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The use of pesticides and the development of cancer in farmers: A scoping review

O uso de agrotóxicos e o desenvolvimento do câncer em agricultores: uma revisão de escopo

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ABSTRACT Giving the problem that involves the complex relationship between the use of pesticides and the onset of cancer, several studies have been developed around the world searching for evidence to prove it. The objective is to analyze the relationship between the use of pesticides and the onset of cancer in farmers, according to specialized literature. It is a scoping review. The search was carried out in three databases, and the articles were analyzed by two researchers and a third, for dealing with disagreements. Cohen's Kappa value was tested to assess agreement regarding the data extracted from the studies. A total of 29 bibliographies made up the sample. The studies came from five continents. Case-control and cohort research dominated the review landscape, using inferential statistics with different types of statistical tests. A variety of cancer types were studied, and most of the articles pointed to a predisposition to cancer, referring to biomarkers for early prediction of this chronic disease. In conclusion, being a farmer and being exposed to pesticides confers a greater risk of developing cancer compared to those who are not exposed.

KEYWORDS Pesticides. Neoplasms. Farmers. Health risk. Environmental health.

RESUMO *Diante da problemática que envolve a complexa relação entre o uso de agrotóxicos e o aparecimento de câncer, diversos estudos vêm sendo desenvolvidos no mundo em busca de evidências que a comprovem. Objetivou-se analisar a relação entre a utilização de agrotóxicos e o aparecimento de câncer em agricultores, segundo a bibliografia especializada. Trata-se de uma revisão de escopo. A busca foi realizada em três bases de dados, e os artigos foram analisados por dois pesquisadores e um terceiro, para as discordâncias. Foi testado o valor de Kappa de Cohen para avaliar concordância quanto aos dados extraídos dos estudos. Um total de 29 bibliografias compuseram a amostra. Os estudos foram provenientes de cinco continentes. Pesquisas de caso-controle e coorte dominaram o cenário da revisão, utilizando estatística inferencial com diferentes tipos de testes estatísticos. Uma variedade de tipologias de câncer foi estudada, e grande parte dos artigos apontou para uma predisposição ao câncer, remetendo a biomarcadores para previsão precoce dessa doença crônica. Conclui-se que ser agricultor e estar exposto aos agrotóxicos conferem um maior risco de desenvolvimento de câncer em relação aos não expostos.*

PALAVRAS-CHAVE *Agroquímicos. Neoplasias. Agricultores. Risco à saúde humana. Saúde ambiental.*

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Introduction

Pesticides are products, according to Law No. 14,785, whose purpose is to modify the composition of flora or fauna, with the aim of protecting them from the harmful interference of other living beings[1]. They are used to maintain control or eliminate insects, larvae, weeds and other pests that can affect plantations[2,3], however, their effects are not selective and affect flora and fauna in general.

The use of pesticides has increased by 93% worldwide in recent years, with the increase in Brazil corresponding to 190%[4]. Brazil is considered one of the largest agricultural producers in the world and the second largest exporter of these products5. In 2008, it rose to the ranking of the largest consumer of pesticides in the world[5], maintaining this position since then. Its excessive use increases the risks to Public Health, Occupational Health and the Environment.

Study mapped the use of pesticides in Brazil, demonstrating that, while the consumption of pesticides in the world, between 2000 and 2010, increased by 100%, in Brazil, it reached 200%; and that from 2012 to 2014, approximately 8.33 kg per hectare were applied, with glyphosate being the most consumed in all Brazilian regions[6].

Pesticides are classified based on their purpose, chemical group and toxicity. After exposure to pesticides, poisoning may occur, which, depending on the time of onset of symptoms, may be: i) acute, resulting from exposure to concentrations of one or more toxic agents capable of causing damage within 24 hours; ii) chronic, resulting from continued exposure to relatively low doses of one or more products, the symptoms of which may appear weeks, months, years or generations after their use[5,7].

Chronic damage resulting from exposure includes different types of cancer[8]. Cancer appears as a result of the disorderly growth of cells, which can invade adjacent tissues or distant organs. Because they divide rapidly, cancer cells tend to be very aggressive and uncontrollable, forming tumors that can spread to other areas of the body[8].

The potential for cancer development – despite the large number of variables to be considered (types of substances and their associations, handling, use of Personal Protective Equipment (PPE), genetic factors, among others) – is recognized by the Ministry of Health[9] and by different authors[2,5,10]. Some of these studies seek evidence that indicates the relationship between specific types of pesticides and genetic mutations[11,12] or the carcinogenic potential of certain types of products[13,14]; others still research the relationship between the use of pesticides and cancer morbidity and mortality rates[15,16]. It is important to emphasize that the probability increases when these farmers do not use PPE properly[17].

Given the evidence presented, the objective of this review is to analyze the relationship between the use of pesticides and the appearance of cancer in farmers, according to specialized bibliography.

Material and methods

A scoping review[18-20] was conducted following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) approach[21]. The study protocol for the scoping review was registered on the Open Science Framework (OSF) platform on August 22, 2022[22].

Inclusion criteria

The inclusion criteria for selecting articles were: original articles; applied research articles; published in full, from 2012 to 2021; with open access; in English and Portuguese; that addressed the relationship between the use of pesticides and the onset of cancer in the farming population. Systematic reviews; editorials; experience reports; annals; theses and dissertations; government manuals and documents; studies with other types of workers other than agricultural workers or that treated cancer in animals; and those that focused on acute damage or other chronic damage other than cancer were excluded. It was decided to include in the analysis original articles, published in journals and submitted to peer review, as they directly seek to contribute to the construction of responses regarding the effects of pesticides on the health of farmers.

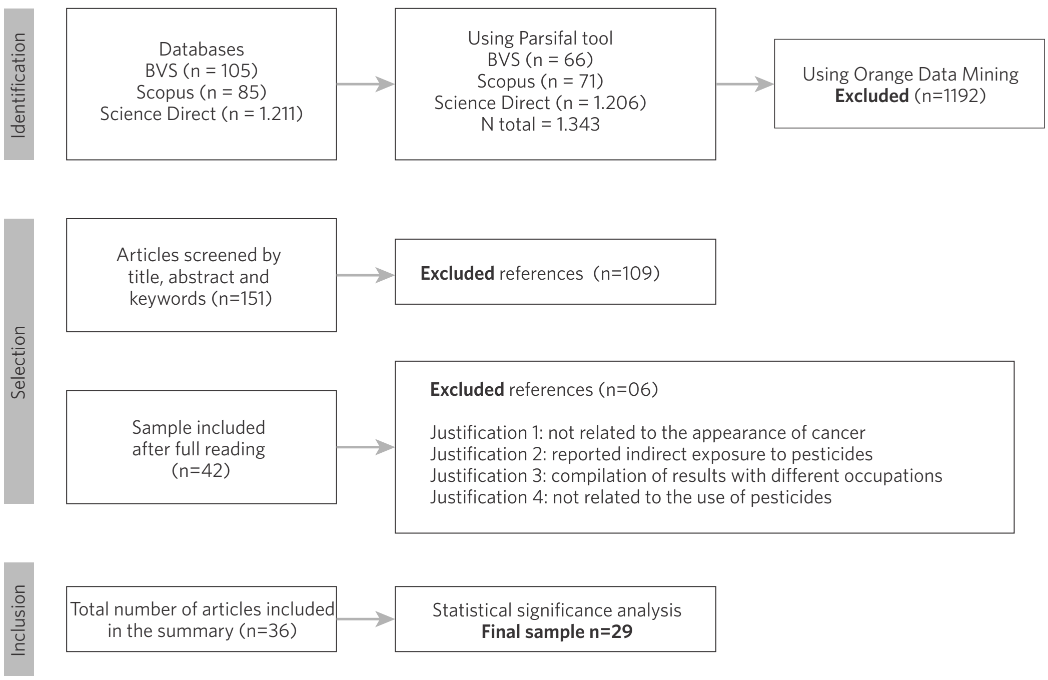
Search scheme

The data search was developed in the BVS, Scopus and ScienceDirect databases, from the CAFe access of the CAPES' Portal of Journals, using the keywords indexed in the Health Sciences Descriptors (DeCS) and with Boolean expressions, on 07/14/2021: "*agrotóxicos* OR agrochemicals OR pesticides", AND "*câncer*", AND "*agricultores* OR farmers".

Study selection

Figure 1 presents the search results, inclusions and exclusions of articles that deal with the relationship between cancer and the use of pesticides, with the respective justifications.

Figure 1. Flowchart representing the selection of articles



Source: Prepared by the authors based on PRISMA-ScR[21].

The search for articles in the databases yielded 1,401 references. Using the Parsifal and Orange Data Mining tools, the search resulted in 1,192 studies. After screening (Kappa 0.774, p = <0.01) and reading the articles in full (Kappa 0.627), based on the criteria defined for this study, a total of 29 bibliographies were pre-selected, with the final sample comprising of articles that presented statistical significance (n = 29) for the relationship between the onset of cancer in farmers and the use of pesticides.

As a strategy for screening the articles, the Orange Data Mining platform was used in the first phase for 'text mining', with descriptors assigned based on the analysis of titles, abstracts and keywords. The selection of studies in the screening and eligibility phases was carried out by two researchers who were experts in the subject and a third reviewer in case of disagreements.

As a parameter for the evaluation – inclusion/exclusion criteria and selection of articles by researchers –, Cohen's Kappa test was applied to verify the agreements between the evaluators[23,24]. A Kappa value between 0.6 and 0.8[25] was considered satisfactory.

Data analysis

After extracting the data of interest, they were organized into tables and treated using thematic analysis. Thematic analysis consists of three stages: a) pre-analysis, which is subdivided into skimming, corpus formation, and formulation and reformulation of hypotheses and objectives; b) exploration of the material; and c) processing of the results obtained and interpretation[26].

The study is part of the research project 'The use of pesticides in family farming and its implications for farmers' health and environmental health', approved by the Research Ethics Committee, Opinion No. 3,481,277 (CAAE 17010519.1.0000.5341).

Results

The characteristics related to the studies, such as authors and year, title, country of origin, journal and qualis are described in *table 1*, only for the studies that presented statistical significance for the association between pesticides and cancer 81% (n=29).

Table 1. Description of the articles that make up the scoping review

Author, Year	Title	Country	Journal	Qualis
A1 Miranda-Filho AL, Monteiro GT, Meyer A. (2012)[27]	Brain cancer mortality among farm workers of the State of Rio de Janeiro, Brazil: a population-based case-control study	Brazil	International journal of hygiene and environmental health	A1
A2 Boccolini P de MM, Asmus CIRF, Chrisman J de R, Câmara V de M, Markowitz SB, Meyer A. (2014)[28]	Stomach cancer mortality among agricultural workers: results from a death certificate-based case-control study	Brazil	Cadernos de Saúde Coletiva	B1
A3 Amr S, Dawson R, Saleh DA, et al. (2015)[29]	Pesticides, gene polymorphisms, and bladder cancer among Egyptian agricultural workers	Egypt	Archives of environmental & occupational health	B1
A4 Andreotti G, Hoppin JA, Hou L, et al. (2015)[30]	Pesticide Use and Relative Leukocyte Telomere Length in the Agricultural Health Study	United States	PloS One	-
A5 Gómez-Martín A, Altakroni B, Lozano-Paniagua D, et al. (2015)[31]	Increased N7-methyldeoxyguanosine DNA adducts after occupational exposure to pesticides and influence of genetic polymorphisms of paraoxonase-1 and glutathione S-transferase M1 and T1	Spain	Environmental and molecular mutagenesis	A2

Table 1. Description of the articles that make up the scoping review

Author, Year	Title	Country	Journal	Qualis
A6 Jones RR, Barone-Adesi F, Koutros S, et al. (2015)[32]	Incidence of solid tumours among pesticide applicators exposed to the organophosphate insecticide diazinon in the Agricultural Health Study: an updated analysis	United States	Occupational and environmental medicine	A1
A7 Lemarchand C, Tual S, Boulanger M, et al. (2016)[33]	Prostate cancer risk among French farmers in the AGRICAN cohort	France	Scandinavian journal of work, environment & health	A2
A8 Presutti R, Harris SA, Kachuri L, et al. (2016)[34]	Pesticide exposures and the risk of multiple myeloma in men: An analysis of the North American Pooled Project	United States	International journal of cancer	A1
A9 Salerno C, Carcagnì A, Sacco S, et al. (2016)[35]	An Italian population-based case-control study on the association between farming and cancer: Are pesticides a plausible risk factor?	Italy	Archives of environmental & occupational health	B1
A10 Bonner MR, Freeman LE, Hoppin JA, et al. (2017)[36]	Occupational Exposure to Pesticides and the Incidence of Lung Cancer in the Agricultural Health Study	United States	Environmental health perspectives	A1
A11 Fallahi P, Foddis R, Cristaudo A, Antonelli A. (2017)[37]	High risk of brain tumors in farmers: a mini-review of the literature, and report of the results of a case control study	Italy	La Clinica terapeutica	-
A12 Kachuri L, Harris MA, MacLeod JS, Tjepkema M, Peters PA, Demers PA. (2017)[38]	Cancer risks in a population-based study of 70,570 agricultural workers: results from the Canadian census health and Environment cohort (CanCHEC)	Canada	BMC cancer	A3
A13 Lemarchand C, Tual S, Levêque-Morlais N, et al. (2017)[39]	Cancer incidence in the AGRICAN cohort study (2005-2011)	France	Cancer epidemiology	A2
A14 Rusiecki JA, Beane Freeman LE, Bonner MR, et al. (2017)[40]	High pesticide exposure events and DNA methylation among pesticide applicators in the agricultural health study	United States	Environmental and molecular mutagenesis	A2
A15 Ahluwalia M, Kaur A. (2018)[41]	Modulatory role of GSTT1 and GSTM1 in Punjabi agricultural workers exposed to pesticides	India	Environmental science and pollution research international	A2
A16 Benedetti D, Lopes Alderete B, de Souza CT, et al. (2018)[42]	DNA damage and epigenetic alteration in soybean farmers exposed to complex mixture of pesticides	Brazil	Mutagenesis	A2
A17 Boulanger M, Tual S, Lemarchand C, et al. (2018)[43]	Lung cancer risk and occupational exposures in crop farming: results from the AGRIculture and CANcer (AGRICAN) cohort	France	Occupational and environmental medicine	A1
A18 Jacobsen-Pereira CH, Dos Santos CR, Troina Maraslis F, et al. (2018)[44]	Markers of genotoxicity and oxidative stress in farmers exposed to pesticides	Brazil	Ecotoxicology and environmental safety	A1

Table 1. Description of the articles that make up the scoping review

Author, Year	Title	Country	Journal	Qualis
A19 Tomiazzi JS, Judai MA, Nai GA, Pereira DR, Antunes PA, Favareto APA. (2018)[45]	Evaluation of genotoxic effects in Brazilian agricultural workers exposed to pesticides and cigarette smoke using machine-learning algorithms	Brazil	Environmental science and pollution research international	A2
A20 Ch R, Singh AK, Pathak MK, et al. (2019)[46]	Saliva and urine metabolic profiling reveals altered amino acid and energy metabolism in male farmers exposed to pesticides in Madhya Pradesh State, India	India	Chemosphere	A1
A21 Mills PK, Dodge JL, Bush J, Thompson Y, Shah P. (2019)[47]	Agricultural Exposures and Breast Cancer Among Latina in the San Joaquin Valley of California	United States	Journal of occupational and environmental medicine	A2
A22 Ordoñez-Beltrán V, Frías-Moreno MN, Parra-Acosta H, Martínez-Tapia ME. (2019)[48]	Estudio sobre el uso de plaguicidas y su posible relación con daños a la salud	Mexico	Revista de toxicología	-
A23 Piel C, Pouchieu C, Carles C, et al. (2019)[49]	Agricultural exposures to carbamate herbicides and fungicides and central nervous system tumour incidence in the cohort AGRICAN	France	Environment international	A1
A24 Saad-Hussein A, Beshir S, Taha MM, et al. (2019)[50]	Early prediction of liver carcinogenicity due to occupational exposure to pesticides	Egypt	Mutation research. Genetic toxicology and environmental mutagenesis	A3
A25 Cepeda S, Forero-Castro M, Cárdenas-Nieto D, Martínez-Agüero M, Rondón-Lagos M. (2020)[51]	Chromosomal Instability in Farmers Exposed to Pesticides: High Prevalence of Clonal and Non-Clonal Chromosomal Alterations	Colombia	Risk management and healthcare policy	-
A26 Hutter HP, Poteser M, Lemmerer K, et al. (2020)[52]	Indicators of Genotoxicity in Farmers and Laborers of Ecological and Conventional Banana Plantations in Ecuador	Ecuator	International journal of environmental research and public health	A1
A27 Jacobsen-Pereira CH, Cardoso CC, Gehlen TC, Regina Dos Santos C, Santos-Silva MC. (2020)[53]	Immune response of Brazilian farmers exposed to multiple pesticides	Brazil	Ecotoxicology and environmental safety	A1
A28 Pardo LA, Beane Freeman LE, Lerro CC, et al. (2020)[54]	Pesticide exposure and risk of aggressive prostate cancer among private pesticide applicators	United States	Environmental health	A1
A29 Salazar-Flores J, Pacheco-Moisés FP, Ortiz GG, et al. (2020)[55]	Occupational exposure to organophosphorus and carbamates in farmers in La Cienega, Jalisco, Mexico: oxidative stress and membrane fluidity markers	Mexico	Journal of occupational medicine and toxicology	-

Source: Prepared by the authors, 2024.

A geographic distribution of publications was identified that covers almost all continents. Most studies were concentrated in the American continent (22, with n = 12 in North America and n = 10 in South America). The United States of America (n = 9) and Brazil (n = 8) are worth highlighting, as they concentrated the largest number of published articles. In Europe, France had the largest number (n = 4). Publications in Africa and Asia were less prominent. There were no publications in Oceania. This distribution suggests that the use of pesticides and their effects on health is a concern that deserves attention at a global level.

The papers selected for the research are distributed across international and national scientific journals. The 29 articles come from 24 different journals, with 24 articles also published in journals included in the Qualis/CAPES system, with significant impact metrics, and the majority published in A1 and A2 journals.

The characteristics relating to methodological aspects, such as design, participants and statistical analyses used, are described in *table 2*.

Table 2. Designs, participants and main statistics present in the selected studies

Art.	Design	Number of participants	Statistical analyses used
A1	Case-control study based on death certificates of men, over 18 years old, living in RJ	2,040 cases of male cancer deaths, 4,140 random controls. Of the total of 6180 deaths, 233 were linked to agriculture, with 95 being cases and 138 controls.	Descriptive statistics, inferential statistics with chi-square test and odds ratio and Hosmer-Lemershow test
A2	Case-control, with analysis of death certificates of farmers exposed to pesticides and mortality from stomach cancer	Cases 11,766 (stomach cancer) and controls 11,557 (any other diagnosis)	Inferential statistics, with chi-square test, odds ratio and logistic regression
A3	Multicenter case-control study with blood samples processed for DNA extraction	953 cases and 881 controls. Genotyping for 419 cases and 358 controls	Descriptive statistics, chi-square inferential statistics, Student's t test and odds ratio
A4	Prospective population cohort study at AHS in pesticide applicators, with: 1) measurement of telomeres in leukocyte DNA; 2) self-administered questionnaire; 3) comparison between oral and blood cells, RTL calculation	568 cancer-free participants and 40 blood comparisons	Inferential statistics, using multivariate linear regression, Spearman correlation
A5	Longitudinal prospective cohort study for changes in DNA level of N7-MedGels lymphocytes between low and high level spray exposures. Blood samples were collected for each harvest period	39 workers	Inferential statistics, with Pearson's correlation test and Student's t test
A6	Prospective cohort	22830 farmers or pesticide applicators	Inferential statistics with Poisson regression, Spearman correlation and Wald tests
A7	Prospective cohort study, which sought data on lifetime agricultural exposures in the AGRICAN enrollment questionnaire	Among 181,842 registered, 81,961 were identified after applying exclusion criteria and 1496 were selected because they had prostate cancer	Inferential statistics, with risk ratios and Cox regression

Table 2. Designs, participants and main statistics present in the selected studies

Art.	Design	Number of participants	Statistical analyses used
A8	Three population-based case-control studies in the United States and Canada	547 cases of multiple myeloma and 2,700 controls, totaling 3,247 participants	Descriptive statistics, inferential statistics, with logistic regression and odds ratio
A9	Population-based case-control study	241 (cases), 1240 (controls), totaling 1,481	Inferential statistics, with Fisher's exact test, odds ratio, multiple logistic regression and t-test
A10	Population study, with data updated by follow-up questionnaire	546 cases of lung cancer	Inferential statistics, with cox regression
A11	Case-control study of patients recruited from the Department of Neurosurgery at Univ. of the Hospital of Pisa, Italy	174 cases and 522 controls, totaling 696 participants	Descriptive statistics, inferential statistics, with chi-square, odds ratio and logistic regression
A12	Cohort study	70,570 farmers, 9515 of whom had an incidence of cancer	Inferential statistics, with risk ratios and Cox regressions
A13	Prospective cohort study	11065 with a cancer incidence of 181,842 enrolled in the cohort	Inferential statistics, with chi-square and Poisson regression
A14	Prospective, population-based cohort of applicators from Iowa and North Carolina, with DNA laboratory examination and questionnaire response	596 applicators	Inferential statistics, with Student's t test, Wilcoxon Rank Sum test, linear regression and logistic regression, with bootstrapping technique and intraclass correlation coefficients
A15	Case-control study with blood collection for laboratory tests	513 individuals (250 agricultural workers and 263 occupationally unexposed)	Descriptive statistics, inferential statistics, with Student's t test, chi-square and odds ratio
A16	Prospective cohort, with questionnaire response and face-to-face interview. Blood, urine and buccal cell samples were collected	Rural workers (n = 137) exposed to different types of pesticides compared to an unexposed group (control; n = 83), totaling 220 participants	Inferential statistics, with Student's t test (Welch test), Pearson correlation and non-parametric Mann-Whitney tests and Spearman correlation
A17	Cohort study, with farmers registered with health insurance (AGRICAN)	897 cases of lung cancer	Inferential statistics, with Cox regression and Wald test
A18	Retrospective cohort, case-control, blood analysis	41 men and 9 women (case group) and 75 from the control group, totaling 115 participants	Inferential statistics, with Mann-Whitney, Kruskal-Wallis tests, one-way ANOVA and Spearman correlations
A19	Case-control, observational, prospective and cross-sectional study carried out with material collected from oral mucosa cells for cytogenetic analysis	60 farmers and 60 controls, totaling 120 participants	Inferential statistics, with ANOVA test, Wilcoxon test, linear regression, Tukey's post-hoc test and Fisher's exact test
A20	Case-control study, with collection of urine and saliva samples and response to a questionnaire	51 pesticide applicators and 52 controls, totaling 103 participants	Inferential statistics, with multivariate statistical analysis, with Pareto scale, PLS-D and unpaired t-test
A21	Epidemiological case-control study. Both cases and controls completed a detailed questionnaire	101 patients and 88 controls, totaling 189 participants	Descriptive statistics, inferential statistics, with Student's t test, chi-square, odds ratio and logistic regression
A22	Descriptive study	58 farmers	Descriptive statistics, inferential statistics, with Pearson Correlation
A23	Prospective cohort, carried out through the AGRICAN database	57847 farmers exposed to fungicides and herbicides	Inferential statistics, with risk ratios, Cox regression, univariate, backward, multivariate analyzes and sensitivity analysis

Table 2. Designs, participants and main statistics present in the selected studies

Art.	Design	Number of participants	Statistical analyses used
A24	Field research, case-control, carried out by blood collection and laboratory research of various tumor biomarkers	50 urban researchers exposed and 50 unexposed and 50 rural sprayers occupationally exposed to pesticides and 50 unexposed, totaling 200 participants	Inferential statistics, with ANOVA test, multivariate analysis and Pearson correlation
A25	Laboratory case-control study to verify the frequency of chromosomal alterations and the level of chromosomal instability in peripheral blood lymphocytes	5 farmers occupationally exposed to pesticides and 5 individuals not exposed	Inferential statistics, with Student's t test, Fisher's exact test, Wilcoxon test and Shapiro–Wilk test
A26	Comparative study, with application of a questionnaire and collection of buccal cells in workers in conventional and ecological agriculture	34 from conventional agriculture and 37 from ecological agriculture, totaling 71 farmers	Descriptive statistics, inferential statistics, with Poisson correlation and chi-square
A27	Case-control study, with collection of peripheral blood samples. A questionnaire was also administered to farmers	43 farmers and 30 controls, totaling 73 participants	Inferential statistics, with Mann-Whitney test
A28	Epidemiological cohort study, with data from the AHS database and questionnaire application in three phases	734 cases of aggressive prostate cancer among farmers	Inferential statistics, with Cox regression, risk ratios, Pearson correlation, logistic regression, Wald test, likelihood ratio test and multivariate logistic regression
A29	Cross-sectional case-control study	113 exposed and 93 control group, totaling 216 participants	Descriptive statistics, inferential statistics, with Student's t test, ANOVA test and Tukey's post-hoc test

Source: Prepared by the authors, 2024.

Case-control and cohort studies dominated the review scenario. There was a diverse number of participants in each study, sources and forms of data collection, which shows diversity in the number and types of methodologies used, making the analysis of the studies as a whole complex.

As for statistical tests, different and diverse types of tests were used, especially for quantitative data. Most studies used descriptive and inferential statistics.

The objectives and conclusions of the studies are presented in *table 3*.

Table 3. Objectives and conclusions presented in the selected studies

Art	Objective	Conclusions
A1	To estimate the risk of mortality from brain cancer in agricultural workers exposed to pesticides in the state of Rio de Janeiro, Brazil.	A statistically significant association was observed between brain cancer mortality and agricultural activity in male rural workers, aged 18 or over. Furthermore, the risk of mortality from brain cancer was greater for those workers who lived in regions with more intense use of pesticides.
A2	To investigate the risk of death from stomach cancer in agricultural workers living in the state of Rio de Janeiro.	Agricultural workers had a significantly higher risk of death from stomach cancer than non-agricultural workers. This risk in agricultural workers may be associated with exposure to pesticides.

Table 3. Objectives and conclusions presented in the selected studies

Art	Objective	Conclusions
A3	To examine associations between bladder cancer risk and pesticide exposure among male farmers, and potential interactions between exposures and genetic polymorphism of NQO1 and SOD2.	Male agricultural workers in Egypt are at higher risk than other men of developing bladder cancer, linked to exposure to pesticides. The contribution of susceptible genetic origins is possible.
A4	To examine cumulative and most recent pesticide use with relative telomere length measured in blood DNA from Agricultural Health Study participants.	The findings suggest that more recent, cumulative use of certain pesticides may be linked to changes in RTL, which may be a potential intermediary in certain diseases. The strongest association was for 2,4-D and shorter TL, which was borderline significant after accounting for multiple comparisons.
A5	To assess DNA damage in intensive agricultural workers exposed to pesticides by determining N7-methyldeoxyguanosine (N7-MedG) levels.	In intensive agriculture workers, greater exposure to pesticides increased DNA alkylation levels, demonstrating genotoxicity. Exposed individuals with inherited susceptible metabolic genotypes (particularly, null genotype for GSTM1 and PON1 192 Ralelo) appear to be at increased risk for genotoxic DNA damage.
A6	To assess the risk of solid tumor in AHS on exposure to diazinon.	The updated assessment of diazinon provides additional evidence of an association with lung cancer risk.
A7	Identify occupational risk factors for prostate cancer in farmers, focusing on specific tasks.	The analysis suggests that the risk of prostate cancer is increased in several agricultural activities (cattle and pig farming, pastures and fruit growing) and for some tasks, including the use of pesticides.
A8	Investigate associations between pesticide use and hematological cancer risk.	In this large North American study of MM and pesticide use, significant increases in MM risk were observed for the use of carbaryl, capitan, and DDT.
A9	Investigate the association between agriculture (a proxy for pesticide exposure) and cancer in the suburban area of Vercelli (Northwest Italy).	The population-based case-control study showed that farmers, compared to non-farmers, have a greater chance of developing several types of cancer, suggesting a plausible association between exposure to pesticides and the occurrence of the disease.
A10	To evaluate the use of 43 pesticides and 654 cases of lung cancer after 10 years of additional follow-up at AHS.	The analyzes provide additional evidence for an association between the use of pendimethalin, dieldrin, and parathion and lung cancer risk. An association was found between chlorimuron ethyl and lung cancer. Prolonged exposure to low-level pesticide mixtures can be critical for the development of cancer.
A11	Investigate the impact of agricultural work on cancer morbidity (malignant brain tumors) in the agricultural population.	A significant relationship was observed between brain tumor and agricultural activity in Italy.
A12	Systematic analysis of cancer incidence by occupational subgroup of farmers.	Exposure to pesticides may have contributed to increased risks of hematopoietic cancer, while increased risks of lip cancer and melanoma may be attributed to sun exposure.
A13	Compare cancer incidence in the cohort (overall, by sex, by farm work, occupational status, and pesticide use) with the general population.	An increase in the incidence of prostate cancer, melanoma and multiple myeloma (MM) was found. The risk was higher in males, in rural workers for prostate and lip cancer, in agricultural workers for melanoma and for MM. The incidence of MM and melanoma was higher among men and women who used pesticides.
A14	To evaluate the association between exceptionally high pesticide exposure events (HPEEs) and DNAm among pesticide applicators in the Agricultural Health Study (AHS).	Non-specific HPEEs may contribute to increased DNAm in GSTp1 and, in some groups, reduced DNAm in MGMT and LINE-1. The impacts of these changes on disease development are unclear, but elevated GSTp1 promoter DNAm and subsequent gene inactivation have been consistently associated with prostate cancer.

Table 3. Objectives and conclusions presented in the selected studies

Art	Objective	Conclusions
A15	To determine the frequency distribution of GSTT1 and GSTM1 in agricultural workers in Punjab, India, and investigate their contribution to susceptibility to genetic damage, environmental risk factors, cancer predisposition and risk of future diseases.	The absence of both copies of GSTM1 can lead to decreased marital activity. Consequently, the resulting accumulation of pesticides or their intermediate products may be a potential risk factor for increased cytogenetic damage, various types of cancer, reproductive disorders, and other adverse health effects.
A16	To evaluate the genetic and epigenetic effects in soybean farmers exposed to pesticides and their relationship with oxidative stress mechanisms.	There is interference from the pesticide mixture in different cellular regulatory processes (signaling, cell communication and differentiation, mitotic cycles and apoptosis, organization of mitochondria and chromatin). Exposure of soybean farmers may be associated with the induction of DNA damage, observed in peripheral blood and oral cells. MN. Data indicate that persistent genetic instability associated with DNA hypermethylation following prolonged exposure to low-level pesticide mixtures may be critical for adverse health outcomes such as cancer.
A17	To evaluate associations between various cultures and related tasks and lung cancer risk, overall and by histological subtypes.	The results suggest associations between lung cancer and several harvest-related tasks, even if we cannot rule out some incidental findings due to multiple comparisons.
A18	Investigate the relationship between occupational exposure to various pesticides and the presence of DNA damage and oxidative stress.	Individuals exposed to pesticides are more subject to genetic damage and, consequently, more susceptible to diseases resulting from this damage.
A19	Evaluate the genotoxic effects on rural workers exposed to cigarette smoke and/or pesticides and identify possible classification patterns in exposure groups.	Exposure of Brazilian agricultural workers to pesticides and/or tobacco increased nuclear abnormalities in exfoliated oral epithelial cells. However, concomitant exposure to these xenobiotics did not lead to an additive or potentiating effect. This genotoxic potential is alarming and indicates an increased risk of oral cancer.
A20	Using mass spectrometry-based metabolomics to investigate pesticide-induced metabolic perturbations in urine and saliva samples from farmers in Madhya Pradesh, India.	It is suggested that oxidative stress due to complex pesticide exposure causes disturbances in amino acid and energy metabolism.
A21	To evaluate the role of agricultural work, pesticide exposure, and age at first exposure to agricultural work on breast cancer risk among Hispanic women in Central California.	Agricultural work may be associated with increased risk of breast cancer in Hispanic female agricultural workers.
A22	To analyze the frequency of use and knowledge about the negative effects of pesticide application and its relationship with damage to the health of the inhabitants of Ejido Guadalupe Victoria, Nuevo Casas Grandes.	There is a high incidence of cancer cases, especially in adults, who handle this type of product (pesticides) throughout their lives.
A23	To evaluate associations between potential exposures to carbamate herbicides and fungicides and the incidence of CNS tumors, overall and by histological subtype.	Although some associations need to be corroborated in further studies and should be interpreted cautiously, these findings provide additional evidence of carcinogenicity for several carbamate fungicides and herbicides.
A24	To estimate new biomarkers for the early prediction of liver malignancy due to occupational exposure to pesticides in two groups of workers with different socioeconomic status.	There was a significant increase in DNA damage, with shortening of telomere length and variation in the activity of the telomerase enzyme, with the majority of this damage being related to high levels of BuChE. Furthermore, the results illustrated that pesticide-exposed individuals with GSTT1 genotype were suggested to be more susceptible to hepatotoxicity and carcinogenicity.

Table 3. Objectives and conclusions presented in the selected studies

Art	Objective	Conclusions
A25	To evaluate CIN (chromosomal instability level) in farmers exposed to pesticides in the department of Cundinamarca, Colombia.	Identified previously unreported chromosomal variants (CVs) and CAs in farmers exposed to pesticides. It suggests a deleterious effect of pesticides on chromosomes, as well as an association between them and a significant increase in CIN.
A26	Investigate the occupational health of workers in conventional and ecological agriculture.	Conventional farmers exposed to pesticides on banana plantations manifest an increased level of acute genotoxic and cytotoxic damage, considered as an indicator of increased risk of developing cancer.
A27	To investigate the relationship between occupational exposure to pesticides and the immunological profile of 43 farmers exposed to mixtures of pesticides for at least 15 years.	The constant antigenic stimulus during exposure to pesticides may favor the recruitment of dendritic cells and macrophages in the skin and respiratory system. In secondary lymphoid organs, CD4T and B cells are undergoing proliferative exhaustion, with consequent depletion of all mature B subpopulations. It results in a decrease in humoral immunity due to its cytotoxic action.
A28	To evaluate associations between aggressive PCa and the use of 39 additional pesticides not previously considered, adding 13 years of follow-up time and 811 additional cases of aggressive PCa.	A significantly elevated risk of aggressive PCa was found among users of the insecticide OP dimethoate and an inverse association between the use of the herbicide triclopyr.
A29	Determine markers of oxidative stress levels (GSH, GSSG, carbonyl groups, nitric oxide metabolites and lipid peroxides), as well as changes in mitochondrial membrane fluidity caused by occupational exposure to organophosphates and carbamates in farmers.	Exposure to OPs and carbamates showed an increase in carbonyl levels, NO 2−/NO 3 −, lipoperoxidation and high fluidity of the mitochondrial membrane and a decrease in the concentration of GSH and GSSG in exposed/unexposed farmers. When evaluating groups A, B, C and D by years of exposure, a slight increase in oxidative markers and membrane fluidity was observed in those with more than 21 years of use (C and D). The results show increased levels of oxidative stress in exposed farmers, particularly at membrane fluidity levels (3x times in contrast to the unexposed group).

Source: Prepared by the authors, 2024.

Regarding the objectives of the studies presented in the bibliographies, most refer to: 1) biomarkers for early prediction of cancer (case-control studies and clinical trials); and 2) risk associations (sociodemographic data, use of pesticides, types of pesticides, exposure to products, frequency and duration of exposure and agricultural tasks).

Most of the articles point to a predisposition to cancer (n = 14), including epidemiological, case-control and experimental studies, through clinical trials. They use laboratory tests to verify genetic damage[30,40-42,44,45,52] and/or oxidative stress[42,44,45,52,55], in addition to metabolic disorders[46] and immunological profile[53], all factors that contribute to the development of cancer.

Other studies are aimed at specific types of cancer, such as breast[47], prostate[33,40], central nervous system[27,37,49], lung[32,36,43], in addition to risk or incidence for any type of cancer[38,39,41,48,52].

There is a diversity of pesticides used by farmers, with results associated with the use of products in isolation or in combination. The use of different types of pesticides has been shown to be associated with lung[32,36], hematological[34], breast[47] and prostate[54] cancer.

Discussion

It is important to highlight the following cohorts: the Agricultural Health Study (AHS), in the

USA, of licensed pesticide applicators enrolled between 1993 and 1997; and the AGRIculture and CANcer (AGRICAN), in France, of members of the agricultural health insurance scheme, enrolled between 2005 and 2007, from which several studies in this review were derived. Cohort studies are the most capable of raising etiological hypotheses, providing incidence and risk measures, and, for the most part, are based on groups exposed to a risk factor presumed to be the cause of a disease to be detected in the future[56]. In this context, they constitute predictive factors that, if controlled, can delay or even prevent the onset of a disease.

Brazil stands out for its large agricultural market. The April 2023 estimate for the Brazilian harvest of cereals, legumes, and oilseeds reached 302.1 million tons, which corresponds to an increase of 14.8% compared to 2022, growth of 39.0 million tons. Rice, corn, and soybeans are the three main products in this group, which together account for 92.3% of the production estimate and occupy 87.3% of the area expected to be harvested[57]. Soybeans are the crop with the highest use of pesticides and accounted for 55.69% of total pesticide sales[58]. The number of hectares cultivated and large monocultures are responsible for the consumption of most pesticides used in the country, which justifies the significant number of studies developed and the warning produced by the Brazilian Association of Public Health (ABRASCO)[5] regarding the cumulative and gradually increased use of pesticides and their consequent risks, including the development of different types of cancer.

It can be seen that most studies presented statistical significance for the association between pesticides and cancer, 81% (n = 29). The predominant number of articles that validate the existence of this relationship points to the increased risk of cancer for those exposed to these products.

In the articles analyzed, the association between cancer development and pesticide use highlighted factors such as male gender[27-29,38,39], being an agricultural worker[28,35,37-39], frequency and duration of exposure to pesticides[29,30,31,43], specific types of pesticides[32,34,36,47,54] and the use of pesticides[33,47,48,52] as variables that predispose the onset of this disease. The vast majority of studies indicated exposure to pesticides[35,40-42,44-46,49-53,55] as a cause or determining factor for cellular damage contributing to the onset of cancer.

Thus, being a farmer confers a higher risk of developing cancer compared to non-agricultural workers[28,37], that is, the greater the exposure, the greater the risk[29]. Several studies that confirm the relationship between exposure to pesticides and the risk of developing cancer indicate that this is increased when farmers do not use the personal protective equipment recommended in each country[33,42,44,47,48,52,53]. The number of studies that show the non-use of this protective equipment as one of the determinants of the development of cancer allows us to state that this is a behavior that needs to be changed worldwide (regardless of the level of development), through appropriate and effective educational actions and technological support.

In addition to exposure to pesticides, the professional activities carried out by farmers at each stage of planting, such as preparing the spray, applying it, spraying it, and harvesting[33,37], as well as their lifestyle[30,31,33,36,39,45,51,54] and environmental characteristics, may be factors that increase the risk of the disease[27,28]. Other studies, in smaller numbers, have not observed any difference in the incidence of cancer between farmers and the general population[38,39].

Several authors conclude that exposure to pesticides increases the chance of developing cancer[29,32-34,49] or present them as the main inducer of tumors[37]. In this sense, research must be developed to produce substances that are increasingly less aggressive to the environment and to living beings in general, in addition to producing international protocols that prohibit extremely toxic pesticides from being used worldwide[5].

It is important to highlight that 12 of the 29 studies analyzed made adjustments for risk factors for the development of cancer. This is important to increase the quality of the evidence and attests to the researchers' concern with the accuracy of the data presented. Thus, due to the complexity of the topic in question, the adjustment of variables allows analyses that reinforce the evidence between occupational exposure and the development of the disease[28,29,49]. The most commonly used adjustments were for sociodemographic data: age, sex, ethnicity, education; smoking and alcohol habits; and family history of cancer.

It is worth noting that skin cancer, such as melanoma, non-melanoma and lip cancer, were evidenced in three of the studies[35,38,39], but were not considered in this analysis, due to the strong relationship with sun exposure[38], which may result in another analysis bias, compromising the results obtained in the aforementioned studies.

Conclusions

The relationship between the use of pesticides and the development of cancer has been the subject of several studies on different continents over the last decade. For the present study, were selected 36 bibliographies, of which 81% (n = 29) obtained statistical significance for this relationship, which demonstrates the possibility of a cause-and-effect link, especially with adjustments for confounding factors.

Thus, the data set of this scoping review shows that being a farmer and being exposed to pesticides confers a greater risk of developing cancer compared to unexposed individuals.

Different types of cancer have been reported, in particular lung, hematopoietic and prostate cancer. It is also important to highlight that farmers used a variety of products and combinations of compounds.

In addition to the types of cancer highlighted, n = 14 (48%) studies indicated biomarkers for early cancer prediction. Therefore, there is evidence of the differentiations (or cellular impairment) that the products can cause in the human body, especially in relation to cellular metabolism, such as DNA damage and oxidative stress.

Case-control and cohort studies dominated the review scenario, using inferential statistics with several different types of statistical tests. There were a diverse number of participants in each study.

It is important to emphasize that it is the responsibility of health professionals to relate the various risk factors that involve the health condition of users, such as the profession of being a farmer. Professionals must be able to identify, analyze and implement measures that minimize risks based on the evidence found and knowledge of professional practice, as well as to diagnose early and offer appropriate treatment to this population.

Given the problem involving public health due to the incorrect use of pesticides, Public Policies need to be implemented in order to control and guarantee safety in the handling of products by farmers, considering that, according to the literature, the relationship between the use of pesticides and the development of cancer is established.

Collaborators

Cioato FM (0000-0003-1184-7947)* and Stedile NLR (0000-0001-6658-5353)* contributed to the acquisition, analysis and interpretation of data for the work, critical revision for important intellectual content and final approval of the manuscript. Lucas JIP (0000-0002-6307-1338)* contributed to ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved and final approval of the manuscript. ■

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