Appropriate Description of Probability Distribution of Prostrate Specific Antigen (PSA): An Aid to Early Detection of Prostrate Cancer

Chrysogonus Chinagorom Nwaigwe [a*], Chukwudi Justin Ogbonna [a] and Emmanuel Uchechukwu Oliwe [b]

[a] Department of Statistics, Federal University of Technology, Owerri, Nigeria.
[b] Department of Statistics, Federal University of Technology, Owerri, Imo State Polytechnic, Omuma, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

Abstract

Prostrate cancer has been observed to be a worrisome ailment among adult males across the globe over some decades. Just like any other ailment, its early detection and treatment gives the patient a better chance of survival. Measuring the Prostrate specific antigen (PSA) of the patients at specified intervals is one of the techniques of detecting the onset of prostrate cancer. This paper attempts to obtain the most appropriate probability distribution of prostrate specific antigens (PSA) that gives the best estimates of the parameters of the distribution. The age specific probabilities of patients with prostrate specific antigen (PSA)>4.0ng/ml were calculated. The results show that the most appropriate distribution among the distributions fitted is the Burr distribution. The probability of observing a PSA greater than 4.0 ng/ml in adult males above the age of

---

Corresponding author: Email: chrysogonusnwaigwe@gmail.com, chrysogonus.nwaigwe@futo.edu.ng;

45 years was seen to be moderately high (0.68) with a median PSA of 8.30 ng/ml and an inter quartile range of 16.40. The results also show that PSA of 60.0 ng/ml and above were exceptional cases that require urgent attention. It was observed that men whose ages are between 60 and 80 years have higher chances of having PSA values greater 4.0ng/ml with men between 60 and 75 years having the highest chances. It is therefore suggested that men with PSA higher than 4.0ng/ml between 60 and 80 years of age may not be subjected to needle biopsies but be referred directly for digital rectal examinations.

1 Introduction

One of the characteristics of living things is growth. Postlethwait et al. [1] defined growth as the division and enlargement of cells [1]. Gene is responsible for the control of the growth of this cell. When these genes are affected by some factors which disturb its proper functioning, it loses control to regulate cell growth and therefore allows cells to grow awkwardly which endangers its surrounding. This mutation of genes, regulating cell proliferation is called CANCER [2].

Carol et al. [3] defined cancer as a group of diseases that causes cells in the body to change and grow out of control, in other words, a growth disorder of cells [3]. It starts when an apparently normal cell grows uncontrollably and invasively, resulting to a cluster of cells (lump) called tumour, mostly move or metastases to distance site [2]. Cancer is named after the part of the body where the tumour originated, for instance prostate cancer, breast cancer, etc.

According to [4], National Cancer Institute (NCI) defined Prostate cancer as the cancer formed in the tissues of the prostate. In human being, the prostate gland which is about the size of a golf ball and spongy in texture is located at the base of the bladder, and it holds the fusion of the ejaculatory duct with the urethra from the urinary bladder [2]. It secretes an alkaline fluid in the semen that neutralises the acids in the female reproductive system, [1]. The most common type of prostate cancer is Adenocarcinomas. Other types include Small Cell Carcinomas, Neuroendocrine tumors, Transitional Cell Carcinomas and Sarcomas (American Cancer Society).

Some other risk factors that predispose a male child to suffer from prostate cancer during his life time include: excessive drinking of alcohol, smoking, heredity, genetic changes, occupation, obesity, prostatitis, vasectomy [5]. It has been hypothesized that androgenic hormones play a role in its pathogenesis due to the fact that men with 5-alpha reductase deficiency do not develop prostate cancer [6].

The world is saddened with the rising incidence of Prostate Cancer. An estimated 913000 men were diagnosed of Prostate Cancer worldwide in 2008 and developed countries had more than two-third of these cases [7]. In Nigeria, Prostate Cancer was the most common cancer among men with about 21.7 percent from Ibadan Cancer Registry (IBCR) report and 28 percent from Abuja Cancer Registry (ABCR) report [8].

There are different tests available for early detection of prostate cancer. These include: Prostate Specific Antigen (PSA) test, Digital Rectal Examination (DRE) test and Tissue Biopsy. PSA was discovered in the late 1970s and was introduced as a serum test in 1980 after it was demonstrated to be related positively to the presence of prostate cancer [9]. PSA is a 34kDa glycoprotein enzyme produced by the columnar and ductal prostatic epithelial cells of the prostate tissue which liquidizes the semen. It consists of 240 amino acid residues and 4 sugar chains, and its half-life in Blood is relatively long, spanning 2.2 – 3.2 days [10]. It circulates at low levels in the Blood stream where it can be measured. Elevated levels can occur in men with benign prostatic hypertrophy (BPH), prostatitis, urinary tract infection, prostatic infarction and prostate cancer. It has also been observed that, its increase may occur after prostate biopsy, aggressive digital rectal examination (DRE), ejaculation, urethral catheterization, physical exercise and other kind of stimulation [11].

The high plasmatic levels of this PSA (PSA > 4 ng/mL) is used as a biomarker in diagnosing, staging and monitoring prostate cancer patients [6]. In 1986, the US Food and Drug Administration approved its use for monitoring men with prostate cancer. Ever since then, serum PSA with clinical symptoms, digital rectal examination (DRE) and sometimes ultrasound examination has become the most ways for screening men of

prostate cancer [9]. This threshold of 4.0 ng/ml was recommended as the level at which a man should undergo prostate biopsy, though it has a probability of 25% that a man having a PSA of 4.0 ng/ml has prostate cancer [12]. It is also worthy of note that PSA of a healthy elderly male with no evidence of prostate cancer increases by 3.2% annually [13].

The digital rectal examination (DRE) involves the doctor placing a gloved and lubricated finger inside the rectum of his patient and feels for lumps or abnormal firmness in the prostate gland. However, men without cancer have also shown an elevated level of PSA. Tissue biopsy seems to be more effective for diagnosis and confirmation of the presence of prostate cancer. It involves the removal of a small tissue from the suspected affected region of the disease (prostate) as a sample for further examination about the suspected disease [14]. It is worthy of note that early detection of prostate cancer increases the chance of effective treatment.

The effects of biological and medical variables, occasioned by random factors have prolonged the anticipated solution to prostate cancer, thereby creating more room for research. When events or factors are random, it is known that deterministic approaches to their studies yield less accurate results and lack predictive power. This drawback can be circumvented by undertaking probabilistic approaches to their study. Although, there are great research works on clinical practises, pathology, diagnosis and management of prostate cancer via its biomarker, the serum PSA level, some of these research works used descriptive statistics such as tables and chats to undertake their studies. Others applied statistical tools such as logistic regression, correlation and ratio for the relationship between PSA and other biological factors. However, research works that describe the probability distribution of PSA of prostate cancer patients remain uncommon. Nonetheless, understanding the appropriate probability distribution of PSA will facilitate its prediction and early dictation of prostate cancer. When the probability distribution of PSA is known, the probability that a man with a given PSA level has prostrate cancer can be calculated.

2 Literature Review

Prostate – Specific Antigen (PSA) has been used for prostate cancer detection since 1994 [12]. Nogueira et al. [12] opined that since the last two decades, the usage of PSA has revolutionized abilities to diagnose, treat and manage prostate cancer patients which led to a substantial reduction in the proportion of men suffering from the metastatic of this disease and also accounted for about 32.5% reduction in the Age – adjusted prostate cancer mortality rate through 2003 [12].

Farazi et al. [15] observed that prostate cancer has a prevalence of 1046 per 100, 000 in men over the age of 40 years in Lagos [15]. They observed that the contributing factors include: gaps in awareness and perception of susceptibility to prostate cancer, and low level of screening which were due to age, educational level, and income of these men.

Akakura [10] observed that "higher levels of PSA were associated with a higher probability of diagnosing prostate cancer" [10]. According to [10], needle biopsies detect prostate cancer in 20% – 30% of cases with PSA level of 4.1 – 10.0ng/ml and 30% – 50% or more of cases higher than 10.0ng/ml. He recommended that all cases showing PSA levels of 4.1ng/ml or more be referred to specialist urologist as well as those showing PSA levels of 4.0ng/ml or less for positive findings on digital rectal examination (DRE).

Erol et al. [16] showed that the use of free/total PSA ratio in patients with PSA levels of 4 – 10 ng/ml enhances the specificity of PSA screening and decreases the number of unnecessary biopsies [16].

Atish et al. [17] evaluated the free to total PSA ratio to distinguish between the Benign Prostate Hyperplasia (BPH) and prostate cancer patients in and around SRM University and found that though they were diagnosed as BPH and as cancer, using PSA determination, the free to total PSA ratio were decreased significantly in cancer patients than BPH. They suggested that PSA should be used more appropriately to distinguish between BPH and prostate cancer and to detect cancer of the prostate at an early stage.

Kim [18] performed a linear regression to analyse a relationship between PSA fluctuation and other factors such as Age, PSA, PSA density (PSAD) and prostate volume, and found out that PSA level was significantly correlated with PSA fluctuation [18].

Vollmer [9] used Bayes probability rule to calculate age and serum prostate – specific antigen (PSA) and specific positive predictive values (PPVs) for prostate cancer [9]. According to [9], the PPV was the conditional probability of having prostate cancer, given a value of PSA and a particular Age group. He found out that Bayes PPV suggested that in younger men, cut off points defining an elevated PSA level should be raised rather than lowered as could be seen from the three age groups (50 – 59, 60 – 69, and 70 – 79 years).

3 Methodology

The methods employed in this study are: (i) using histogram and probability plots to identify the probability distributions similar to the empirical distribution; (ii) comparison of the empirical cumulative density function with theoretical cumulative density function of some identified probability distribution functions with similar shapes and (iii) test of goodness of fit of the empirical data using Kolmogorov –Smirnov (K-S) test.

3.1 Data collection

The data used for this study are secondary data, collected from unpublished record of one hundred and two (102) patients' case files from Jone Medical Centre, Owerri; a specialist hospital for the treatment and management of Prostate Cancer. The variable of interest was the Prostate-Specific Antigen (PSA in ng/ml) of the patients. A mere inspection of the data collected show that there were outliers in the data which could lead to a positively skewed distribution. Therefore, in fitting distributions to the data, positively skewed distributions such as the Burr, Gamma and Weibull distributions would be considered.

3.2 Empirical cumulative distribution function (ECDF)

Let a given random sample of size n be $x_1, x_2, \ldots, x_n$ and let $x_{(1)} < x_{(2)} < \cdots < x_{(n)}$ be the ordered statistics. Suppose that the distribution of X is $F(x)$, then, the empirical cumulative distribution function (ECDF) is $F_n(x)$ as defined by [19]:

$$F_n(x) = P(X \leq x)$$
(3.1)

$$P(X \leq x) = \frac{X_i \leq x}{n}$$
(3.2)

where,

X_i = number of observations less than or equal to x.
n = total number of observations.

3.3 Determination of age specific probabilities

Age specific probabilities are helpful in determining the age group in which an abnormal condition has a higher chance of occurring.

Let X denote the event that a patient's PSA is greater than 4.0.

Let Z_i denote the number of PSA>4.0 ng/ml in age group i;

Let n be the total number of PSA>4.0ng/ml in the sample; then, the probability that PSA>4.0ng/ml in age group i is given by

$$P_i(X > 4.0) = \frac{Z_i}{n}$$
(3.3)

3.4 Kolmogorov – smirnov test

According to [19], Kolmogorov – Smirnov test statistic is based on measuring the vertical difference between the empirical cumulative distribution function of the sampled data $F_n(x)$ and the hypothesised theoretical probability distribution $F(x)$.

Let,

$$D_n = d_n(X_n ..., X_n) = \sup_{-\infty < x < \infty}[F_n(x) - F(x)]$$

(3.4)

The test statistic is given as,

$$K_n = \sqrt{n} \sup_{-\infty < x < \infty}[F_n(x) - F_0(x)],$$

(3.5)

where, $F_0(x)$ is the theoretical probability distribution stated under the null hypothesis.

3.4.1 Test of hypothesis

The following set of hypotheses is tested:

H_0: The PSA data fit the stated probability distribution.
H_1: The PSA data do not fit the stated probability distribution.

3.4.2 Decision rule

The null hypothesis H_0 would be rejected if *p–value* is less than 0.05 at 5% level of significance, otherwise the null hypothesis would not be rejected. Among the theoretical distributions, the distribution with the highest *p–value* would be considered the most appropriate distribution that fits the PSA data. On the other hand, reject H_0 if and only if $K_n > K_{1-\alpha}$, where, $K_{1-\alpha}$ is the tabulated value of Kolmogorov-Smirnov statistic.

3.4.3 Burr distribution

Let *X* be a positive random variable having Burr distribution, the probability density function is given by [20]:

$$kcx^{c-1}(1+x^c)^{-(k+1)}, \quad x > 0$$

(3.6)

where k and c are shape parameters.

According to [20], the maximum likelihood estimators of k and c can be obtained by solving the following equations numerically,

$$\hat{k} = \frac{n}{\sum_{i=1}^{n} \ln(1 + x_i^{\hat{c}})}$$

(3.7)

and

$$\frac{n}{\hat{c}} + \sum_{i=1}^{n} \ln(x_i) - \left[\frac{n}{\sum_{i=1}^{n} \ln(1 + x_i^{\hat{c}})} + 1 \right] \sum_{i=1}^{n} \frac{x_i^{\hat{c}} \ln(x_i)}{1 + x_i^{\hat{c}}} = 0$$

(3.8)

3.4.4 Gamma distribution

Suppose $X_1, X_2, \dots, X_n$ are random sample of size n from a population that is a Gamma distribution, the probability density function (PDF) is defined by [21] and [22] as:

$$f(x \mid \alpha, \beta) = \frac{x^{\alpha-1}}{\beta^\alpha \Gamma(\alpha)} e^{-\frac{x}{\beta}}, \ x > 0, \ \beta > 0 \tag{3.9}$$

Where:

α = shape parameter;
β = scale parameter.

The maximum likelihood estimators of α and β are as given in [22]:

$$\hat{\alpha} = \frac{n\sum_{i=1}^{n} x_i}{n\sum_{i=1}^{n} x_i \ln(x_i) - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} \ln(x_i)} \tag{3.10}$$

$$\hat{\beta} = \frac{1}{n^2}\left[n\sum_{i=1}^{n} x_i \ln x_i - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} \ln x_i \right] \tag{3.11}$$

3.4.5 Weibull distribution

Considering the Weibull probability density function (pdf) given by [23] and [24]:

$$f_X(x) = \frac{\beta}{\alpha}\left(\frac{x}{\varepsilon}\right)^{\beta-1} e^{-\left(\frac{x}{\alpha}\right)^\beta}, \ \alpha > 0, \ \beta > 0, \ x > 0 \tag{3.12}$$

where β is the shape parameter and α is the scale parameter.

Thus, the maximum likelihood estimators of the scale and shape parameters of a Weibull distribution are given as in [25]:

$$\hat{\alpha}^2 = \frac{1}{n}\sum_{i=1}^{n} x_i^\beta \tag{3.13}$$

$$\frac{1}{\beta} = \frac{\sum_{i=1}^{n} x_{ii}^{\hat{\beta}} \log(x_i)}{\sum_{i=1}^{n} x_i^{\hat{\beta}}} - \frac{1}{n}\sum_{i=1}^{n} \log(x_i) \tag{3.14}$$

where n is the sample size.

4 Results and Discussion

In this section, PSA data collected from the hospital folders of some male patients were described and fitted to probability distributions. Kolmogorov - Smirnov goodness of fit test was used to identify the best probability distribution suitable for the PSA data. Description and analysis of the data were done with the help of Statistical Package for Social Sciences Version 20.0 (SPSS 20.0) and MATLAB R2016a.

Table 1. Data on prostate specific–antigen (PSA in ng/ml) of 102 patients

6.7	5.2	0.4	5.5	9.9	4.7	13.8	12.3	53.2	27.
3.5	4.2	0.5	4.1	5.9	5.5	10.9	0.1	0.2	50.0
120.0	40.8	8.6	12.5	37.2	3.6	2.0	50.3	6.7	14.5
5.7	5.1	4.0	1.1	0.2	10.3	10.9	5.0	7.4	15.6
0.1	7.2	5.3	17.4	1.9	2.1	78	0.5	8	3.5
0.2	88.2	16.2	0.4	14.3	20.2	13.0	12.4	4.0	6.0
37.0	7.8	20.0	14.5	10.4	5.3	9.3	3.0	35.0	3.5
3.8	32.3	36.7	1.5	35.0	32.2	36.2	1.0	4.9	18.0
44.7	8.0	0.1	63.5	4.6	115.0	0.7	118.0	80.2	0.1
12.4	22.7	0.2	16.7	7.9	10.0	83.0	0.4	8.8	25.0
10.0	40.4								

Source: Unpublished Record of Jone Medical Centre, Owerri, Imo State, Nigeria

4.1 Description and estimation of the parameters of the PSA data

In this section the PSA data are described graphically and the parameters of the distribution estimated.

Table 2. Description of the data on the PSA of the patients

	N	Minimum	Maximum	Median	Inter quartile Range	Skewness	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error
PSA	102	0.1000	120.00	8.30	16.40	2.331	0.239

Table 2 shows that the minimum and maximum values of PSA recorded from the patients were 0.1ng/ml and 120ng/ml respectively with a median PSA value of 8.30ng/ml and inter quartile range of 16.40 ng/ml. Rawla et al. (2019) opined that a PSA > 4.0ng/ml is a biomarker for diagnosing, staging and monitoring prostate cancer patients [6]. Akakura (2004) stated that a higher level of PSA was associated with a higher chance of prostate cancer with a needle biopsy detecting prostate cancer in 30% to 50% or more cases higher than 10.0ng/ml [10]. Thus, this median level of PSA 8.30ng/ml in Table 2 suggests a high risk of prostate cancer.

The coefficient of skewness of 2.331 shows that the distribution is positively skewed (this accounts for the use of the median as the measure of central tendency);. a distribution whose coefficient of skewness is greater than zero is positively skewed, while coefficient of skewness of less than zero is negatively skewed distribution [19]. This implies that the PSA values are not evenly clustered around their mean value; but rather, majority of the values are less than the mean value.
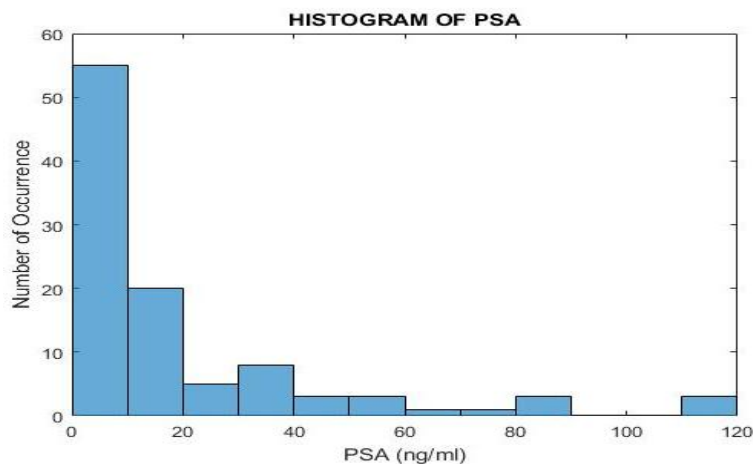

Fig. 1. Graphical representation of the PSA Data

Fig. 1.shows that men whose PSA values are within the range, 0.0ng/ml ≤ PSA < 10.0 ng/ml are 55 in number, followed by 20 men whose PSA are within the range, 10.0ng/ml ≤ PSA < 20.0ng/ml. The histogram also shows that PSA above 60ng/ml are exceptional and rare cases. The histogram depicts the positive skewed nature of the PSA data.
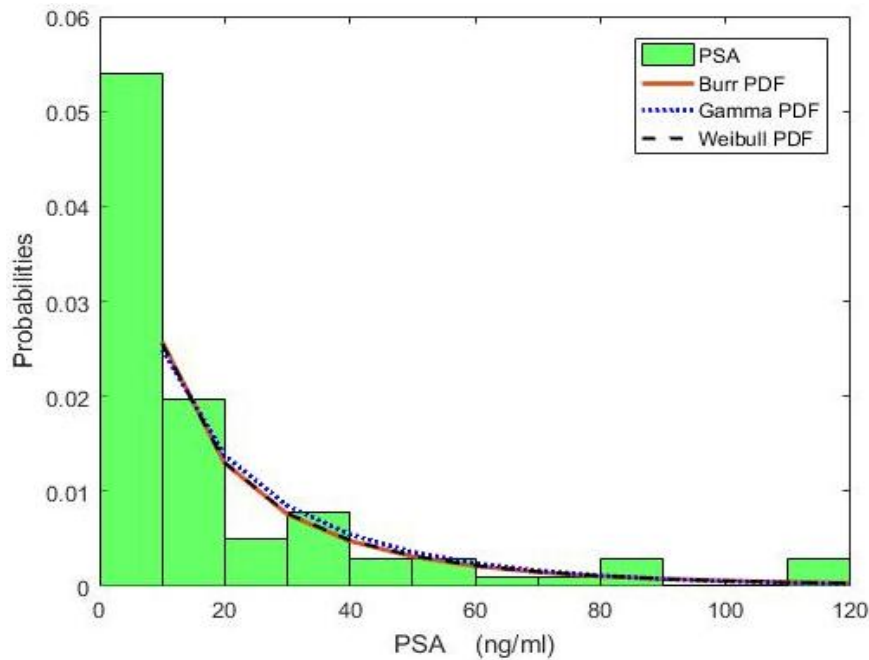

Fig. 2. Graphical Representation of the Fit of Some Probability distributions to the PSA Data

Fig. 2 shows that the Webull and Burr distributions seem to fit the data better than the Gamma distribution. This is because, the polygon showing the empirical distribution of the PSA data coincided with the polygons showing the theoretical distributions of the Burr and Weibull distributions at most points on the graph.

4.2 Test of hypothesis on the PSA data

The estimates of the parameters for the hypothesized probability distributions as well as Kolmogorov – Smirnov test are given in Table 3 below:

Table 3. Parameter estimates and kolmogorov – smirnov test from the PSA data

Probability Distribution	Parameters	Log-Likelihood Estimate	Kolmogorov – Smirnov Test		
			H	**P**	**KSSTAT**
Burr	$\hat{\tau} = 0.736557$ $\hat{\alpha} = 31.1091$	–389.925	0	0.4002	0.0870
Gamma	$\hat{\alpha} = 0.6164$ $\hat{\beta} = 30.279$	–390.839	0	0.3675	0.0894
Weibull	$\hat{\alpha} = 15.1348$ $\beta = 0.7229$	–389.937	0	0.3959	0.0873

The "p" column in the Kolmogorov– Smirnov Test of Table 3. shows that *p–values* for all the distributions are greater than 0.05, suggesting that we do not have enough evidence to reject the null hypothesis (H$_0$) which stated that PSA fits all the hypothesized probability distributions.

Although all the hypothesized distributions could describe the PSA data well, the distribution with the shortest Kolmogorov – Smirnov distance D_n (KSSTAT) is the Burr distribution with KSSTAT =0.0870 and is followed

by Weibull distribution (KSSTAT = 0.0873). This implies that the maximum vertical difference between the empirical cumulative distribution function of the PSA and Burr distribution is 8.7% and 8.73% for Weibull distribution. Therefore, the Burr distribution with probability density function described in (3.6) is the most appropriate distribution for the PSA data. Thus, using equation 3.2, the probability that a patient whose PSA is more than 4.0ng/ml will be at risk and diagnosed of prostate cancer is given as: $P(x > 4) = 1 - F(x \leq 4)$. Therefore, $P(x > 4) = 0.68$.
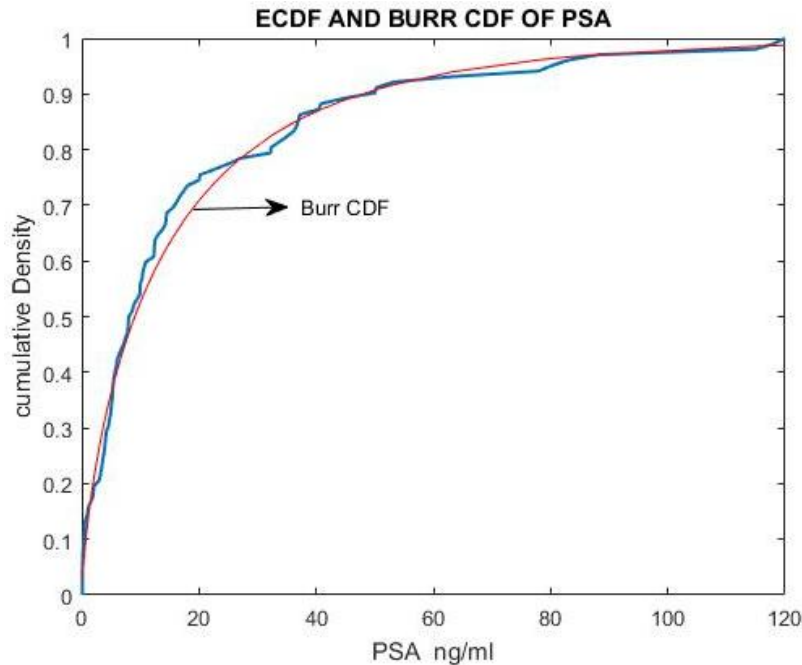

Fig. 3. Graphical Representation of the Fit of the Burr distribution with the Empirical Distribution of the PSA

Table 4. Age specific probabilities

Age group	PSA>4.0	$P_X(x)$
$45 \leq y < 50$	0	0
$50 \leq y < 55$	5	0.068
$55 \leq y < 60$	7	0.095
$60 \leq y < 65$	12	0.162
$65 \leq y < 70$	16	0.216
$70 \leq y < 75$	14	0.189
$75 \leq y < 80$	10	0.135
$80 \leq y < 85$	6	0.081
$85 \leq y < 90$	3	0.041
$90 \leq y < 95$	0	0
$95 \leq y < 100$	1	0.014
Total	74	

Fig. 3 shows that the Burr distribution is a very good fit to the empirical distribution of the PSA data.It can also be observed that the Burr distribution may give slightly different cumulative densities when the PSA values fall between 20.0ng/ml and 40.0ng/ml.

4.3 Calculation of the age specific probabilities

The PSA values greater than 4.0ng/ml were classified according to the ages of the patients whose PSA readings were taken. The age specific probabilities were calculated using (3.3). The results are given in Table 4.

The results in Table 4 show that men between the ages of 60 and 80 years have higher chances of having their PSA readings increased above 4,0ng/ml. Men between 65 and 70 years of age were observed to have the highest chances of having their PSA values increased beyond 4.0ng/ml. Since, needle biopsies detect prostrate cancer in 20 -30% of cases with PSA level of 4.1-10.0ng/ml and 30-50% or more of the cases higher than 10.0ng/ml , needle biopsies may not therefore be necessary for men between 60 and 80 years of age with PSA greater than 4.0ng/ml but should be referred for digital rectal examinations [10].

5 Conclusion

In this research, sample data consisting of Prostate Specific Antigen (PSA) of 102 patients were collected from patients' folders in a specialist hospital on Prostrate cancer. The data consisted of the PSA readings of patients who were diagnosed of prostrate cancer and those not diagnosed of prostrate cancer. Analyses of the data show that the median PSA of patients is 8.30ng/ml with an inter quartile range of 16.40 and coefficient of skewness of 2.331. A test of hypothesis was carried out using Kolmogorov – Smirnov goodness of fit test. The purpose was to identify the most appropriate distribution that fitted the PSA data. The Burr, Gamma and Weibull distributions were fitted to the data. These distributions were chosen because the data contain outliers capable of resulting to positively skewed distributions. The results obtained show that the Burr distribution is the best distribution for the PSA data among the three distributions fitted to the data. Furthermore, the probability that a patient's PSA is greater than 4.0ng/ml was calculated. This gave an approximate probability of 0.68, which indicates a higher chance of having the prostrate cancer. The PSA readings of the patients whose PSA values were greater than 4.0ng/ml were then grouped according to the ages of the patients and the age specific probabilities calculated. The results obtained show that men between the ages of 65 and 70 years have the highest chances of having their PSA readings increased beyond 4.0ng/ml, though high probabilities of PSA greater than 4.0ng/ml spanned from men between 60-80years of age. It is then suggested that since, needle biopsies detect prostrate cancer in 20 -30% of cases with PSA level of 4.1-10.0ng/ml and 30-50% or more of the cases higher than 10.0ng/ml , needle biopsies may not therefore be necessary for men between 60 and 80 years of age with PSA greater than 4.0ng/ml but should be referred for digital rectal examinations.

Acknowledgement

Competing Interests

Authors have declared that no competing interests exist.

References

[1]   Postlethwait JH, Hopson JL. Modern biology. Holt, Rinehart and Winston., a Harcourt Education Company, USA; 2006.

[2]   Raven PH, Johnson GB, Losos JB, Singer SR. Biology. McGraw-Hill Publishing Company, New York, America. 2005;7th Ed.

[3]   Carol D, Rebecca S, Ahmedin J. Breast Cancer Facts and Figures 2015-2016. American Cancer Society Atlanta Georgia; 2015.

[4]   Peterdana NR, Mochtar CA, Umbas R, Hamid AR. the risk factors of prostate cancer and its prevention: A literature review. The Indonesian Journal of Internal Medicine. 2016;48 (3).

[5] Sadeghi-Gandomani HR, Yousefi MS, Rahim S, Yousefi SM, Rahim S, Karimi-Rozveh A. The incidence, risk factors and knowledge about the prostrate cancer through worldwide and Iran. World cancer Research Journal. 2017;4(4):e972.

[6] Rawla P. Epidemiology of Prostate Cancer. World J Oncol, Elmer Press Inc. 2019;10(2):63-89.

[7] Kheirandish P, Chinegwundoh F. Ethnic differences in prostate cancer. British Journal of Cancer. 2011;105:481-485.

[8] Jedy-Agba EE, Curado MP, Ogunbiyi O, Oga E, Fabowale T, Igbinoba F, ... Cancer Incidence in Nigeria: A Report from Population-based Cancer Registries. Cancer Epidemiol. 2012; 36(5).

[9] Vollmer RT. Predictive Probability of Serum Prostate–Specific Antigen for Prostate Cancer: An Approach Using Bayes Rule. Am J Clin Pathol. 2006;125:336–342.

[10] Akakura K. Clinical use of prostate specific antigen (PSA). Japan Medical Association. 2004;47(12):549–554.

[11] Brett T. Prostate Specific Antigen. Australian Family Physician. 2011;40(7):497-500.

[12] Nogueira L, Corradi R, Eastham JA. Prostatic specific antigen for prostate cancer detection. International Brazil Journal of Urology. 2009;35(5):521–531.

[13] Pudasaini S, Subedi N, Shrestha NM. Evaluation of prostate specific antigen levels and its correlation with histopathological findings. Journal of Pathology of Nepal. 2019;9:1485–1489.

[14] Kenny PA, Bozzone DM. The biology of cancer: stages of cancer development. Infobase Publishing, Inc; Chelsea House, New York; 2007.

[15] Farazi PA, Siahpush M, Maloney S, Dinkel D, Michalek A, John R , et al. Awareness and attitudes of nigerian men living in abuja on prostate cancer. Screening. Journal of Cancer Education. 2019;34:1107–1111.

[16] Erol B, Gulpinar MT, Bozdogan G, Ozkanli S, Onem K, Mungan G, et al. The cutoff level of free/total prostate specific antigen (f/t PSA) ratios in the diagnosis of prostate cancer: A validation study on a Turkish patient population in different Age categories. Kaohsiung journal of Medical Science. 2014;30:545 – 550.

[17] Atish C, Prasad SD, Mukesh R, Surendran K, Sundaresan S, Thangapannerselvem T. A study on prostate specific antigen (PSA) with the ratio of free to total PSA. African Journal of Biochemistry Research. 2010;4 (1);013–016.

[18] Kim JS, Ryu JG, Kim JW, Hwang EC, Jung S, Kang TW, et al. Prostate–Specific antigen fluctuation and prostate cancer. Original Article. 2015;41(2):258–264.

[19] D'Agostino RB and Stephens MA. Goodness – of – Fit – Techniques. Marcel Dekker, Inc. New York USA; 1986.

[20] Hakim AA, Fithriani I, Novita M. Properties of burr distribution and its application to heavy-tailed survival time data. Journal of Physiccs: Conference series; 2021.

[21] Stewart WJ. Probability, markov chains, queues, and simulation. Princeton University Press, New Jersey, UK; 2009.

[22] Khamkong M. Parameter estimation method for the two parameter gammadistribution based on transformation. International Journal of Applied Engineering Research. 2018;13(2):1261–1264.

[23] Soong TT. Fundamentals of probability and statistics for engineers. John Wiley and Sons, Ltd, England; 2004.

[24] Bhattacharya P, Bhattacharjee R. A study on Weibull Distribution for Estimating the Parameters.Journal of Applied Quantitative Methods. 2010;5(2):234–241.

[25] Alexopoulos A. One-parameter weibull type distribution, its relative entropy with respect to weibull and a fractional two-parameter exponential distribution. MDPI Journal, Switzerland; 2019.

_____