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SYSTEMATIC REVIEW

Organochlorine pesticide exposure and risk of prostate cancer development and progression: a systematic review

[version 1; peer review: 2 approved with reservations]

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Abstract

Background: There is an increasing body of evidence linking the exposure of an individual to pesticides such as organochlorine pesticides (OPCs) and an increased risk of developing diseases such as cancer. Exposure to OPCs has been suggested to increase the risk of developing hormone-dependant cancers such as prostate cancer (PCa). However, there is a relative paucity of information about the influence of exposure to these pesticides on the evolution of PCa, including risk of tumour development, progression to metastasis, and disease recurrence following therapy.
Methods: We used several databases such as PubMed MEDLINE Database, Web of Science, and Scopus, in order to conduct a systematic review of the available epidemiological data implicating an association between exposure to OCPs and biochemical recurrence (BCR) of PCa. We searched all peer-reviewed articles published up to July 31st 2020. Pre-defined eligibility criteria for the inclusion of studies were that they be original studies, reviews, previous meta-analyses, or case–control or cohort studies.
Results: Agent Orange is the most widely-studied OCP in the context of any possible causal role in the recurrence of PCa following radical prostatectomy, or in the progression to advanced disease. Only two studies didn't demonstrate a significant association between exposure to OCPs and subsequent BCR following radical prostatectomy. Another study identified a significant association between exposure to Oxychlordane and PCB44 and progression to advanced PCa.
Conclusion: This review confirmed a relative lack of high-quality evidence regarding this topic. However, the available evidence to date suggests the presence of a potential causal relationship between exposure to OPCs and PCa development and progression.

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords
Organochlorine pesticides, prostate cancer, biochemical recurrence, advanced disease

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Abbreviations

AO: Agent Orange; BCR: Biochemical Recurrence; OCs: Organochlorines; OCPs: Organochlorine Pesticides; PCa: Prostate Cancer

Introduction

Prostate cancer (PCa) is the second most common non-cutaneous malignancy diagnosed among men worldwide, and the most common cancer type detected in men in developed countries[1]. Several risk factors for the development of PCa have been established, including increasing age, positive family history, and accumulated environmental exposure to several hormones[2,3]. Some pesticides can influence the hormonal milieu *in vivo* by functioning to mimic the effect of hormones, regulate enzyme systems involved in hormone metabolism, and affect androgenic stimulation of the prostate gland, potentially leading to increased cellular proliferation and progression to malignancy[4–6]. Organochlorines (OCs) comprise a large number of pesticides, and these have been used extensively throughout the world for several decades. Whilst their use has been banned or severely restricted in many countries, they remain in use in many areas of the world, and this has the potential to adversely affect the health of individuals in countries where OCs are still in use. OCs are highly-persistent organic pollutants, with a high serum level being reported in several distinct populations[7–10]. The International Agency of Research on Cancer (IARC) has classified many OCPs as being Class 2B agents, implicating them as being possible carcinogens[11]. Moreover, a large number of OCPs have been demonstrated to have the potential to disrupt endocrine function[12,13], suggesting that exposure to these specific types of pesticides may increase the risk of developing hormone-dependant cancers such as PCa[14]. Several OCPs including chlordecone, DDE, DDT and Lindane have been implicated as potential independent risk factors for PCa development[15–18]. However, to date there is a relative lack of information about the impact of exposure to OCPs upon on the development of aggressive metastatic PCa, or influences on PCa disease-free survival, and potential BCR following radical treatment. The aim of this review article is to provide a contemporary update of the epidemiologic evidence implicating exposure to OCPs upon the recurrence of PCa following radical therapy.

Methods

Design and inclusion criteria

We conducted a systematic review of the available epidemiological data investigating a potential relationship between exposure to OCPs and the development of recurrent PCa following radical therapy. We searched all peer-reviewed articles published up to July 31st 2020. Pre-defined eligibility criteria for the inclusion of studies were that they be original studies, reviews, previous meta-analyses, or case–control or cohort studies. Moreover, it was mandatory that they contain information about association measures, including odds ratios (OR), relative risks (RR), and confidence intervals (CI) in order to facilitate an analysis of possible relationships between exposure to specific OCPs and development of recurrent PCa following treatment. Finally, it was necessary for the included studies to provide sufficient data and be written in English, French, or Spanish. Exclusion criteria included *in vitro* experimental and mechanistic studies, editorials, or letters, and as such these reports were not included in this review.

Search strategy and selection of articles

The initial search strategy included PubMed MEDLINE Database, Web of Science, and Scopus, utilising different "key words" to order identify studies investigating potential associations between exposure to OCPs and development of recurrent PCa following treatment (Figure 1).

MeSH controlled vocabulary was utilised, including combinations of the following key words: ''organochlorine pesticides'', ''exposure'', ''DDT'', ''DDE'', ''hexachlorocyclobenzene'', ''lindane'', ''chlordecone'', ''kepone'', ''chlordan'', ''dicofol'', ''mirex'', ''dieldrin'', ''endrine'', ''aldrine'', ''PCB'', ''dioxine'', ''endosulfan'', ''heptachlor'', ''methoxychlor'', ''toxaphene'', ''prostate cancer'', ''biochemical recurrence'', ''biochemical failure'', ''prostatic carcinoma'', ''prostatic neoplasm'', ''prostatic adenocarcinoma'', ''case – control studies'' and ''cohort studies.''

Extracted domains included sttudy design, demographics, findings

Results

An overview of five available studies investigating a potential relationship between exposure to OCPs and development of recurrent PCa following radical treatment is provided in Table 1. Two studies did not observe any significant relationship between the exposure of American Veterans to Agent Orange (AO) and subsequent BCR following radical prostatectomy[19,20]. Li *et al.* reported that exposure to AO significantly increased the Dioxin-TEQ level in blood samples ($p < 0.001$), but high dioxin-TEQ levels were not associated with an increased risk of subsequent BCR (p=0.23). A study by Ovadia *et al.* found that men exposed to AO did not have an increased risk of BCR following radical prostatectomy in both a univariate analysis (HR 1.03; 95% CI 0.84 – 1.25; p=0.80) and a multivariate analysis (HR 1.21; 95% CI 0.99–1.49; p=0.07). However, a study by Shah *et al.* reported a significant positive association between exposure to AO and BCR following radical prostatectomy. In this study of 206 men, those with documented exposure to AO had a significantly increased risk of subsequent BCR following radical prostatectomy (RR 1.55; 95% CI 1.15 – 2.09; p=0.004 when adjusted for clinical characteristics, and RR: 1.47; 95% CI 1.08 – 2.00; p=0.02 when adjusted for clinical plus pathological characteristics)[21]. Another study by Brureau *et al.* revealed a significant positive association between exposure to Chlordecone and BCR following radical prostatectomy and no associations for DDE or PCB-135. In this study of 326 men, those with documented exposure to Chlordecone had a significantly increased risk of subsequent BCR following radical prostatectomy (adjusted HR = 2.51; 95% CI: 1.39 – 4.56; for the highest versus lowest quartile of exposure; p trend = 0.002). In addition, sensitivity analysis revealed that Chlordecone exposure was still significantly associated with a risk of BCR after excluding patients with positive surgical margins or prostatectomy ISUP Gleason grade 3 or higher, or advanced pathological stage[22].

A report by Koutros *et al.* suggests that other pesticides, such as Oxychlordane and PCB44, may be implicated in modifying the

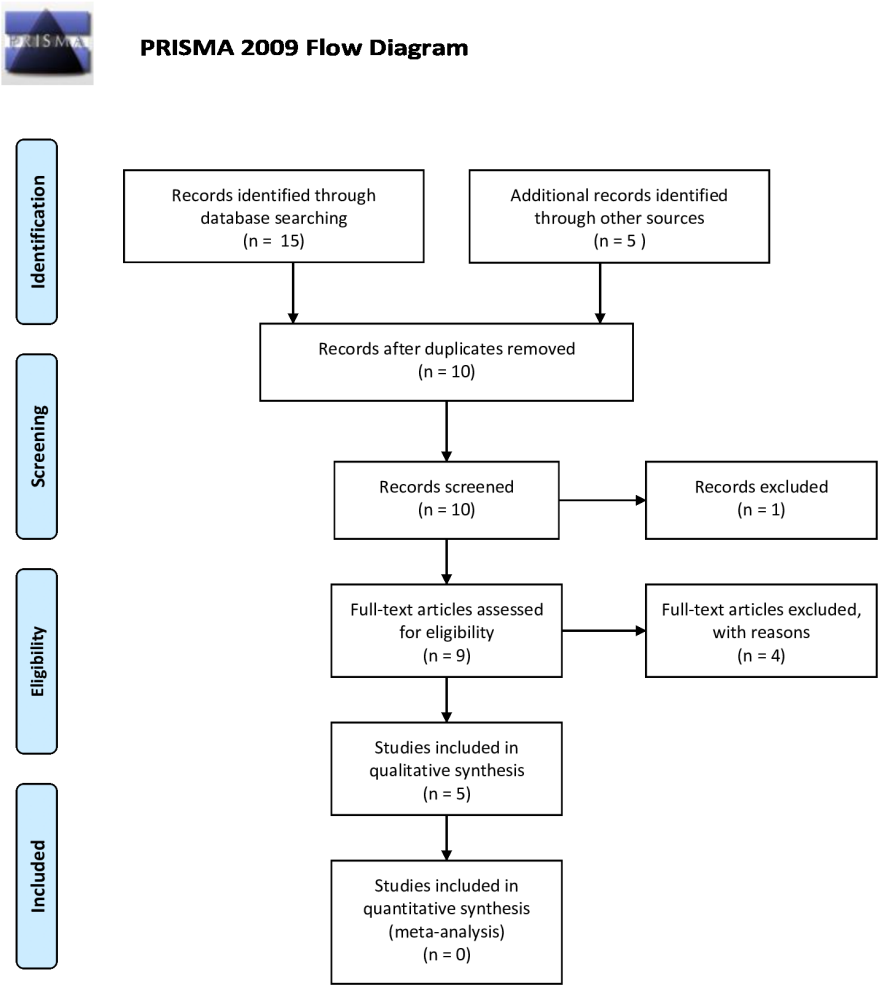


Figure 1. Flowchart summarising the selection process of the articles included in this review.

risk of developing advanced PCa. For example, the development of metastatic PCa was twice as likely among men with a serum concentration of Oxychlordane in the highest quartile when compared against those in the lowest quartile (OR 2.03; 95% CI 1.03 – 4.03; *p*-trend=0.05). Findings for specific PCB-related chemicals showed a significant inverse association between natural log–transformed lipid-adjusted PCB44 and metastatic PCa (OR 0.74; 95% CI 0.56–0.97; *p*-trend=0.02)[23]. All characteristics of OCPs involved in BCR or metastatic PCa are summarised in Table 2.

Discussion

This systematic review confirms that there is a relative lack of high-quality evidence implicating a potential association between exposure to OCPs and BCR of PCa. However, the available evidence suggests that there may be a potential causal relationship between exposure to OCPs and development and progression of this malignancy. Agent Orange is the most widely-studied OCP in the context of any possible causal role in the recurrence of PCa following radical prostatectomy, or in the progression to advanced disease[24]. However, only two studies demonstrated a significant association between exposure to OCPs and subsequent BCR following radical prostatectomy. Two pesticides were involved: Chlordecone and Agent Orange[21,22]. Another study by Koutros *et al*. identified a significant association between exposure to Oxychlordane and PCB44 and progression to advanced PCa[23]. However, each of these studies are limited by their inclusion of a relatively small number of cases. Larger prospective clinical studies would be necessary to confirm these potential associations, however it is recognised that such studies would be very difficult to conduct, and are not presently feasible.

This review highlights the relative lack of evidence on the potential causal role of OCPs in PCa development and progression, despite the observation that a large number of pesticides exist and continue to be in use in many countries worldwide (Table 3). As such, this topic has potential impacts in aspects of global healthcare, and there is widespread public concern

Table 1. Details of available studies investigating potential relationship between exposure to OCPs and progression of PCa.

Author	Population study	Exposure characteristics	Definition of BCR	Association with BCR
Li *et al.* Prostate cancer and prostatic diseases (2013)[19]	93 men (37 with pesticides exposure and 56 without) from American Veterans administration treated by radical prostatectomy for prostate cancer between April 2005 and September 2009 with a median follow-up of 5.3 years	37 men were exposed to Agent O during the Vietnam War. Exposure evaluation by measurement Dioxin-TEQ level in blood.	Not defined	No significant association
Ovadia *et al.* Urologic Oncology: Seminars and Original Investigation (2015)[20]	1882 men (333 with pesticides exposure and 1549 without) from American Veterans administration treated by radical prostatectomy for prostate cancer between 1998 and 2011 with a median follow-up of 85 months	333 men were exposed to agent O during the Vietnam War. Agent O exposure was determined by veteran self-reported verified by Veterans Affairs committee in order to determine Veterans exposure according to his location during the war.	1 PSA level > 0.2 ng/ml, 2 levels of 0.2 ng/ml or secondary treatment for a detectable PSA after radical prostatectomy	No significant association
Shah *et al.* British Journal of Urology International (2009)[21]	1495 men (206 with pesticides exposure and 1289 without) from the Shared Equal Access Research Cancer Hospital database Veterans Affairs treated by radical prostatectomy for prostate cancer between 1988 and 2007 with a median follow-up of 49 months.	206 men were exposed to agent O during the Vietnam War. Agent O exposure was determined by veteran self-reported	Biochemical progression was defined as one PSA level of > 0.2 ng/mL, two of 0.2 ng/mL, or secondary treatment for an elevated PSA level after radical prostatectomy.	Significant association
Brureau *et al.* International Joural of Cancer (2020)[22]	326 men with pesticides exposure from University Hospital of Guadeloupe (FWI) treated by radical prostatectomy for prostate cancer between 2004 and 2007 with a median follow-up of 73 months.	326 men were exposed to Chlordecone, PCB 135 and DDE	Biochemical progression was defined as one PSA level of > 0.2 ng/mL, two of 0.2 ng/mL	Significant association for Chlordecone No significant association for DDE and PCB 135.
Author	**Study population**	**Exposure characteristics**	**Advanced disease**	**Association with metastatic disease**
Koutros *et al.* Environmental Health Perspectives (2015)[22]	Case control study included 150 cases and 314 controls in a population-based cohort in Norway, who were diagnosed from enrolment through 31 December 1999 and were diagnosed at least 2 years after serum collection.	150 men with metastatic prostate cancer from Janus Serum Bank cohort in Norway. 11 organochlorine pesticides and their metabolites and 34 PCB congeners were analysed	Metastasis and histologic grade were caracterized according to the American Cancer Society's. All 184 incident metastatic prostate cancer cases didn't have history of cancer (except non melanoma skin cancer)	Significant association for: Oxychlordane. PCB44 (inverse association)

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Table 2. Organochlorine pesticide characteristics involved in BCR and metastatic prostate cancer.

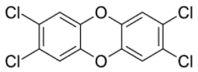
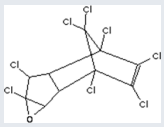
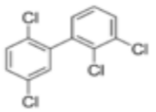
Name	Molecular structure	Comments
Agent Orange contaminated by TCDD (2,3,7,8-tétrachlorodibenzo-para-dioxine)		Lipophilic molecule hence its stability when it's in a living organism. It's resistant to the mechanisms of detoxification and remain stored in the adipose tissue of animals. It's chemically very stable molecule and is therefore bio-accumulated. His half-life is 5–10 years in human body[25].
Oxychlordane		Because of their lipophilic properties and their persistence in the environment, chlordane and related compounds bioaccumulate and biomagnify along the food chain[26].
PCB44 2,2',3,5'-Tetrachlorobiphenyl		PCBs appeared to early twentieth century chemists interesting for their dielectric properties. These are ubiquitous and persistent pollutants. Highly fat soluble, they are part of the bioaccumulative contaminants commonly found in fatty tissue in humans. Food is the primary source of PCB exposure. They have endocrine disruptor properties[27].
Chlordecone		Chlordecone interferes with estradiol signaling through binding to the nuclear estrogen receptors α (ERα) and β (ERβ), eliciting agonistic and antagonistic effects, respectively[28].

Table 3. Organochlorine pesticides involved in prostate cancer risk.

References	Study design	Pesticides	OR (95% CI)	Intensity of exposure
Alavanja *et al.* American Journal of Epidemiology (2003)[27]	Cases-Controls 566 cases and 54766 controls	Chlorinated pesticides[a]	1.3 (1.0 – 1.6) 1.5 (1.2 – 2.0)	T2 T3L
Mills *et al.* Journal of occupational and environmental medicine (2003)[15]	Cases-Controls 222 cases and 1110 controls	Lindane Heptachlor	1.9 (1.1 – 3.2) 2.4 (1.2 – 4.6) 2.1 (1.2 – 3.5) 2.0 (1.1 – 3.6)	Level 3 Level 4 Level 3 Level 4
Settimi *et al.* International journal of cancer (2003)[28]	Cases-Controls 124 cases and 659 controls	DDT Dicofol	2.2 (1.1 – 4.8) 2.8 (1.5 – 5.0) 2.8 (1.5 – 5.0) 2.4 (1.2 – 5.3) 3.0 (1.3 – 7.0)	Ever ≤ 15 years Ever ≤ 15 years > 15 years
Xu *et al.* Environmental Health Perspectives (2010)[24]	Cases-Controls 65 cases and 1920 controls	beta-Hexachlorocyclohexane	3.4 (1.2 – 2.9)	T3U
Band *et al.* The Prostate (2011)[16]	Cases-Controls 1153 cases and 3999 controls	DDT Lindane	1.7 (1.0 – 2.7) 2.0 (1.2 – 3.6)	High High
Cockburn *et al.* American Journal of Epidemiology (2011)[29]	Cases-Controls 173 cases and 162 controls	Organochlrorine pesticides[b]	1.6 (1.0 – 2.6) 2.0 (1.2 – 3.5)	Ever High
Multigner *et al.* Journal of Clinical Oncology (2011)[17]	Cases-Controls 623 cases and 671 controls	Chlordecone	1.8 (1.2 – 2.6)	Qu4
Emeville *et al.* Environmental Health Perspectives (2015)[18]	Cases-Controls 576 cases and 655 controls	DDE	1.5 (1.0 – 2.3)	Qu5

T3L = lower tertile 3, T3U = uppertertile3, Q1, Q2, Q3, Q4 = Quartiles, Qu1, Qu2, Qu3, Qu4, Qu5 = Quintiles
[a] Included aldrin, chlordane, DDT, dieldrin, heptachlorandtoxaphene
[b] Dicofol, dieldrin, dienochlor, endosulfan, heptachlor, lindane, methoxychlor, and toxaphene

regarding pesticide exposure and negative impacts on health[29]. There is a well-documented causative relationship between exposure to pesticides and increased risk of development of many types of malignancy. It is therefore important to understand in greater detail the potential influence of OCP exposure upon aspects of PCa risk, and to identify the molecular pathways and mechanisms implicit in this increased risk (Figure 2).

Some OCPs, such as PCBs and Chlordecone, have functional properties that disrupt various endocrine pathways, including the synthesis, secretion, transport, and binding of hormonal ligands to their cognate receptors, whilst in addition they may result in the elimination of natural human hormones[30]. Phthalte pesticides are endocrine disruptor molecules with demonstrable estrogenic effects in breast and PCa cells, and these may also be implicit in the etiology of hormone-independent PCa cancer[31]. Given that phthalates are estrogen-like substances, they can positively regulate the proliferation of human hormone dependent PCa cells by acting on the crosstalk between TGF-β and oestrogen receptor signaling pathways[32]. In addition, some studies suggest that estrogen and xenobiotic carcinogens may play an important role in PCa progression via oxidative estrogen metabolism. For example, the CYP1B1 enzyme is involved in the hydroxylation of estrogens, and this reaction is of key relevance to the regulation of estrogen metabolism[33]. The over-production of estrogen-like E2, or the bioconversion of E2 into genotoxic metabolites such as estradiol-3,4-quinone or 4-hydroxyestradiol by CYP1B1, may lead to the generation of reactive oxygen species which subsequently cause DNA damage and enhance PCa progression[34]. In support of this hypothesis, Gu *et al.* observed that men with the CY1B1 rs1056836 CC genotype had an increased risk of PCa recurrence following radical prostatectomy when compared against a combined CG and GG genotype[35].

Conclusion

In conclusion, this review highlights the relative lack of studies regarding the potential influence of OCPs on the recurrence and progression of PCa following radical therapy. An increased understanding of the pathways and mechanisms through which pesticides may influence the natural history of PCa progression could influence the clinical management of men with this ubiquitous and common malignancy. It is important that the current relatively small body of evidence demonstrating a negative influence of OCPs on PCa risk should be added to in as timely a

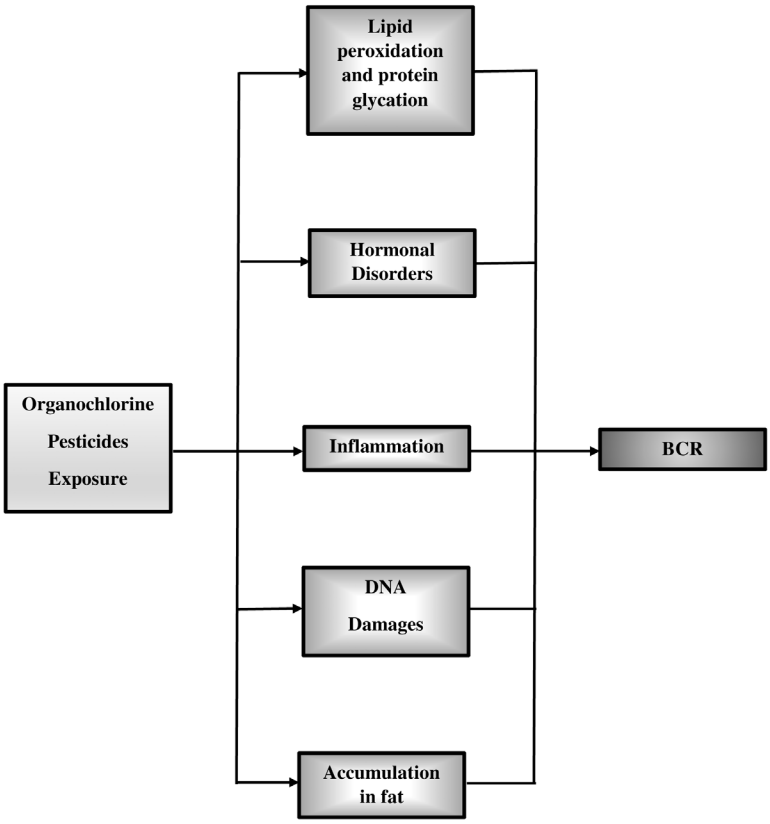


Figure 2. Putative molecular effects of organochlorine pesticides.

fashion as possible so that knowledge of this important health topic can increase, with a resultant positive health benefit for a significant number of individuals worldwide.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for 'Organochlorine pesticide exposure and risk of prostate cancer development and progression: a systematic review', https://doi.org/10.6084/m9.figshare.14245694.v1[36].

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

References

1. Center MM, Jemal A, Lortet-Tieulent J, *et al.*: **International variation in prostate cancer incidence and mortality rates.** *Eur Urol.* 2012; **61**(6): 1079–92.
PubMed Abstract | Publisher Full Text
2. Chen C, Weiss NS, Stanczyk FZ, *et al.*: **Endogenous sex hormones and prostate cancer risk: a case-control study nested within the Carotene and Retinol Efficacy Trial.** *Cancer Epidemiol Biomarkers Prev.* 2003; **12**(12): 1410–1416.
PubMed Abstract
3. Hsing AW: **Hormones and prostate cancer: what's next?** *Epidemiol Rev.* 2001; **23**(1): 42–58.
PubMed Abstract | Publisher Full Text
4. Keller-Byrne JE, Khuder SA, Schaub EA: **Meta-analyses of prostate cancer and farming.** *Am J Ind Med.* 1997; **31**(5): 580–586.
PubMed Abstract | Publisher Full Text
5. Janssens JP, Van Hecke E, Geys H, *et al.*: **Pesticides and mortality from hormone-dependent cancers.** *Eur J Cancer Prev.* 2001; **10**(5): 459–467.
PubMed Abstract | Publisher Full Text
6. Parent ME, Siemiatycki J: **Occupation and prostate cancer.** *Epidemiol Rev.* 2001; **23**(1): 138–143.
PubMed Abstract | Publisher Full Text
7. Yang L, Li X, Zhang P, *et al.*: **Concentrations of DDTs and dieldrin in Long Island Sound sediment.** *J Environ Monit.* 2012; **14**(3): 878–885.
PubMed Abstract | Publisher Full Text
8. Park MJ, Lee SK, Yang JY, *et al.*: **Distribution of organochlorines and PCB congeners in Korean human tissues.** *Arch Pharm Res.* 2005; **28**(7): 829–838.
PubMed Abstract | Publisher Full Text
9. Jaga K, Dharmani C: **Global surveillance of DDT and DDE levels in human tissues.** *Int J Occup Med Environ Health.* 2003; **16**(1): 7–20.
PubMed Abstract
10. Jakszyn P, Goñi F, Etxeandia A, *et al.*: **Serum levels of organochlorine pesticides in healthy adults from five regions of Spain.** *Chemosphere.* 2009; **76**(11): 1518–1524.
PubMed Abstract | Publisher Full Text
11. IARC, IARC monographs on the evaluation of carcinogenic risks to humans Volume 100F: **A review of human carcinogens: chemical agents and related occupations.** *International Association for Research on Cancer (IARC), Lyon.* 2012.
12. De Coster S, Van Larebeke N: **Endocrine-disrupting chemicals: associated disorders and mechanisms of action.** *J Environ Pub Health.* 2012; **2012**: 713696.
PubMed Abstract | Publisher Full Text | Free Full Text
13. McKinlay R, Plant JA, Bell JNB, *et al.*: **Endocrine disrupting pesticides: implications for risk assessment.** *Environ Int.* 2008; **34**(2): 168–183.
PubMed Abstract | Publisher Full Text
14. Landau-Ossondo M, Rabia N, Jos-Pelage J, *et al.*: **Why pesticides could be a common cause of prostate and breast cancers in the French Caribbean Island, Martinique. An overview on key mechanisms of pesticide-induced cancer.** *Biomed Pharmacother.* 2009; **63**(6): 383–395.
PubMed Abstract | Publisher Full Text
15. Mills PK, Yang R: **Prostate cancer risk in California farm workers.** *J Occup Environ Med.* 2003; **45**(3): 249–58.
PubMed Abstract | Publisher Full Text
16. Band PR, Abanto Z, Bert J, *et al.*: **Prostate Cancer Risk and Exposure to Pesticides in British Columbia Farmers.** *Prostate.* 2011; **71**(2): 168–183.
PubMed Abstract | Publisher Full Text
17. Multigner L, Ndong JR, Giusti A, *et al.*: **Chlordecone Exposure and Risk of Prostate Cancer.** *J Clin Oncol.* 2010; **28**(21): 3457–3462.
PubMed Abstract | Publisher Full Text
18. Emeville E, Giton F, Giusti A, *et al.*: **Persistent organochlorine pollutants with endocrine activity and blood steroid hormone levels in middle-aged men.** *PLoS One.* 2013; **8**(6): e66460.
PubMed Abstract | Publisher Full Text | Free Full Text
19. Li Q, Lan L, Klaassen Z, *et al.*: **High level of dioxin-TEQ in tissue is associated with Agent Orange exposure but not with biochemical recurrence after radical prostatectomy.** *Prostate Cancer Prostatic Dis.* 2013; **16**(4): 376–81.
PubMed Abstract | Publisher Full Text
20. Ovadia AE, Terris MK, Aronson WJ, *et al.*: **Agent Orange and long-term outcomes after radical prostatectomy.** *Urol Oncol.* 2015; **33**(7): 329.e1–6.
PubMed Abstract | Publisher Full Text
21. Shah SR, Freedland SJ, Aronson WJ, *et al.*: **Exposure to Agent Orange is a significant predictor of prostate-specific antigen (PSA)-based recurrence and a rapid PSA doubling time after radical prostatectomy.** *BJU Int.* 2009; **103**(9): 1168–1172.
PubMed Abstract | Publisher Full Text | Free Full Text
22. Brureau L, Emeville E, Helissey C, *et al.*: **Endocrine disrupting-chemicals and biochemical recurrence of prostate cancer after prostatectomy: A cohort study in Guadeloupe (French West Indies).** *Int J Cancer.* 2020; **146**(3): 657–663.
PubMed Abstract | Publisher Full Text
23. Koutros S, Langseth H, Grimsrud TK, *et al.*: **Prediagnostic Serum Organochlorine Concentrations and Metastatic Prostate Cancer: A Nested Case-Control Study in the Norwegian Janus Serum Bank Cohort.** *Environ Health Perspect.* 2015; **123**(9): 867–72.
PubMed Abstract | Publisher Full Text | Free Full Text
24. Chang ET, Boffetta P, Adami HO, *et al.*: **A critical review of the epidemiology of Agent Orange/TCDD and prostate cancer.** *Eur J Epidemiol.* 2014; **29**(10): 667–723.
PubMed Abstract | Publisher Full Text | Free Full Text
25. Sorg O, Zennegg M, Schmid P, *et al.*: **2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) poisoning in Victor Yushchenko: identification and measurement of TCDD metabolites.** *Lancet.* 2009; **374**(9696): 1179–1185.
PubMed Abstract | Publisher Full Text
26. Abdallah MAE, Zaky AH, Covaci A: **Levels and profiles of organohalogenated contaminants in human blood from Egypt.** *Chemosphere.* 2017; **176**: 266–272.
PubMed Abstract | Publisher Full Text
27. Van den Berg M, Birnbaum L, Bosveld AT, *et al.*: **Toxic Equivalency Factors (TEFs) for PCBs, PCDDs, PCDFs for Humans and Wildlife.** *Environ Health Perspect.* 1998; **106**(12): 775–792.
PubMed Abstract | Publisher Full Text | Free Full Text
28. Eroschenko VP: **Estrogenic activity of the insecticide chlordecone in the reproductive tract of birds and mammals.** *J Toxicol Environ Health.* 1981; **8**(5–6): 731–742.
PubMed Abstract | Publisher Full Text
29. Mostafalou S, Abdollahi M: **Pesticides and human chronic diseases: evidences, mechanisms, and perspectives.** *Toxicol Appl Pharmacol.* 2013; **268**(2): 157–77.
PubMed Abstract | Publisher Full Text
30. Quagliariello V, Rossetti S, Cavaliere C, *et al.*: **Metabolic syndrome, endocrine disruptors and prostate cancer associations: biochemical and pathophysiological evidences.** *Oncotarget.* 2017; **8**(18): 30606–30616.
PubMed Abstract | Publisher Full Text | Free Full Text
31. Harris CA, Henttu P, Parker MG, *et al.*: **The estrogenic activity of phthalate esters in vitro.** *Environ Health Perspect.* 1997; **105**(8): 802–11.
PubMed Abstract | Publisher Full Text | Free Full Text
32. Lee HR, Hwang KA, Choi KC: **The estrogen receptor signaling pathway activated by phthalates is linked with transforming growth factor-β in the progression of LNCaP prostate cancer models.** *Int J Oncol.* 2014; **45**(2): 595–602.
PubMed Abstract | Publisher Full Text

33. Gajjar K, Marin-Hirsch PL, Martin FL: ***CYP1B1* and hormone-induced cancer.** *Cancer Lett.* 2012; **324**(1): 13–30.
PubMed Abstract | Publisher Full Text

34. Go RE, Hwang KA, Choi KC: **Cytochrome P450 1 family and cancers.** *J Steroid Biochem Mol Biol.* 2015; **147**: 24–30.
PubMed Abstract | Publisher Full Text

35. Gu CY, Qin XJ, Qu YY, *et al.*: **Genetic variants of the *CYP1B1* gene as predictors of biochemical recurrence after radical prostatectomy in localized prostate cancer patients.** *Medicine (Baltimore).* 2016; **95**(27): e4066.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Brureau L, Multigner L, Hamdy F, *et al.*: **PRISMA 2009 checklist.doc.** *figshare.* Journal contribution. 2021.
http://www.doi.org/10.6084/m9.figshare.14245694.v1

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Pradeep Kumar Sharma
CSIR-Indian Institute of Toxicology Research, Lucknow, India

Brureau et al, in their work titled "Organochlorine pesticide exposure and risk of prostate cancer development and progression: a systematic review" have attempted to provide an evidence for causality between OCPs exposure and prostate cancer development, which is really pertinent in the current scenario where humans are being exposed to several different types of environmental chemicals that may affect their health in multiple ways including risk of hormone-dependent cancers such as breast and prostate cancer. While the authors have executed their work plan very nicely and covered all the articles available at the time of compilation of this study with appropriate exclusion/Inclusion criteria, yet I feel that the data insufficiency is a limitation in this study to derive concluding remarks on potential causal role of OCPs and PCa development. There are some comments that authors may consider for the comprehensiveness and better understanding the causal role of OCPs in PCa development.

1. The study compiles the data till July 2020, so authors should consider recent studies published in the subject area (e.g. PMID: 36949525 [1], PMID: 36526827 [2]).

2. While referring to the epidemiological studies in Table 1, authors should also indicate the exposure levels and/exposure window of OCPs (probable route of exposure to these OCPs in the cohorts).

3. Authors have restricted their study to a chemical group of OCPs only, while, given the fact that a number of other endocrine disrupting chemicals are routinely being identified, and known to have exposures in humans, it would be better to consider other potential EDCs for their causal relationship with PCa (preferably the epidemiological studies). It would give a comprehensive analysis of identifying substantial risk factors by considering the chemicals that are in frequent use as well, besides the OCPs.

4. In the introduction section, and accumulated environmental exposure to several hormones, it is not clear to what exogenous hormones human beings are exposed to? As exogenous substances (natural or synthetic) can mimic the action of natural ligands but are not the ligands for nuclear receptors particularly for estrogen- and androgen-receptors,

5. Check the clarity in this sentence in the introduction section "*However, to date there is a relative lack of information about the impact of exposure to OCPs **upon on the development** of aggressive metastatic PCa*",

6. Though authors have mentioned several mechanistic reasons for these chemicals to cause PCa, their effects on androgen receptor (that is predominantly involved in the development of hormone-sensitive pCa) are largely missing and therefore authors should also consider this limitation in this study to highlight the limited understanding of OCPs like EDCs with respect to their androgen-mimicking potential.

References

1. Iwasaki M, Itoh H, Sawada N, Tsugane S: Exposure to environmental chemicals and cancer risk: epidemiological evidence from Japanese studies.*Genes Environ*. 2023; **45** (1): 10 PubMed Abstract | Publisher Full Text
2. Modica R, Benevento E, Colao A: Endocrine-disrupting chemicals (EDCs) and cancer: new perspectives on an old relationship.*J Endocrinol Invest*. 2023; **46** (4): 667-677 PubMed Abstract | Publisher Full Text

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Environmental Carcinogenesis and hormone-dependent cancers

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 28 February 2022

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Matthew J Roberts
Department of Urology, Royal Brisbane and Women's Hospital, Brisbane, Qld, Australia

Thank you for asking me to review this systematic review. The topic is interesting, especially as many men are exposed to OCPs that may be implicated in PC pathogenesis. The literature is limited, which is acknowledged. For the most part, the authors have done a good job at including and discussing the relevant data from included studies.

Some comments below that I hope improve the manuscript:

1. Given the paucity of data, no firm conclusions can be drawn. The authors have written to this for the most part, but some passages may overstate a potential association: - Abstract - "However, the available evidence to date suggests the presence of a potential causal relationship between exposure to OPCs and PCa development and progression" - this is unbalanced given the other half of the data showed no association. Could the authors please check the other potential passages and amend to reflect appropriately?

2. The results table is very brief, suggest expanding the results more than significant association so that readers can assess for themselves (e.g. the HRs seem much higher in the smaller studies, thus I would be more inclined to be influenced by the larger studies which are split in their conclusions)

3. Figure 2 is ok but could be more informative - I would place a pathological/biological focus e.g. cancer spread and proliferation in between BCR (a clinical endpoint, I would also include metastasis); "hormonal disorders" is extremely vague, which of these are relevant to PC? it may also be helpful to show what downward effects these aspects cause to result in biological change

4. There is no limitations paragraph, there are many and so this should be included and lengthy. A major limitation is the assessment of association only, association does not equal causation in the absence of robust biological data. It does not appear from the paper content that such biological data exists. There are many causes for the associations seen, e.g. healthcare seeking behaviour, use of other medications (statins etc.). Also, men who are exposed may be more anxious, so more likely to opt for adjuvant radiotherapy after RP (before recent RADICALS/RAVES data..)

5. I don't think that I could replicate this study as the exclusion reasons were not included. Could this be included as a supplementary table?

6. Some minor spelling errors (e.g. "Extracted domains included sttudy design.. and in Table 1 International Joural of Cancer..)

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Prostate cancer - clinical research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 28 Feb 2022

Laurent BRUREAU

Thank you for reviewing this work. The objective of this review is to warn against the risk of exposure to pesticides and in particular organochlorines on prostate cancer. Indeed, most of the data concern the impact of pesticides on the occurrence of cancer. However, there are few data on the impact of pesticides on the course and progression of the disease after diagnosis. This question is important because it is legitimate to think that prolonged exposure can have an impact on the progression of the disease. Our review, presents little data but it is the reality on the subject. We hope that this review will encourage other authors to carry out work on the same theme.

Competing Interests: No competiting interests

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