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Exposure to pesticides and prostate cancer: systematic review of the literature

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Abstract

Introduction: Investigations about the association between prostate cancer and environmental and/or occupational pesticide exposure have evidenced a possible role of these chemical substances on tumor etiology, related to their action as endocrine disruptors.
Objective: To assess the association between pesticide exposure and prostate cancer by conducting a systematic review of the scientific literature.
Materials and methods: Articles published until August 18, 2015 were searched in the databases MEDLINE/Pubmed, Scielo, and Lilacs using the keywords "pesticides" and "prostate cancer". Only the analytical observational studies whose methodological quality met the criteria established by the New Castle-Ottawa scale were included in this review.
Results: The review included 49 studies published between 1993 and 2015. All studies were in English and analyzed exposure to pesticides and/or agricultural activities. Most studies (32 articles) found a positive association between prostate cancer and pesticides or agricultural occupations, with estimates ranging from 1.01 to 14.10.
Conclusion: The evidence provided by the reviewed studies indicates a possible association between the development of prostate cancer and pesticide exposure and/or agricultural occupations.

Keywords: agriculture; environmental exposure; occupational exposure.

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Introduction

Prostate cancer is the second most common cancer in men and is an important cause of mortality in many countries (1). Aging and family history of prostate cancer are two factors associated with the development of this disease (2, 3). Many other factors, both internal and external (environmental and/or lifestyle-related), have been investigated, but the evidence of their role on prostatic carcinogenesis remains inconclusive (4–7).

Pesticide exposure is among these factors (8–11). These chemical substances have the potential of interfering with the endocrine system of animals and humans, acting as endocrine disruptors (12), and consequently, they have been associated with various health outcomes, such as prostate cancer (5, 13).

In the last decades, the number of studies on the association between environmental and/or occupational pesticide exposure and prostate cancer has increased. Many studies identified a higher risk of developing prostate cancer in individuals with pesticide exposure, while others have not found this association (14–16). The present study attempted to assess this association by conducting a systematic review of the literature on this subject.

Materials and methods

The articles were searched in the databases MEDLINE/Pubmed, Scielo, and Lilacs, using the keywords "prostate cancer" and "pesticides."

All articles published in scientific journals until August 18, 2015 were identified, in addition to all the references of the studies found by the search. Abstracts of the said references were searched in the same databases and included in the first analytical phase.

The titles and abstracts of all articles were read to select the ones eligible for the next phase of the review.

The first selection phase used the following inclusion criteria:

- Articles published in Portuguese, English, Spanish, French, and Italian;
- Articles whose exposure of interest was pesticide or agricultural occupation;
- Articles with prostate cancer as outcome;
- Articles that presented risk estimates and their respective confidence intervals.

This phase also included the following exclusion criteria:
- Articles that did not include the study subject;
- Book chapters, technical manuals, monographies, theses, and dissertations;
- Articles whose methods were not pertinent to the scope of the review (clinical assays, descriptive studies, basic research studies);
- Articles whose subjects had also participated in larger studies with longer follow-up periods;
- Case-control studies whose control subjects had benign prostate hyperplasia (BPH) or any type of cancer;
- Literature reviews.

The articles selected for the next phase were read in full and their quality was assessed as recommended by the New Castle-Ottawa scale (NOS). This scale was developed to assess the quality of observational studies, aiming at the incorporation of its parameters on the definition of inclusion/exclusion of studies in systematic reviews (17).

This scale considers three main aspects: selection of the study groups; group comparability; and determination of any exposure or outcome of interest for case-control or cohort studies, respectively. Each NOS item receives a score, with the final score of an article ranging from 1 to 9 points. According to these criteria, articles that score 6 or more points have good methodological quality.

Two independent researchers assessed the quality of the studies based on NOS criteria. Only articles that scored 6 or more points were included in the review. Whenever the researchers disagreed with respect to the score, the articles were reread and discussed, until an agreement was reached.

The research project that originated this study was approved by the Ethics Committee on Human Research of the Federal University of Mato Grosso do Sul, according the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals.

Results

Figure 1 summarizes the articles search strategy, selection, and quality assessment.

The search conducted in the three databases initially returned 598 studies with the two MeSH terms cited in the methodology. The databases Pubmed/Medline, Scopus, and Lilacs returned 319, 275, and four references, respectively. Of the total, seven studies were excluded because they were in languages other than the eligible ones (five were in Japanese and two were in German), so 591 studies remained.

Of these 591 studies, 142 were repeated and 22 had no abstract, so they were excluded. A total of 123 references of the remainder 427 studies were added to the latter, totaling 550 studies.

A total of 462 studies were excluded after reading their titles and abstracts. The remaining 88 articles were fully read. At this phase, another 38 articles were excluded because they did not meet the selection criteria, but their abstracts had not provided enough information to exclude them at the anterior phase. At the end of this phase, 50 studies remained, which were then submitted to methodological quality assessment. In this final phase, one article was excluded because it did not reach the minimum score of 6. Hence, 49 articles were included in this systematic review.

The oldest study selected for the systematic review was published in 1993, and the newest, in 2015. Only two studies were published between 1993 and 2002. The other studies were published after 2002, 22 between 2003 and 2007 and 25 between 2008 and 2012. All these studies were in English.

Most studies had been conducted in North America (41 articles), followed by Europe (four articles), Asia (two articles), and Oceania and Central America (one article each). Studies from South America were not found. Regarding countries, most studies were conducted in the United States (38 articles), followed by Canada (three articles) and Italy (two articles).

The journals with the highest article frequency were the *Environmental Health Perspectives* (12 articles), *Journal of Occupational and Environmental Medicine* (JOEM, seven articles), *International Journal of Cancer* (five articles), and *American Journal of Epidemiology* (four articles).

With respect to design, 15 were case-control studies (Table 1), and 34 were cohort studies (Table 2).

Of the 15 reviewed case-control studies, three had agricultural occupations as the exposure variable, and the other studies analyzed exposure to specific chemical substances (Table 1). Twelve of these studies found a positive association between prostate cancer and pesticide exposure and/or agricultural occupations. In these studies the risk estimates (odds ratios) varied from 1.74; 95% confidence interval (CI, 1.01–3.13) to 14.10; 95% CI (2.55–77.9) (Table 1).

Of the 34 analyzed cohort studies (Table 2), 29 used data from the agricultural health study (AHS), which included a large cohort of more than 50,000 farmers and pesticide applicators from the United States. Studies based on AHS data analyzed possible associations between specific pesticide exposure and many types of cancer. Some of these studies found that individuals exposed to the organophosphate insecticides fonofos and coumaphos, and to the herbicide butylate were at higher risk of developing prostate cancer, with relative risks of 1.83, 95% CI (1.12–3.00); 1.65, 95% CI (1.13–2.38), and 2.09, 95% CI (1.27–3.44), respectively (41, 54, 58). Another study done within

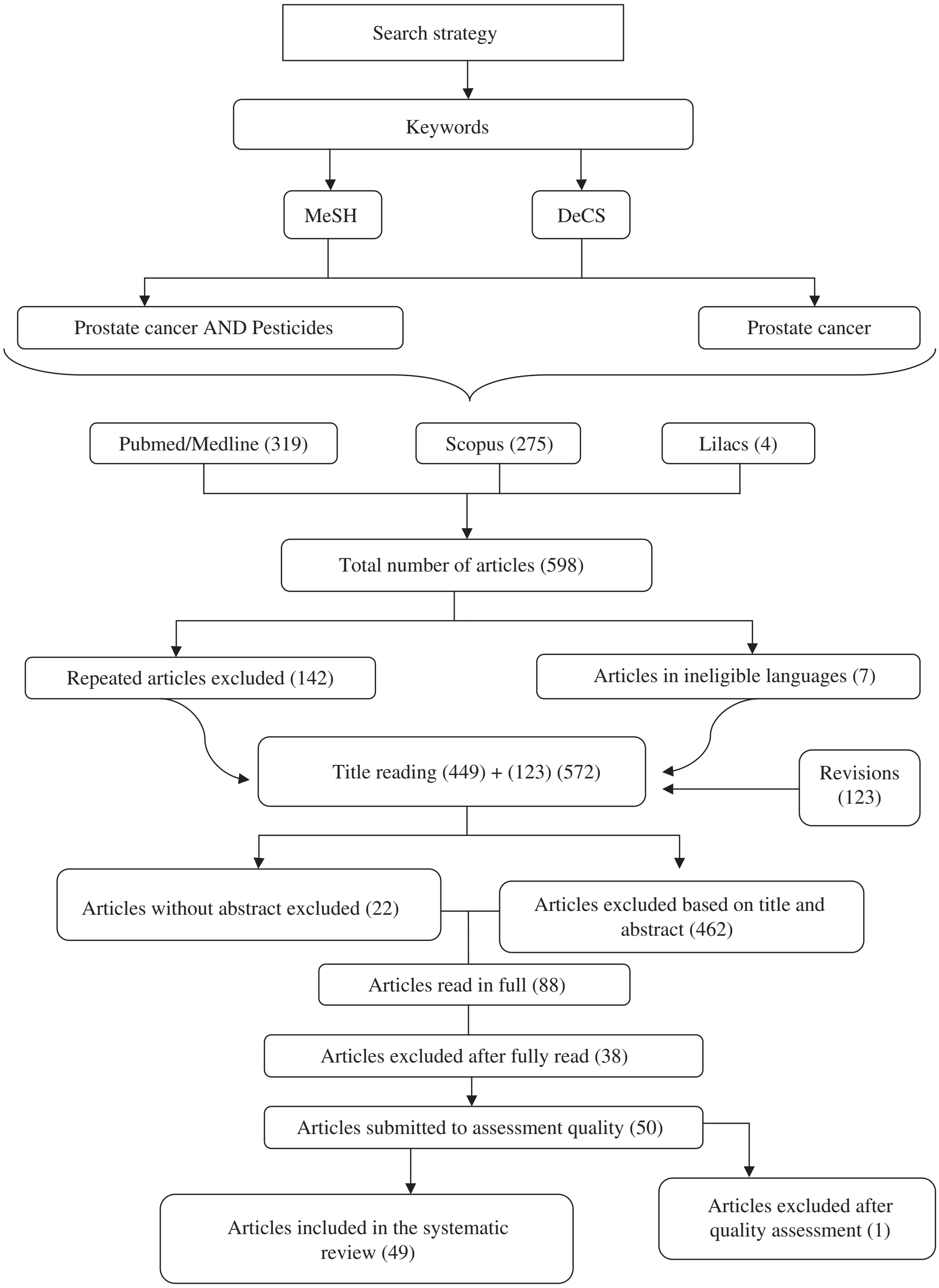

Figure 1: Article search and selection strategy for the systematic review.

this cohort found a negative association between exposure to the herbicide metolachlor and prostate cancer. The other studies did not find statistically significant associations between the analyzed substances and prostate cancer, except for a study that included only individuals with more aggressive prostate cancer (Gleason≥7). The said study found associations between prostate cancer and fonofos, malathion, terbufos, and aldrin, with relative risks of 1.63, 95% CI (1.22–2.17); 1.43, 95% CI (1.08–1.88); 1.29, 95% CI (1.02–1.64); and 1.49, 95% CI (1.03–2.18), respectively (60) (Table 2). The other five cohort studies analyzed exposure to pesticides in general, not specifying any particular substance. One of them, conducted in the Netherlands, found a negative association between prostate cancer and pesticide exposure, with a relative risk of 0.60, 95% CI (0.37–0.95) (35). Another Dutch study found a negative association between prostate cancer and exposure to agriculture at some point in life, with a relative risk

Table 1: Characterization of the reviewed case-control studies.

References	Authors, country, and year of publication	Study population	N	Type of exposure	Results odds ratio and 95% confidence interval (CI)	Adjustment variables
(18)	Franceschi et al. Italy, (1993)	Men seen in hospitals located in northeast Italy aged <80 years. 161 cases of prostate cancer	1669	Agricultural occupation	Born in 1930 or later: OR: 3.0 (0.7–12)	Smoking, age, and alcohol intake
(19)	Sharpe et al. Canada, (2001)	Men from metropolitan Montreal aged 45 to 70 years. 398 cases of prostate cancer	1140	Gardening pesticides or sprays used during non-work-related activities	OR: 2.3 (1.3–4.2)	Age, ethnicity, family history of cancer, body mass index, smoking, and alcohol intake
(20)	Ritchie et al. US, (2003)	Men recruited from two Iowa clinics with a mean age of 64.5 years (47 to 85 years). 58 cases of prostate cancer	157	Organochloride pesticides[a]	Group exposed to oxychlordane OR: 3.11 (1.27–7.63)	Age, body mass index, history of prostatitis
(21)	Mills et al. US, (2003)	Cohort of farmers from California with a mean age of 70 years. 222 cases of prostate cancer	1332	16 organochloride pesticides[b]	Simazine OR: 2.16 (1.15–4.04)	Age, date of affiliation to the rural union and affiliation duration
(22)	Fleming et al. US, (2003)	Farmers and pesticide applicators with a mean age of 39.2 years. 199 deaths by prostate cancer	238,844	Agricultural occupation	OR: 1.3 (0.8–2.2)	Age
(23)	Giri et al. US, (2004)	Cohort of military personnel born between January 1935 and December1953 old enough to fight in the Vietnam War. 47 cases of prostate cancer	189	TCDD (Agent Orange)	OR: 2.06 (0.81–5.23)	Race and age
(24)	Meyer et al. US, (2007)	Men from South Carolina aged 65 to 79 years. 405 cases of prostate cancer	797	Agricultural occupation	Caucasian farmers OR: 1.8 (1.3–2.7)	Age and region
(9)	Fritschi et al. Australia, (2007)	Australian men aged 45 to 70 years. 606 cases of prostate cancer	1077	Exposure to synthetic and natural fertilizers and pesticides[c]	Organophosphate: OR: 0.69 (0.43–1.12) Organochloride: OR: 0.76 (0.33–1.75)	Age
(25)	Parent et al. Canada,(2009)	Men who worked as farmers when young. The cases and controls had mean ages of 63 and 61 years, respectively. 49 cases of prostate cancer	232	Pesticides (unspecified) and many other chemical substances not related to agriculture	Substantial level of pesticide exposure: OR: 2.3 (1.1–5.1)	Age, ethnicity, education level, and respondent status
(26)	Subahir et al. Malasia, (2009)	Men seen at a university hospital with a mean age of 71.7 years (50 to 86 years). 56 cases of prostate cancer	112	Pesticides (unspecified)	OR: 5.57 (1.74–17.78)	Daily physical activity, family history of cancer, frequency of sexual activity, vegetable intake, fruit intake, tomato intake, meat intake, physical activity

Table 1 (continued)

References	Authors, country, and year of publication	Study population	N	Type of exposure	Results odds ratio and 95% confidence interval (CI)	Adjustment variables
(27)	Xu et al. US, (2010)	American adults (1499 < 65 years old and 486≥65 years old). 58 cases of prostate cancer	1985	13 organochlorides[d]	BHCH: OR: 3.36 (1.24–9.10) Trans-nonachlor: OR: 14.1 (2.55–77.9) Dieldrin: OR: 2.74 (1.01–7.49)	Age, education level, smoking, marital status, race, ethnicity
(11)	Sawada et al. Japan, (2010)	Japanese men aged 40 to 69 years. 201 cases of prostate cancer	14,203	9 organochlorides[e]	Plasma level of BHCH+ high quartile: OR: 0.56 (0.30–1.01)	Smoking, alcohol intake, marital status, green tea intake, body mass index, miso soup intake
(10)	Aronson et al. Canada, (2010)	Men aged 50–80 years seen by five urologists from Ontario. 79 cases of prostate cancer	408	Organochloride pesticides[f]	Mirex In concentration (5.6 to 10.0) only including clinical controls. OR: 0.44 (0.23–0.85)	Age, smoking, alcohol intake, and physical activity
(28)	Multigner et al. Guadeloupe, (2010)	Cases and controls from Guadalupe with mean ages of 66.2 and 60.6 years, respectively. 623 cases of prostate cancer	1294	Chlordecone	Plasma level of chlordecone (+ high tertile) in the multivariate model. OR: 1.77 (1.21–2.58)	Age
(29)	Cockburn et al. US, (2011)	White non-Latins from California. Controls aged >65 and cases aged 60–74 years. 173 cases of prostate cancer	335	13 Pesticides	Group of 8 organochlorides (high level of exposure) OR: 2.03 (1.17–3.52) Captain (high level of exposure) OR: 1.74 (1.01–3.13)	Age, race/ethnicity, use of pesticides athome.

[a]B-BHC, p,p′-DDE, p,p′-DDT, dieldrin, heptachlor epoxide, hexachlorobenzene, trans-nonachlor, oxychlordane. [b]Chlorothalonil, diazinon, dichloropropene, dichlorvos, dicofol, heptachlor, lindane, malathion, mancozeb, maneb, methyl bromide, propargite, propoxur, propyzamine, simazine e trifluralin. [c]Organophosphates, organochlorides, phenoxy herbicides, other pesticides, synthetic fertilizers, natural fertilizers. [d]Hexachlorobenzene, *B*-HCH,/-HCH, p,p′-DDT, p,p′-DDT, oxychlordane, trans-nonachlor, heptachlor epoxide, mirex, aldrin, dieldrin, endrin. [e]*o,p′*-DDT, *p,p′*-DDT, *p,p′*-DDE, trans-nonachlor, cis-nonachlor, oxychlordane, HCB, mirex, *B*HCH. [f]*p,p′*-DDE, *p,p′*-DDT, trans-nonachlor, oxychlordane, HC.

Table 2: Characterization of the reviewed cohort studies.

References	Authors, country, and year of publication	Study population	n	Type of exposure	Results relative risk and 95% CI	Adjustment variables
(30)	Lee et al. US, (2004)	Farmers and pesticide applicators from North Carolina and Iowa. 571 cases of prostate cancer	47,738	Alachlor	RR: 1.13 (0.91–1.41)	Age, alcohol intake, smoking status, education level, family history of cancer, recruitment year, state of residence, and the five pesticides most correlated with alachlor (atrazine, cyanazine, metolachlor, trifluralin, 2,4-D)
(31)	Rusiecki et al. US, (2004)	Farmers and pesticide applicators from North Carolina and Iowa. 554 cases of prostate cancer	52,470	Atrazine	Weighted exposure intensity (+ high quartile) RR: 0.89 (0.63–1.25)	Age, alcohol intake, smoking status, education level, family history of cancer, recruitment year, state of residence, and the five pesticides most correlated with atrazine
(32)	Lee et al. US, (2004)	Farmers and pesticide applicators from North Carolina and Iowa. 820 cases of prostate cancer	52,910	Chlorpyrifos	Only applicators who answered the home questionnaire RR: 1.02 (0.50–2.06)	Age, alcohol intake, smoking status, education level, family history of cancer, recruitment year, state of residence, and the four pesticides most correlated with chlorpyrifos (alachlor, carbofuran, fonofos and trifluralin)
(33)	Zeegers et al. The Netherlands, (2004)	Men who work or worked in agriculture	2355	Agricultural occupation	Works or worked as farmer RR: 0.86 (0.53–1.40). Worked longest as farmer RR: 0.70 (0.36–1.36)	Age, fruit intake, smoking status, meat intake, alcohol intake, education level, family history of prostate cancer, and physical activity
(34)	Cocco et al. Italy, (2005)	Antimalarial applicators from Sardinia between 1946 and 1950. 49% were aged 30 years or less. There were 71 deaths from prostate cancer	4552	DDT	RR mean accumulated exposure (+ high quartile): RR: 0.90 (0.40–1.90)	Age, age at first exposure, and ethnic origin
(35)	Boers et al. The Netherlands, (2005)	Dutch men aged 55 to 69 years. 1386 cases of prostate cancer	3711	Pesticides	Pesticide exposure 3rd tertile: RR: 0.60 (0.37–0.95)	Age, history of prostate cancer in first-degree relative, meat, vegetable, fruit, and alcohol intakes, smoking status, education level, and physical activity
(36)	Bonner et al. US, (2005)	Pesticide applicators from North Carolina and Iowa. 551 cases of prostate cancer	48,586	Carbofuran	Exposure time in days (+ high quartile): RR: 0.88 (0.53–1.47)	Age, alcohol intake, smoking status, education level, family history of cancer, recruitment year, state of residence, and the five pesticides most correlated with carbofuran (EPTC, fonofos, trichlorfon, chlorpyrifos, and permethrin)

Table 2 (continued)

References	Authors, country, and year of publication	Study population	n	Type of exposure	Results relative risk and 95% CI	Adjustment variables
(37)	De Roos et al. US, (2005)	Farmers and pesticide applicators from North Carolina and Iowa. 825 cases of prostate cancer	52,207	Glyphosate	Exposure time in days (+ high tertile): RR: 1.10 (0.90–1.30)	Age, demographic factors, lifestyle, and other pesticides
(38)	Pavuk et al. US, (2006)	Vietnam War veterans. 81 cases of prostate cancer	2516	TCDD (Agent Orange)	Higher levels of serum TCDD in military personnel who stayed >789 days in Southeast Asia: RR: 2.18 (1.27–3.76)	Age, body mass index during the mission, occupation, smoking status
(39)	Pardue et al. US, (2006)	Farmers and pesticide applicators from North Carolina and Iowa. 472 cases of prostate cancer	21,807	Aldrin, chlordane, DDT, Dieldrin, heptachlor, lindane, toxaphene	The seven insecticides were analyzed together. Exposure time in days (+ high quartile) RR: 1.0 (0.70–1.40)	Age at recruitment, family history of prostate cancer, state of residence, education level, smoking status, alcohol intake, total number of days applying organochlorides
(40)	Lynch et al. US, (2006)	Farmers and pesticide applicators from North Carolina and Iowa. 267 cases of prostate cancer	49,013	Cyanazine	Exposure time in days (+ high tertile): RR: 1.23 (0.87–1.70)	Age at recruitment, family history of prostate cancer, state of residence, education level, smoking status, alcohol intake, total number of days applying organochlorides
(41)	Mahajan et al. US, (2006)	Farmers and pesticide applicators from North Carolina and Iowa. 149 cases of prostate cancer with family history of this disease	41,151	Fonofos	Only men with family history of prostate cancer. Weighted exposure intensity (+ high tertile) RR: 1.83 (1.12–3.00)	Age
(42)	Rusiecki et al. US, (2006)	Farmers and pesticide applicators from North Carolina and Iowa. 299 cases of prostate cancer	49,803	Metolachlor	Exposure time in days (+ high tertile) RR: 0.59 (0.39–0.89)	Age, alcohol intake, smoking status, education level, family history of cancer, applicator status (private or commercial), state of residence, and the pesticides most correlated with metolachlor
(43)	Hou et al. US, (2006)	Farmers and pesticide applicators from North Carolina and Iowa. 561 cases of prostate cancer	34,374	Pendimethalin	Exposure time in days (tertile>half) Unexposed reference group RR: 1.0 (0.50–2.10)	Age, education level, alcohol intake, smoking status, family history of cancer, recruitment year, state of residence, and the five pesticides most correlated with pendimethalin
(44)	Samanic et al. US, (2006)	Farmers and pesticide applicators from North Carolina and Iowa. 694 cases of prostate cancer	41,969	Dicamba	Unexposed reference group Exposure time in days (+ high tertile): RR: 1.08 (0.81–1.46)	Age, education level, alcohol intake, smoking status, family history of cancer, recruitment year, state of residence, and total number of days applying pesticides

Table 2 (continued)

References	Authors, country, and year of publication	Study population	n	Type of exposure	Results relative risk and 95% CI	Adjustment variables
(45)	Mahajan et al. US, (2006)	Farmers and pesticide applicators from North Carolina and Iowa. 401 cases of prostate cancer	21,016	Phorate	Exposure time in days (+ high quartile) Reference group with low exposure: RR: 1.31 (0.72–2.37)	Age, smoking status, family history of cancer, recruitment year, state of residence, education level, type of applicator (commercial or private) and use of aldicarb, ethylene dibromide, aldrin, 2,4,5-TP, and butylate
(46)	Bonner et al. US, (2007)	Farmers and pesticide applicators from North Carolina and Iowa. 413 cases of prostate cancer	19,200	Malathion	Unexposed reference group Exposure time in days (+ high tertile): RR: 1.04 (0.79–1.37)	Age, alcohol intake, smoking status, education level, family history of prostate cancer, recruitment year, and state of residence
(47)	Mahajan et al. US, (2007)	Farmers and pesticide applicators from North Carolina and Iowa. 541 deaths by prostate cancer	20,077	Carbaryl	Intensity of exposure to carbaryl, days of use per year: RR: 0.69 (0.47–1.03)	Age, alcohol intake, smoking status, family history of cancer, recruitment year, state of residence
(48)	Lee et al. US, (2007)	Farmers and pesticide applicators from North Carolina and Iowa. 57 deaths by prostate cancer	53,587	Chlorpyrifos	Intensity of exposure to Chlorpyrifos: RR: 0.90 (0.46–1.74)	Age at recruitment, education level, alcohol intake, smoking status, family history of cancer, state of residence, and the four pesticides most correlated with chlorpyrifos (alachlor, carbofuran, fonofos, and trifluralin)
(49)	Koutros et al. US, (2008)	Farmers and pesticide applicators from North Carolina and Iowa. 1180 cases of prostate cancer	48,480	Dichlorvos	Unexposed reference group Weighted exposure intensity, days throughout life (+ high tertile): RR: 0.99 (0.71–1.37)	Age, recruitment year, type of applicator (commercial or private), chlordane, petroleum, family history of prostate cancer, state of residence, smoking status
(50)	Greenburg et al. US, (2008)	Farmers and pesticide applicators from North Carolina and Iowa. 1171 cases of prostate cancer	47,718	Captan	Unexposed reference group Weighted exposure intensity, days throughout life (+ high tertile): RR: 1.02 (0.73–1.44)	Age, family history of prostate cancer in first-degree relative, and recruitment year
(51)	Bemmel et al. US, (2008)	Farmers and pesticide applicators from North Carolina and Iowa. 927 cases of prostate cancer	48,378	S-Ethyl-N,N-dipropylthiocarbamate	Exposure time in days (+ high tertile): RR: 1.17 (0.89–1.53)	Age, race, smoking status, alcohol intake, type of applicator (commercial or private), history of prostate cancer, state of residence, and total number of days using pesticides

Table 2 (continued)

References	Authors, country, and year of publication	Study population	n	Type of exposure	Results relative risk and 95% CI	Adjustment variables
(52)	Mozzachio et al. US, (2008)	Farmers and pesticide applicators from North Carolina and Iowa. 1100 cases of prostate cancer	46,625	Chlorothalonil	Unexposed reference group Weighted exposure intensity, days throughout life (+ high tertile): RR: 0.79 (0.52–1.21)	Age, smoking status, state of residence, family history of cancer, type of applicator (commercial or private)
(53)	Kang et al. US, (2008)	Farmers and pesticide applicators from North Carolina and Iowa. 740 cases of prostate cancer	48,834	Trifluralin	Reference group with low exposure Weighted exposure intensity (+ high tertile): RR: 1.18 (0.89–1.57)	Age at recruitment, smoking status, education level, alcohol intake, state of residence (Iowa/North Carolina), family history of cancer in first-degree relatives, type of applicator (commercial/private)
(54)	Lynch et al. US, (2009)	Farmers and pesticide applicators from North Carolina and Iowa. 543 cases of prostate cancer	18,555	Butylate	Unexposed reference group Reference group with low exposure Exposure time in days (+ high tertile): RR: 2.09 (1.27–3.44)	Age, education level, race, smoking status, family history of cancer in first-degree relative
(55)	Koutros et al. US, (2009)	Farmers and pesticide applicators from North Carolina and Iowa. 1161 cases of prostate cancer	48,106	Aromatic amine	Unexposed reference group Weighted exposure intensity, days throughout life (+ high tertile): RR: 1.06 (0.81–1.40)	Age, recruitment year, family history of cancer in first-degree relative, type of applicator (commercial or private), use of alachlor and carbofuran
(56)	Rusiecki et al. US, (2009)	Farmers and pesticide applicators from North Carolina and Iowa. 1032 cases of prostate cancer	47,823	Permethrin	Weighted exposure intensity (+ high tertile): RR: 0.87 (0.65–1.16)	Age, recruitment year, race, family history of cancer in first-degree relative, smoking status, state of residence
(57)	Bonner et al. US, (2010)	Farmers and pesticide applicators from North Carolina and Iowa. 1131 cases of prostate cancer	43,522	Terbufos	Unexposed reference group Weighted exposure intensity (+ high tertile): RR: 1.21 (0.99–1.47)	Age, recruitment year, family history of prostate cancer, state of residence, education level, smoking status, alcohol intake, atrazine, 2,4-D, fonofos, carbofuran, and phorate
(58)	Christensen et al. US, (2010)	Farmers and pesticide applicators from North Carolina and Iowa. 1311 cases of prostate cancer	44,133	Coumaphos	Individuals who used Coumaphos and had a family history of prostate cancer: RR: 1.65 (1.13–2.38)	Age

Table 2 (continued)

References	Authors, country, and year of publication	Study population	n	Type of exposure	Results relative risk and 95% CI	Adjustment variables
(59)	Barry et al. US, (2012)	Farmers and pesticide applicators from North Carolina and Iowa. 1851 cases of prostate cancer	53,588	Methyl bromide	Weighted exposure intensity (+ high tertile): RR: 1.01 (0.72–1.41)	Age, race, alcohol intake, education level, state of residence, family history of cancer, five pesticides most correlated with methyl bromide (metalaxyl, ethylene dibromide, carbaryl, aldicarb, and maneb/mancozeb)
(60)	Koutros et al. US, (2012)	Farmers and pesticide applicators from North Carolina and Iowa. 1962 cases of prostate cancer	54,412	50 types of pesticides	Only for prostate tumors with Gleason≥7 Fonofos-RR: 1.63 (1.22–2.17) Malathion- RR: 1.43 (1.08- 1.88) Terbufos- RR: 1.29 (1.02–1.64) Aldrin- RR: 1.49 (1.03–2.18)	Age, smoking status, fruit intake, residence location, and leisure-time physical activity
(61)	Ansbaugh et al. US, (2013)	Vietnam War veterans. 896 cases of prostate cancer	2720	TCDD (Agent Orange)	OR: 1.52 (1.07–2.13)	Age, PSA level, and result of digital rectal examination
(62)	Lerro et al. US, (2015)	Farmers and pesticide applicators from North Carolina and Iowa. 1362 cases of prostate cancer	33,484	Acetochlor	RR: 0.99 (0.82–1.20)	Age, race, state of residence, type of applicator, smoking status, family history of prostate cancer, alcohol intake, body mass index, use of tractor with closed cabin, and use of pesticides correlated with acetochlor
(63)	Jones et al. US, (2015)	Farmers and pesticide applicators from North Carolina and Iowa. 1292 cases of prostate cancer	22,830	Diazinon	RR: 1.16 (0.95–1.43).	Age, state of residence, smoking status, alcohol intake, family history of prostate cancer, education level

of 0.86, 95% CI (0.53–1.40) (33). A study conducted in Italy (34) did not find an association between prostate cancer and dichlorodiphenyltrichloroethane (DDT) exposure during antimalarial campaigns. Additionally, two other studies that investigated the association between prostate cancer and 2,3,7,8-tetrachlorodibenzodioxin (TCDD, also known as agent orange), an herbicide used as a chemical weapon during the Vietnam War, found that military personnel exposed to TCDD were at higher risk of prostate cancer, with a relative risk of 2.18, 95% CI (1.27–3.76) (38) and odds ratio of 1.52, 95% CI (1.07–2.13) (61).

Only two of the reviewed studies did not find an association between prostate cancer and exposure to pesticides or agricultural occupations (39, 43), although many studies, especially the cohort studies, found associations without statistical significance. Fifteen studies found a negative association between prostate cancer and the analyzed exposure. However, most studies (32) found a positive association between prostate cancer and exposure to pesticides or agricultural occupations.

In Figure 2, it is possible to observe the risk estimates and respective confidence intervals of all the studies included in this review.

Considering this set of studies, we can see that there was no association between prostate cancer and exposure to pesticides or activities related to agriculture in only two of them (39, 43), although many studies, mainly cohort studies, have found associations with no statistical significance. In 15 studies, the authors observed negative associations between prostate cancer and the analyzed exposure. However, in most studies (32) there were positive associations between prostate cancer and pesticide exposure or work in activities related to agriculture.

For more restricted analysis purposes, we evaluated separately the subgroup of 42 studies that only looked at exposure to one or more pesticides in agricultural activities (Figure 3). In this smaller group, although there was a more specific characterization of exposure, a wide variation in risk estimates is nevertheless observed.

Discussion

Agricultural occupations leads to the exposure to numerous chemical substances, which can be associated with some types of cancer, including prostate tumors (64, 65). Thus, an expressive number of occupational studies have investigated the association between pesticide exposure and prostate cancer, especially in farmers and related occupations (66). A literature review combined the results of epidemiological studies and general occupational surveys of cancer mortality and morbidity in farmers from developed countries. The authors concluded that farmers are at greater risk of developing prostate cancer, even though no associations were found with specific types of pesticides. Nevertheless, the studies included in that review were conducted between the late 1960s and early 1970s, and most used mortality data (67).

The present systematic review found that pesticide exposure is associated with a moderate increase in the risk of developing prostate cancer. Other literature reviews found similar results. In a meta-analysis of 37 studies on pesticide exposure and cancer published between 1963 and 1994, Acquavella et al. (1998) found that farmers had a higher risk of prostate cancer: 1.07, 95% CI (1.02–1.13) (14). The said meta-analysis analyzed 30 studies with prostate cancer as outcome, 11 of which were cohort studies, eight were case-control studies, and 11 used the proportional mortality ratio. Another literature review of 22 studies published between 1995 and 2001, including cohort, case-control, proportional mortality ratio, standardized mortality ratio and standardized incidence ratio studies, found that individuals with pesticide exposure had an estimated prostate cancer risk of 1.13, 95% CI (1.04–1.22) (65). Nonetheless, it is important to consider that the period covered by the present systematic review is unique and that it included only cohort and case-control studies, which are methodologically sounder than the set of studies evaluated in the cited literature reviews and so one must exercise caution when comparing its results.

The risk estimates reported by the reviewed case-control studies vary widely, and that may be related to the diversity of the study populations, the way certain variables were treated by the statistical analyses performed, and the definition of exposure. Only two case-control studies adjusted the measure of association for family history of prostate cancer, even though children and siblings of individuals who had these tumors are two or three times more likely to develop the disease than those without a family history (7). Xu et al. (2010) found that White men aged 65 years or more exposed to the organochloride trans-nonachlor had a 14-fold risk of prostate cancer (27). However, the authors did not adjust the measure of association for family history of prostate cancer, which could be a confounder. On the other hand, since case-control studies assess past exposure, they may be more susceptible to exposure classification errors. Most studies analyzed herein classified exposure based on self-reports. Self-reports may be affected by memory bias if the recollection of cases and controls differed with respect to past pesticide exposure. However, a study with a cohort of

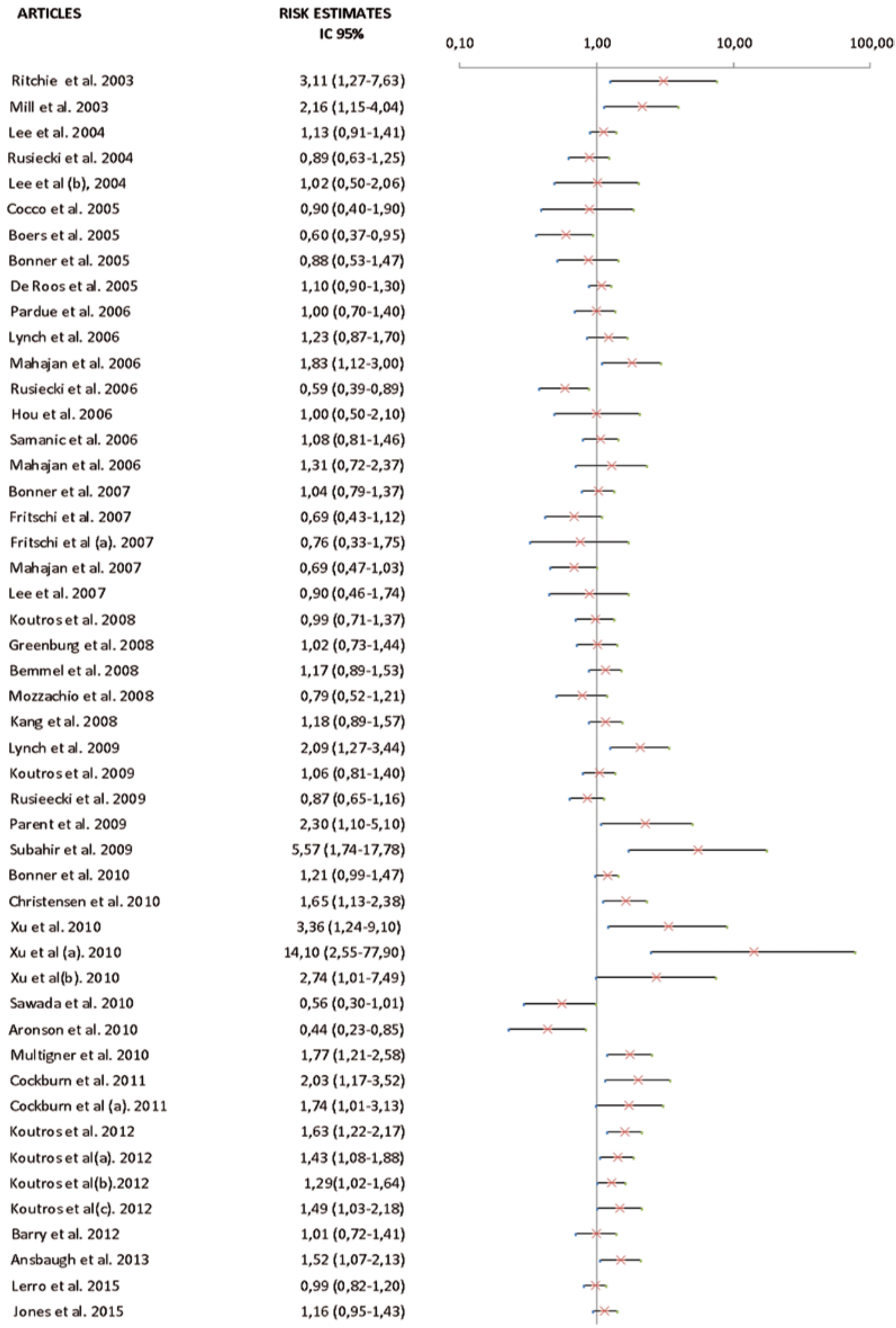

Figure 2: Risk estimates and 95% CIs observed in the reviewed articles the review.

pesticide applicators in the United States analyzed their recollection of these substances and compared it with the recollection of other variables, such as food habits and alcohol intake, and did not find statistically significant differences (68).

The present review chose not to include case-control studies with controls diagnosed with BPH or any type of cancer. This is justified by the fact that, although the two diseases seem to have distinct natural histories, with BPH developing in the transitional zone and cancer in the

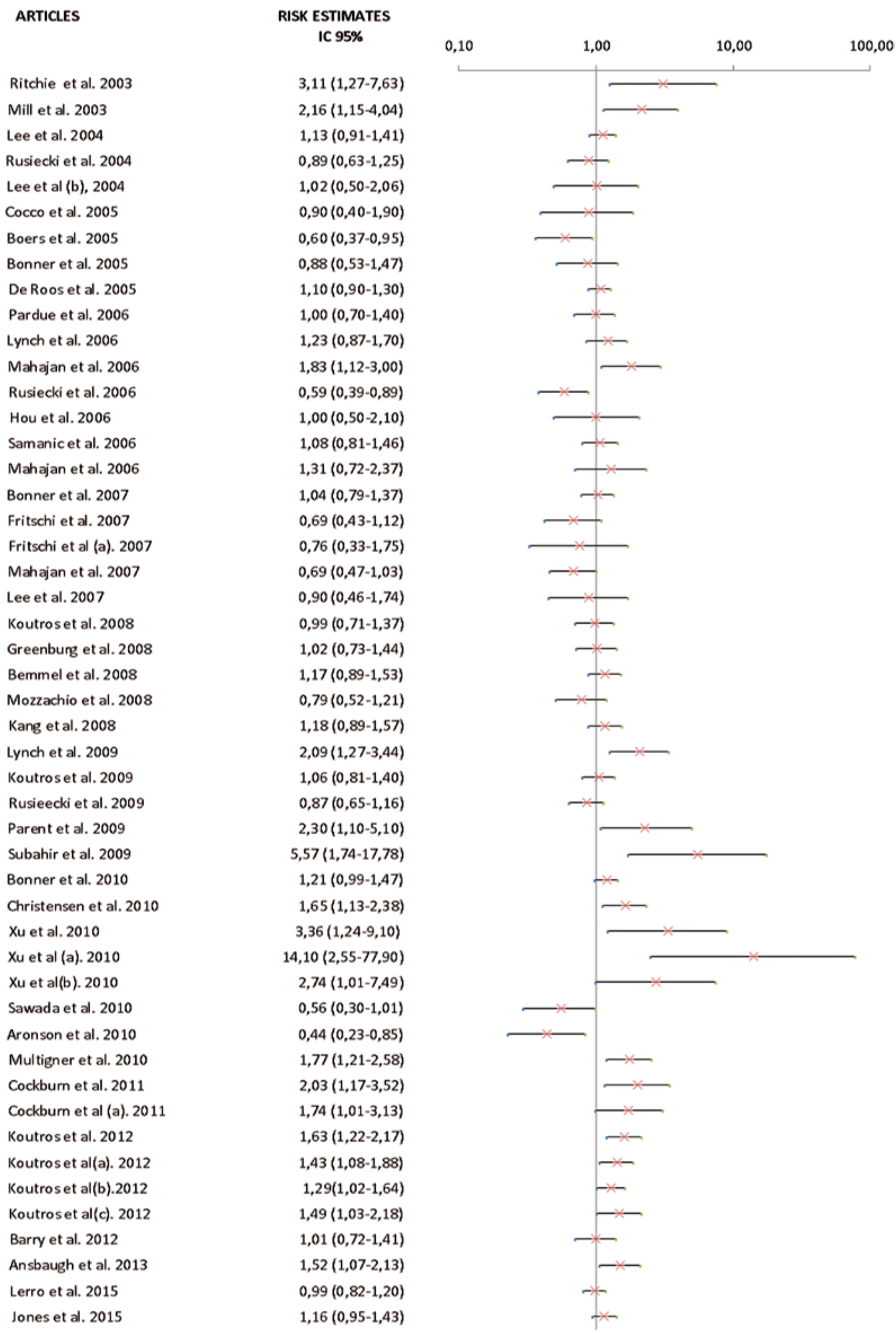

Figure 3: Risk estimates and 95% CIs, including only studies that analyzed pesticide exposure due to agricultural activities.

peripheral zone of the prostate, the relationship between BPH and prostate cancer has not yet been clearly and accurately defined (69, 70). The two diseases have some common characteristics: both are hormone dependent, their incidences increase progressively with age, and they often co-occur (71). Necropsy studies suggest that 83% of prostate cancer cases develop in men with BPH. A study from Taiwan found a positive association between prostate cancer and BPH (72). Another case control study only found an association between prostate cancer and BPH in individuals whose BPH diagnosis preceded prostate cancer diagnosis by up to 6 months (73). A meta-analysis of 12 case-control studies published between 1987 and 2007, which investigated the association between prostate cancer and exposure to pesticides and/or agriculture, found a risk estimate of 3.83, 95% CI (1.96–7.48) when the controls had BPH; when these individuals were excluded, the odds ratio decreased to 1.38, 95% CI (1.16–1.64) (74).

Most studies reviewed herein were conducted in the United States, and publications on the subject became more frequent from 2003. High interest on the subject may reside on the fact that the United States has very high pesticide use, and an important part of its population is occupationally or environmentally exposed to these substances. It is estimated that the United States used 22% of the global pesticide consumption between 2005 and 2007 (75).

Of the cohort studies analyzed in the present review, most (29 articles) were based on a cohort of more than 50,000 American farmers and pesticide applicators, aimed to investigate the effects of pesticide exposure on human health. Twenty-seven of these studies analyzed exposure to a single substance, and three of these studies found positive associations of prostate cancer with fonofos, butylate, and coumaphos. However, these farmers may have been exposed to other pesticides, so it is very difficult to attribute these findings to any particular substance. Farmers and pesticide applicators are infrequently exposed to a single pesticide, and as there are numerous pesticides, most studies cannot determine the contribution of specific compounds (76).

The wide variation in the risk estimates reported by the studies analyzed herein may be related to the heterogeneity of their samples and methodologies. The criteria used for determining exposure were diverse, ranging from individuals exposed to gardening pesticides during leisure time (19) to military personnel exposed to the herbicide Agent Orange during the Vietnam War (38, 61). Likewise, another literature review on the subject found that occupational exposure tends to be very heterogeneous and depends on many factors, such as type of crop, crop area, time of exposure, and use or not use of personal protective equipment, among others (14).

The majority of studies included in their source population, men of different ethnic backgrounds, precluding an analysis of the association based on this variable. The participation of different racial groups was quite heterogeneous and related to the geographic area in which the studies were conducted. While in the studies within the cohort of farmers and pesticide applicators in the US, predominated white men, in those developed in Asia and Central America there was a predominance of individuals of the yellow and black racial groups, respectively. Some articles did not provide specific information about the ethnic origin of the study subjects.

The diversity in the criteria used to determine exposure, including from individuals exposed to the use of pesticides in gardening during leisure time (19) to military men exposed to the herbicide Agent Orange during the Vietnam War (38, 61) was another difficulty. We attempted a stratification, according to the type of exposure analyzed in the studies, in order to restrict exposure only to pesticides in agricultural settings. However, even so, the diversity of analyzed pesticides hampered, partially, their comparability.

One limitation, which is common to systematic reviews, is the possible occurrence of publication bias (77). Studies that do not support a given hypothesis may be less likely to be published. The comparison between unpublished studies on the subject and those included in the present review would allow the verification of this type of bias, but this is a very challenging and difficult task to execute (14). However, since the associations identified in many studies included in this review were not statistically significant, publication bias was likely very small.

The methodological limitations of the reviewed epidemiological studies prevent a more accurate definition of many individual exposure factors, such as exposure intensity and amount of exposure, among others. Moreover, other factors, such as little detail on the exposure of agricultural populations, type of occupation, and work duration, the use of indirect exposure measurements, and short intervals between exposure and end of the follow-up period prevent a more accurate analysis of the association of interest and the execution of a meta-analysis (78, 79).

Thirty-two of the reviewed studies found prostate cancer to be positively associated with pesticide exposure or agricultural occupation, and in 11 of these studies, exposed individuals were more than twice as likely to develop prostate cancer in comparison to unexposed individuals. However, some studies found weak associations, and sometimes, without statistical significance.

The evidence provided by the studies systematically reviewed herein indicates that individuals exposed to pesticides or who have agricultural occupations are at greater risk of developing prostate cancer.

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