RESEARCH

Correlations between risk factors for prostate cancer: an epidemiological analysis

Correlações entre fatores de riscos para o câncer de próstata: uma análise epidemiológica

Correlaciones entre factores de riesgo de cáncer de próstata: un análisis epidemiológico

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ABSTRACT
Objective: To establish correlations between risk factors for prostate cancer. **Method**: 155 Medical records of patients with prostate cancer were analyzed regarding the tumor characteristics and risk factors. **Results**: The patients on average were 70 years of age, incomplete grade school (70%), exposed to pesticides (68.56%), non-smokers (93.8%), and alcohol consumption (71.2%), patients with adenocarcinoma (98.71%) and metastases (12.90%). Positive correlations (0.001) were evidenced with occupational exposure (r= 0.588), use of medications (r= 0.569) and radiation exposure (r= 0.609). No correlations were observed for diet, smoking and alcoholism. **Conclusion**: The data show that for associations between genetic factors and occupational exposure, with emphasis to the mutagenicity and carcinogenicity. **Descriptors**: Prostate cancer, Risk factors, Mutagenicity, Carcinogenicity.

RESUMO
Objetivo: Estabelecer correlações entre fatores de risco para o câncer de próstata. **Método**: 155 prontuários de pacientes com câncer de próstata foram analisados quanto às características do tumor e aos fatores de risco. **Resultados**: Os pacientes apresentavam em média 70 anos de idade, primário incompleto (70%), expostos a agrotóxicos (68,56%), sem hábitos para tabagismo (93,8%), e etilismo (71,2%), portadores de adenocarcinoma (98,71%) e metástases (12,90%). Correlações (0,001) positivas foram evidenciadas com exposição ocupacional (r=0,588), uso de medicamentos (r=0,569) e exposição a radiações (r=0,609). Não foram observadas correlações para dieta, tabagismo e etilismo. **Conclusão**: Os dados apontam para associações entre fatores genéticos e exposição ocupacional, com ênfase para a mutagenicidade e carcinogenicidade. **Descritores**: Câncer de próstata, Fatores de risco, Mutagenicidade, Carcinogenicidade.

RESUMEN
Objetivo: Establecer correlaciones entre los factores de riesgo para el cáncer de próstata. **Método:** 155 registros médicos de pacientes con cáncer de próstata fueron analizados por las características del tumor y los factores de riesgo. **Resultados:** Los pacientes tenían una edad mediana de 70 años, primaria incompleta (70%), expuesta a los pesticidas (68,56%), sin que el hábito de fumar (93,8%) y el consumo de alcohol (71,2%) que adenocarcinoma (98,71%) y metástasis (12,90%). Correlación (0.001) Correlación (0.001) positivas fueron observados con la exposición ocupacional (r=0,588), el uso de medicamentos (r=0,569) y la exposición a la radiación (r=0,609). No se observó la correlación con la dieta, el tabaquismo y consumo excesivo de alcohol. **Conclusión:** Los datos sugieren asociaciones entre los factores genéticos y la exposición ocupacional, con énfasis en la mutagenicidad y la carcinogenicidad. **Descriptores**: Cáncer de próstata, Factores de Riesgo, Mutagenicidad, Carcinogenicidad.

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INTRODUCTION

Cancer will be the main cause of mortality in the world in the coming decades. Associated with this forecast, cancer has a strong impact on society, a time that results in a public health problem, causing productive individuals disabilities that affect social and economic segments. [1] Since 2003, malignant neoplasms are the second cause of death in the population, representing almost 17% of deaths of known causes, notified in Mortality information System in 2007. It is estimated that, in 2030, the number of new cases per year in the world will be 27 million, of which approximately 60% occur in developing countries. In addition, 257,870 new cases will be expected, in 2013, for the males, and 260,640 for females. In this context, it is estimated that most incidents will be non-melanoma skin cancer (134,000 new cases), prostate (60,000), female breast (53,000), colon and rectum (30,000), lungs (27,000), stomach (20,000) and cervical (18,000). [2]

Currently, it is known that at least one-third of the new cases of cancer that occur every year in the whole world could be prevented. [3] Among these, the prostate cancer - one of the malignant neoplasms more frequent in the world and that further increases incidences in the male population in virtue of an extension in life expectancy, which estimates exceed 70 years, in Brazil, in 2020. [4] Allied to this it is configured as the second leading cause of death in Brazil. [5]

Prostate cancer is the second most common malignant neoplasm in men observed in different ethnic groups. The Americas and Africa has a high prevalence (137 cases per 100,000 inhabitants), while in Asian populations, the prevalence is less than 10 cases per 100,000 people. These data suggest that genetic factors may contribute to these differences in susceptibility. [6] However, a positive correlation with the family history has been recognized as one of the most important risk factors, as well as the age. [7] More than any other cancer, this is considered a cancer of third age, since about three-quarters of the cases occur in the world after 65 years of age. [8-9]

The early diagnosis signals a better prognosis for the patient that offers of therapies with chances of cure. [10] There are opportunities for the prevention of most cancers, because about 80-90% of them are related to lifestyle and environmental factors, some of which are well known, such as smoking, alcohol consumption, excessive exposure to ionizing radiation and sunlight, chemicals in food and other exposures to carcinogenic agents. [11-12]

In this context, this study aims to examine the records of the Department of Health Statistics (SAME), in a Care Center for Cancer in the city of Teresina, Piaui, Brazil, in the period 2010/ 2012. With the objective of characterizing the socio-economic and clinical profiles of patients with prostate cancer, performing the mapping of probable risk factors associated with cancer, from information to patients undergoing chemotherapy and/or radiotherapy, as a strategy to improve the prevention of cancer in Piaui.

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METHODOLOGY

Characterizations of the study

The research was exploratory and descriptive, once that were observed facts, recorded, analyzed, classified and interpreted without the interference of the researcher, who sought to gather information about a particular object, delimiting, thus, a fieldwork and mapping the manifestation conditions of this object. With regard to procedures, the study was carried out by means of collecting data from medical records of patients with prostate cancer, as well as the application of a health questionnaire.

Ethical Aspects

The research was carried out with the authorization of the direction of Hospital Sao Marcos and obeyed the resolution 466/12 of the National Council of Ethics, which regulates the operational issues and ethical scientific research involving human beings. The patients who agreed to participate in the study signed a Free and Informed Consent Term (FICT). The approval by the UNINOVAFAPI Research Ethics Committee is registered under the number 0151.0.043.000-11.

Data Collection and sample characterization

The health service chosen for the research was the Sao Marcos Hospital, which is a reference center for diagnosis and treatment of cancer in Teresina, Piauí. In addition it meets the population of several states of Brazil, especially the states of Maranhão, Pará, Ceará and Tocantins The database query aimed to identify which type of malignant tumor more present among patients, as well as the socio-economic aspects and clinical treated at the institution during the period of 2010/2012. We analyzed 155 medical records of patients with prostate cancer. Of these, 20 patients agreed to participate in the second stage of the research by responding to a questionnaire for public health in obeying the protocol published by the International Commission for Environmental Protection the Mutagens and Carcinogens (ICPEMC). [13] The questionnaire was applied after prior authorization of patients upon the signature of the Free and Informed Consent Form. Patients were excluded who did not undergo chemotherapy and/or radiotherapy, or didn't accept to participate in the research.

Statistical analysis

For data analysis, the Spearman's test was used through the program SPSS 20.0 for correlation between potential risk factors in patients with prostate cancer and the analysis of variance (ANOVA) by the Tukey test, through the program Graph Pad Prism 5.0.

RESULTS AND DISCUSSION

According to epidemiological studies, carried out in the Sao Marcos Hospital, in the period 2010/2012, 155 patients with prostate cancer were recorded. The general

characteristics of the subjects are presented in Table 1. The data recorded in the medical records, as well as those reported by patients indicate that the majority of patients with cancer is brown ethnicity (43.8%), with incomplete elementary education (70%). The patients with prostate cancer, on average were 70 years of age.

Table 1. General characteristics of the research subjects

Parameters	Patients (n=155)	Significance (p)
Age (years; mean ± dp; minimum-maximum)	69.69 ± 7.28 (58-82)*	0.000
Ethnic Group		
Brown	86 (43.8%)*	0.000
Caucasian	38 (31.3%)	
Black	31 (25.0%)	
Schooling		
Illiterate	16 (10.0%)	
Incomplete Elementary	108 (70.0%)*	0.023
Complete Elementary	31 (20.0%)	

* Significance for P<0.05. *One Sample Chi-Square test.*

The data relating to clinical aspects are presented in Table 2, including the location of the cancer and their subtypes, as well as indicative of metastasis and clinical treatment. In their majority, the patients had adenocarcinoma and treatment focused on surgery and radiotherapy. The percentage of metastasis for prostate cancer was 12.9%. The implementation of mechanisms for monitoring treatment, in relation to the damage in normal cells, as well as for the process of angiogenesis is a strategy for the prevention of metastasis and new neoplasms.

Table 2. Clinical characteristics of patients with prostate cancer in relation to subtypes for prostate cancer, metastasis confirmed clinical treatment and family history

Characteristics	Patients
Metastasis confirmed	
Yes	12.90%
no	87.10%
Subtypes of Cancer	
Prostate adenocarcinoma	98.71%
Urothelial carcinoma	0.65%
Small cell carcinoma and adenocarcinoma	0.65%
Type of treatment	
Radiotherapy	43.75%
Surgery	6.25%
Surgery and radiotherapy	43.75%
Surgery, chemotherapy and radiotherapy	6.25%
Family History	
There are no cases of cancer in the family	37.5%
	6.25%
Cousin	18.75%
Brothers	6.25%
Father and brother	6.25%
Brother and son	

* Significance for P<0.05. *One Sample Chi-Square test.*

Currently, it is known that at least one-third of all new cases of cancer that occur annually in the world could be avoided. [14-15,3] This possibility to prevent many cancers is related to the fact that approximately 80-90% of them are related to environmental factors and the style of life, some of which are well known, such as smoking, alcohol consumption, excessive exposure to sunlight and the ionizing radiation, chemicals in foods, as well as occupational exposure to carcinogenic agents.[11,16]

Until now, only three risk factors for prostate cancer has been well established: age, race and family history.[8,17] In studies with animals, testosterone may induce the prostate cancer, acting as a promoter of genotoxicity, as well as estradiol, derived from testosterone, which can lead to DNA adducts, but also generates reactive oxygen species that lead to mutations.[18]

Family history of prostate cancer presents significance representing a potential risk factor. Several lines of evidence indicate

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that the human tumorigenesis is a process that involves several steps and these are reflected in genetic alterations that lead to the gradual transformation of human cells.[19] Thus, the initiation and progression of carcinogenesis involving the accumulation of many mutations.[20]

In Table 3 are presented the epidemiological data relating to the main risk factors identified in patients with prostate cancer. As noted, smoking and drinking habits of the patients are in focus. However, the diet low in micronutrients worrisome, as well as the question of the use of medicines without medical prescriptions.

Table 3. Risk Factors associated with lifestyle, environmental and occupational in patients with prostate cancer.

Risk Factors	Patients (n=155)	Significance (p)
Smoking		
Yes	8 (6.8 %)	
no	147 (93.8 %)*	0.000
Alcoholism		
Currently drinks	29 (18.8 %)	0.724
Drank before the disease	29 (18.8 %)	
Doesn't drink	136 (62.4%)	
Fruits and vegetables in the diet		
Yes	31 (20%)	
no	124 (80%)*	0.007
Red meat Consumption		
Yes	124 (80%)*	0.007
no	31 (20%)	
Self-Medication		
Yes	135 (62.3%)*	0.008
no	20 (37.7 %)	
Type of medication		
Analgesic	59 (49.3%)	0.035
Anti-inflammatory	48 (25.1%)	
Do not take	48 (25.1%)	
Exposure to chemicals		
Pesticides	59 (38 %)	0.006
Paints	19 (12.5 %)	
Smoke	10 (6.4 %)	
Kitchen gas	10 (6.4 %)	
Construction material	19 (12.5%)	
Not informed	38 (24.2 %)	
Exposure to ionizing radiation		
X-Ray therapy	155 (100 %)	0.011
X-Ray diagnostics	155 (100 %)	
Occupational Exposure		
Family Agriculture	39 (25.16%)	0.000
Retired as farmer	67 (43.4%)	
Trade	19 (12.25%)	
Self-employed	10 (6.4%)	
Construction	10 (6.4%)	
Not informed	10 (6.4%)	

* Significance for P<0.05. *One Sample Chi-Square test.*

It is known that tobacco contains more than 4720 substances, 60 are known carcinogens: polycyclic aromatic hydrocarbons, nitrosamines, aromatic amines, aldehydes and volatile organic compounds and other metals. Such substances may produce DNA adducts that can cause damage to genetic material, contributing to the process of carcinogenesis.[21,22]

The World Health Organization (WHO) considers smoking as the main cause of death that can be prevented in the world and a risk factor for cancer. According to the WHO, more than 5 million people die each year around the world due to smoking, being that the majority of these deaths are concentrated in people with low and medium incomes. It also shows that, in 2030, the number of deaths will exceed the home of 8 million, reaching one billion deaths by the end of this century. Smoking is a predictive cancer variable by inducing significant changes in genetic material, observed by cytogenetic biomarkers.[23] The mechanism used by these factors to trigger the emergence of neoplasms is related to imbalance in production process and elimination of ERO, capable of damaging the DNA and compromising important genes in systems such as repair.[24] Tumor suppressor Genes such as *p53* and *PTEN* when deregulated can lead to impairment of important functions such as apoptosis induction, activation of the repair system and cell cycle arrest.[25]

Alcoholism has been associated with cancer of the esophagus, larynx, pharynx, but can also be a risk factor for prostate cancer. Although the ethanol is not a direct carcinogen, one of its metabolites, acetaldehyde, may act as a tumor promoter.[26] Alcohol abuse of shows synergy with chronic hepatitis B or an infection with the hepatitis C

virus, predisposing the body for the development of hepatocellular carcinoma.[11]

Diets poor in micronutrients increases the risk of degenerative diseases, including cancer. [27-28] It is known that the vitamins and minerals are essential for the maintenance of genomic stability, in addition to exercise influence on the metabolism, in many aspects, including DNA synthesis, repair, the methylation and apoptosis. [28-30] epidemiological Evidences indicate the protective factors, such as a diet rich in vitamin E, selenium, lycopene, soybeans and products made from milk and meat.[31-32] Obesity, low physical activity and low consumption of antioxidants, vitamin D and calcium, coffee are risk factors.[33-34]

There are reports of carcinogenicity resulting from pharmaceutical drugs both in animals and in human beings with positive responses in several tests for genotoxicity, mutagenicity and carcinogenicity, with suggestions for a better assessment of the risks and benefits of medicines.[35-36]

It is worth mentioning that the patients in this study also consume drugs not prescribed by doctors, with emphasis on analgesics and anti-inflammatory (Table 3). In most cases, the damage is repaired by the body, when it does occur, it can result in mutations that may be perpetuated into daughter cells during the replication process.[37-38]

Oncologic therapy have evolved and reached achievements relevant as the development and implementation of antineoplastic agents that ensure a better prognosis for the patient. Although the benefits are unquestionable, we should not

underestimate a profile that offers security, once again that these drugs cause imperiling effects on critical systems to interact with the DNA. [39-40] In chemotherapy, which has been used is the combined therapy, which consists in combinations of surgery, radiotherapy and chemotherapy, seeking to eradicate both the neoplasm primary as their occult micrometastases, before one can detect the occurrence of macroscopic distribution in the physical or radiological examination.[41]

Numerous epidemiological studies have reported that, in most cases, the cancers are caused by continuous exposure to mutagenic and carcinogenic agents. Individual susceptibility may depend on the genetic predisposition, the differences in eating habits and lifestyle. The individual response to stress may vary according to conditions, such as the function and the particular combination of genes, absorption and metabolism, the cell death apoptosis/necrosis, cell cycle control, DNA repair and immune response and micronutrient deficiencies.[41-42]

Thus, the identification of risk factors can contribute routinely in the diagnosis and treatment of patients with prostate cancer. Despite the lack of evidence of other factors, such as the consumption of alcohol, diseases, infections, exercise, the biomass body and genotypes may also influence the data interpretation. These analyzes are required for the consideration of genetic instability in studies of correlations between chemical exposure occupational and environmental.[43]

The majority of cancer cases (80 %) are related to the environment, holding a large number of risk factors. It is understood as the

general environment (water, land and air), the occupational environment (chemical industries and related), the environment of consumption (food, medicines). Changes in the environment caused by man himself, the life style adopted by persons can determine different types of cancer.[14-15]

In terms of occupation of the patients interviewed, approximately 70% are related to family farming or being active or retired farmers. The patients were also exposed to physical agents, such as the use of radiation in clinical diagnoses and treatments (Table 3).

During the diagnosis and cancer therapy, humans are exposed to high linear energy transfer, which cause various biological effects, including inactivation of cells, genetic mutations, which can result in the induction of cancer.[44] Despite of ionizing radiation have applicability medical and non-medical, constitute a threat to Human Health worldwide. Knowledge of their changes in gene expression of irradiated cells can be of paramount importance to establish paradigms for radiation protection[45]

In addition, the exposure of the DNA molecule to radiation triggers a complex cascade of signal transduction causing damage to the genetic material. Recently, studies have demonstrated deletions and alterations in the genome with alterations in the expression of genes after exposure to delayed response radiation doses having malignant transformations in human fibroblasts.[45] Therefore, ionizing radiation is known for its carcinogenicity potential.[46]

Chemical Agents that initiate carcinogenesis are extremely varied including

both synthetic and natural products.[19] exposure to pesticides (organochlorine pesticides, dioxins polychlorinated) can also be a risk factor associated with cancer.[47] The occupational exposure to pharmaceutical products, herbicides and fungicides have been associated with the development of lung cancer.[48,22]

As seen in Tables 3, numerous epidemiological aspects relating to risk factors such as the risks of self-medication, occupational exposure to pesticides were evidenced as predictors for prostate cancer; in addition to the importance of family history. To determine the correlations between the probable risk factors, the data were submitted to Spearman's statistical correlations.

Table 4 shows positive correlations between the type of work, in their majority involved with agriculture with exposure to pesticides, medicines, exposure to X-Rays, family history and the patient with prostate cancer, with a factor of correlation of 0.588 and significance level of 0.016 (p < 0.05). It must be emphasized that, in this occupational exposure, patients are exposed to various chemicals, potentially mutagenic.

Table 4. Statistical Correlations between the risk factors for prostate cancer patients (n= 155), met in a reference Hospital for cancer treatment

Cancer versus Risk Factors	Correlation Factor (r)	Significance (p)
Occupation	0.588	0.016*
Medication	0.569	0.023**
Other diseases	0.516	0.004*
Place of employment	0.603	0.001**
Alcoholism	0.094	0.692
Smokes	-0.214	0.425
Exposure to X-Rays	0.609	0.001**
Diet	0.122	0.653
Family History	0.516	0.001**

Spearman's Coefficient with significance for 0.05.

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No correlations were found between smoking and prostate cancer studied (Table 4). Although the literature does not record the specific association between smoking and prostate cancer, [49-52] recent studies suggest that the habit of smoking as a major risk factor for a considerable number of neoplasms in humans.

Associations between smoking and cancer, due to the diversity of chemical products that comprise the tobacco, are considered as genotoxic and carcinogenic. [16,19] Smoking is associated with the occurrence of several malignant diseases in the oral cavity, pharynx, esophagus, stomach, pancreas, colon, rectum, liver and biliary tract, kidneys, bladder, breast, cervix, vulva, myeloid leukemia, among others. [21-22] Numerous evidences indicate an association between active and passive smokers with cancer. However, this correlation is not yet well established due to possible interactions between smoking, alcohol and influences of hormonal factors, [50,52] one aspect that can also be found in the presented data.

In relation to the general characteristics of health, patients with prostate cancer reported the onset of cardiovascular diseases (62.5%), genetic (50%), bacterial infection (93.5%). However, it was observed that low percentage for hepatitis (6.45%), meningitis (6.45%) and mononucleosis (6.45%), in addition to other genetic diseases. It is worth emphasizing that, after application of the test of correlations were found significant statistical data for other diseases related to the development of prostate cancer (Table 5).

Table 5. General Characteristics of patient health with prostate cancer

Diseases	Patients (n=155)	Significance (p)
AIDS		
Yes	-	0.000
no	155 (100%)	
Diabetes		
Yes	29 (18.8%)	0.000
no	126 (81.3%)	
Cardiovascular Diseases		
Yes	97 (62.5%)	0.000
no	58 (37.5%)	
Genetic Disorders		
Yes	77 (50%)	0.000
no	78 (50%)	
Hepatitis		
Yes	10 (6.45%)	0.000
no	145 (93.5%)	
Bacterial Infections		
Yes	145 (93.5%)	0.208
no	10 (6.45)	
Herpes		
Yes	10 (6.45%)	0.000
no	145 (93.5%)	
Meningitis		
Yes	10 (6.45%)	0.000
no	145 (93.5%)	
Mononucleosis		
Yes	10 (6.45%)	0.000
no	145 (93.5%)	
Other diseases		
Yes	49 (31.1%)	0.000
no	106 (68.8%)	

* Significance for P<0.05. One Sample Chi-Square test.

Cardiovascular diseases and cancer are the leading causes of mortality in the world. Risk factors are smoking and diet, as well as the pathogenic processes, such as chronic inflammation and oxidative stress that cause genetic instability. [28]

CONCLUSION

The notoriety of cancer as one of the main causes of death suggests the need for an in-depth approach to their intrinsic biological aspects of presentations and the risk factors involved in its etiology. In this light, this work extends the discussion on the main risk factors identified in patients diagnosed with prostate cancer. Age is well established as a risk factor for prostate cancer, whose prevalence is observed from 70 years of age forward, as shown in the literature. Age is associated with

the risk factors from environmental and occupational for the study population.

However, the positive correlations were also observed as family history. Taking into account the risks of genetic instability associated with DNA damage, another important aspect is correlated with environmental exposure and / or occupational reported by patients. The majority of patients with prostate cancer were farmers or retired as such. Significant exposure to pesticides can result in genomic instability that may trigger a carcinogenic process. A significant Percentage of patients with prostate cancer had a family history, especially father and grandfather. Other risk factors described in the literature are related to lifestyle, such as smoking and alcohol consumption that, in this study, were not correlated. However, the use of drugs, especially those prescribed by doctors can be mentioned as a risk factor.

We should also emphasize that in the study in focus, nutrition was not associated with risk factors. However, other studies should be conducted due to the importance of micronutrients for genetic stability. Considering cancer as a multifactorial genetic disease, with strong influences of age, ethnicity, socioeconomic factors, lifestyle, family history, micronutrients and epigenetic factors associated with occupational and environmental risk, the findings obtained in this epidemiological study corroborate as the main risk factors that guide the etiology of prostate cancer. The results obtained can be used as indicators of public policies related to the treatment and prevention of prostate cancer.

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