

Relationship between the Use of Agrochemicals and the Development of Prostate Cancer in the State of Santa Catarina

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ABSTRACT

Prostate cancer (PCa) is considered the second most common type of cancer among men. It is a pathology that is commonly asymptomatic in the early stages, a factor that causes patients to seek medical help only when the disease is already at an advanced stage. Some risk factors have well-established bases, such as age, family history and obesity. However, new studies suggest a possible relationship with environmental and occupational factors, mainly in agricultural areas. It is believed that this fact may be related to exposure to pesticides, so that rural areas are the places where the population is most exposed. Thus, the objective is to identify the relationship between the main risk factors and the development of PCa and investigate a possible relationship with exposure to pesticides. Data regarding epidemiology were collected from the Hospital Cancer Records (RHC), while data regarding mortality were collected from the Mortality Information System (SIM). The information has national coverage and, as its main focus, the State of Santa Catarina, in the period from 2012 to 2022. After analysis, it was identified that the etiology of PCa, despite not being well defined, is compatible with what was described in the literature and has advanced age as the main risk factor. When analyzing data relating to occupation, there is a marked prevalence of cases in rural workers, which represents a third of cases, with a predominance in 8 of the 12 micro-regions.

KEYWORDS: Prostate cancer. Risk factors. Pesticides. Rural workers. Early diagnosis.

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INTRODUCTION

Prostate cancer (PCa) is the second most commonly diagnosed cancer among men worldwide and is considered the fifth leading cause of cancer deaths. It is estimated that in 2020 there were around 1,4 million new cases of prostate cancer, of which approximately 375 thousand resulted in death. Furthermore, it is the most frequently diagnosed disease in 112 countries and the main cause of death in 48 of them (WANG *et al.*, 2022).

In Brazil, according to data provided by the *Instituto Nacional de Câncer* (INCA), approximately 704 thousand new cases of cancer are expected to occur in each year of the 2023-2025 triennium. Of these, around 70% are believed to occur in the Southeast and South regions. Regarding prostate cancer, approximately 72 thousand new cases are expected in the same period, so that, with the exception of non-melanoma

skin cancer, it is the most prevalent cancer throughout the country (INCA, 2022).

Due to the fact that it presents itself as a silent and usually asymptomatic disease in the initial stages, it is common for patients to seek medical help only in advanced stages of the disease, a fact that demonstrates how harmful not performing preventive exams can be (TEIXEIRA *et al.*, 2022). For this reason, there has been a considerable increase in the number of screening exams and, as a form of early detection, the dosage of prostate-specific antigen (PSA) has been adopted in conjunction with digital rectal examination (DRE) (BRAVO *et al.*, 2022).

As a consequence of the high number of PCa cases and the demand for help in advanced stages of the disease, the World Health Organization (WHO) is eager to develop public policies aimed at early diagnosis, especially in Primary Health Care (PHC) (QUEIROZ *et al.*, 2022). However, with

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regard to the progression of the disease, each type of cancer has its own characteristics, which makes early diagnosis unfeasible for some patients. Thus, there is a need to use variables that are part of the *hall* of the main risk factors for the development of the disease in order to obtain a well-defined target population for screening (INCA, 2022).

Regarding the main risk factors for the development of PCa, through the carcinogenesis process, there is a predominance of non-modifiable factors, such as advanced age and heredity, which already have well-established bases (QUEIROZ *et al.*, 2022). However, in recent decades, numerous factors have been associated, such as obesity, smoking, endocrine alterations and, recently, exposure to environmental and occupational factors (RUTHS *et al.*, 2022).

Regarding environmental and occupational factors, there has been an increase in the incidence of this pathology among agricultural producers. This fact supports the hypothesis of a possible relationship between the development of the disease and the use of agrochemicals, as well as demonstrating itself as a factor that causes vulnerability for the rural population (BRITO; WELLER, 2022).

In this same context, it is observed that there is a greater exposure of the rural population to agrochemicals, so that workers who work directly with the handling of these inputs are the most affected. However, it is not only rural producers who suffer the consequences of this exposure. The contamination of water and food, indirectly, causes a large portion of the population to be exposed to such agents. However, there is still a lack of studies that directly point to a relationship between this exposure and the development of PCa (SANTOS, 2022).

Given this scenario, it is clear that it is necessary to observe the environmental and occupational context in which individuals are inserted, in order to identify the main risks involved and enable the adoption of more effective preventive measures. Thus, the objective of this article was to identify the main risk factors associated with the development of prostate cancer and to verify the existence of a possible correlation with exposure to agrochemicals in the population of the State of Santa Catarina.

MATERIAL AND METHODS

This study was conducted through a cross-sectional, descriptive and quantitative research. The data sources used to carry out the work were the *Registro Hospitalar de Câncer* (RHC), available at INCA, for the collection of epidemiological data and the *Sistema de Informações Sobre Mortalidade* (SIM), available at DATASUS, for the collection of data on deaths in the national territory related to PCa.

Regarding the number of deaths due to PCa (ICD 10 – C61), data were collected for the period from 2012 to 2022, which present the total number of deaths that occurred throughout Brazil. These numbers were also collected, in the same period, for the State of Santa Catarina, with data covering all Health Microregions.

The collection was carried out through the variable 'Municipality of the Hospital Unit' and all cities that have institutions with oncology qualifications and are references in the various health regions of the state were selected, such as: Blumenau, Chapecó, Criciúma, Florianópolis, Itajaí, Jaraguá do Sul, Joaçaba, Lages, Porto União, Rio do Sul, São Bento do Sul and Tubarão.

To collect data, the primary location of the cancer was considered to be in the prostate. The independent variables studied were mortality, age, smoking, race, family history, alcohol consumption, histological type and occupation, a factor that stood out in the study.

It is worth noting that, for the statistical analysis of the data, according to the variables, only those that presented pertinent information about the patients, entered in the RHC and SIM, were considered valid. The remaining cases, those that were not classified or did not have information, were used only to estimate the number of people affected by the disease.

Based on the data obtained, mortality rates were analyzed at national and state levels, as well as the main risk factors for the development of prostate cancer and the existence of a possible relationship with the use of agrochemicals. All population data used in the research were extracted from the Brazilian Institute of Geography and Statistics (IBGE), also available on DATASUS.

RESULTS AND DISCUSSION

In Brazil, according to data made available by INCA (2023), through the RHC, it is estimated that, in the period between 2012 and 2022, there were around 332,636 cases of prostate cancer, with emphasis on the South and Southeast regions of the country, which, together, account for 67.5% of all cases and occupy the first position in the *ranking*, if demographic density is considered (Table 1).

In the same sense, in the southern region of Brazil, from 2012 to 2022, 57,105 cases of PC were recorded, figures that are equivalent to 17.17% of cases throughout Brazil. However, when analyzing the numbers in relation to the population average, a prevalence of around 4 cases for every 1,000 men is noted (INCA, 2023). In the *ranking*, in first place is the State of Rio Grande do Sul, with 25,639 cases and an average of 0.23% of the total population of the State. Next come the States of Paraná, with 18,923 cases, and Santa Catarina, with 12,543 cases, both with an average involvement of 0.16% of the State's population.

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Table 1: Number of prostate cancer cases in Brazil, from 2012 to 2022. Absolute number of cases by region, percentage of involvement based on the demographic density of each region and the respective proportion in relation to the total number of cases in the country.

<i>Region</i>	<i>No. of cases</i>	<i>Population</i>	<i>% of involvement in the region</i>	<i>% of cases in relation to the country</i>
<i>North</i>	11,239	17,349,623	0.065	3.38
<i>North East</i>	86,358	54,644,534	0.158	25.96
<i>Midwest</i>	7,918	13,470,741	0.059	3.17
<i>Southeast</i>	167,404	84,847,187	0.197	50.33
<i>South</i>	57,105	29,933,315	0.191	17.17

Source: Database of the Hospital Cancer Registry System (SisRHC), 2023.
Brazilian Institute of Geography and Statistics (IBGE), 2023.

In the State of Santa Catarina, PC represents 10.09% of cancer cases affecting the male population. In the period from 2012 to 2022, the occurrence of 12,543 cases was observed, with a predominance in the microregions of Chapecó, in first place, with 2,274 cases, followed by Florianópolis, with 2,115 cases. However, when the population density, updated by the IBGE in 2022, is taken into account, it is noted that the incidence is higher in the microregions of Chapecó and Lages (Table 2, Graph 1).

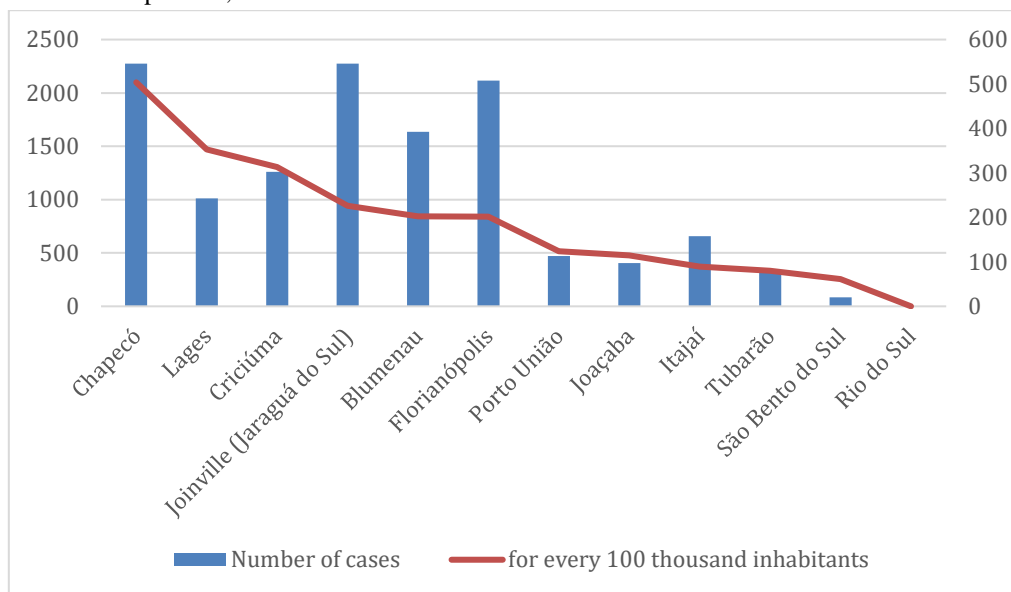
Table 2: Number of cases of prostate cancer in the State of Santa Catarina, from 2012 to 2022. Absolute numbers and based on the demographic density of each microregion.

<i>Microregion</i>	<i>No. of cases</i>	<i>Population</i>	<i>% total location</i>	<i>for every 100 thousand inhabitants</i>
<i>Chapecó</i>	2274	451.331	0.50	504
<i>Lages</i>	1011	286,208	0.35	353
<i>Criciúma</i>	1261	402,494	0.31	313
<i>Joinville (covers Jaraguá do Sul)</i>	2276	1,007,538	0.23	226
<i>Blumenau</i>	1634	808.228	0.20	202
<i>Florianópolis</i>	2115	1,047,383	0.20	202
<i>Porto União</i>	472	380,572	0.12	124
<i>Joaçaba</i>	404	352.143	0.11	115
<i>Itajaí</i>	656	735,527	0.09	89
<i>Tubarão</i>	325	404,645	0.08	80
<i>São Bento do Sul</i>	85	138,787	0.06	61
<i>Rio do Sul</i>	0	228,414	0	0

Source: Database of the Hospital Cancer Registry System (SisRHC), 2023.
Brazilian Institute of Geography and Statistics (IBGE), 2023.

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Graph 1 – Number of prostate cancer cases in the State of Santa Catarina, from 2012 to 2022, Comparison between the total number of cases and the relative cases per 100,000 inhabitants.



Source: Database of the Cancer Hospital Registry System (SisRHC), 2023.
Brazilian Institute of Geography and Statistics (IBGE), 2023.

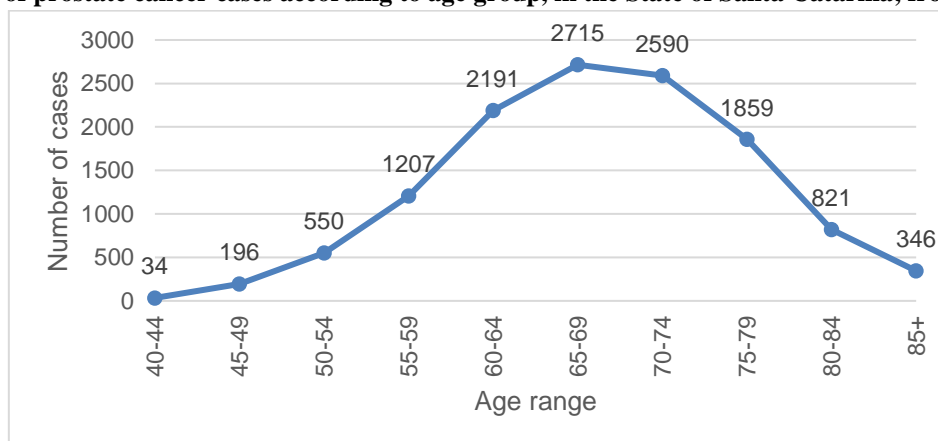
According to the *Ministério da Saúde* (MS) (2023), some risk factors for the development of PCa already have scientifically proven evidence. Among these, the main ones to be considered are age, with greater relevance from the age of 55, family history of cancer, as long as it occurred before the age of 60 and involves first-degree relatives, and, according to more recent studies, patients diagnosed with obesity or who are overweight or have increased abdominal circumference (BRASIL, 2023).

Regarding these data, in the State of Santa Catarina, between 2012 and 2022, it is observed that, in relation to the age group, 93.51% of the cases occurred after 55 years of age, data that corroborate the information presented by the MS (BRASIL, 2023). Furthermore, there is a predominance of the disease between 65 and 69 years of age, which corresponds

to 21.64% of the cases. Patients under 40 years of age represent only 0.27% of the cases and, for this reason, were not included in the graph (INCA, 2023) (Graph 2).

Regarding family history of cancer, this fact was confirmed in 55.3% of cases, however, without discrimination regarding the location of the neoplasia. The RHC Manual: Routines and Procedures (BRASIL; 2000, p. 46), specifies only the degree of kinship, this item “*should consider exclusively consanguineous, ascending or collateral relatives up to the second generation, that is: parents, grandparents, uncles and aunts and uncles and siblings*”. On the other hand, data regarding obesity and overweight are not part of the hall of variables available in the RHC, which makes it impossible to carry out a detailed analysis of this risk factor.

Graph 2 – Number of prostate cancer cases according to age group, in the State of Santa Catarina, from 2012 to 2022.



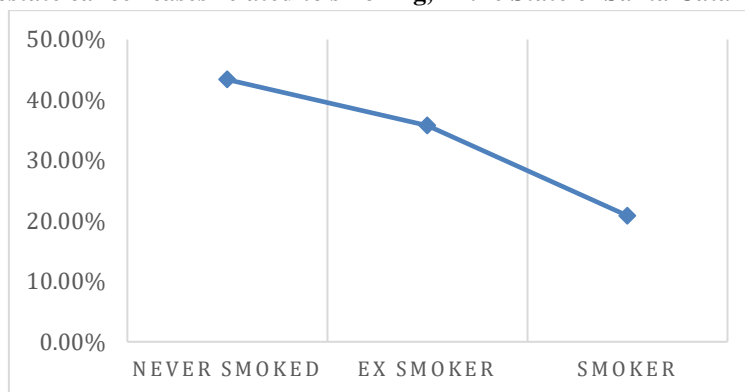
Source: Database of the Hospital Cancer Registry System (SisRHC), 2023.

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In this same context, regarding smoking, it is observed that this is still a relationship that is not very well established, since, according to data available at the RCH, most patients with prostate cancer claim to have never smoked in their lives (43.37%). Next, there are those who are classified as ex-smokers (35.75%), however, without

information on the tobacco load, exposure time and form of presentation. Finally, there are patients who declare themselves to be smokers, who represent only 20.86% of the total number of patients with confirmed symptoms. (INCA, 2023).

Graph 3 – Percentage of prostate cancer cases related to smoking, in the State of Santa Catarina, from 2012 to 2022.



Source: Database of the Hospital Cancer Registry System (SisRHC), 2023.

However, to date, despite the existence of research, there is still no exact definition of the etiology of prostate cancer. There are a large number of new factors that have been studied and added to the *list* of possible causes. Among these, a new trend is observed, mainly with regard to exposure to environmental and occupational factors, with emphasis on the use of agrochemicals (RUTHS *et al.*, 2022).

Regarding agrochemicals, according to cohort studies carried out in the United States by the *Agricultural Health Study (AHS)*, there is evidence that there is a strong association between exposure to these products and the development of the disease, either directly or indirectly. In the same sense, a recent study indicated that, among the participants, around 32% of patients diagnosed with prostate

cancer were farmers. This fact, in addition to reinforcing this possible association, points to the need to include agricultural producers as a population at risk, due to their level of vulnerability (BRITO; WELLER, 2022).

In Brazil, through an analysis of data available in the RHC, from 2012 to 2022, it was observed that the results corroborate the previous report. Regarding occupation, the two professions that appear at the top of the list of patients who most developed prostate cancer were multipurpose agricultural workers and agricultural workers, which when added together, correspond to approximately 35.52% of cases. Of these, multipurpose agricultural workers come first, with 19.82% of cases, followed by agricultural workers, with an incidence of 15.70% of cases (Table 3).

Table 3: Number of prostate cancer cases according to occupation, in Brazil, from 2012 to 2022. Only cases with recorded information are counted.

<i>Occupation</i>	<i>Absolute frequency</i>	<i>Relative frequency</i>
<i>Multipurpose Agricultural Works</i>	27,628	19.82%
<i>Agricultural Works</i>	21,885	15.70%
<i>Vehicle Driver</i>	12,276	8.80%
<i>Bricklayer / Plasterer</i>	9,494	6.81%
<i>Trader</i>	6,716	4.81%
TOTAL	139,387	100%

Source: Database of the Hospital Cancer Registry System (SisRHC), 2023.

In the same sense, within the State of Santa Catarina, with regard to occupation, it is observed that agricultural workers correspond to 29.14% of PCa cases. A total of 2,145 cases were recorded, which corresponds to 9.80% of all cases that occurred in Brazil in the same period. Thus, in addition

to reinforcing the data described above, it presents an incidence around 3 times higher than the second placed, vehicle drivers, who appear with only 9.84% of cases. Nevertheless, it presents itself as the main cause in 8 of the

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12 microregions that have data available on the RHC platform (Table 4).

Table 4: Number of cases of prostate cancer according to occupation, in the State of Santa Catarina, from 2012 to 2022. Only cases with recorded information are counted.

<i>Occupation</i>	<i>Number of cases at the level SC</i>	<i>Frequency (%) at level SC</i>	<i>Number of cases in Brazil</i>	<i>Frequency (%) at level Brazil</i>
<i>Agricultural Worker</i>	2,145	29.14%	21,885	15.70%
<i>Vehicle Driver</i>	698	9.48%	12,276	8.80%
<i>Bricklayer / Plasterer</i>	400	5.43%	9,494	6.81%
<i>Trader</i>	388	5.27%	6,716	4.81%
<i>Guard / Security</i>	168	2.28%	1,920	1.37%
TOTAL <i>(with recorded information)</i>	7,359	58.60% of the total	139,387	41.90% of the total

Source: Database of the Hospital Cancer Registry System (SisRHC), 2023.

According to data provided by the Brazilian Agricultural Research Corporation (EMBRAPA), the consumption of agrochemicals varies according to the region of the country. Data indicate that the regions that use the most are the Southeast, with around 38% of all national consumption, and the South, with approximately 31% of the total. Therefore, this information reinforces the suspicion of a possible link with the development of prostate cancer, given that these are the two regions that have the highest number of cases expressed per number of inhabitants (SPADOTTO; GOMES, 2021).

Regarding the forms of exposure, it is observed that direct exposure is the one that presents the greatest risks involved, mainly during the handling and application of such products. It is believed that the carcinogenesis process is induced due to hormonal changes resulting from the genotoxicity caused by agrochemicals, so that an attack occurs on the nucleus of DNA molecules, which are caused by free radicals, which are responsible for the mutations that occur in tumor suppressor genes and proto-oncogenes (RUTHS, 2022).

In this same context, the action of agrochemical products as endocrine disruptors is observed, so that such manifestations result in changes in both hormonal activities and functions, which are responsible for leading to the emergence of numerous types of cancer, as well as causing malformations, infertility and neurotoxicity (DUTRA et al., 2021).

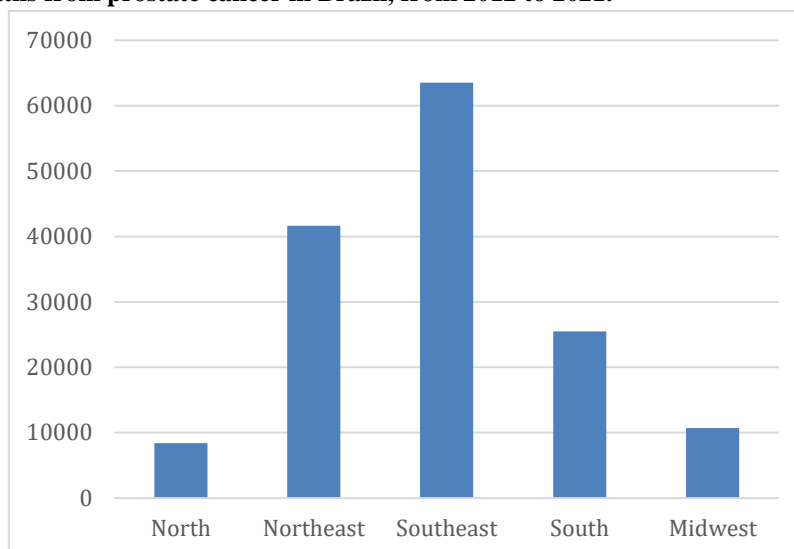
An example of this is the insecticide Dimethoate, a supposed causative agent of PCa found in the composition of several insecticides, which has contact, deep and systemic action and is widely used for pest control. The mechanism of action is similar to other organophosphates, occurring through the inhibition of the enzyme acetylcholinesterase, which, once inhibited, prevents the degradation of the neurotransmitter acetylcholine, which, as a consequence, accumulates in the nerve endings. As a result, there is hyperstimulation of several cell types that result in effects on the parasympathetic, sympathetic, motor and central nervous systems (FMC, 2020).

Regarding mortality, according to data from the Ministry of Health (2023), at a national level, prostate cancer ranks second, behind only lung cancer. According to data from the RHC, between 2012 and 2021, around 149,788 patients died, which represents a mortality rate of approximately 45% of cases.

In Santa Catarina, data from the *Boletim Epidemiológico Barriga Verde* (2021) report that in 2019, prostate cancer was the second neoplasm with the highest number of deaths, with a rate of approximately 10.6% of the total. Regarding the mortality rate among those with the disease, according to data from the RHC, it is estimated that, in the period from 2012 to 2021, there were 4,621 deaths, equivalent to 8.09% of PCa cases.

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Graph 4 – Number of deaths from prostate cancer in Brazil, from 2012 to 2021.



Source: Mortality Information System (DATASUS) database, 2023.

However, INCA and MS do not recommend screening for prostate cancer. This approach is based on scientific studies that have shown high false positive rates, which can lead to emotional destabilization, as well as the need for new tests and the risk of an excessive increase in the number of cases diagnosed and requiring treatment. Therefore, they consider early diagnosis, through signs and symptoms, to be the main strategy to be used (BRASIL, 2023).

However, such information is controversial and questionable, since some documents state that since it is a silent and asymptomatic disease in the early stages, it is extremely important to carry out screening in at-risk populations. In this same context, recent research indicates that, in recent decades, there has been a considerable increase

in the encouragement of prostate cancer screening and the use of diagnostic tests, so that it has become common practice to measure PSA, together with RT, in order to enable early detection of the disease. (BRAVO et al., 2022).

In this regard, the official note issued by the Brazilian Society of Urology (SBU) in 2018 classifies the guidance not to perform PCa screening as mistaken and claims that the consequences, as expected, have already begun to appear. Furthermore, they reinforce that early identification of more aggressive forms of cancer, with a high risk of progression, allows them to be adequately treated, even in the initial stages, as well as that late diagnosis can result in a negative impact on public health and a worsening of the outcomes of oncological cases.

Table 5: Status of prostate cancer case records in Brazil and the State of Santa Catarina, from 2012 to 2022. Absolute frequency and relative frequency.

BRAZIL	332,636	100%
<i>NO INFORMATION</i>	139,212	41.85%
<i>UNCLASSIFIED</i>	43,938	13.20%
<i>NOT APPLICABLE</i>	10,099	3.03%
<i>CLASSIFIEDS</i>	139,387	41.90%
SAINT CATHERINE	12,543	100%
<i>NO INFORMATION</i>	3,786	30.18%
<i>UNCLASSIFIED</i>	1,091	8.69%
<i>NOT APPLICABLE</i>	307	2.44%
<i>CLASSIFIEDS</i>	7,359	58.60%

Source: Database of the Hospital Cancer Registry System (SisRHC), 2023.

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It is worth noting that the information systems used for the research, like others, present a large deficit in relation to patient information. Within the State of Santa Catarina, only 58% of patients have their occupation recorded, with emphasis on the microregion of Chapecó, which presents data from 96.04% of the patients treated (Table 5).

This fact was not a limitation for the research, however, it exposes the difficulties encountered in defining priorities and conduct based on existing data and the need to improve the insertion of registration data.

FINAL CONSIDERATIONS

The etiology of PCa, although not well defined, based on the data analyzed, both at the national and state levels, appears to be compatible with that described in the literature. Advanced age is the main factor associated with the development of the disease, with prevalence above 55 years. Family history, although not establishing a relationship with the primary location, is found in more than half of the patients.

Regarding smoking, further studies are needed to prove a direct relationship with the development of PCa. Isolated data shows that most patients are not smokers, however, there is a gap that needs to be better explored when it comes to former smokers, since data such as smoking history, exposure time and form of presentation can alter this relationship.

One fact that deserves to be highlighted is the high prevalence of PCa cases in the South and Southeast regions of Brazil, the two that use the most agrochemicals. When analyzing the data related to occupation, it is noted that both at the national level and in the State of Santa Catarina, there is a high prevalence of PCa cases in workers in rural areas, so that, within the State of Santa Catarina, it represents almost one third of the cases and is the main risk factor found in 8 of the 12 microregions. Therefore, the existence of a relationship between exposure to these agents and the development of PCa becomes evident.

Thus, given the high prevalence in rural workers, who are often not even part of the risk factor *group*, there is a need for clinical studies to better clarify this relationship. It is also expected that new public policies will be developed with the aim of improving screening and prevention methods to mitigate the occurrence of new cases of PCa in this target population.

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