

Phytosanitary products from agriculture associated with the development of bladder cancer among farm owners and farm workers: a systematic review

N. Belcaid¹, I. Dassar², A. Abdellaoui¹, M. Taleb¹

¹Engineering, Electrochemistry, Modeling and Environment Laboratory; Faculty of Sciences Dhar El Mahraz; Sidi Mohamed Ben Abdellah University; Fez, Morocco;

²Ministry of Agriculture, Maritime Fisheries, Rural Development and Water and Forests; Morocco

Contacts: Nouredine Belcaid drbelcaidnouredine@gmail.com

Context. Increased bladder cancer prevalence among farm owners and farm workers has been linked to high use of phytosanitary agents in agricultural activities. These results suggested that exposure to phytosanitary products and the risk of bladder cancer may be related.

Objective. Examining the connection between phytosanitary products and the risk of bladder cancer was the goal of the current systematic review and meta-analysis.

Methods. Through PubMed, Scopus, Science Direct, and Web of Science, a thorough literature searches of works updated to 2022 was carried out. The estimates of odd ratio (OR) with 95 % confidence intervals for the highest *versus* the lowest exposure to pesticide were compiled using fixed- or random-effect models. A prevalence meta-analysis was performed using Cochrane Revman Software.

Results. According to the pooled OR estimates, exposure to phytosanitary conditions was linked to a higher risk of bladder cancer (OR 1.59; 95 % confidence interval 0.51–5.02). Results in the cohort and case–control groups both showed a connection.

Conclusion. According to the majority of studies, exposure to phytosanitary agents and the risk of bladder cancer are directly correlated. According to certain research, smoking may increase the risk of bladder cancer.

Keywords: bladder cancer, phytosanitary product, smoking, farm-owner, farm-worker, malignant tumor, insecticide, pesticide, ungicides, aromatic amines, polycyclic aromatic hydrocarbons, chemical exposure

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Фитосанитарные продукты, ассоциированные с риском развития рака мочевого пузыря у работников сельскохозяйственных предприятий: систематический обзор

N. Belcaid¹, I. Dassar², A. Abdellaoui¹, M. Taleb¹

¹Engineering, Electrochemistry, Modeling and Environment Laboratory; Faculty of Sciences Dhar El Mahraz; Sidi Mohamed Ben Abdellah University; Fez, Morocco;

²Ministry of Agriculture, Maritime Fisheries, Rural Development and Water and Forests; Morocco

Контакты: Nouredine Belcaid drbelcaidnouredine@gmail.com

Введение. В последние годы наблюдается рост выявляемости рака мочевого пузыря у работников сельскохозяйственных предприятий, отмеченный также с широким использованием фитосанитарных продуктов в агрокультурной деятельности. Предположительно, существует связь между воздействием фитосанитарных продуктов и риском развития рака мочевого пузыря.

Цель – провести систематический обзор литературы и метаанализ в целях изучения взаимосвязи между фитосанитарными продуктами и риском развития рака мочевого пузыря.

Методы. Проведен поиск статей, опубликованных до 2022 г. включительно, в базах данных PubMed, Scopus, Science Direct и Web of Science. Оценку отношения шансов (ОШ) с 95 % доверительными интервалами для самого

высокого и низкого уровней контакта с пестицидами проводили с использованием моделей с фиксированными и случайными эффектами. Метаанализ частоты встречаемости выполнен с помощью программного обеспечения Cochrane Revman.

Результаты. Согласно объединенным оценкам ОШ, контакт с фитосанитарными продуктами был связан с повышенным риском рака мочевого пузыря (ОШ 1,59; 95 % ДИ 0,51–5,02). Результаты в когортных группах и группах «случай–контроль» показали наличие ассоциации.

Заключение. Согласно данным большинства исследований, взаимодействие с фитосанитарными агентами напрямую коррелирует с повышенным риском развития рака мочевого пузыря. Результаты некоторых исследований показывают, что курение может повышать этот риск.

Ключевые слова: рак мочевого пузыря, фитосанитарный продукт, курение, владелец ферм, сельскохозяйственный рабочий, злокачественная опухоль, инсектицид, пестицид, фунгициды, ароматические амины, полициклические ароматические углеводороды, химическое воздействие

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Research question

Numerous pieces of evidence from earlier years have shown that bladder cancer and phytosanitary products may be related. Evaluation of the link between bladder cancer and phytosanitary products was the goal of the recent meta-analysis and systematic review.

The current analysis research question was set up using the PICO approach.

Population — bladder cancer patients.

Intervention — no intervention.

Comparison — no comparison.

Outcome — exposure-related danger of bladder cancer to phytosanitary products from agriculture.

Question: What is the relationship between exposure to phytosanitary products from agriculture and risk of bladder cancer?

Introduction

A condition known as cancer is a situation where a small percentage of body cells grow out of control and invade other physical regions and out of it cancerous tumors or malignant tumors exist [1]. Cancer can appear almost anywhere in one of the billions of cells that comprise the human body [2]. According to world health organization, the tenth most common type of cancer worldwide is bladder cancer. Every year, around 600,000 human beings worldwide are identified as having bladder cancer, and out of those about 200,000 pass away from it [3]. It has been reported by experts that bladder cancer is more prevalent in males than females. For example, between 1997 to 2002 the Canary Islands, a group of islands off the coast of Spain had 338 instances of bladder cancer in males and 202 females per 100,000 people, according to the National Epidemiology Centre [4] and Urinary bladder malignancy is the highest frequent malignancy in males in the United States, compared to women [5]. Apart from gender, in United States,

increased cancer mortality among farmers varies by race, and geographic area as well [4].

The most recent epidemiological research connects occupation and environmental biochemical (carcinogens) exposures to approximately 30 different forms of cancer [4]. There has been significant research about the linked danger factors with bladder cancer in farmers, nicotine is the leading danger factor for illness development [4].

The use of insecticides, aromatic amines, or polycyclic aromatic hydrocarbons in the workplace is a substantial significant predictor for bladder cancer. Indeed, numerous jobs involving chemical exposure, such as farming and other jobs involving pesticide exposure, appear to be significant risk factors [4].

Because of the potentially hazardous substances (eg, phytosanitary products, solvents, paints, and engine exhaust) farmers are exposed to, the occurrence of bladder cancer among farmers has been studied. A non-statistically significant increase in risk is also considered among women who live in a household with agricultural laborers, because these women are more likely to be exposed to pesticide and other pollutant residues brought home on the farmers' clothes or shoes, as well, through their customary responsibilities for cleaning the clothes and house [6]. Furthermore, agriculturalists and their families reside in neighborhoods close to where they work, exposing family members to additional hazards such as dirty air and poisoned food or drink [6].

Meta-analysis is seen as a useful tool for signifying trends that may not be visible in a solo study. As a result, brief separate studies boosts confidence in the findings. We are aware of no meta-analysis has previously been published on the correlation between phytosanitary products from agriculture and the jeopardy of bladder cancer. The current study sought to objectively assess the relationship between phytosanitary products from agriculture and the danger of bladder cancer by synthesizing the findings of previously published case–control and cohort studies.

Methods

Literature exploration

The following databases were consulted for literature: PubMed, Scopus, Science direct and Web of science for articles evaluating bladder cancer patients associated with phytosanitary products from agriculture until October 2022. In order to create search strings, the selected words and phrases or keywords used were: “pesticides” OR “fungicides” OR “insecticides” AND “bladder cancer” in Title Abstract Keyword.

Search strategy

Using a standardized form, two reviewers separately browsed the following databases’ titles and summaries: PubMed, EMBASE databases, Scopus, Science direct, articles on the Web of Science were looked up and evaluating bladder cancer patients associated with phytosanitary products from agriculture until 2022. In order to create search strings, the selected words and phrases or keywords used were: “pesticides” OR “fungicides” OR “insecticides” AND “bladder cancer” in Title Abstract Keyword.

Eligibility criteria and study selection

Cohort studies, intervention studies, case–control studies, random-controlled trials, and cross-sectional studies were among the study categories that were all eligible to be considered in the evaluation. There weren’t any limitations on the location of studies. All studies related to phytosanitary products from agriculture allied with the growth of bladder cancer among farm owners and farm workers were included in the research. The titles and abstracts of the selected publications were rapidly skimmed to see how relevant they were to the research issue. Other criteria observed were:

- the complete article can be accessed in English authorship;
- published between 1990 and 2022 in a peer-reviewed journal;
- owners and employees of farms participated in the survey;
- only studies involving human participants were allowed;
- studies that presented the full results.

For this systematic review, many exclusion standards were established, including the following:

- duplicates, abstract-only, not for publication or peer review;
- articles from wikis and encyclopedias, case studies, review articles, opinion essays, and systematic reviews;
- studies using non English language.

Talk with a third reviewer who acted as an arbiter helped the reviewers come to an agreement when they couldn’t. Cross references between the chosen studies and pertinent papers were examined. Independently reading the entire texts of the remaining articles, they were graded. Any disagreements among the authors on the articles were resolved throughout the article selection and data extraction phase.

Extraction of data

Using a standardized form (Microsoft Excel), the two reviewers’ separately extracted data. When the data from the evaluated papers were available, the following factors were noted: study design, the nation in which the study was aromatic, sample size, features of the control group, exposure and outcomes, and findings.

Quality assessment

Depending on the type of study that was accessible, the danger of bias was evaluated. The threat of bias in non-randomized studies of intervention (ROBINS-I) instrument was used to assess the risk of bias because there were no randomized-controlled trials on this subject. Participant recruitment for the study, categorization of interventions, deviations from intended interventions, missing data, measurement of outcomes, and choice of the stated results are all included. The possibility of bias brought on by confounding circumstances (lack of knowledge on pacifier kind, beginning and ending of habit, initial malocclusion), and presence of digital or object sucking) is also included. Each included study was rated individually by the reviewers, and any disagreements were settled through consultation between them.

Data synthesis

Using the Cochrane Review Manager Software, a meta-analysis of the various sub-group data gathered from the chosen studies was carried out. This meta-analysis employed a random-effects model to account for the heterogeneity between studies because different studies’ research designs and measuring periods varied, the summary measurements were combined and visualized as forest plots. The review calculated the level of heterogeneity using the I^2 statistic. In order to ensure that the included studies were highly homogeneous, a level of heterogeneity 25 % was acceptable. The distribution of the studies’ results’ symmetry was evaluated using a funnel plot. A sensitivity analysis was also done to identify any possible sources of heterogeneity.

Results

Study selection

A literature searches from e-databases turned up 3618 papers. One hundred and twenty-seven studies from Scopus, 1809 from Science Direct, 106 from Web of Science, and 1576 from PubMed. Due to duplication, a total of 237 records were eliminated. The remaining 3381 studies were submitted for titles and abstract screening and a total 3306 publications were omitted at this stage. The next step was full-text reading which looked into 75 articles. After full text read, 67 articles were eliminated. Of the 67 articles eliminated 24 were reviews, 36 did not report the desired outcome and 7 were removed due to lack of full text. Finally, 8 studies were available for inclusion and these studies are [4, 5, 7–12].

The study selection procedure is summarized in Fig. 1.

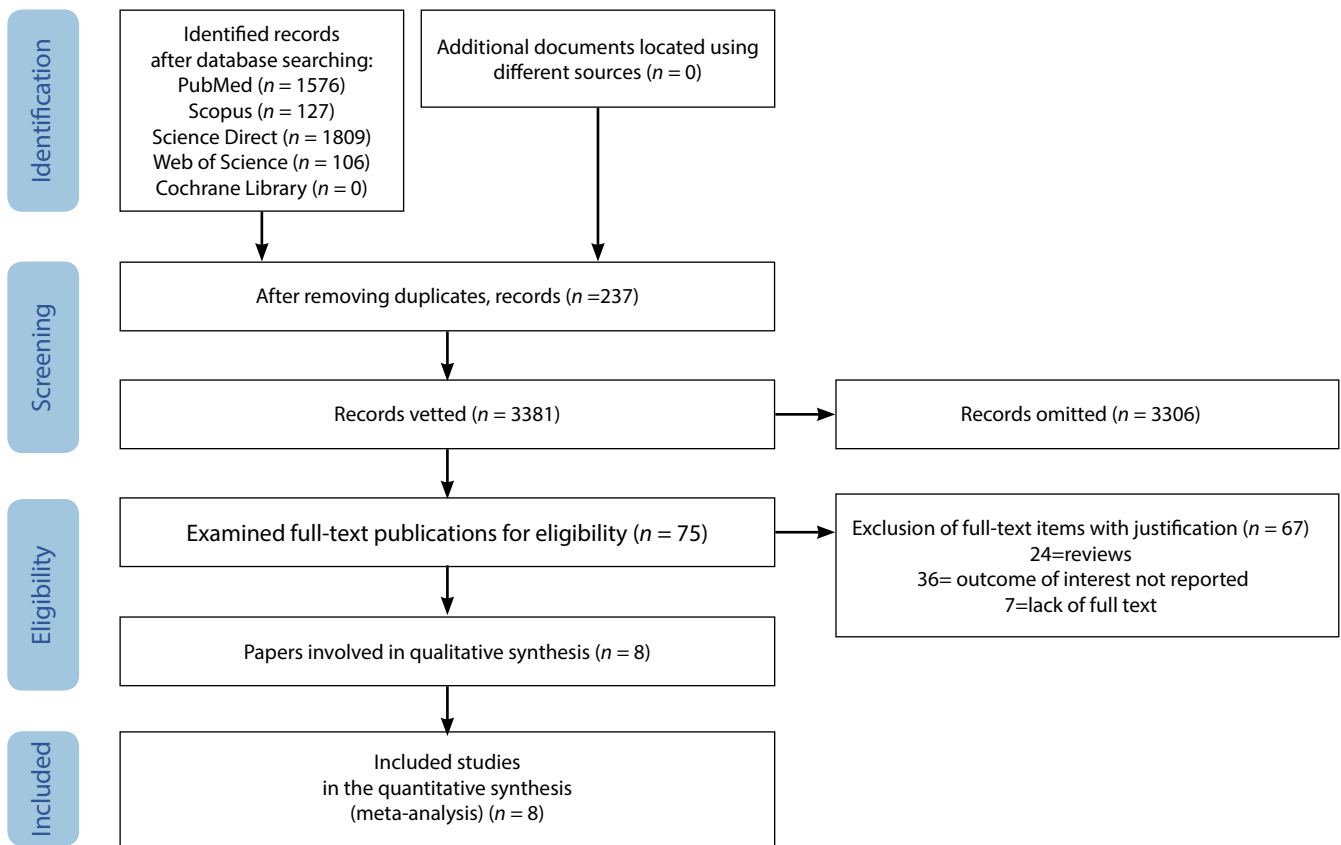


Fig. 1. PRISMA flow diagram for the study selection process

Characteristics of included studies

All of these articles were published between 1993 to 2022. The size of the sample in these research varied from 341 to 839 947 with a total of 992 350 participants. They were all adults of various ages. Among the 8 studies, 7 were case–control studies, and 1 was a cohort study. Table 1 gives a summary of the eight studies encompassed in the analysis.

Quality assessment results

Table 2 depicts the pre-, during-, and post-intervention domains of the ROBINS-I may be subject to bias judgments. Two studies [6, 9] were found to have a high risk of bias, whereas five of the non-randomized studies [4, 5, 7, 10, 11] were at moderate risk of bias and one case–control study [8] was found to have a low risk of bias.

Meta-analysis

Incidence of bladder cancer due to phytosanitary products

This analysis's quantitative data comes from eight studies [4–9, 11, 12]. When evaluating the results from bladder cancer prevalence, the overall total of members was 997 350, 969 875 in the phytosanitary products group and 27 475

in the non-phytosanitary group. The prevalence rates of bladder cancer were 62 % in the phytosanitary products group vs. 5.5 % in the non-phytosanitary products group.

It made use of a random-effect model. The calculated odd ratio (OR) was 1.59 with 95 % confidence interval (CI) 0.51–5.02 ($p = 0.43$). The collected research showed significant heterogeneity of $p < 0.00001$ and $I^2 = 99\%$. The overall results showed that phytosanitary products is linked with the growth of bladder cancer among farm workers and farm owners. These findings, however, are statistically insignificant. Fig. 2 shows a forest plot that gives a summary of the results of this analysis.

Publication bias

The standard error of each study is plotted against the average effect size in the funnel plot below to highlight how variable each study is (Fig. 3). Because studies were scattered more asymmetrically around the mean, visual analysis of the funnel plot revealed that there was publication bias or small study bias. The publication bias might have been caused by insignificant findings, small effect size, and/or unfavorable outcomes.

Table 1. *Featured studies' characteristics*

Author	Year of study	Study design	Country	Total sample size	Age of participants	Male participants	Findings
S. Amr et al.	2014	Case—control	Egypt	1834	45–65 years	1834	Bladder cancer risk was dose-dependently increased by pesticide exposure, according to our findings (the odds increased with the length of exposure)
A. Cassidy et al.	2009	Case—control	Texas	1208	35–74 years	928	This analysis shows that urinary bladder cancer risk has increased for jobs that were previously considered at risk. Workers in a number of occupations and industrial groupings are much more likely to develop urinary bladder cancer, especially if they have worked there for 10 years or more
S. Amr et al.	2013	Case—control	Egypt	4456	Not specified	3594	Egyptians were more likely to get bladder cancer due to farming-related occupational and environmental exposures
M. Boulanger et al.	2017	Cohort study	French	148 051	53–76 years	82 700	Our research raises the possibility that there is a connection between farming, especially greenhouse farming, the growing of field vegetables, and bladder cancer
S.S. Jackson et al.	2016	Case—control	Egypt	1167	19–80 years	0	Living with an agricultural worker, as defined by non-occupational exposure to agricultural employment, among Egyptian women who are married, bladder cancer incidence has increased
L.D. Boada et al.	2015	Case—control	Spain	346	50–80 years	288	The role of genes encoding xenobiotic-metabolizing enzymes in bladder cancer is confirmed by these findings, which add to the evidence for gene-environment connections between organochlorine pesticides and the disease
F. Forastiere et al.	1993	Case—control	Italy	341	35–80 years	Not specified	According to the study, stomach cancer is on the rise while bladder cancer fatality rates are generally low among farmers in central Italy
J.F. Viel, B. Challier	1995	Case—control	French	839 947	35–74 years	Not specified	Given that vines are largely concentrated in Southern France, these findings may help to explain the French south-north gradient in bladder cancer. They also increase the body of indication suggesting that pesticides in grapes cause bladder cancer mortality among farmers

Table 2. Uses the ROBINS-I method to determine whether any included research may be biased

Study	Confound- ing	Selection of partici- pants	Sorting of interven- tion	Deviance from intended	Missing data	Dimension of outcome	Choice of conveyed result	Overall
S. Amr et al., 2014	Low	Low	Low	Low	Low	Low	Low	Low
A Cassidy et al., 2009	Low	—	Low	Moderate	Low	Moderate	Moderate	Moderate
S. Amr et al., 2013	Low	Low	Moderate	Low	Low	Low	Low	Moderate
M. Boulanger et al., 2017	Serious	Serious	Low	Low	Moderate	Low	Moderate	Serious
S.S. Jackson et al., 2016	Serious	Low	Low	Moderate	low	Moderate	Moderate	Serious
L.D. Boada et al., 2015	Moderate	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
F. Forastiere et al., 1993	Low	Moderate	Low	Moderate	Low	Low	Low	Moderate
J.F. Viel, B. Challier, 1995	Low	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate

Note. Low compared to a well-conducted randomized trial. Moderately sound for a non-randomized study, but insufficient to compare to a rigorous randomized trial. Serious is far too complicated to produce any good evidence on the impacts of action. The greatest amount of bias ever detected in any domain is equivalent to the overall bias risk.

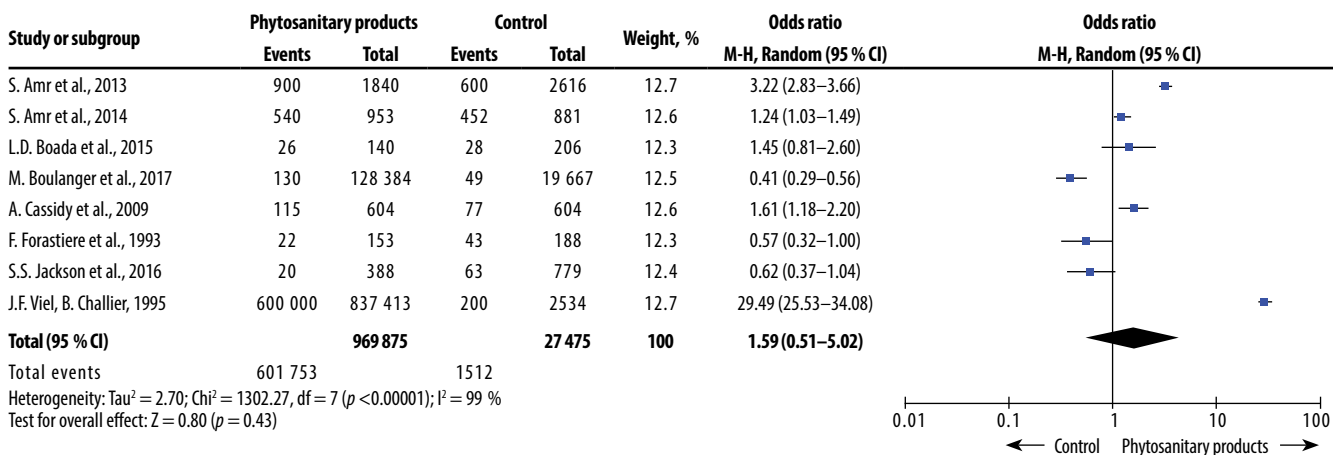


Fig. 2. The forest plot of phytosanitary products from agriculture associated with the development of bladder cancer among farm owners and farm workers. CI – confidence interval

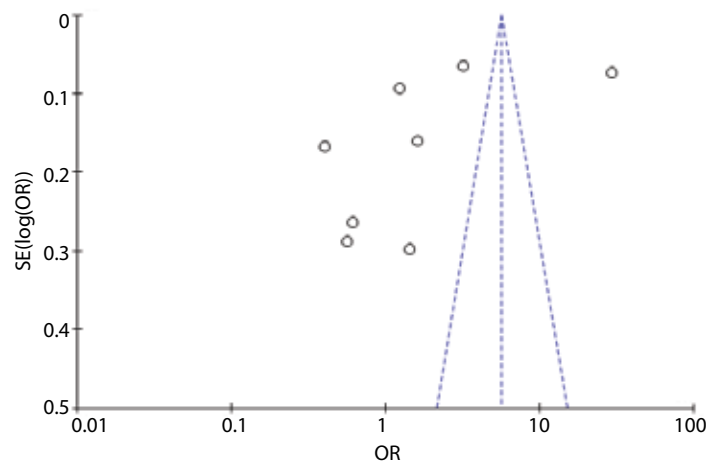


Fig. 3. Analysis of a funnel plot for publication bias. OR – odds ratio

Sensitivity analysis

From the forest plot, the heterogeneity of the pooled effect of all studies included was high as shown by $I^2 = 99\%$. Using “eyeball” test, the variability was clearly displayed and this affirmed the reported figure of I^2 . The need to find out the reason behind high heterogeneity arose. To see how deleting single study at a time affected the aggregate effect, the sensitivity examination was done. One study [4] after being deleted, the heterogeneity lessened from 99 % to 97 %, this shows it had the potential for extraordinary values. The calculated OR, changed to 1.06 with 95 % CI 0.57–1.96 ($p = 0.86$).

Studies were gradually removed and examined, another study [5] was discarded and the variability reduced as I^2 changed from 97 % to 90 %, the calculated OR, changed to 0.87 with 95 % CI 0.54–1.4 ($p = 0.56$). The two studies show substantial significant influence on the pooled heterogeneity. Different studies were removed but not much effect on I^2 could be noticed. When third study by M. Bou-langer et al. was removed I^2 drastically changed from 90 % to 76 %, the calculated OR became 1.05 with 95 % CI 0.74–1.5 ($p = 0.79$) [9]. In both instances the results didn't differ significantly with the ones obtained in the main analysis meaning the high heterogeneity have significant impact on the findings.

Discussion

This systematic review and meta-analysis assessed the association of phytosanitary products from agriculture with the development of bladder cancer among farm owners and farm workers. According to the findings from most of the studies that passed the inclusion criteria, there is a direct correlation between phytosanitary products from agriculture and bladder cancer. Some studies showed that phytosanitary products is not only the danger of bladder cancer, there is other contributing factors to the danger of bladder cancer including tobacco smoking, older age and genetic composition. The findings from the study conducted showed that compared to people that have never been exposed to phytosanitary products before, those that were exposed a long period had high chances of developing bladder cancer, so long as other factors remain constant.

There were very few studies that focused exclusively on types of bladder cancer; most of them looked into all types without specificity. According to the findings, the risk of bladder cancer generally was higher as the exposure increased. The findings suggest that there may be a correlation between gender, type of phytosanitary products and threat of bladder cancer. The data also proposes that the relationship may be more pronounced in men compared to women; this may also be affected by the fact that conventionally, heavy smokers are mostly male and also they engage in farming more than women, therefore, the assumption may hold.

In terms of the most impactful type of phytosanitary products that is linked with risk of bladder cancer is pesticides,

most of the studies proposed that pesticides increase the risk more significantly. There may be a statistically significant correlation between the type of phytosanitary products and the risk of bladder cancer.

The statistical analysis justified that indeed the bladder cancer can be caused by phytosanitary products which include pesticides, fungicides, herbicides and insecticides (OR 1.59; 95 % CI 0.51–5.02).

Most of the studies focused on pesticides and not whole phytosanitary products, this could be a source of bias.

It was clear that even those who do not smoke but exposed to the chemicals from agriculture are at risk of bladder cancer. Countries that engage in agriculture as one of the main economic activities (Egypt, France, Spain, Italy) are at risk of bladder cancer nevertheless care can be taken while conducting their business.

Because there were no randomized controlled trials, assessing the relationship between agricultural phytosanitary products and the growth of bladder cancer, we had to incorporate non-randomized, in this review, we included case–control and cohort studies.

There was no research done to reduce the effects that confounding factors might have. Then it will of use to take this into consideration while analyzing the findings of the meta-analysis.

Limitations of the study

The examination of within-study confounders was severely constrained in the studies that met the qualifying requirements for exposure to phytosanitary products and the risk of bladder cancer by allowing only certain research designs while excluding others. Additionally, the studies that met the eligibility requirements had a moderately high degree of variability; the heterogeneity to variations in the length of follow-up and different aspects of focus such as age, gender, and smoking among others. Unfortunately, there were very few studies that exclusively looked into the different types of bladder cancer. Upcoming studies should consider reducing the scope of research to focus on a particular type of bladder cancer such as urothelial carcinoma, squamous cell carcinoma and adenocarcinoma; most of them have not been exclusively researched in terms of their association with phytosanitary products.

Some studies concluded that the relationship between phytosanitary products and bladder cancer may be strong in men compared to their women counterparts; in such cases, the varied circumstances are a significant limitation; men are conventionally heavy smokers and work at ranch while women are mostly light smokers and concentrate in house work. Such a fact should be taken into account when carrying out a study.

The absence of several research design types was one of the most glaring flaws in the execution of this meta-analysis. 7 out of 8 included studies were of type case–control, only 1 was a cohort study.

Another drawback may be the size of the study population, which was over 150,000 participants in some included studies but only 341 in others [10]. The statistical heterogeneity was high, as manifested by variability of the intervention effect being evaluated in different studies. The small number of papers that matched the inclusion requirements might have contributed.

All of the constraints had a harmful effect on the validity of the results and the whole quality of the study. Future studies investigating the connection between phytosanitary products and the danger of bladder cancer will be built on the results of the current systematic review. Future research should consider more clinical aspects of the association such as predictive factors.

Conclusion

The papers that were part of the present systematic review and meta-analysis all provided information on the

relationship between bladder cancer risk and phytosanitary products.

It was clear that phytosanitary products raised the incidence of bladder cancer. The link between bladder cancer and various agricultural and general use of these products was stronger in never smokers, highlighting the difficulty in understanding the effect of additional exposures on malignancies brought on by smoking.

Few researchers have investigated whether phytosanitary chemicals, which easily go via the bladder, could be threat features for bladder cancer as farmers have high incidences of the disease than the general population.

Our findings show that phytosanitary products exposure might be an underappreciated danger feature in bladder carcinogenesis. Future research should include precise phytosanitary products information on specific active components, as well as studies that look at risks, regardless of smoking status.

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Вклад авторов

N. Belcaid: разработка дизайна исследования, разработка теории и выполнение расчетов;
I. Dassar: утверждение аналитических методов, помощь в проведении метаанализа, контроль результатов работы;
A. Abdellaoui: разработка дизайна исследования, утверждение аналитических методов;
M. Taleb: разработка дизайна исследования.
Все авторы обсудили результаты и внесли вклад в окончательную версию статьи.

Authors' contributions

N. Belcaid: conceived the study design, developed the theory and performed the computations;
I. Dassar: reviewed and validated the analytical methods, provided guidance on conducting the meta-analysis and supervised the findings of this work;
A. Abdellaoui: conceived the study design, reviewed and validated the analytical methods;
M. Taleb: conceived the study design.
All authors discussed the results and contributed to the final manuscript.

ORCID of authors

N. Belcaid: <https://orcid.org/0000-0002-0368-5899>

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