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On Share Frailty Cure Model: An Application On Cervical Cancer

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Abstract : *Survival analyses are greatly used in medical research especially frailty models which are mostly used to account for heterogeneity in time-to-event. Over the years treatment of cancer has progressed with some patients being cured from different type of cancer. Survival analysis is more focused on subjects that are less at risk of recurrences, metastasis or death after the first treatment as these set of subjects are regarded as being cured. The general assumption of standard frailty model is that all subjects have the same frailty. These assumptions ignore the heterogeneity of such frailties and will lead to incorrect results and conclusions. To address the identified deficiencies in previous studies, this research will propose a shared frailty cure model. Shared frailty assumes that within a cluster the value of frailty term is improved with constant and common frailty to all subjects in the same group clusters by measuring the correlation between event times within the cluster, hence representing changes over time in clusters or population heterogeneity. These structures can be achieved by introducing covariates that are rank specific by the process Shared frailty model, addressing the weakness of the cure frailty model by considering the homogeneity in groups or clusters were failure can be similar by having the same frailty.*

Keywords: *survival, frailty, cure, cervical cancer.*

I. Introduction

Survival analysis with cure fraction are becoming common to epidemiological and clinical trials. Univariate cure rate model has been used for failure time data for various types of cancer such as leukemia, prostrate, breast head, neck cancer and also in studying effect of a particular drug on different subjects were we have a significant proportion of the patients cured. Survival analysis goal now has shifted towards cure of disease (curative therapy) rather than prolongation of time to death (life-prolonging therapy) the proportion of cured patients has become an important measure of the long term benefit driven from the therapy(Maetani & Gamel, 2013). To achieve cure choosing the right regimen is very vital, these especially in younger women, for curative treatment can yield many years of healthy life, while the prolongation of life offers only limited benefits before relapse takes the life completely, and hence cured subjects are saved from all related sufferings which would be unbearable to the subjects than death itself.

Frailty models can be improved by its applications to multivariate survival data without using the notion of standard frailty.frailty was first introduced by (Vaupel, Manton, & Stallard, 1979) Shared frailty models for multivariate data used to extend frailty for univariate data analysis and can be used when modelling intragroup or between group correlation. Early considerations of the shared frailty was considered by (Clayton & Cuzick, 1985; Hougaard, 1995). The frailty model is used with univariate data and is also used to model heterogeneity among individuals. Shared frailty model can be applied on multivariate survival data where the unobserved frailty is shared among clusters or groups of individuals, shared frailty model can be regarded as a random effects model for survival data. A natural extension for the univariate frailty is a multivariate frailty where individuals are allowed to share the same frailty value within clusters of a group. Sharing a frailty value also generates dependence between those individuals with the same shared frailty.

Relapse are treated as recurrent events and death as terminal event this event can be analyzed separately or jointly (Mazroui, Mathoulin-Pélissier, MacGrogan, Brouste, & Rondeau, 2013) Frailty models are extension of proportional hazard model which is aimed at accounting for potential heterogeneity caused by prognostic factors that are unmeasured and are time dependent recurrent events. (Box-Steffensmeier, Linn, & Smidt, 2014) Repeated events processes has a lot of challenges for estimation of covariate effects on event history models. Mostly in repeated events analysis there are usually within the subject correlation in event times due to heterogeneity within the groups, were we have higher or lower event rate than other reasons that cannot be measured or event dependence, where the occurrences of an event itself may raise or lower the event rates. The within subject correlation violates within the cox models assumptions of independent events. Recurrent events are observed in clinical, industrial and social research. (Mauguen et al., 2013) Recurrent events in this study are defined as relapse of cervical cancer, these event do not impact the risk of death. When studying recurrent event, different time scale can be used. Time event such as the calendar and gab time are used. Gap time is the time-between-event, it implies the time the time to the next event corresponds to the number of days elapsed between two successive events that is after an event the subject the subject will start again at time zero

(0). Duration of the time at risk for an event corresponds to the duration of time at risk for the gap time. The starting time of the period at risk is not reset to the starting point zero, hence the subject is not considered to be at risk for the jth event until after time (j-1). Calendar time is also referred to as counting process approach, which keeps track of time since randomization, it is also known as time-to-event(Mauguen et al., 2013)Mazroui et al., 2013,Unkel, Farrington, Whitaker, & Pebody, 2014).

Cure model dates back as (Arbutiski, 1985; Berkson & Gage, 1952; Boag, 1949; Farewell & Sprott, 1988; Laska & Meisner, 1992) with parametric mixture model has been used to describe distributions in a mixed population, were we have a fraction of the population being cure that is free from recurrences (Gorny et al., 2014).

Although cervical cancer is preventable It remains a major concern in sub-Saharan Africa(organisation, 2014).Cervical cancer are caused by human papilloma virus (HPV), sexual contact. It is diagnosed by Pap test (finding changes in cervical cells before the turn to cancer), symptoms of cervical cancer are vagina bleeding (between period, during sex, or after menopause), pain during sex, vagina discharge that is not normal, lower abdominal pain. It is treated by surgery (removal of cancer tissues, hysterectomy), chemotherapy, radiation therapy. Hysterectomy is not usually needed especially when detected early.(Choices, 2014). Cervical cancer as classified by FIGO has for stages 1, 2, 3 and 4, stages defines how far the cancer cells have covered, it has three grades 1(well defined), 2 (moderately defined), and stage 3 (poorly defined or undifferentiated).

II. Problem Statement

Clinical trials and simulation studies have shown that standard survival analysis suffer a number of disadvantages such as research tend to lose power as the follow- up on individual increases, When follow-up is limited, individuals are more sensitive to an increase in failure time than to an increase in cure rate, most of these research do not distinguish between Curative and life-pro-longing treatments, As a result, death-delaying treatment may have a greater advantage than is curative.cervical cancer is at the high side in most African countries especially in sub-Saharan Africa, Which accounting for 22 percent of all worldwide cervical cancer. There are few literatures regarding cure for cervical cancer, Most of the studies conducted on cervical cancer are done on the prevalence rate.

This research used a mixture cure will account for the proportion of the population that are cured as well as the fraction of the population that die as a resultof cancer of the cervics.

III. Cure Model

Cure model represents an interesting method for studying patient's outcome, it makes it possible to know if and when patients are alive and disease free or without a recurrence, and hence they are considered cured. Majority of patients with disease that has a possibility of recurrence are concerned about relapse and have learn to live with the uncertainty of being able to return to life free of cancer. The possibility of giving a precise estimation of the probability of being alive without recurrences would be of great importance to clinicians to enable them give a more precise answer to patients request for such information. Modelling survival data with a cure fraction is an important issue in many clinical studies, it can be used in studies such as different types of cancer such as leukemia, head and neck cancer, and also in studying the effect of certain drugs in which significant proportion of the patients can be regarded as being cured after treatment or corrective surgery.

They cure model can also be used for proper modelling of two confounded traits, such as susceptibility and endurance. In analyzing recurrent data a study by (Price & Manatunga, 2001) used cure frailty models to analyze the recurrence and a cure fraction in leukemia considering only a time to even the random effect explained the heterogeneity between the observed risk factor on individual patients. (Wu, Lin, Lu, Li, & Shih, 2014) hence proposed a frailty mixture cure model for hospital readmission, parameters were estimated using expectation maximization (EM) algorithm, using also standard error to calculate bootstrap method, the model showed people with recurrence, having a recurrence implies a patient cannot belong to the group that are regarded cured.(Rondeau, Schaffner, Corbière, Gonzalez, & Mathoulin-Pélissier, 2013) in its study extended the cure model with application on breast cancer and hospital readmission showing possibility of having cure after each relapse, indicating the probability of cure can be possible with time.

IV. Shared Frailty Cure Model

This research will extend the frailty cure model to shared frailty cure model on cervical cancer recurrences with possibility cure, using a case of multiple event on cervical cancer allowing the shared frailty model to be different for each event rank.This structures can be introduced by introducing rank specific covariates, through adapting the process introduced in(Rondeau et al., 2013) and adopting the procedure of shared frailty in (Callegaro & Iacobelli, 2012; Hirsch & Wienke, 2012) to take care of the weakness of the cure frailty model in accounting homogeneity in groups or clusters were failure times has common ingredients, that is individuals with common frailty.

The subject i (i=1,2,…N),X_{ijk} with jth recurrence time (j=1,2,…n_i) with cluster k (k=1,2,…n_i), c_i the censoring time of the event, the follow up time T_{ijk} =min (X_{ijk}, c_i) and δ_{ijk} is a binary indicatore for event recurrence is zero when observation is censored and 1 when X_{ijk} is observed. Let $Z_{ijk} = (Z_{1ij}, \dots Z_{nij})$ be a vector of n covariate which can be fix or time dependent for individual i at cluster k at time j. let ω_ia random effect normally distributed with mean 0 and variance θ^2. The standerd frailty assumes all individuals experiences the event of interest with varying risk greater than zero, the frailty model extends the cox proportional hazard accounting for unobservable heterogeneity among individuals, the shared frailty accounts for the heterogeneity among group of clusters.

The hazard at t_{ijk} for individual with random effect and shred frailty is given by

$$\lambda_{ijk}(t_{ijk}/\omega_i) = \lambda_0(t_{ijk})\exp(\beta' z_{ijk} + \omega_i) \qquad \text{Equ 1.2}$$

λ_0 Is the baseline hazard function ω_i is the random effect that takes account for dependency between successive event within a patient in a specified cluster. The model corresponds to the survival function,

$$s(t_{ijk}/\omega_i) = \exp(-\Lambda_0(t_{ijk})\exp(\beta' z_{ijk} + \omega_i)), \qquad \text{Equ 1.3}$$

Where $\Lambda_0(.)$ is the cumulative hazard function,

When the population is a mixture of susceptible and non-susceptible individuals cure model is used to extend the shared frailty model. Let $\pi(Z^*)$=P (U=1/Z^*) be the proportion of the uncured individuals depending on covariate vector $Z^* = (Z_1^*, \dots Z_q^*)$ associated by logistic form with the incidence, $(Z^*) = \frac{\exp(b'z^*)}{1+\exp(b'z^*)}$. Let T be a time to event which is defined only when u=1 with conditional survival function s (t/u=1) =p (T>t/u=1) for the uncured subject. Let Z be a covariate vectored associated with latency. Hence the marginal distribution is, S (t) =1-$\pi(Z^*) + \pi(Z^*)S(t/u = 1)$ there for the equation of shared frailty cure model is

$$\begin{cases} s(t_{ijk}/\omega_i) = 1 - \pi_{ik}(z_{ik}^*) + \pi_{ik}(z_{ik}^*)\exp(-\Lambda_0(t_{ijk}/U_{ik} = 1)\exp(\beta' z_{ijk} + \omega_j)) \\ \pi_i(z_{ik}^*) = p(U_{ik} = 1/z_{ik}^*)\dfrac{\exp(\beta' z_{ik}^*)}{(1+\exp(\beta' z_{ik}^*))} \\ \omega_i \text{ i. i. d} N(0;\theta^2) \end{cases} \qquad \text{Equ 1.4}$$

For one event for an individual. The model can be extended to having more than one event for an individual that is possibility of being cured after each event.

$$\begin{cases} s(t_{ijk}/\omega_i) = 1 - \pi_{ij}(z_{ijk}^*/\omega_i)\exp\left(-\Lambda_0(t_{ijk}/U_{ijk})\exp(\beta' z_{ijk} + \omega_i)\right) \\ \pi_{ij}(z_{ijk}^*/\omega_i) = p(U_{ijk} = 1/z_{ijk}^*) = \dfrac{\exp(b' z_{ijk}^* + \alpha\omega_i)}{\left(1+\exp(b' z_{ijk}^* + \alpha\omega_i)\right)} \\ \omega_i \sim \text{i. i. d. } N(0;\theta^2) \end{cases} \qquad \text{Equ1.5}$$

The model can be used to account for infect of intervention on the individual, the intervention in this research will be hysteroscopy as a result of cervical cancer. Incorporating model with two random effects ω_{1ik} *and* ω_{2ik} is assumed independent, $\omega_{1ik} + \omega_{2ik}$ *and* ω_{2ik} are correlated. Variance of random effectω_{2ik}, θ_2^2represent similar heterogeneity for both event, that is the recurrence and cure rates. Hence we can assume that rate and cured fraction are correlated with the same random effectω_{2ik}. The other random effect ω_{1ik} is independent of ω_{2ik} accounting for heterogeneity between recurrent event times due to random effect not including the cured fraction

$$\begin{cases} s(t_{ijk}/\omega_{1ki}\omega_{ik}) = 1 - \pi_{ijk}(z_{ijk}^*/\omega_{2ik})exp\left(-\Lambda_0(t_{ijk}/U_{ijk})exp(\beta' z_{ijk} + \omega_{1ik} + \omega_{2ik})\right) \\ \pi_{ij}(z_{ijk}^*/\omega_{2k}) = p(U_{ijk} = 1/z_{ijk}^*) = \dfrac{\exp(b' z_{ijk}^* + \alpha\omega_{2ik})}{\left(1+\exp(b' z_{ijk}^* + \alpha\omega_{2ik})\right)} \\ \omega_{1i} \sim N(0;\theta_1^2) \\ \omega_{2i} \sim N(0;\theta_2^2) \end{cases}$$

through the application of cure shared frailty to model cure and recurrences to cervical cancer at the four different stages owing to the similarity in clusters or cancer grade, hence using the multiple approach through introduction of rank specific covariates and allowing stage of cancer to be different from each event rank as well as cluster

Research Hypothesis

A multivariate hypothesis being tested is,

H_0; The recurrent and cure rate are the same for all the stages

H_1; the recurrentt and cure rate are not the same for all the stages

V. Rationale of The Study

Cure fraction in survival data are becoming increasingly commonin clinical trials,Considering the

disease naturally, a lot of events arise after the first treatment for same subject, in patients with breast cancer and treated with breast cancer conserving surgery some of the subjects may experience reoccurrences, metastases or death. Unless the disease is always fatal, the primary measure of survival benefit should be proportion of subjects cured rather than measuring hazard ratio that is on cure model not on a life-prolonging model. Special attention has to be attached to cure in the analysis of survival data. A multivariate extension of the cure model estimate the impact of treatment and other variables on the likelihood of cure. Hence providing both subjects and clinicians the information the need for vital decisions.An extension multivariable of the estimated cure model for impact of treatment and other variables on the cure likelihood.

Hence providing both subjects and clinicians with the information the need for vital decisions showed the time to death is studied to assess the effect of treatment, this would be just like counting the coins in a cash transaction while leaving the bills uncounted or unattended to. Cure model represents an interesting method for studying patient's outcome, it makes it possible to know if and when patients are alive and disease free or without a recurrence, and hence they are considered cured. The clinical utility of the cure fraction lies in the possibility of informing a patient the possibility of success of a specific treatment. Majority of patients with disease that has a possibility of recurrence are concerned about relapse and have learn to live with the uncertainty of being able to return to a normal life. The possibility of giving a precise estimation of the probability of being alive without recurrences can help clinicians to give a more precise answer to patients request for such information.

VI. Methodology

All registered cervical cancer patients in the medical record for the period of at least fifteen years (25yrs) of the hospitals, considering the stages (0,1,2,3,4) of cancer at diagnosis and first treatment with all necessary vital data will be included in the study. The stages in figure 3.1 below show the stages of cervical cancer

These study is amid at evaluating the number of patients with cervical cancer that will survive a minimum of 5years (remission) without recurrences, metastasis or death as a result of cervical cancer at the four different stages of the cancer after the first treatment.

Independent variables (Covariate):Entry date (ED),Age at menarche, Parity status(YES ;1 NO ; 0), Marital status (YES ; 1 NO ; 0), Lost of follow-up (YES ; 1 NO ; 0) and recurrent event times (0,1,2,3)

Dependent variables: recurrences, metastasis and death

Cure in this context means being free of symptoms of cervical cancer for the period of at least five years (5yrs). The diagram shown below, shows the possible out-come after the event of failure.Figure 3.1 present the transition from treatment to either recurrence, metastasis or death

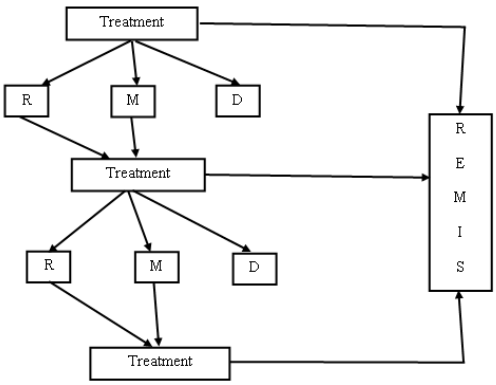

Figure 3.2 Transition

VII. Statistical Analysis

Shared frailty cure model formulation for recurrent time-to-event data for cervical cancer to account for the four different stages of cervical cancer accounting for the cured fraction and also recurrence time. Patients with no recurrences and lost to follow-up alive at the end of the study of who died (not from cervical cancer) will be considered to be cured Statistical analysis will be carried out with the use of statistical software, Secondly the maximum likelihood estimation method will be used to estimate the cure fraction in the population, the two random effect needed to take into account the between subject correlation, and hence calculate the probability to develop a new event after each already developed event.

VIII. Statistical Software

SAS and R software are the most used statistical packages, SAS is mostly used by researchers in the social science environment, and it is fast and can accommodate large data set. R is greatly appreciated by science based academicians mostly statisticians as the package gives room for contributions through the use of ready-to-use functions and also advanced statistical tools that are most recent. (Rondeau et al., 2015) a frailty package for shared frailty.

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