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 OPCs 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 OPCs 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.
**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 countries1. Several risk factors for the development of PCa have been established, including increasing age, positive family history, and accumulated environmental exposure to several hormones2,3. 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 malignancy4,5. 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 populations5–10. The International Agency of Research on Cancer (IARC) has classified many OCPs as being Class 2B agents, implicating them as being possible carcinogens11. Moreover, a large number of OCPs have been demonstrated to have the potential to disrupt endocrine function12,13, suggesting that exposure to these specific types of pesticides may increase the risk of developing hormone-dependant cancers such as PCa14. Several OCPs including chlordecone, DDE, DDT and Lindane have been implicated as potential independent risk factors for PCa development15–18. However, to date there is a relative lack of information about the impact of exposure to OCPs upon 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 development of recurrent PCa following radical treatment. 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).


Extracted domains included study 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 prostatectomy19,20. 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 stage22.

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.

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. 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. Another study by Koutros et al. identified a significant association between exposure to Oxychlordane and PCB44 and progression to advanced PCa. 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.

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). All characteristics of OCPs involved in BCR or metastatic PCa are summarised in Table 2.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>Exposure characteristics</th>
<th>Definition of BCR</th>
<th>Association with BCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al.</td>
<td>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.</td>
<td>37 men were exposed to Agent O during the Vietnam War. Exposure evaluation by measurement Dioxin-TEQ level in blood.</td>
<td>Not defined</td>
<td>No significant association</td>
</tr>
<tr>
<td>Ovadia et al.</td>
<td>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.</td>
<td>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.</td>
<td>1 PSA level &gt; 0.2 ng/ml, 2 levels of 0.2 ng/ml or secondary treatment for a detectable PSA after radical prostatectomy</td>
<td>No significant association</td>
</tr>
<tr>
<td>Shah et al.</td>
<td>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.</td>
<td>206 men were exposed to agent O during the Vietnam War. Agent O exposure was determined by veteran self-reported.</td>
<td>Biochemical progression was defined as one PSA level of &gt; 0.2 ng/mL, two of 0.2 ng/mL, or secondary treatment for an elevated PSA level after radical prostatectomy.</td>
<td>Significant association</td>
</tr>
<tr>
<td>Brureau et al.</td>
<td>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.</td>
<td>326 men were exposed to Chlordecone, PCB 135 and DDE. Biochemical progression was defined as one PSA level of &gt; 0.2 ng/mL, two of 0.2 ng/mL</td>
<td>Significant association for Chlordecone No significant association for DDE and PCB 135.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>Exposure characteristics</th>
<th>Advanced disease</th>
<th>Association with metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koutros et al. Environmental Health Perspectives (2015)</td>
<td>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.</td>
<td>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.</td>
<td>Metastasis and histologic grade were characterized 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).</td>
<td>Significant association for: Oxychlordane. PCB44 (Inverse association)</td>
</tr>
</tbody>
</table>
### Table 2. Organochlorine pesticide characteristics involved in BCR and metastatic prostate cancer.

<table>
<thead>
<tr>
<th>Name</th>
<th>Molecular structure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent Orange contaminated by TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxine)</td>
<td><img src="image" alt="Molecular structure" /></td>
<td>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.</td>
</tr>
<tr>
<td>Oxychlordane</td>
<td><img src="image" alt="Molecular structure" /></td>
<td>Because of their lipophilic properties and their persistence in the environment, chlordane and related compounds bioaccumulate and biomagnify along the food chain.</td>
</tr>
<tr>
<td>PCB44 2,2',3,5'-Tetrachlorobiphenyl</td>
<td><img src="image" alt="Molecular structure" /></td>
<td>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.</td>
</tr>
<tr>
<td>Chlordcone</td>
<td><img src="image" alt="Molecular structure" /></td>
<td>Chlordcone interferes with estradiol signaling through binding to the nuclear estrogen receptors α (ERα) and β (ERβ), eliciting agonistic and antagonistic effects, respectively.</td>
</tr>
</tbody>
</table>

### Table 3. Organochlorine pesticides involved in prostate cancer risk.

<table>
<thead>
<tr>
<th>References</th>
<th>Study design</th>
<th>Pesticides</th>
<th>OR (95% CI)</th>
<th>Intensity of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alavanja et al. American Journal of Epidemiology (2003)</td>
<td>Cases-Controls 566 cases and 54766 controls</td>
<td>Chlorinated pesticides</td>
<td>1.3 (1.0 – 1.6) 1.5 (1.2 – 2.0)</td>
<td>T2 T3L</td>
</tr>
<tr>
<td>Mills et al. Journal of occupational and environmental medicine (2003)</td>
<td>Cases-Controls 222 cases and 1110 controls</td>
<td>Lindane Heptachlor</td>
<td>1.9 (1.1 – 3.2) 2.4 (1.2 – 4.6)</td>
<td>Level 3 Level 4</td>
</tr>
<tr>
<td>Settimi et al. International journal of cancer (2003)</td>
<td>Cases-Controls 124 cases and 659 controls</td>
<td>DDT Dicofol</td>
<td>2.2 (1.1 – 4.8) 2.8 (1.5 – 5.0)</td>
<td>Ever ≤ 15 years</td>
</tr>
<tr>
<td>Xu et al. Environmental Health Perspectives (2010)</td>
<td>Cases-Controls 65 cases and 1920 controls</td>
<td>beta-Hexachlorocyclohexane</td>
<td>3.4 (1.2 – 2.9)</td>
<td>T3U</td>
</tr>
<tr>
<td>Band et al. The Prostate (2011)</td>
<td>Cases-Controls 1153 cases and 3999 controls</td>
<td>DDT Lindane</td>
<td>1.7 (1.0 – 2.7) 2.0 (1.2 – 3.6)</td>
<td>High High</td>
</tr>
<tr>
<td>Cockburn et al. American Journal of Epidemiology (2011)</td>
<td>Cases-Controls 173 cases and 162 controls</td>
<td>Organochlorine pesticides</td>
<td>1.6 (1.0 – 2.6) 2.0 (1.2 – 3.5)</td>
<td>Ever High</td>
</tr>
<tr>
<td>Multignier et al. Journal of Clinical Oncology (2011)</td>
<td>Cases-Controls 623 cases and 671 controls</td>
<td>Chlordcone</td>
<td>1.8 (1.2 – 2.6)</td>
<td>Qu4</td>
</tr>
<tr>
<td>Emeville et al. Environmental Health Perspectives (2015)</td>
<td>Cases-Controls 576 cases and 655 controls</td>
<td>DDE</td>
<td>1.5 (1.0 – 2.3)</td>
<td>Qu5</td>
</tr>
</tbody>
</table>

T3L = lower tertile 3, T3U = upper tertile 3, Q1, Q2, Q3, Q4 = Quartiles, Qu1, Qu2, Qu3, Qu4, Qu5 = Quintiles

a Included aldrin, chlordane, DDT, dieldrin, heptachlor and toxaphene

b Dicofol, dieldrin, dienochlor, endosulfan, heptachlor, lindane, methoxychlor, and toxaphene
regarding pesticide exposure and negative impacts on health\textsuperscript{30}. 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\textsuperscript{30}. Phthalate 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\textsuperscript{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-\(\beta\) and oestrogen receptor signaling pathways\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.](image)
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


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

References


Open Peer Review

Current Peer Review Status:  

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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, PMID: 36526827).

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 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

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

**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
https://doi.org/10.5256/f1000research.33040.r125204

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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:

   "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 sstudy 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?
Are the conclusions drawn adequately supported by the results presented in the review?
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 competing interests

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