P450, Cancer

INTRODUCTION

Cancer has a complicated and multifactorial aetiology that includes both hereditary and sustainable or environmental components.¹ According to various research, hormone-mediated actions of both endogenous and exogenous hormonal drugs enhance the risk of prostate cancer.^{2,3} According to Sonnenschein and Soto (1998), endocrine disruptors are exogenous chemicals that imitate hormones and interfere with physiological working of endogenous hormones. They may also operate as tumour promoters.^{4,5} p,p'-dichlorodiphenyl- dichloroethylene (p,p'-DDE), hexachlorohexane (HCH), dieldrin and p,p'-dichlorodiphenyl- trichloroethane (p,p0-DDT) are examples of OCPs and their derivatives that have modest androgenic and estrogenic effects.²

India has recently been identified as one of the top producers and consumers of OCPs among nations that still use them. Due to their low cost and adaptability, organochlorine pesticides (OCPs), particularly DDT and

HCH, have been widely utilised in India for both agricultural and health purposes over the past several decades. However, there is a propensity to use OCPs in excess. In India, the output of pesticides- particularly insecticides like DDT and HCH- rose from 5000 to 85,000 metric tonnes between 1958 and 2004.⁶ Organochlorine pollutants are currently one of the major environmental concerns, along with exposure to persistent organic pollutants (POPs).

Organochlorine pesticides are flammable and can be applied to crops, used in homes, disposed of in landfills, either legally or illegally, or released into the air by factories or stockpiles. These substances can stick to soil, airborne particles, and aquatic systems. OCPs adsorb to sediments and bioaccumulate in fish and other aquatic species.⁷ These substances are pervasive anthropogenic environmental pollutants that have been connected to a number of health hazards and environmental harm. OCP applications, such as DDT and HCH, have raised concerns in tropical Asian nations because they account for a

significant portion of pesticide usage.⁸ Widespread human exposures are probably to blame for the so-called 'silent pandemic' of neurodevelopmental problems.⁹ Exposure to various categories of organochlorine (OC) pesticides has been linked to adverse health effects such as cancer, birth defects, reproductive defects, neurological and developmental impairment, immunotoxicity, and disruption of the endocrine system, according to epidemiological and other laboratory studies in animals.¹⁰ These substances offer a major health danger, especially to young children whose enzymatic and metabolic systems are still developing.¹¹ Numerous epidemiological research indicates that maternal employment in agriculture may increase the incidence of birth abnormalities when pregnant women are exposed to OCPs.¹² They linger in the body for a long time because they are lipophilic. These chemicals are persistent and considerably more dangerous to people because of their long biological half-lives in both humans and the environment.¹³ Additionally, studies indicate that these endocrine disrupting herbicides may contribute to cancer.¹⁴ Prostate cancer risk and ED use has recently become the subject of in-depth research.¹⁵ Results, however, are contradictory and are not particular.

Human xenobiotic metabolising gene polymorphism exhibits parallel behavior in ethnical, geographic and racial distribution, and the CYP and GST genes' ethnic-specific effects are well-known.¹⁶ A significant separate ethnic group that makes up one-sixth of the global population is the Indian population.¹⁷ The Caucasoid Aryan population of North India differs ethnically from the Caucasoid Dravidian population of South India.¹⁸ Therefore, research is needed to determine the frequency of gene variation in various populations that may be related to the risk of developing certain cancers.

A crucial phase I xenobiotic metabolising enzyme called cytochrome P450 (CYP) 1A1 is in charge of the anabolism of steroidal hormones and several carcinogens, inclusive of oestrogen.^{19,20} It is recognised that CYP1A1 polymorphisms can modify the activity of the enzymes and potentially change how steroidal hormones and carcinogens are metabolised. As a result, CYP1A1 polymorphisms have been linked to an increased risk of many malignancies, including prostate cancer.²¹ In our prior investigation from the same group, we observed that some of the CYP1A1 polymorphisms were common.²⁰ As a result, exposure to increased concentrations of these 'carcinogenic chemicals', particularly in 'high-risk genotypes', could further raise prostate cancer risk.

CANCER

A pathologic build-up of clonally grown cells that share a common ancestor is cancer. Genetic damage, which is often acquired but can occasionally be congenital, is the underlying cause of all malignancies. In most cases, the genetic instability that results in unchecked cell proliferation is caused by the activation of oncogenes that promote growth and/or the deletion or inactivation of

tumour suppressor genes that limit growth. Genes that control DNA repair and programmed cell death (apoptosis) also contribute to the development of cancer. The most generally accepted theory of how cancer develops is the Knudson '2-hit' hypothesis, which asserts that a mutation in one predisposing gene is necessary but insufficient for malignancy and that invasive cancer will only emerge after the occurrence of a second mutation.²² It is now commonly acknowledged that the accumulation of driver gene alterations that progressively boost cell proliferation results in cancer.²³ Environmental variables play a significant role in the progression of cancer, according to epidemiological research, and this has important implications for primary prevention. Both twin studies and the discovery of the genes responsible for cancer risk syndromes have decisively shown the importance of heredity.^{24,25}

TYPES OF CANCER

Breast cancer

Women were frequently diagnosed with breast cancer, which has become one of the most prevalent cancers in women.²⁶ The incidence of breast cancer has been rising globally recently, according to the GLOBOCAN report. India is a subcontinent with significant differences in its health care system and in terms of its ethnic, cultural, religious, and economic diversity. The distribution of health care facilities is uneven, with many areas still lacking access to the advantages of programmes for early detection, education, and multimodal treatment. Due to growing incidence and awareness, breast cancer is frequently found in females in Indian urban areas and it is second most common among those in rural areas.²⁷ Previous research has found a strong correlation between organochlorine pesticides (OCPs) and an increased risk of breast cancer among environmental pollutants connected to the disease.²⁸ Pesticides are a class of chemical substances used to kill and/or control a variety of pests, such as weeds, bacteria, fungi, and insects.²⁹ Breast cancer has been divided into five classes based on gene expression profiles. Two of them (luminal A and luminal B) are caused by ER-positive tumours, and three of them (basal-like, HER2-positive, and normal-like) are caused by ER-negative tumours.³⁰

Lung cancer

The most frequent cancer in men is lung cancer, which poses a serious public health issue in India. In comparison to women, men are more affected. The most likely causes could be more exposure to tobacco smoke, air pollution, and other risks that men encounter more frequently than women. HBCR statistics from RCC Trivandrum reveal that men are more often than women to develop lung cancer, with a male to female ratio of 4.7 to 1.³¹ Thiruvananthapuram, Kerala, India; 2015). In both men and women, lung cancer is the most prevalent type of cancer, accounting for 17% and 8%, respectively, of new

cancer cases and 18% of all cancer-related deaths worldwide.³² Lung cancer risk factors are tobacco smoking and other environmental variables (such as ionising radiation, asbestos, metals, silica, polycyclic aromatic hydrocarbons, and air pollution).³³

Prostate cancer

High serum levels of OCPs, which are highly persistent organic pollutants, have been observed in a number of populations.³⁴ The IARC classed large number of OCPs as Class 2B (possible carcinogens).³⁵ In addition, it has been demonstrated that several OCPs have the ability to alter the endocrine system.³⁶ Because of this, it has been suggested that exposure to these particular pesticides may raise the risk of malignancies that depend on hormones.³⁷ The most prevalent malignant tumour and the second leading cause of cancer death in males is prostate cancer (PCa).³⁸

Tumour metastasis, in which cancerous cells migrate from the main tumour to nearby organs such as the bone, lung, and brain, is a factor in the poor prognosis of prostate cancer.³⁹ Although prostate cancer is the most frequently detected malignancy in men in North America, little is known about its origin.⁴⁰ In accordance with Stanford and Ostrander (2003), environmental risk variables such as lifestyle, vasectomy, medical history, employment history, and nutritional variables have also been looked at. Genetic factors account for about 10% of instances of prostate cancer.⁴¹ Given that both estrogens and androgens may play a role in the aetiology of prostate cancer (PC), this disease has recently gained a lot of attention.⁴² Additionally, due to the disease's rising occurrence around the globe, unidentified origin, and high prevalence among farmers and in regions with heavy pesticide usage, research into the effects of environmental and occupational exposures was necessary.⁴³

Colorectal cancer

The third most frequent cause of cancer-related death worldwide for both males and females is colorectal cancer.⁴⁴ However, death rates are higher in less developed nations because they have poor infrastructure and scarce resources for healthcare. The death rates in various Western Countries have been declining because of numerous other factors, including timely discovery thanks to screening and improved CRC care.⁴⁵ The ASR in India for CRC is quite down, 5.1 per 100,000 females and at 7.2 per 100,000 males (Fact sheet). The absolute number of CRC patients is high in a nation with a resident of more than 1 B people. India has one of the lowest rates of CRC survival after five years, at less than 40%. In reality, the CONCORDE-2 study shows that in some registries, the 5 year survival rate for rectal cancer in India is decreasing.

In most parts of the world, men are more likely than women to develop CRC.⁴⁶ Our patients made up 65 percent of men. However, there can be a bias against going to a referral centre for treatment in this situation. The

average age of those who participated in our study was 47.2 years. 35% of the patients had an average patient age of under 40 and under 60. In an eastern Indian study of 168 patients with sporadic CRC, the mean age at presentation was 47.01 years; however, in a retrospective descriptive analysis of 220 instances of sporadic CRC diagnosed by colonoscopy over a five-year period, the mean age at presentation was 58.4 years.⁴⁷ Even though they only involved a limited number of patients, other Indian research have produced comparable findings, raising the question of whether CRC develops earlier in India.⁴⁸ Some incidences of CRC in the initial phases are asymptomatic and can be diagnosed by screening. Patients who are symptomatic may show up in an emergency scenario with bleeding, pain or obstructive symptoms, or, in rare instances, obstruction or perforation. Although the majority of prominent societies in industrialised countries recommend colon cancer screening, adoption rates are often low, and the majority of CRC would be detected when symptomatic. With a median symptom duration of 4 months, rectal bleeding was the most common symptom among our patients. It was followed by altered bowel habits (25.6%) and pain (44%). Most studies have found that CRC patients experience similar characteristic symptoms.⁴⁹

Cervical cancer

Due to its extremely toxic nature and ecological accumulation, pollution from OCP and potentially toxic elements (PTE) is a problem for people all over the world.⁵⁰ As a result, they may seriously harm the public's health as well as ecological cycles. Some PTEs and OCPs operate as endocrine disruptors, altering hormonal balance, primarily through chronic exposure, and causing malignancies in addition to immunological and reproductive problems. The second most frequent type of cancer among women in developing nations is uterine cervix cancer.⁵¹ Following the discovery of a significant correlation between high-risk persistent human papillomavirus (HPV) infections and the development of cervical cancer, HPV-related control strategies for its prevention were created.⁵² The annual burden of cervical cancer has decreased by 50-70% in a number of wealthy nations that have established the HPV DNA or Pap test as the principal technique of detection.⁴⁵ Using VIA every five years for women between the ages of 30 and 65, the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS) of the GOI in recent past started a resident based cervical cancer diagnosis programme (in hundred districts as a preliminary programme) (Indian Government).

Ovarian cancer

With the greatest fatality rate of any disease of the female reproductive system, the 5th most ordinary cancer is ovarian cancer.⁵³ Cancer of ovary has been identified as the 3rd most common malignancy among women in India.⁵⁴ Epithelial ovarian cancer (EOC) accounts for 80-

90% of ovarian cancer instances.⁵⁵ Ovarian cancer is brought on by the alteration of ovarian surface epithelial cells, germ cells or sex cord and stromal cells. EOC is far more frequent than the embryonal or germinal ovarian cancers frequently seen in adult age women and becoming more common in pre-menopausal women and post-menopausal women.⁵⁶ EOC has a significant mortality rate due to its clinical silence, non-specific symptomatology, and typical late-stage diagnosis. Age at menopause and menarche (late menopause or early menarche), oral contraceptive consumption (progesterone and/or oestrogen), past record of family, genetic variables, environmental exposure, occupational exposure and inflammation are the main etiological factors that have been identified. Environmental toxins created by humans are multiplying, and many of them pose real health risks. Pesticides are one of the largest and most dangerous types of poisons used globally among ubiquitous organic environmental toxins.⁵⁷

There is data that suggests one of the main environmental causes of EOCs is the use of organochlorine pesticides (OCPs).⁵⁸ OCPs have been routinely utilised for at least 60 years, which has contributed to the current level of environmental day.⁵⁹ In India, insecticides, herbicides, and fungicides are majorly employed in agrarian practises and initiatives for public safety or health.⁶⁰ In addition to the targeted species, more than 95% of sprayed herbicides and 98% of sprayed insecticides reach the non-target living systems, food, bottom sediments, air and water.⁶¹ According to several recent studies, these OCs may change the assertion of a number of transcripts across the genome, which could lead to the development of numerous etiopathologies, including cancer.⁶² Given that there appears to be a rise in the prevalence of ovarian cancer instances in North India, it is important to comprehend the alterations in the transcriptome expression of ovarian cancer individuals in combination with their tissue OCP levels as well as the widespread application of OCs in this area.^{63,64}

Bladder cancer

In the world, bladder cancer (BC) is the twelfth most prevalent kind of cancer.³² The most common kind of BC, transitional cell carcinoma (TCC), accounts for around 90% of all BC cases. It has been noted that uroepithelial cells are extremely vulnerable to the by-products of several chemical chemicals, such as those that cause cancer.⁶⁵ One of the most common symptoms of BC is blood in the urine (haematuria), which can either be tiny or visible to the naked eye (macroscopic).⁶⁶ Bladder cancer is the second most common malignancy in middle-aged and older men, behind prostate cancer.⁶⁷ UBC has a complex aetiology that is caused by both external and endogenous (patient-related) causes. Exogenous risk factors include smoking, exposure to pesticides such organochlorine pesticides (OCPs), aromatic amines, heavy metals, and environmental contaminants. Additionally, dietary variables may play a protective or causal role in the

development of UBC.⁶⁸ The usage of pesticides in agriculture is crucial in causing oxidative stress or an imbalance of antioxidants.⁶⁹ They have been interacting with life and eventually leading to genetic and chromosomal defects such single-strand and double-strand DNA breakage, improper insertion into the DNA structure, DNA adduct creation, and epigenetic changes of the genes.⁷⁰ OPs are phosphorus-containing organic compounds. They consist of a lateral side chain and two organic chains.⁷¹ Ops are quickly digested by the human body, making it impossible to test them in their intact form in the blood or urine.⁷² Biological monitoring using the right biomarkers is one of the finest approaches to gauge OP exposure levels and, subsequently, identify their biochemical consequences on the human body.⁷³

Kidney cancer

The natural history of kidney cancer, also known wrongly as renal cell carcinoma, is uncommon. It is the tenth most frequent cancer in the USA, and since 1973, both the incidence and death rate have climbed by 43% and 16%, respectively.⁷⁴ 95 000 fatalities per year are thought to be caused by kidney cancer worldwide. Men are two to three times as likely as women to develop cancer.⁷⁵ 10% of people with chronic kidney disease (CKD) worldwide and 16% in the Indian subcontinent have an aetiology that is unclear. CKD's pathogenesis is still unknown, despite epidemiological research suggesting that environmental pollutants may have a factor.⁷⁶ The extensive use of organochlorine compounds on crops and generally in public health occasions makes it more persistent in environment for too long. The half-life in terms of biological sense of OCPs is very lengthy and they are lipophilic i.e., dissolvable in fats or lipids by nature, which causes biological accumulation of OCPs in body and growing worries about their potentially harmful impacts on health of human population.

The detrimental effects of OCPs consists various systems, including the reproductive system, the integumentary system and the respiratory system.^{70,77} Experimental animals have shown that OCP causes histological changes in the kidney, including the glomerular cells and renal tubular parenchymatous degeneration.⁷⁸ Patients with chronic renal illness may accumulate OCPs for unknown reasons. In addition to the decreased kidney excretory function associated with CKD, it's probable that the multiformity of xenobiotic metabolising macromolecules may contribute to the elevated presence of OCPs in these patients. In the detoxification procedure, the xenobiotic stage I metabolising macromolecule enzymes that is cytochrome P450 transforms the organochlorine compounds to the glutathione (GSH) binders that are susceptible in-between metabolites. This process is then accelerated by glutathione S-transferases (GSTs), allowing GSH final excretion.⁷⁸ Organochlorine pesticides, such as a-HCH, c-HCH, a-endosulfan, b-endosulfan, and p,p0 - DDE, significantly increased the risk of CKD in the population of North India. Number of these OCPs also had

a negative correlation with the patients' eGFR. DDE and HCH blood levels were found to be greater in CKD patients earlier research by Rutten et al (1988). This finding is consistent with our study's interim report.⁸⁰

DISCUSSION

As we have studied number of cases consisting pesticidal residues and its positive co-relation with cancer (Table 1), it is quite clear that there are harmful effects of pesticidal remnants on human health. Studies shows prominent health effects of pesticides and other major carcinogenic risks associated with pesticides usage. Earlier, we have witnessed so many cases of organochlorines compounds

causing cancer among humans in India. India is agriculture dominant country. For achieving a vast yield, farmers are rushing towards various insecticides to prevent their crops from insects. But lack of information of protocols and dosage, the use of insecticides becomes a danger for farmers itself as well as environment and others well beings. Indian government had banned various chemical compounds in recent times because of their harmful effects on environment and human health. Organochlorine compounds are the most dangerous one and have a detrimental effect on environment. For safeguarding the country's environment and health of public, it is recommended to minimize the application of these compounds and move towards organic farming.

Table 1: Studies resembling different observations in association with different types of cancers.

| Type of cancer | No. of studies found | No. of studies included | Positive association of OCPs to cancer | Summary of results |
|----------------|----------------------|-------------------------|--|----------------------|
| Breast | 4 | 4 | 3 | Positive co-relation |
| Lung | 3 | 3 | 2 | Positive co-relation |
| Prostate | 7 | 5 | 4 | Positive co-relation |
| Colorectal | 2 | 2 | 0 | Negative co-relation |
| Cervical | 3 | 2 | 1 | Negative co-relation |
| Ovarian | 3 | 3 | 2 | Positive co-relation |
| Bladder | 4 | 3 | 2 | Positive co-relation |

CONCLUSION

The review of available literature suggests a potential association between the application of organochlorine pesticides and the incidence of certain types of cancer in India. Additionally, there is evidence to suggest that xenobiotic metabolizing gene polymorphisms may play a role in individual susceptibility to the carcinogenic effects of these pesticides. Further research is needed to confirm these findings and to better understand the mechanisms underlying this association. It is important to note that the use of these pesticides should be evaluated in the context of their potential health risks, as well as their potential benefits in terms of pest control.

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