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A Mathematical Model for the Genetic Variation of Prolactin and Prolactin Receptor in Relationship with Serum Prolactin Concentrations and Breast Cancer Risk

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Abstract
The Weibull distribution is a widely used model for studying fatigue and endurance life in engineering devices and materials. Recent advances in Weibull theory have also created numerous specialized Weibull applications. Modern computing technology has made many of these techniques accessible across the engineering spectrum. Despite its popularity, and wide applicability the traditional 2 – parameter and 3- parameter Weibull distribution is unable to capture all the lifetime phenomenon for instance the data set which has a non – monotonic failure rate function. Recently several generalization of Weibull distribution has been studied. An approach to the construction of flexible parametric model is to embed appropriate competing models into a larger model by adding shape parameter. Some recent generalizations of Weibull distribution including the Exponentiated Weibull, Extended Weibull, Modified Weibull are discussed and references **[5]** therein, along with their reliability functions. In this paper a new generalization of Weibull distribution called the transmuted Weibull distribution is utilized for our medical application. For example, Prolactin and prolactin receptors are present in normal breast tissue, benign breast disease, breast cancer cell lines, and breast tumour tissue, leading to speculation that the proliferative and antiapoptotic effects of prolactin in breast epithelial cells could be a factor in breast carcinogenesis. In this paper, a test for the distribution of prolactin concentrations in controls, by menopausal status and relationships with Serum Prolactin Levels and Breast Cancer Risk was investigated in the application part, by using Transmuted Weibull Distribution. As a result the mathematical curves for the Probability Density Function, Reliability Function and Hazard Rate Function are obtained for the corresponding medical curve given in the application part.

Keywords: Prolactin (PRL), Prolactin Receptor (PRLR), Single Nucleotide Polymorphism(SNP), Transmuted Weibull Distribution, Reliability Function, Hazard Rate Function.
Mathematics Subject Classification: 62N05, 90B25

I. Mathematical Model

1.1 Introduction

Some recent generalizations of Weibull distribution including the exponentiated Weibull, extended Weibull, modified Weibull are discussed and references **[5]** therein, along with their reliability functions. In this article a new generalization of Weibull distribution called the transmuted Weibull distribution is presented **[8].**

A random variable X is said to have transmuted distribution if its cumulative distribution function is given by

$$F(x) = (1+\lambda)G(x) - \lambda G(x)^2 \, , |\lambda| \leq 1 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1.1)$$

where G(x) is the cdf of the base distribution. Observe that at $\lambda = 0$ we have the distribution of the base random variable. Aryal et al **[4]** studied the transmuted Gumbel distribution and it has been observed that transmuted Gumbel distribution can be used to model climate data. In the present study we will provide mathematical formulation of the transmuted Weibull distribution and some of its properties.

1.2 Transmuted Weibull Distribution

A random variable X is said to have a Weibull distribution with parameters $\eta > 0$ and $\sigma > 0$ if its probability density function is given by

$$g(x) = \frac{\eta}{\sigma}\left(\frac{x}{\sigma}\right)^{\eta-1} exp\left(-\left(\frac{x}{\sigma}\right)^{\eta}\right), x > 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1.2)$$

The cdf of X is given by

$$G(x) = 1 - exp\left(-\left(\frac{x}{\sigma}\right)^{\eta}\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots (1.3)$$

Now using (1.1) and (1.3) the cdf of a transmuted Weibull distribution is

$$F(x) = \left[1 - exp\left(-\left(\frac{x}{\sigma}\right)^{\eta}\right)\right]\left[1 + \lambda exp\left(-\left(\frac{x}{\sigma}\right)^{\eta}\right)\right] \quad \ldots\ldots\ldots\ldots\ldots\ldots (1.4)$$

Hence, the pdf of transmuted Weibull distribution with parameters η, σ and λ is

$$f(x) = \frac{\eta}{\sigma}\left(\frac{x}{\sigma}\right)^{\eta-1} exp\left(-\left(\frac{x}{\sigma}\right)^{\eta}\right)\left[1 - \lambda + 2\lambda exp\left(-\left(\frac{x}{\sigma}\right)^{\eta}\right)\right] \quad \ldots\ldots\ldots\ldots (1.5)$$

Note that the transmuted Weibull distribution is an extended model to analyze more complex data and it generalizes some of the widely used distributions. In particular for η=1we have the transmuted exponential distribution as discussed in Shaw et al **[8].** The Weibull distribution is clearly a special case for λ = 0. When η = λ = 1 then the resulting distribution is an exponential distribution with parameter $\frac{\sigma}{2}$.

In this section we shall present the moments and quantiles for the transmuted Weibull distribution. The k[th] order moments of a transmuted Weibull random variable X, in terms of gamma function Γ(.) is given by

$$E(X^k) = \sigma^k \Gamma\left(1 + \frac{k}{\eta}\right)\left\{1 - \lambda + \lambda 2^{\frac{-k}{\eta}}\right\} \quad \ldots\ldots\ldots\ldots\ldots (1.6)$$

Moreover, if $k/\eta = r$ is a positive integer then,

$$E(X^k) = \sigma^k r!\{1 - \lambda + \lambda 2^{-r}\}$$

Therefore, the expected value E(X) and variance Var(X) of a transmuted Weibull random variable X are,

$$E(X) = \sigma\Gamma\left(1 + \frac{1}{\eta}\right)\left\{1 - \lambda + \lambda 2^{\frac{-1}{\eta}}\right\} \quad \ldots\ldots\ldots\ldots (1.7)$$

$$Var(X) = \sigma^2\left\{\Gamma\left(1 + \frac{2}{\eta}\right)\left[1 - \lambda + \lambda 2^{\frac{-2}{\eta}}\right] - \Gamma^2\left(1 + \frac{1}{\eta}\right)\left[1 - \lambda + \lambda 2^{\frac{-1}{\eta}}\right]^2\right\} \quad \ldots\ldots\ldots\ldots (1.8)$$

Note that when η = k,

$$E(X^k) = \sigma^k\left[\frac{2-\lambda}{2}\right]$$

The q[th] quantile x_q of the transmuted Weibull distribution can be obtained from (1.4) as

$$x_q = \sigma\left[-ln\left\{1 - \left(\frac{1 + \lambda - \sqrt{(1+\lambda)^2 - 4\lambda q}}{2\lambda}\right)\right\}\right]^{\frac{1}{\eta}} \quad \ldots\ldots\ldots\ldots (1.9)$$

The transmuted Weibull distribution can be a useful characterization of failure time of a given system because of the analytical structure. The reliability function R(t), which is the probability of an item not failing prior to some time t, is defined by R(t) = 1 – F(t). The reliability function of a transmuted Weibull distribution is given by

$$R(t) = exp\left(-\left(\frac{t}{\sigma}\right)^{\eta}\right)\left[1 - \lambda + \lambda exp\left(-\left(\frac{t}{\sigma}\right)^{\eta}\right)\right] \quad \ldots\ldots\ldots\ldots\ldots (1.10)$$

The other characteristic of interest of a random variable is the hazard rate function defined by $h(t) = \frac{f(t)}{1-F(t)}$ which is an important quantity characterizing life phenomenon. It can be loosely interpreted as the conditional probability of failure given it has survived to the time t. The hazard rate function for a transmuted Weibull random variable is given by

$$h(t) = \frac{\eta}{\sigma}\left(\frac{t}{\sigma}\right)^{\eta-1}\left\{\frac{1 - \lambda + 2\lambda exp\left(-\left(\frac{t}{\sigma}\right)^{\eta}\right)}{1 - \lambda + \lambda exp\left(-\left(\frac{t}{\sigma}\right)^{\eta}\right)}\right\} \quad \ldots\ldots\ldots\ldots\ldots\ldots (1.11)$$

From equations (1.5), (1.10) & (1.11) the mathematical representations of the Probability Density Function, Reliability Function and Hazard Rate Functions are given in Mathematical Result.

II. Application

The reproductive hormone prolactin is produced primarily by the pituitary gland **[6]** and in lesser amounts by several other tissues, including breast tissue. Prolactin plays a central role in breast development, differentiation and lactation **[1]** but experimental data suggest that, in addition to having a role in normal development, prolactin may have procarcinogenic effects **[2,9]**. Prolactin and prolactin receptors are present in normal breast tissue, benign breast disease, breast cancer cell lines, and breast tumour tissue, leading to speculation that the proliferative and antiapoptotic effects of prolactin in breast epithelial cells could be a factor in breast carcinogenesis.

There is a growing body of epidemiologic evidence supporting an association between circulating prolactin levels and breast cancer risk, although data are not conclusive. Large prospective studies have reported a positive association between prolactin levels and breast cancer risk **[10].** No association was reported by smaller prospective studies, although the number of breast cancer cases was limited **[13].** Results from case – control studies are inconsistent. It is also found that increased serum prolactin levels were associated with nulliparity in premenopausal women and with current or recent use of hormone therapy (HT) and lower body mass indices (BMI) in postmenopausal women **[3].**

In addition to reproductive and environmental factors, genetic variation in the prolactin (PRL) and prolactin receptor (PRLR) genes may be associated with increased prolactin levels and breast cancer risk. Exploration of genetic variants in prolactin and prolactin receptor has identified single – neucleotide polymorphisms (SNPs) that alter transcription factor binding, modify prolactin receptor activity, and may be associated with breast cancer risk **[11]** or circulating prolactin levels. In a recent study of finding the relationship between serum prolactin and breast cancer risk, it is investigated that the association between common genetic variation in prolactin and prolactin receptor and breast cancer in the Breast Cancer Study. Additionally, the association between prolactin and prolactin receptor single – neucleotide polymorphisms and serum prolactin levels among controls, hypothesizing that altered serum prolactin levels may be an intermediate marker between genetic variation in prolactin and prolactin receptor and breast cancer risk.

2.1 Study population

Briefly, eligible cases included women (age range of 20 to 74 years) whose primary invasive or in situ breast cancer was diagnosed. Cases were identified by means of a rapid identification system. Eligible controls were identified from a population registry containing demographic information and were frequency – matched to cases on the basis of age (5 –year categories) and study site. A total of 2,502 controls (69% of eligible) were enrolled in the study.

Study participants provided information on demographics, reproductive and medical history, oral contraceptive and postmenopausal hormone use, and other potential breast cancer risk factors. A blood sample was provided by 84% of cases and 92% of controls.

2.2 Serum Prolactin Measurement

Serum prolactin concentration was measured in a subset of cases and controls, whose selection was described in detail by Faupel – Badger and colleagues **[3].** Controls were matched to cases by menopausal status, age (5- year categories), time of blood collection (within 2 hours) study site, and day of menstrual cycle (within 2 days, premenopausal women only). Only control prolactin concentration were used in this analysis.

Serum prolactin levels were measured by Quest Diagnostics by using the Bayer ADVIA Centaur Immunoassay and were calculated after caliberation with known prolactin concentrations. One control subject was excluded from further serum prolactin analyses because of a concentration outside the assay limits of detection(0.3 to 200 ng/mL).

Women were classified as premenopausal if they reported that they were still having natural menstrual periods; medical records were used to determine menopausal status for women who did not know whether they were still experiencing natural menstrual periods. Among postmenopausal women, oral hormone therapy use was based on self – reported use of estrogen and progesterone pills for purposes other than birth control. Family history of breast cancer was based on female first – degree relatives with breast cancer.

Time of blood collection was included in models by using 2 – hour categories. Time since last menstrual period was the number of days between blood draw and the participant's most recent menstrual period and was used as a continuous variable.

Previous studies have shown that prolactin levels are higher in premenopausal compared with postmenopausal women and that prolactin levels vary with the day of menstrual cycle in premenopausal women. Owing to the differences in average prolactin levels and cycling patterns, the data are presented on mean prolactin levels by genotype stratified by menopausal status. Models were adjusted for age, time of blood collection, and time since last menstrual period (premenopausal women only).

2.3 Association between Prolactin, Prolactin Receptor Single – Neucleotide Polymorphisms and Breast Cancer Risk

By examine the association between variant alleles in 25 single neucleotide polymorphisms – 7 prolactin and 18 prolactin receptor and breast cancer risk, prolactin receptor single – neucleotide polymorphisms rs7718468 and rs13436213 were associated with postmenopausal breast cancer risk. For both single – neucleotide polymorphisms, the association was strongest for women carrying the minor allele homozygous genotype. One single – neucleotide polymorphism was associated with premenopausal breast cancer.

Serum prolactin was measured in 773 controls, and levels were higher in premenopausal women compared with postmenopausal women (Figure 2.3.1). Several single – neucleotide polymorphisms in prolactin receptor were significantly associated with prolactin levels in premenopausal controls. Closer examination of the prolactin distributions showed that there was several outlier values among postmenopausal controls, and so it is necessary to perform a sensitivity analysis to determine the effect of these outliers on the association between rs849872 and prolactin in postmenopausal controls (Figure 2.3.1)

A sliding window approach was used to identify global haplotype associations with breast cancer. An association was detected for a region encompassing prolactin receptor single – neucleotide polymorphisms rs873456, rs7718468, rs34024951, and rs9292575 and postmenopausal breast cancer. Five haplotypes in this region had estimated frequencies of greater than 0.05, and haplotype G-C-G-C was positively associated with breast cancer risk when compared with the referent haplotype G-T-G-C. These haplotypes were not associated with serum prolactin levels in postmenopausal controls. There was no association between prolactin receptor haplotypes and premenopausal breast cancer or between prolactin haplotypes and premenopausal or postmenopausal breast cancer.

The distribution of serum prolactin concentrations in controls, by menopausal status

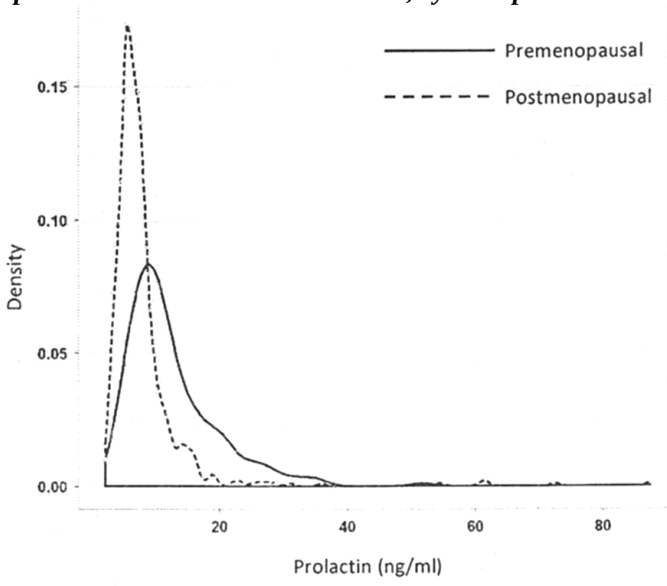

Figure 2.3.1

Prolactin concentrations in Breast Cancer Study control subjects ranged from 2.1 to 348.4 ng/mL and the majority were less than 50 ng/mL. The unadjusted geometric mean (interquartile range) prolactin concentrations were 10.89 ng/mL (7.80 to 15.30) in premenopausal controls and 6.99 ng/mL (5.30 to 8.60) in postmenopausal controls.

Several breast cancer risk factors have been reported to be associated with prolactin levels **[7]** and estrogen has been shown to stimulate the prolactin extrapituitary promoter in breast cancer cell lines. Furthermore, prolactin act through both autocrine and endocrine pathways. Refinement of tissue – level prolactin and prolactin receptor expression assays may provide a more accurate estimate of the prolactin levels surrounding breast epithelial cells from autocrine and endocrine sources.

III. Mathematical Results

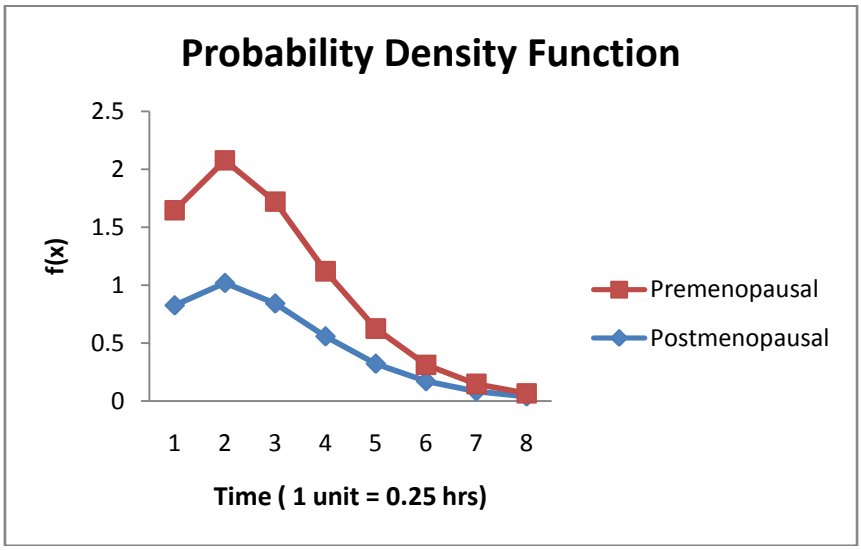

Figure 3.1

In testing the distribution of serum prolactin concentrations in controls, by menopausal status: The Probability Density Function f(x) increases in the interval of 15 to 30 minutes and it decreases suddenly from the 30th minute to the end (2nd hour)

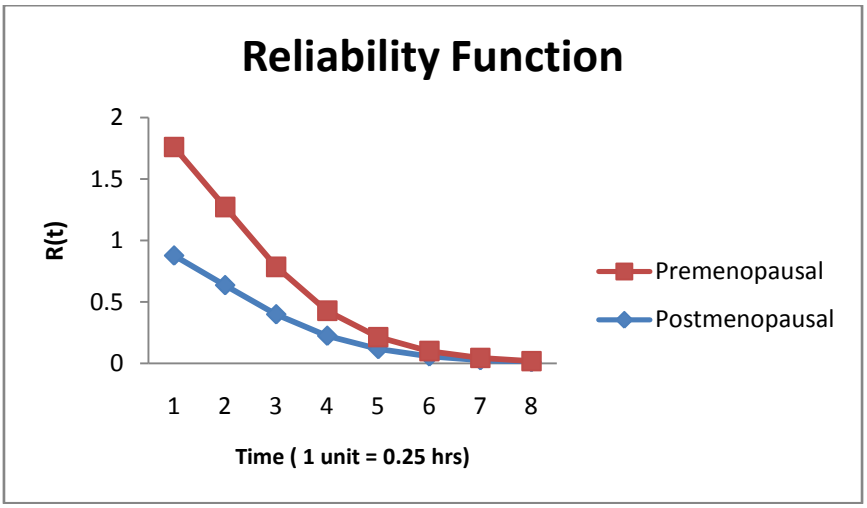

Figure 3.2

In testing the distribution of serum prolactin concentrations in controls, by menopausal status: The Reliability Function R(t) reaches its maximum value in the 15th minute and it decreases gradually from the 15th minute to the end (2nd hour.

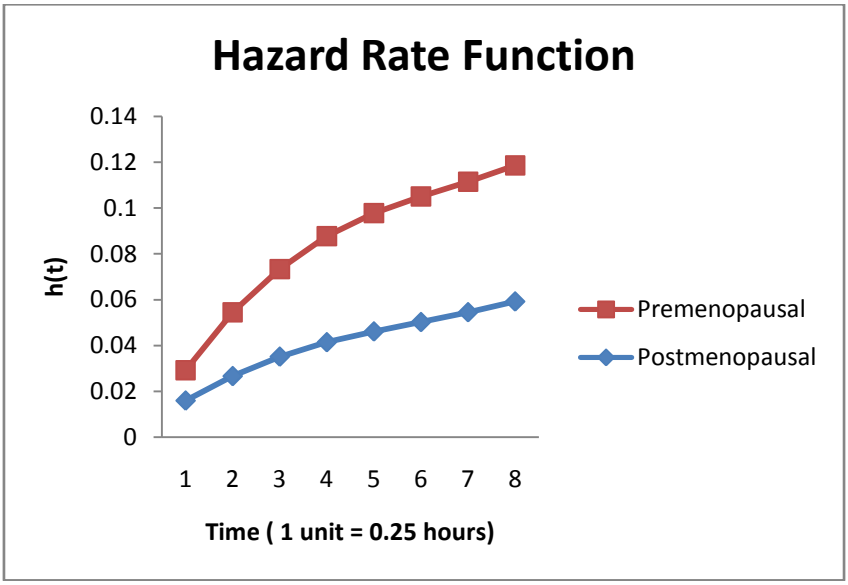

Figure 3.3
In testing the distribution of serum prolactin concentrations in controls, by menopausal status: The Hazard Rate Function h(t) increases from the 15th minute till the end (2nd hour).

IV. Conclusion

As a result the curves for the PDF, Reliability Function and the Hazard Rate Function are obtained in Figures (3.1, 3.2 & 3.3) for the corresponding medical figure given in the application part. During the investigation of serum prolactin concentrations (in a period of 2hours) the Hazard Rate Function increases from the 15th minute till the end (2nd hour), the PDF increases in the interval of 15 to 30 minutes and it decreases suddenly from the 30th minute to the end (2nd hour) and the Reliability Function reaches its maximum value in the 15th minute and it decreases gradually from the 15th minute to the end (2nd hour). In this study it is observed that: In testing the distribution of serum prolactin concentrations in controls, by menopausal status the hazard rate density is found to be higher for premenopausal stage than the postmenopausal stage. Thus, the Genetic Variation of Prolactin and Prolactin Receptor in Relationship with Serum Prolactin Concentrations and Breast Cancer Risk is more for the Premenopausal Cases and very low for Postmenopausal cases.

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