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Risk Factor Analysis of Residential Topography and Age on Prostate Cancer Incidence

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Abstract

GLOBOCAN stated that prostate cancer is the third most common type of cancer in the world. Previously, prostate cancer incidence rates in Asian populations were lower than Western populations. In recent years, the incidence rate of prostate cancer in Asia has increased rapidly. Indonesia ranks 10th out of 32 Asian countries. Prostate cancer is a multifactorial disease, including age and topographical factors of residence. Prostate cancer risk factors need to be identified to target primary and secondary prevention. Pesticide-specific exposure in rice field areas accumulates in the environment and becomes a pathology. Literature studies from various sources related to these risk factors are still very limited. This study aims to analyze the risk factors of residential topography and age on prostate cancer incidence. An observational analytic study was conducted with a case-control design. 177 samples were obtained by total sampling method, with prostate cancer as the case group and benign prostate hyperplasia as the control group. Age variable parameters are less than or more than 65 years. The residential topography criteria are narrow and large rice fields around the sample residence. The chi-square test result found a significant correlation between residential topography with prostate cancer incidence (p= 0.028, OR= 2.155) and correlation between age factor with prostate cancer incidence (p=0.018, OR=2.187). Age had a 2.009-fold higher risk of prostate cancer incidence than the topography of residence. In conclusion, the topographic profile of the rice field area around the residence and age has a significant risk factor on prostate cancer incidence.

Keywords: age, pollutant, prostate cancer, residence, rice field

Introduction

Prostate cancer (PCa) is one of the most common cancers worldwide, accounting for the majority of all cancer-related deaths. (Bergengren et al., 2023). In 2020, the Global Cancer Statistics (GLOBOCAN) states that prostate cancer is the third leading cancer type. The highest number of new cases and mortality from this cancer is 7.3%, after breast cancer (11.7%) and lung cancer (11.4%) (Sung et al., 2021). Previously, prostate cancer incidence rates in Asian populations were lower than those in Western populations. However, in recent years PCa incidence and mortality rates in some Asian countries have increased rapidly. Prostate cancer incidence and mortality in Indonesia is ranked 10th out of 32 Asian countries (Chen et al., 2014). The Indonesian Society of Urologic Oncology (ISUO) in 2015, stated that there were 1,102 patients with prostate cancer with an average age of 67.18 years in three central teaching hospitals (Jakarta, Bandung, and Surabaya), more patients came with an advanced stage of 59.3% (ISUO, 2015). In recent years, individual growth patterns have independent prognostic value and can be used for better risk personalization (Leenders et al., 2020).

Prostate tumors can be categorized into malignant prostate cancer and benign prostatic hyperplasia (BPH). BPH is a non-cancerous enlargement of the prostate gland, commonly affecting men over 40. It is prevalent globally, with estimates suggesting that around 50% of men in their 50s and up to 90% in their 80s experience BPH (Shrivastava & Gupta, 2012). In Asia, the incidence mirrors global trends, with similar rates of BPH observed among Asian men (Xia et al., 2012). BPH is

characterized by the proliferation of prostate glandular and stromal tissues, leading to urinary symptoms due to urethral compression (Kishanrao, 2022). Histological examination reveals hyperplastic changes in both glandular and stromal components, with increased cellularity and altered architecture (Mostofi et al., 2014). Magnetic resonance spectroscopy has shown distinct metabolic profiles in BPH tissues, aiding in differentiation from malignant tumor (Hahn et al., 2014).

Prostate Cancer risk factors need to be identified to target primary and secondary prevention (Bergengren et al., 2023). Age, race, and family history are non-modifiable risk factors. Whereas physical activity and sleep, dietary intake, history of disease and surgery, smoking, and environmental and occupational factors were identified as modifiable risk factors (Bergengren et al., 2023).

In 2017-2019 in the United States, prostate cancer had a high probability in the age range of 65-84 years (10.4%), followed by age 50-64 years (3.9%), age over 85 years (3.1%), and age 0-49 years (0.2%) (Siegel et al., 2024). The cancer statistics center in the United States, also recently showed that the likelihood of PCa increased from 1.8% in men aged 60-69 years to 9% in men aged 70 years and above (Bergengren et al., 2023). The findings also suggest that only 1 in 350 men aged less than 50 years may be diagnosed with prostate cancer. The incidence rate of the disease is closer to 60% in men over 65 years old (Rawla, 2019). Adulthood is the peak of circulating testosterone and decreases gradually in old age (Moreau et al., 2020). A decrease in testosterone androgens in men can increase the expression of the BCL-2 (B Cell Lymphoma 2) family of proteins which are anti-apoptotic as a form of compensation (Ali & Kulik, 2021). Androgen-induced prostate epithelial growth and invasion appear in embryogenesis and will be reactivated in cancer and form masses in the prostate (Toivanen & Shen, 2017).

Research by Romadhon et al. (2024) found a strong association between age and cancer development and considered socio-environmental variables when assessing risk factors for cancer occurrence (Romadhon et al., 2024). Rice fields are a crucial staple food source in Asia, but the use of pesticides in agriculture raises significant environmental and health concerns. The reliance on pesticides to enhance rice fields, which can reach up to 10 t/ha, is prevalent in many Asian countries (Gianessi, 2014). However, this practice leads to pesticide residues that can persist in the environment (Song & Kuo, 2021). Siegel et al. (2024) found that most cancers in men reflect greater exposure to carcinogenic environmental and lifestyle factors. (Siegel et al., 2024). Epidemiologic studies have evaluated workplace exposure, as well as exposure to pesticides and other chemicals (Ledda et al., 2021). Research by Ragin et al. suggests that the duration of pesticide exposure plays an important role in the development of prostate cancer (Ragin et al., 2013). Although most pesticide exposures are not mutagenic, certain pesticides contain EDs (Endocrine Disruptors) that can block testosterone hormonal receptors (Habibi et al., 2021). Under pathological conditions, AR (Androgen Receptors) mutation or unspecific AR binding by ligands modulate different target genes leading to altered regulation of cell proliferation and triggering the onset and progression of prostate cancer (Corti et al., 2022).

Empirical experience of researchers when conducting literature reviews on PubMed and Scopus with the search "Prostate Cancer AND Environment AND Age AND Gleason" without year restrictions, only 50 journals were found on PubMed and 37 on Scopus. In addition, a literature review on Google Scholar only found 36 journals. This proves that few studies still discuss this matter at the national and international levels. Based on this background, the researcher is interested in examining how the influence of the topographic profile factor of the rice field area around the residence and age on prostate cancer incidence.

Methods

Research design

An observational analytic study with a case-control design by comparing prostate cancer as the case group and benign prostate hyperplasia (BPH) as the control group.

Population

The population in the study were medical records that have passed the gold standard test of histopathology preparations in prostate and BPH cases at the Anatomical Pathology Laboratory of PKU Muhammadiyah Surakarta Hospital. The samples in this study were medical records of histopathology preparations with a final diagnosis of prostate cancer from 2018 to 2023.

Sampling Technique and Sample Size Determination

Medical record data obtained by total sampling method were 177 samples of prostate cases, which are 124 cases of prostate cancer and 53 cases of benign prostate hyperplasia (BPH) from 2018 to 2023.

Restriction criteria

The gold standard for tumor examination is a histopathological picture performed in an anatomical pathology laboratory, so this research uses medical record data. Inclusion criteria in this study were medical records with the conclusion of prostate cases and have a complete identity. Exclusion criteria were duplicate cases, residential data not found in the database, and medical records that have a histopathology diagnosis of primary malignancy in other organs such as lung cancer or pancreatic. This study did not have many other exclusions related to the number of rare cases and old age which allow many dropouts.

Measurements

The topography profile variable of the area of rice fields around the residence is the percentage ratio of rice fields area compared to the total sub-district area from the Central Bureau of Statistics data. The distribution of all sample data was analyzed with the 60th percentile (P60) for specific results and a limit of 39% was obtained. The 60th percentile is often considered a specific reference point because it represents a class group that is in the middle of the distribution (Kireyev & Leonidov, 2020). The age variable is the age of the sample when diagnosed with prostate cancer from medical records. Graham's study concluded that prostate cancer is mostly found in men older than 65 years. So, researchers use the 65-year limit as a reference. The measurement criteria were less than and more than 65 years as the median age between at-risk and not (Graham et al., 2023).

Statistical analysis

Univariate analysis was performed to determine the distribution of sample characteristics. Bivariate analysis of the effect between independent and dependent variables was performed using the Chi-Square test. The sig. The P-value is less than 0.05, referred to a statistically significant correlation. Multivariate analysis was performed using a logistic regression test to find out the riskier variable in this study.

Ethical clearance

This study has been approved by the Health Research Ethics Commission of PKU Muhammadiyah Surakarta Hospital with No.13/KEPK/RS.PKU/VI/2024.

Results

Medical record data covering the period from 2018 to 2023, along with the geographical distribution depicted were also included in the analysis. The study encompasses 177 cases of prostate categorized into prostate cancer 124 cases in **Figure 1** and benign prostate hyperplasia (BPH) 53 cases in **Figure 2.**

Table 1 presents the characteristics of the study sample. Most of the prostate cancer samples were more than 65 years old, while most of the BPH samples were less than 65 years old. Both prostate cancer and BPH samples lived mostly in urban areas. The results of the analysis of the topographic profile of the place of residence, most samples are in a residence with a rice field area of less than 39% of the total area. The majority of the samples were private workers. Lymphocyte levels showed that most samples had low lymphocyte levels in prostate cancer and BPH samples. Gleason score in prostate cancer samples, most had a score of more than 8 (poorly differentiated).

Table 2 shows the results of bivariate analysis between topographic characteristics of rice fields around the residence with the incidence of prostate cancer obtained a Chi-square p-value of 0.028. This shows there is a significant influence between the topographic characteristics of rice fields around the residence with the incidence of prostate cancer (OR = 2.155, 95% CI 1.08-4.32). Both prostate cancer and BPH were located in areas with small rice fields (less than 39% of the total area sub-district).

Table 3 shows the bivariate analysis results between age characteristics and the incidence of prostate cancer obtained a Chi-square p-value of 0.018. This shows there is a significant influence between age characteristics with the incidence of prostate cancer (OR = 2.187, 95% CI 1.14-4.21). As many as 66.1% of prostate cancer samples were at risk age of more than 65 years. In contrast to the BPH samples, 52.8% were less than 65 years old.

The results of multivariate analysis are shown in **Table 4**, showing that the age variable had more influence on the incidence of prostate cancer than the topographic profile of rice fields with a significant p-value of 0.040. The age factor has an OR (Odds Ratio) age value of 2.009. This result shows that the age variable provides a 2.009 times greater risk of prostate cancer incidence. The OR value of the age factor is the most significant of the other variables in influencing the incidence of prostate cancer.

Based on the analysis also known as Negelkerke R-square results of 0.072 or 7.2%. This shows that the magnitude of the topographic profile factor of rice fields around the residence and age on the incidence of prostate tumors is 7.2% while other variables outside the model such as family history, race, alcohol and smoking, duration of stay in residence, duration of environmental exposure, type of specific pollutant, and type of daily dietary menu may influence the other 92.8%.

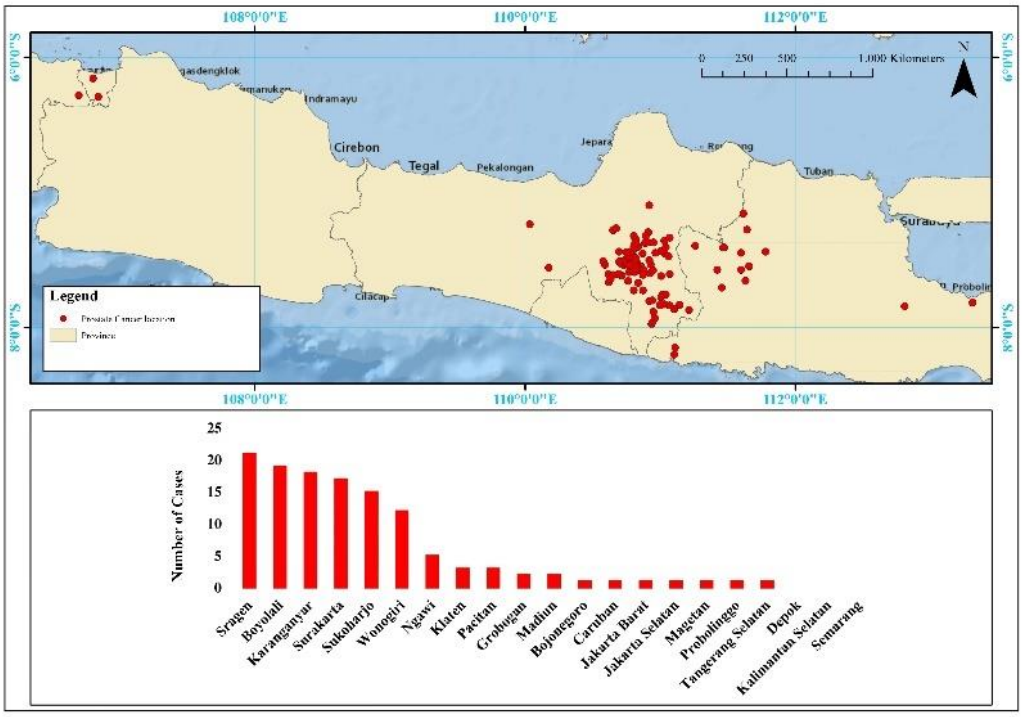

Figure 1. The distribution of prostate cancer cases from 2018 to 2023

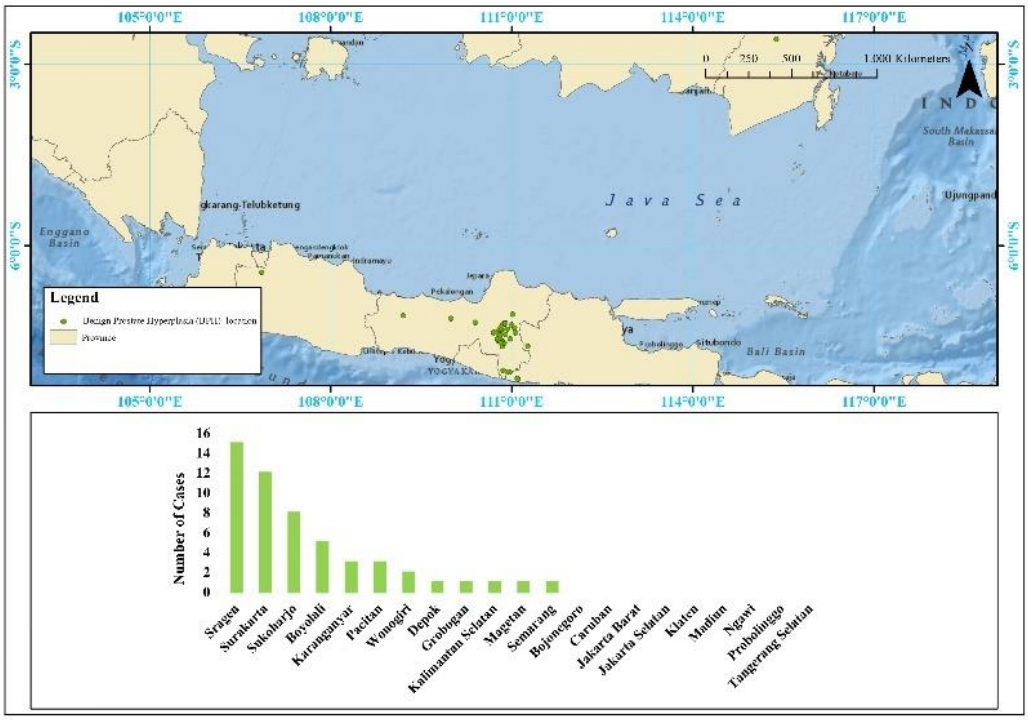

Figure 2. The distribution of BPH cases from 2018 to 2023

Table 1. Characteristics of Study Samples

Characteristic	Prostate Cancer (n= 124)		Benign Prostate Hyperplasia (n=53)	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Age				
<65 years	42	33,9	28	**52,8**
>65 years	82	**66,1**	25	47,2
Place of Residence				
Urban	72	**58,1**	31	**58,5**
Rural	52	41,9	22	41,5
Occupation				
Laborer	11	8,9	2	3,8
Retired	29	23,4	9	17,0
Farmer	18	14,5	10	18,9
Civil Servant	13	10,5	13	24,5
Private Employee	49	**39,5**	17	**32,1**
Self Employed	4	3,2	2	3,8
Topographical Profile of the Area of Rice Fields Around the Residence				
Narrow Rice Field (<39%)	67	**54,0**	38	**71,7**
Large Rice Field (>39%)	57	46,0	15	28,3
Lymphocyte Level				
Low (<25)	99	**79,8**	31	**58,5**
Normal (25-40)	25	20,2	22	41,5
High (>40)	0	0	0	0
Gleason Score				
Well-differentiated (1-6)	23	18,5	0	0
Moderate differentiated (=7)	46	37,1	0	0
Poorly differentiated (8-10)	55	**44,4**	**0**	**0**

Table 2. Risk factor of topographic profile of rice field area around the residence on prostate cancer incidence

Topography Profile Rice Field Area	Prostate Cancer		BPH		OR	CI 95%		P
	F (n)	(%)	F (n)	(%)		Lower	Upper	
<39%	67	**54**	38	**71,7**				
>39%	57	46	15	28,3	**2,155**	1.076	4,315	**0,028**
Total	124	100	53	100				

Table 3. Risk factor of age on prostate cancer incidence

Age	Prostate Cancer		BPH		OR	CI 95%		P
	F (n)	(%)	F (n)	(%)		Lower	Upper	
<65 years	42	33,9	28	**52,8**				
>65 years	82	**66,1**	25	47,2	**2,187**	1,136	4,210	**0,018**
Total	124	100	53	100				

Table 4. Risk factors of topographic profile of rice field area around the residence and age on prostate cancer incidence

Variable	Beta Coefficient	P value	OR (ExpB)	CI 95%		Negelkerke R-square
				Lower	Upper	
Topography Profile Rice Field Area	0,676	0,061	1,966	0,970	3,982	**0,072**
Age	0,698	**0,040**	**2,009**	1,033	3,910	
Constant	0,205	0,442	1,227			

Discussion

The prostate gland is a male hormone-responsive organ that is anatomically located near the urethra and vesica urinary, consisting of different zones such as the peripheral zone and the transitional zone (Coleman, 2018). The main function of the prostate gland is to complete the secretion of semen and keep sperm alive (Wasim et al., 2022). Prostate tumors can be malignant and cause prostate cancer (PCa), or can be benign and cause BPH. (Surya, 2022). More than 95% of prostate cancer cases are adenocarcinomas, mostly of acinar origin, while only a few are of ductal origin. In addition, a total of 80% of prostate adenocarcinomas arise from luminal or basal epithelial cells (with lower prevalence) in the peripheral area, which occupy more than 70% of the total prostate tissue (Wasim et al., 2022). Mutations in the DNA repair genes BRCA1, BRCA2, CDK12, ATM, FANCD2, and RAD51C are associated with prostate cancer incidence (Romadhon & Kurniati, 2024). PCa is a multifactorial disease influenced by genetic mutations, epigenetic changes, and inflammation that contribute to its progression (Pandareesh et al., 2021). Risk factors that are thought to cause prostate cancer consist of non-modifiable and modifiable factors. Non-modifiable factors include age (60-69 years), family history, and genetic predisposition. Modifiable risk factors include physical activity and sleep, dietary intake (specific diet, alcohol, and smoking), disease and treatment (circumcision, vasectomy, and infertility), environmental and occupational factors (environmental and chemical exposure), sexual activity, and marital status (Bergengren et al., 2023).

Influence of topographic profile characteristics of surrounding rice fields on the incidence of prostate cancer

Table 2 shows that prostate cancer samples live more in areas with a topographic profile of rice fields of less than 39% of the total area (67%), compared to areas with a topographic profile of rice fields of more than 39% of the total area (57%) with significant results (p-value = 0.028) between the topographic profile of rice fields around the residence with the incidence of prostate cancer. This shows that there is a significant effect between the incidence of prostate cancer and the topographic profile of rice fields around the residence. The area of Central Java is recorded at 3.25 million hectares, with the use of 30.4% of rice fields and 16.5% of housing and place of residence. This is evidence that the agricultural sector is still more dominant than the building sector (BPS Jawa Tengah, 2018). This is by the study of Pouresmaeili et al. (2015) in two groups of Iranian men diagnosed with prostate cancer and controls aged 50 to 75 years. The study analyzed residence and workplace, smoking habits, and drug consumption history. The results of this study suggest that environmental factors that influence prostate cancer incidence include residential location and exposure to pollutants. In order, the largest number of patients came from provincial capitals, large industrial cities, small towns, and rural areas (Pouresmaeili et al., 2015). A systematic study in the UK has analyzed 49 articles published from 1993 to 2015 with the keywords “pesticides” and “prostate cancer”. The study analyzed pesticide exposure activities and/or agricultural activities. Most (32 studies) showed a positive association between pesticide-specific exposure from agricultural areas and the incidence of prostate cancer, with estimates ranging from 1.01 to 14.1 across studies (Silva et al., 2016). A prospective cohort study in Korea was conducted by identifying 110 men with a diagnosis of prostate cancer and 256 men without prostate cancer. The study was conducted by calculating the serum concentrations of polychlorinated biphenyl (PCB) and organochlorine (OCP) compounds to determine the Hazard Ratio (HR) using the Cox regression model. Exposure to persistent pollutants (POPs) is also associated with etiologic causes of prostate cancer (Lim et al., 2017). In addition, the study of Flores et al. (2023), The study was conducted on black men in West Africa, Cameroon, and Nigeria aged 35 to 70 years. In this research, anthropometric, environmental, and epidemiological analyses were conducted through question surveys. The results of logistic analysis of pesticide exposure as a predictor of cancer diagnosis in the three countries found a significant effect in Nigerian participants with a p-value of 0.013 (Asto-Flores et al., 2023). In contrast to the study of Lemarchand et al. (2014) in farmers in France during the registration period 2005 to 2007 and reanalyzed in December 2009. Occupational risk factors were identified by collecting data on occupational history, agricultural exposures, and livestock exposures collected by questionnaire. Hazard ratios (HR) were determined by Cox regression analysis. Increased risk results were obtained in six activities: pasture, wheat/barley, and tobacco farming, as well as cattle, pig, and horse farming with an HR of 1.07. There was a non-significant relationship between prostate cancer risk

and pesticide use and pasture area (p=0.06) (Lemarchand et al., 2014). The topographic profile of rice fields around the residence shows an effect on the incidence of prostate cancer. Chronic exposure to low doses of pollutant elements in the air, water, and soil environment will accumulate in tissues over time and become an environmental-dependent pathology (Centeno et al., 2013). While most pesticide exposures are not mutagenic, certain pesticides contain EDs (Endocrine Disruptors) that can block testosterone hormonal receptors (Habibi et al., 2021). Androgen receptor (AR) signaling plays a role in the growth and progression of prostate cancer (Achmad, 2022). AR will signal ED within the prostate gland and contribute to the onset of prostate cancer and worsen progression (Corti et al., 2022).

Influence of age characteristics on prostate cancer incidence

Based on **Table 3,** most of the samples who experienced prostate cancer (PCa) were more than 65 years old (66.1%). This indicates that older age groups are more at risk of prostate cancer. Bivariate analysis showed a significant association (p-value = 0.018) between age and prostate cancer incidence. Prostate cancer and BPH respondents in this study had a mean age of 68.27 years with an age range of 45-94 years and a standard deviation of 9.8. This is by research conducted by Rawla (2019) on African-American men of all ages. Researchers analyzed incidence, mortality, etiology, risk factors, and prevention. The results of the study stated that the incidence rate of prostate cancer was close to 60% in men aged over 65 years (Rawla, 2019). In addition, Okebugwu's study (2013) was conducted on prostate cancer patients aged more than 65 years. This research conducted an epidemiological literature study on various countries in the world. The results of this study also showed a significant correlation between aging and the incidence of prostate cancer (p<0.005). The number of elderly men diagnosed with prostate cancer will continue to increase, especially individuals over the age of 65 (Okebugwu, 2023). A study by Abudoubari et al. (2023) was conducted on 105,135 patients with prostate cancer from 1975 to 2019 in the Surveillance, Epidemiology, and End Results Program (SEER) database. The study was not restricted to any particular age, race, and country of the patients. The mean age at diagnosis was 67.9 years with a median age of 68 years. Analysis was performed on the variables of age, tumor stage, race, PSA, and Gleason score as independent risk factors. The results found that the age groups of 15-54 and 55-64 years had a significant increase in prostate cancer incidence (p<0.005). Whereas the over-85 age group experienced a decrease (Abudoubari et al., 2023). In contrast, Somasundaram et al. (2022) in men in the United States from 2000-2018 in the age group of 60 to 85 years had different results. The study conducted an age, race, region, and rural analysis using data obtained from the National Program of Cancer Registries (NPCR) representing patients from all 50 states. The study reported a significant decline in prostate cancer incidence aged 40 years and above, with the steepest decline in the age group above 85 years (Somasundaram et al., 2022). The pathogenesis of prostate cancer has many theories. The most commonly used theory is the dysregulation of androgen receptors which have an important role in regulating prostate cell growth, PCa often progresses to the peripheral zone of the prostate (Coleman, 2018). Prostate cancer shows a complex correlation with age, with older adults being most affected (Okebugwu, 2023). The prostate gland needs the male hormone testosterone known as androgen (Mustafa et al., 2016). One type of androgen, testosterone, is converted to the form of dihydrotestosterone (DHT) by 5α-reductase to ligand to androgen receptors in the cytoplasm (Murray, 2021). DHT plays a role in enhancing macrophage cytotoxicity in prostate cancer cells via TRAIL (Tumor Necrosis Factor Related Apoptosis Inducing Ligand), suggesting a potential link between DHT, immune response, and prostate cancer progression (Lee et al., 2019). Adulthood is the peak of circulating testosterone and declines gradually in middle age and older (Moreau et al., 2020). At the age of 40 most men start to experience andropause (Kim et al., 2020). Decreased androgens in men can increase the expression of the BCL-2 (B Cell Lymphoma 2) family of proteins which are anti-apoptotic in the prostate epithelium. This occurs because increased expression of BCL-2 is a process of compensating for the loss of androgens in the prostate by increasing the induction of prostate luminal epithelial cells (Ali & Kulik, 2021). The study by Calvocoressi highlighted advanced age correlates with more malignant prostate cancer, pointing to increased BCL-2 expression, p53 mutations, and high microvascular density (Calvocoressi et al., 2018). AR gene polymorphisms are associated with prostate cancer incidence, age of onset, and response to therapy, and affect malignancy (Bosch et al., 2002). Malignant cells will continue to proliferate and form macroscopic and enlarged nodules, which can remain in the prostate tissue or penetrate the prostate capsule and extend outside the prostate tissue by hematogenically draining the prostatic venous plexus to the vertebral veins (IAUI, 2022).

Conclusion

The age factor has more risk factors for prostate cancer incidence than the topographic profile of rice fields with a significant p-value of 0.040 and an Odd Ratio of 2.009. In addition, the factors of the topographic profile of rice fields around the residence and age have an influence of 7.2% on the incidence of prostate cancer, while the other 92.8% may be influenced by other variables outside the model.

The implications of this study include the need for preventive measures with early screening in the group of men aged more than 65 years because they have a high risk of prostate cancer. Significant results on residential topography can be used as a reference. Residential topography can be a preliminary finding to look at the specific situation in the residential such as the type of pollutant, duration of exposure, and type of daily diet in the location.

Conflict of Interest

No potential competing interest was reported by the authors. research.

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Author contribution

AN and YPK have been involved in the conception and design of the study, data collection, analysis and interpretation of data, drafting and revising the article, also completion approval of the research manuscript to be submitted.

References

Abudoubari, S., Bu, K., Mei, Y., Maimaitiyiming, A., An, H., & Tao, N. (2023). Prostate cancer epidemiology and prognostic factors in the United States. *Frontiers in Oncology*, *13*. https://doi.org/10.3389/fonc.2023.1142976

Achmad, N. (2022). *Hubungan Ekspresi Programmed Death-Ligand 1 (PD-L1) dengan Grading Adenokarsinoma Prostat*. Fakultas Kedokteran, Universitas Hasanuddin.

Ali, A., & Kulik, G. (2021). Signaling Pathways That Control Apoptosis in Prostate Cancer. *Cancers*, *13*(5), 937. https://doi.org/10.3390/cancers13050937

Asto-Flores, E., Emeka, I., Ademola, P., Jibrin, P., Faruk, M., Sowumi, A., Fatiregun, O., Blaise, N., Oladoyinbo, C., Okoye, I., Salako, A. A., Omonisi, A., Bassey, I. E., Adeniji, K., Asura, N. H., Kaninjing, E., Kukoyi, O., Fathi, P., Enuka, R., … Odedina, F. (2023). Abstract 1213: Impact of pesticide exposure in West African Black men within the United States, Cameroon, and Nigeria. *Cancer Research*, *83*(7_Supplement), 1213–1213. https://doi.org/10.1158/1538-7445.AM2023-1213

Bergengren, O., Pekala, K. R., Matsoukas, K., Fainberg, J., Mungovan, S. F., Bratt, O., Bray, F., Brawley, O., Luckenbaugh, A. N., Mucci, L., Morgan, T. M., & Carlsson, S. V. (2023). 2022 Update on Prostate Cancer Epidemiology and Risk Factors—A Systematic Review. *European Urology*, *84*(2), 191–206. https://doi.org/10.1016/j.eururo.2023.04.021

Bosch, D. N., Galván, J. J. C., Ponce, N. C., & Díaz-Chico, B. N. (2002). Prostate cancer and the androgen receptor gene. *Revista de Oncología*, *4*(5), 228–240. https://doi.org/10.1007/BF02732507

BPS Jawa Tengah. (2018). *Luas Lahan Menurut Kabupaten/Kota di Jawa Tengah Tahun 2010 (ha)*. Badan Pusat Statistik Provinsi Jawa Tengah. https://jateng.bps.go.id/statictable/2015/02/09/656/luas-penggunaan-lahan-menurut-kabupaten-kota-di-jawa-tengah-tahun-2010-ha-.html

Calvocoressi, L., Uchio, E., Ko, J., Radhakrishnan, K., Aslan, M., & Concato, J. (2018). Prostate cancer aggressiveness and age: Impact of p53, BCL-2, and microvessel density. *Journal of Investigative Medicine*, *66*(8), 1142–1146. https://doi.org/10.1136/jim-2018-000804

Centeno, J. A., Mullick, F. G., Ishak, K. G., Franks, T. J., Burke, A. P., Koss, M. N., Perl, D. P., Tchounwou, P. B., & Pestaner, J. P. (2013). Environmental Pathology. In *Essentials of Medical Geology* (pp. 569–596). Springer Netherlands. https://doi.org/10.1007/978-94-007-4375-5_25

Chen, R., Ren, S., Yiu, M. K., Fai, N. C., Cheng, W. S., Ian, L. H., Naito, S., Matsuda, T., Kehinde, E., Kural, A., Chiu, J. Y., Umbas, R., Wei, Q., Shi, X., Zhou, L., Huang, J., Huang, Y., Xie, L., Ma, L., … Sun, Y. (2014). Prostate Cancer in Asia: A Collaborative Report. *Asian Journal of Urology*, *1*(1), 15–29. https://doi.org/10.1016/j.ajur.2014.08.007

Coleman, W. B. (2018). Molecular Pathogenesis of Prostate Cancer. In *Molecular Pathology* (pp. 555–568). Elsevier. https://doi.org/10.1016/B978-0-12-802761-5.00025-0

Corti, M., Lorenzetti, S., Ubaldi, A., Zilli, R., & Marcoccia, D. (2022). Endocrine Disruptors and Prostate Cancer. *International Journal of Molecular Sciences*, *23*(3), 1216. https://doi.org/10.3390/ijms23031216

Gianessi, L. P. (2014, January 1). *Importance of Pesticides for Growing Rice in South and South East Asia*. Crop Life. https://croplife.org/case-study/importance-of-pesticides-for-growing-rice-in-south-and-south-east-asia/

Graham, L. S., Lin, J. K., Lage, D. E., Kessler, E. R., Parikh, R. B., & Morgans, A. K. (2023). Management of Prostate Cancer in Older Adults. *American Society of Clinical Oncology Educational Book*, *43*. https://doi.org/10.1200/EDBK_390396

Habibi, A., Risqiyani, S. Z., & Putri, D. A. S. (2021). Potensi Chimeric Antigen Receptor T Cell (CAR-T Cell) dengan Target Prostate-Specific Membrane Antigen (PSMA) Termodifikasi CRISPR/Cas9 sebagai Terapi Kanker Prostat. *JIMKI: Jurnal Ilmiah Mahasiswa Kedokteran Indonesia*, *9*(1), 23–37. https://doi.org/10.53366/jimki.v9i1.321

Hahn, P., Ian, C., Smith, Leboldus, L., Littman, C., Ray, L., Somorjai, & Bezabeh, T. (2014). The Classification of Benign and Malignant Human Prostate Tissue by Multivariate Analysis of 1H Magnetic Resonance Spectra. *Cancer Research*, *57*(16), 339–401.

IAUI. (2022). *Panduan Penanganan Kanker Prostat*. Ikatan Ahli Urologi Indonesia.

ISUO. (2015). *Panduan Penatalaksanaan Castrate Resistant Prostate Cancer Tahun 2015*. https://iaui.or.id/uploads/guidelines/2015_Panduan_Penatalaksanaan_Castrate_Resistant_Prostate_Cancer.pdf

Kim, D. W., Chen, M.-H., Huland, H., Graefen, M., Tilki, D., & D'Amico, A. V. (2020). Association of Age with Risk of Adverse Pathological Findings at Radical Prostatectomy in Men with Gleason Score 6 Prostate Cancer. *JAMA Network Open*, *3*(4), e202041. https://doi.org/10.1001/jamanetworkopen.2020.2041

Kireyev, A., & Leonidov, A. (2020). *Operationalizing Inclusive Growth: Per-Percentile Diagnostics to Inform Redistribution Policies, WP/20/50, March 2020*.

Kishanrao, S. (2022). Prostate Health in India (BPH & Prostate Cancer). *Archives of Cancer Science and Therapy*, *6*(1), 009–017. https://doi.org/10.29328/journal.acst.1001028

Ledda, C., Bracci, M., Lovreglio, P., Senia, P., Larrosa, M., Martínez-Jarreta, B., & Rapisarda, V. (2021). Pesticide Exposure and Gender Discrepancy in Breast Cancer. *European Review for Medical and Pharmacological Sciences*, *25*(7), 2898–2915. https://doi.org/10.26355/eurrev_202104_25543

Lee, G. T., Kim, J. H., Kwon, S. J., Stein, M. N., Hong, J. H., Nagaya, N., Billakanti, S., Kim, M. M., Kim, W.-J., & Kim, I. Y. (2019). Dihydrotestosterone increases the cytotoxic activity of macrophages on prostate cancer cells via TRAIL. *Endocrinology*. https://doi.org/10.1210/en.2019-00367

Leenders, van G. J. L. H., Verhoef, E. I., & Hollemans, E. (2020). Prostate Cancer Growth Patterns Beyond the Gleason Score: Entering a New Era of Comprehensive Tumour Grading. *Histopathology*, *77*(6), 850–861.

https://doi.org/10.1111/his.14214

Lemarchand, C., Tual, S., Levêque-Morlais, N., Perrier, S., Guizard, A.-V., Velten, M., Rigaud, E., Baldi, I., & Lebailly, P. (2014). 0206 Prostate cancer risk among French farmers in the AGRICAN cohort. *Occupational and Environmental Medicine*, *71*(Suppl 1), A86.3-A87. https://doi.org/10.1136/oemed-2014-102362.269

Lim, J., Nam, C., Yang, J., Rha, K. H., Lim, K.-M., & Jee, S. H. (2017). Serum Persistent Organic Pollutants (POPs) and Prostate Cancer Risk: A Case-Cohort Study. *International Journal of Hygiene and Environmental Health*, *220*(5), 849–856. https://doi.org/10.1016/j.ijheh.2017.03.014

Moreau, K. L., Babcock, M. C., & Hildreth, K. L. (2020). Sex Differences in Vascular Aging in Response to Testosterone. *Biology of Sex Differences*, *11*(1), 18. https://doi.org/10.1186/s13293-020-00294-8

Mostofi, F. K., Isabelll, A. S., Sobin, L. H., & Davis, C. J. Jr. (2014). *Histological Typing of Prostate Tumours* (1st ed., Vol. 1). World Health Organization.

Murray, T. B. J. (2021). The Pathogenesis of Prostate Cancer. In *Prostate Cancer* (pp. 29–42). Exon Publications. https://doi.org/10.36255/exonpublications.prostatecancer.pathogenesis.2021

Mustafa, M., Salih, AF., Illzam, EM., Shafira, A., Suleiman, M., & Hussain, S. (2016). Prostate Cancer: Pathophysiology, Diagnosis, and Prognosis. *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, *15*(6), 04–11. https://doi.org/10.9790/0853-1506020411

Okebugwu, P. N. (2023). AGING: A SYSTEMATIC REVIEW ON THE CORRELATION BETWEEN GERIATRIC DISEASES AND PROSTATE CANCER. *Agrobiological Records*, *11*, 55–66. https://doi.org/10.47278/journal.abr/2023.009

Pandareesh, M. D., Kameshwar, V. H., & Byrappa, K. (2021). Prostate Carcinogenesis: Insights in Relation to Epigenetics and Inflammation. *Endocrine, Metabolic & Immune Disorders - Drug Targets*, *21*(2), 253–267. https://doi.org/10.2174/1871530320666200719020709

Pouresmaeili, F., Hosseini, S. J., Farzaneh, F., Karimpour, A., Azargashb, E., Yaghoobi, M., & Kamarehei, M. (2015). Evaluation of Environmental Risk Factors for Prostate Cancer in a Population of Iranian Patients. *Asian Pacific Journal of Cancer Prevention*, *15*(24), 10603–10605. https://doi.org/10.7314/APJCP.2014.15.24.10603

Ragin, C., Davis-Reyes, B., Tadesse, H., Daniels, D., Bunker, C. H., Jackson, M., Ferguson, T. S., Patrick, A. L., Tulloch-Reid, M. K., & Taioli, E. (2013). Farming, Reported Pesticide Use, and Prostate Cancer. *American Journal of Men's Health*, *7*(2), 102–109. https://doi.org/10.1177/1557988312458792

Rawla, P. (2019). Epidemiology of Prostate Cancer. *World Journal of Oncology*, *10*(2), 63–89. https://doi.org/10.14740/wjon1191

Romadhon, Y. A., & Kurniati, Y. P. (2024). *Pathway Pengaruh Lingkungan dalam Inisiasi dan Progresivitas Kanker Tulang dan Jaringan Lunak* (1st ed., Vol. 1). Muhammadiyah University Press (MUP).

Romadhon, Y. A., Kurniati, Y. P., Jumadi, J., Alesheikh, A. A., & Lotfata, A. (2024). Analyzing Socio-Environmental Determinants of Bone and Soft Tissue Cancer in Indonesia. *BMC Cancer*, *24*(1), 206. https://doi.org/10.1186/s12885-024-11974-8

Shrivastava, A., & Gupta, V. (2012). Various treatment options for benign prostatic hyperplasia: A current update. *Journal of Mid-Life Health*, *3*(1), 10. https://doi.org/10.4103/0976-7800.98811

Siegel, R. L., Giaquinto, A. N., & Jemal, A. (2024). Cancer Statistics, 2024. *CA: A Cancer Journal for Clinicians*, *74*(1), 12–49. https://doi.org/10.3322/caac.21820

Silva, J. F. S., Mattos, I. E., Luz, L. L., Carmo, C. N., & Aydos, R. D. (2016). Exposure to Pesticides and Prostate Cancer: Systematic Review of The Literature. *Reviews on Environmental Health*, *31*(3). https://doi.org/10.1515/reveh-2016-0001

Somasundaram, E., Lang, J., Jambunathan, S., Hadziahmetovic, M., Ukaegbu Oke, O., Petros, F. G., & Ekwenna, O. (2022). National trends in incidence of prostate cancer by age, ethnicity, region, and rurality from 2000-2018: An analysis of US NPCR Database. *Journal of Clinical Oncology*, *40*(16_suppl), e17054–e17054. https://doi.org/10.1200/JCO.2022.40.16_suppl.e17054

Song, J., & Kuo, C. (2021). Do pesticide residues have enduring negative effect on macroinvertebrates and vertebrates in fallow rice paddies. *Cold Spring Harbor Laboratory*.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Surya, K. (2022). Prostate Cancer. In *Fundamentals of Cancer Detection, Treatment, and Prevention* (pp. 355–370). Wiley. https://doi.org/10.1002/9783527838561.ch16

Toivanen, R., & Shen, M. M. (2017). Prostate Organogenesis: Tissue Induction, Hormonal Regulation, and Cell Type Specification. *Development*, *144*(8), 1382–1398. https://doi.org/10.1242/dev.148270

Wasim, S., Lee, S.-Y., & Kim, J. (2022). Complexities of Prostate Cancer. *International Journal of Molecular Sciences*, *23*(22), 14257. https://doi.org/10.3390/ijms232214257

Xia, S.-J., Cui, D., & Jiang, Q. (2012). An overview of prostate diseases and their characteristics specific to Asian men. *Asian Journal of Andrology*, *14*(3), 458–464. https://doi.org/10.1038/aja.2010.137