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EXPONENTIAL MODEL FOR ASSESSING COMPETING RISK IN PATIENT SURVIVAL TIME IN CLINICAL TRIALS

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ABSTRACT: Patients' survival time depends on several concomitant variables that compete for cancer patients' survival. Censored values make parameter estimation difficult. For this reason, an optimal model was developed to estimate patients' paucity entries that generate censored values in survival data. A total of 98 cancer patients were followed to death and their survival times recorded. The data was made up of 80% censored values and 20% uncensored values. The average survival time for patients is 46 months. The presence of tumor in the breast cancer contributed to six times the death of the patients. Simulations show that, median follow-up time is 4.17874 months and the density of incidence of the risk of cancer is 0.0757.

Introduction

In survival analysis several risk factors compete for the death of patients. A patient can die and the risk factors that actuary caused the death may be due to another risk factor different from what is expected to be the cause. For instance, a patient who is being treated for kidney failure rate may die in a gory accident. Accident, heart attack and many competing risk that compete for the life of the patient are all covariates and only one of these risks may cause the death of the patient (Cox, 1972). The term risk is the probability of dying from a given cause prior to death. It should be noted that after the death of the patient the risk among the competing risks is the cause. Analyzing those risks under patients' survival time, two approaches are very useful. First, the survival time of patients can be analyzed separately for each cause. Secondly, those competing risks can be seen as independent entities with the assumption that the hazard rate is constant. This approach is useful if a patient's survival time is analyzed together in one model (Efron, 1977).

METHOD

Suppose n patients are on a study and r failures occur (death) where $n-r$ are censored, then the death density for ith patient is $f(t_i)=\lambda_i e^{-\lambda_i t_i}$ and survival function is $f(t_i)=e^{-\lambda t_j^i}$ where $t_i \geq 0, \lambda_i > 0. t_j^i > 0$. The likelihood is given by

$$f(t) = \lambda e^{-\lambda t_i} \prod_{j=1}^{c_i} e^{-\lambda t_j^i} = \lambda e^{-\lambda (t_i + \sum_{j=1}^{c_i} t_j^{(i)})}$$

Where $(\sum_{j=1}^{m_i} t_j^{(i)}) \ = S$ is the sum of censored observations.

Let X_i be the observed values of covariate such that $E(t_i)= {\lambda_i}^{-1} = a + bx_i$, it follows that

$$f(t) = \prod_{i=1}^{r} (a+bX_i)^{-1} e^{-(a+bX_i)^{-1}} t_i e^{-(a+bX_i)^{-1}} \mathrm{S}$$

The log likelihood of the patients' survival time is

$$\text{Log}\, f(t) = -\sum_{i=1}^{r}(a+bX_i) - \sum_{i=1}^{r} t_i (a+bX_i)^{-1} - S(a+bX_i)^{-1}$$

$$\frac{\partial \text{Log}\, f(t)}{\partial a} = -\sum_{i=1}^{r}(a+bX_i) + \sum_{i=1}^{r} t_i (a+bX_i)^{-2} + S(a+bX_i)^{-2}$$

$$\frac{\partial \text{Log}\, f(t)}{\partial b} = -\sum_{i=1}^{r} X_i (a+bX_i)^{-1} + \sum_{i=1}^{r} X_i t_i (a+bX_i)^{-2} + SX_i (a+bX_i)^{-2}$$

We therefore need to estimate both a and b. This is possible if the constraint $a+bx_i > 0$ is satisfied for every covariate x, the maximum likelihood estimates are therefore the solution of $\frac{\partial \text{Log } f(t)}{\partial a} = 0$ and $\frac{\partial \text{Log } f(t)}{\partial b} = 0$. The presence of censored observations makes the solutions very complicated, and we use the maximum likelihood procedure to find the solutions. Newton – Raphson iterative algorithm can be used to find the solutions. The parameter vector (a, b) can be maximized with respect to the observations but the constraint $a + bX_i > 0$ for every covariate X, imposed on the maximum likelihood can be violated in practical sense. This restriction is violated in practical situation due to the $X's$ ranges involved; b can be close to or less than zero and any attempt to estimate the parameters can run into sticky numerical problems (Cox, 1972). This is the reason why the maximum likelihood procedure is preferred to least square algorithm, but the least square can be used to estimate the initial parameters.

Let $\hat{a}$ and $\hat{b}$ be the maximum likelihood values for the parameters a and b, $\hat{a}$ and $\hat{b}$ can be estimated from the initial parameters $\hat{a}_0$ and $\hat{b}_0$ by using least the square procedure. Assuming that the covariates are linearly related to the to the death of patients, then the expectation of the patients' survival time is $E(t_i) = \lambda^{-1} = a_0 + b_0 x_i$, this means that $E(t_i) = a_0 + b_0 x_i$. From the least square estimate

$$e^2 = \sum_{i=1}^{n} (t_i - a_0 - b_0 x_i)^2$$

Where e^2 is the error sum of squares

$$\frac{\partial e^2}{\partial a_0} = -2(\sum t_i - n a_0 - b_0 \sum x_i)$$

$$\frac{\partial e^2}{\partial b_0} = -2(\sum x_i t_i - a_0 \sum x_i - b_0 \sum x_i^2)$$

$$\text{At } \frac{\partial e^2}{\partial a_0} = 0, \ \ n a_0 + b_0 \sum x_i = \sum t_i$$

$$\frac{\partial e^2}{\partial b_0} = 0 \, , a_0 \sum x_i + b_0 \sum x_i^2 = \sum x_i t_i$$

Setting $x = \sum_i x_i$ and $t = \sum_i t_i$, $\hat{b}_0 = \frac{\sum(x_i - \hat{x})(t_i - \hat{t})}{\sum(x_i - \hat{x})^2}$, $\hat{a}_0 = \bar{t} - \hat{b}_0 \bar{x}$

we can estimate $\hat{a}$ and $\hat{b}$ by expanding $\frac{\partial \text{Log } f(t)}{\partial a}$ and $\frac{\partial \text{Log } f(t)}{\partial b}$ in Taylor series about $\hat{b}_0$ and $\hat{a}_0$ to first order terms. Denote $B_1 = \frac{\partial \text{Log } f(t)}{\partial a}$

$$B_1 = -\sum_{i=1}^{r} \left(\hat{a} + \hat{b}X_i\right) + \sum_{i=1}^{r} t_i (\hat{a} + \hat{b}X_i)^{-2} + S(\hat{a} + \hat{b}X_i)^{-2}$$

And $B_2 = \frac{\partial \text{Log } f(t)}{\partial b}$

$$B_2 = -\sum_{i=1}^{r} X_i (\hat{a} + \hat{b}X_i)^{-1} + \sum_{i=1}^{r} X_i t_i (\hat{a} + \hat{b}X_i)^{-2} + SX_i (\hat{a} + \hat{b}X_i)^{-2}$$

To get the asymptotic variance – covariance matrix for both $\hat{a}$ and $\hat{b}$ it is important to obtain the second partial derivations of $\frac{\partial \text{Log } f(t)}{\partial a}$ and $\frac{\partial \text{Log } f(t)}{\partial b}$.

$$\frac{\partial^2 \text{Log } f(t)}{\partial a^2} = \sum_{i=1}^{r} (\hat{a} + \hat{b}X_i)^{-2} - 2\sum_{i=1}^{r} t_i (\hat{a} + \hat{b}X_i)^{-3} - 2S(\hat{a} + \hat{b}X_i)^{-3}$$

$$\frac{\partial^2 \text{Log } f(t)}{\partial b^2} = \sum_{i=1}^{r} {X_i}^2 (\hat{a} + \hat{b}X_i)^{-2} - 2\sum_{i=1}^{r} {X_i}^2 t_i (\hat{a} + \hat{b}X_i)^{-3} - 2S{X_i}^2 (\hat{a} + \hat{b}X_i)^{-3}$$

$$\frac{\partial^2 \text{Log } f(t)}{\partial a \partial b} = \sum_{i=1}^{r} X_i (\hat{a} + \hat{b}X_i)^{-2} - 2\sum_{i=1}^{r} X_i t_i (\hat{a} + \hat{b}X_i)^{-3} - 2SX_i (\hat{a} + \hat{b}X_i)^{-3}$$

Let $f_{11} = \sum_{i=1}^{r} (\hat{a} + \hat{b}X_i)^{-2} - 2\sum_{i=1}^{r} t_i (\hat{a} + \hat{b}X_i)^{-3} - 2S(\hat{a} + \hat{b}X_i)^{-3}$

$$f_{22} = \sum_{i=1}^{r} {X_i}^2 (\hat{a} + \hat{b}X_i)^{-2} - 2\sum_{i=1}^{r} {X_i}^2 t_i (\hat{a} + \hat{b}X_i)^{-3} - 2S{X_i}^2 (\hat{a} + \hat{b}X_i)^{-3}$$

$$f_{12} = \sum_{i=1}^{r} X_i (\hat{a} + \hat{b}X_i)^{-2} - 2\sum_{i=1}^{r} X_i t_i (\hat{a} + \hat{b}X_i)^{-3} - 2SX_i (\hat{a} + \hat{b}X_i)^{-3}$$

We have writ - up

$$\begin{pmatrix} \hat{a}_k \\ \hat{b}_k \end{pmatrix} = \begin{bmatrix} \hat{a}_{k-1} \\ \hat{b}_{k-1} \end{bmatrix} - \begin{bmatrix} f_{11.k-1} & f_{12.k-1} \\ f_{12.k-1} & f_{22.k-1} \end{bmatrix}^{-1} \begin{bmatrix} B_{1.k-1} \\ B_{2.k-1} \end{bmatrix}$$

Where $\hat{a}_{k-1}$and $\hat{b}_{k-1}$ are the values of $\hat{a}_k$ and $\hat{b}_k$ obtained after $k-1$ iterations and $\hat{a}_0 = \hat{a}_k, \hat{b}_0 = \hat{b}_k$

The unique solution of $\begin{pmatrix}\hat{a}\\ \hat{b}\end{pmatrix}$ depends on the determinant of $\begin{bmatrix} f_{11.k-1} & f_{12.k-1} \\ f_{12.k-1} & f_{22.k-1}\end{bmatrix}$

It is important to start with estimators $\hat{b}_0$ and $\hat{a}_0$ to get $\begin{pmatrix}\hat{a}\\ \hat{b}\end{pmatrix}$. We therefore have to use $\hat{b}_0$ and $\hat{a}_0$ as initial estimators in the New – Raphson iteration algorithm instead of $\hat{a}$ and $\hat{b}$. This is because the two - dimensional New – Raphson procedure can converge easily when least square estimate are used as the initial estimates. We have

$$\hat{a}_n = \hat{a}_{k-1} - \frac{B_{1.k-1}f_{22.k-1} - B_{2.k-1}f_{12.k-1}}{f_{11.k-1}f_{22.k-1} - f_{12.k-1}^2}$$

And

$$\hat{b}_k = \hat{b}_{k-1} - \frac{B_{2.k-1}f_{11.k-1} - B_{1.k-1}f_{12.k-1}}{f_{11.k-1}f_{22.k-1} - f_{12.k-1}^2}$$

Newton - Raphson procedure is iterated until the estimators the procedure converges to the expected value.

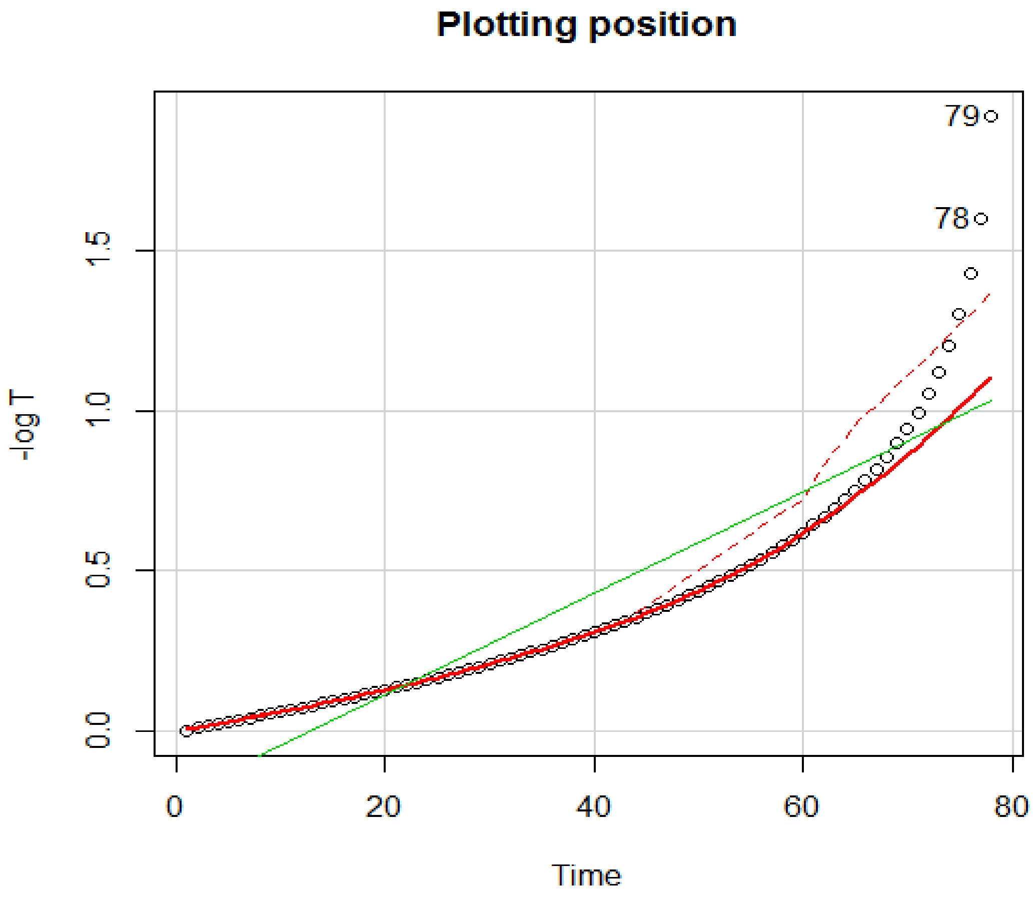
For large samples, the variance –covariance matrix of the estimators $\hat{a}$ and $\hat{b}$ is given by inverting the matrix of the second partial derivatives. This means that the approximate values $Var\hat{a}$, $Var\hat{b}$ and $Cov(\hat{a},\hat{b})$ is the elements of the matrix

$$-\begin{bmatrix} E\left(\frac{\partial^2 \mathrm{Log}\, f(t)}{\partial a^2}\right) & E\left(\frac{\partial^2 \mathrm{Log}\, f(t)}{\partial a \partial b}\right) \\ E\left(\frac{\partial^2 \mathrm{Log}\, f(t)}{\partial a \partial b}\right) & E\left(\frac{\partial^2 \mathrm{Log}\, f(t)}{\partial b^2}\right)\end{bmatrix}^{-1} = \begin{vmatrix} Var(\hat{a}) & Cov(\hat{a},\hat{b}) \\ Cov(\hat{a},\hat{b}) & Var(\hat{b})\end{vmatrix}$$

APPLICATION

A sample of 111 patients with breast cancer was obtained from the Korli-Bu Teaching Hospital in Accra Ghana in 2013. Patients times of entry into the hospital for medical checkup were recorded as well as their time of death (failure), time of absence from the hospital for treatment, time of relocating to a different community.

The survival times of patients during data collection were also recorded. The data is made up of 807 censored observations consisting of 80% of the total observation and 204 failure observations representing 20% of the total observations. The presence of cancer tumor was recorded for patients as covariate factors. The data was arranged in numerical ascendency in an equal interval of t_{i-1} to t_i to ensure that at least every interval has event failure time. This is to avoid truncation of survival times in the intervals. The patients' survival times are arranged from a common start so that patients are assumed to have equal entry time. This removes truncations in the data and puts patients' event times at equal intervals. To test whether the data follows exponential distribution, we used plotting position of the failure times.



The patients' survival time was recorded as well as their covariates. The presence of tumor was recorded against the patients' medical form and used as covariates. This is very important as the patients' survival times largely depend on covariates.

The sum of failure observation= 6154 $\Rightarrow \sum_{i=1}^{r} t_i = 6154$

Mean of $t_i = \bar{t} = 30.16$

The sum of censored values, S = 20629

x is the patients' covariates

$\sum x = 1834.5$

$\hat{x} = 1.81454$

$\sum x^2 = 5027.75$

$\hat{x}^2 = 4.941474$

$\sum x_i t_i = 55377$

$$\hat{b}_0 = \frac{\sum(x_i - \hat{x})(t_i - \hat{t})}{\sum(x_i - \hat{x})^2} = \frac{\sum x_i t_i - n\hat{x}\hat{t})}{\sum x_i{}^2 - n\bar{x}^2}$$

$$\hat{b}_0 = \frac{\sum(x_i - \hat{x})(t_i - \hat{t})}{\sum(x_i - \hat{x})^2} = \frac{\sum x_i t_i - n\hat{t}\hat{x}}{\sum x_i^2 - n\hat{x}^2} = \frac{399.06}{66.51} = 6.2013$$

$$\hat{a}_0 = \bar{t} - \hat{b}_0 \bar{x} = 56.42 - 6.012(1.81454)$$

$$\hat{a}_0 = 56.42 - 6.0(1.81454) = 45.53.$$

The first derivative of the logarithm function with respect to a is

$$B_1 = \frac{\partial \mathrm{Log}\, f(t)}{\partial a} = -\sum_{i=1}^{r}\left(\hat{a} + \hat{b}X_i\right) + \sum_{i=1}^{r} t_i(\hat{a} + \hat{b}X_i)^{-2} + S(\hat{a} + \hat{b}X_i)^{-2} = -148.21$$

The first derivative of the logarithm function with respect to b is

$$B_2 = \frac{\partial \mathrm{Log}\, f(t)}{\partial b} = -\sum_{i=1}^{r} X_i(\hat{a} + \hat{b}X_i)^{-1} + \sum_{i=1}^{r} X_i t_i(\hat{a} + \hat{b}X_i)^{-2} + SX_i(\hat{a} + \hat{b}X_i)^{-2} = -147.42$$

The second derivative of the logarithm function of $f(t)$ with respect to a is

$$f_{11} = \sum_{i=1}^{r}(\hat{a} + \hat{b}X_i)^{-2} - 2\sum_{i=1}^{r} t_i(\hat{a} + \hat{b}X_i)^{-3} - 2S(\hat{a} + \hat{b}X_i)^{-3} = -2.184 \times 10^{-6}$$

The second derivative of logarithm function of $f(t)$ with respect to b is

$$f_{22} = \sum_{i=1}^{r} {X_i}^2(\hat{a} + \hat{b}X_i)^{-2} - 2\sum_{i=1}^{r} {X_i}^2 t_i(\hat{a} + \hat{b}X_i)^{-3} - 2S{X_i}^2(\hat{a} + \hat{b}X_i)^{-3} = -1.087 \times 10^{-4}$$

The second derivative of logarithm function of $f(t)$ with respect to a and b is

$$f_{12} = \sum_{i=1}^{r} X_i(\hat{a} + \hat{b}X_i)^{-2} - 2\sum_{i=1}^{r} X_i t_i(\hat{a} + \hat{b}X_i)^{-3} - 2SX_i(\hat{a} + \hat{b}X_i)^{-3} = -4.0213 \times 10^{-6}$$

$$\begin{bmatrix} f_{11.k-1} & f_{12.k-1} \\ f_{12.k-1} & f_{22.k-1} \end{bmatrix}^{-1} = \begin{bmatrix} -2.184 \times 10^{-6} & -4.0213 \times 10^{-6} \\ -4.0213 \times 10^{-6} & -1.087 \times 10^{-4} \end{bmatrix}^{-1}$$

$$\frac{1}{2.212 \times 10^{-10}} \begin{bmatrix} -2.1844 \times 10^{-6} & -4.0213 \times 10^{-6} \\ -4.0213 \times 10^{-6} & -1.087 \times 10^{-4} \end{bmatrix}^{-1} = -\begin{bmatrix} 9873.4 & 18179.5 \\ 18179.5 & 49141.4 \end{bmatrix}$$

It is easy to see that $f_{11} < 0$, $f_{22} < 0$ but $f_{11}f_{22} - f_{12}^2 > 0$

$$\begin{pmatrix} \hat{a}_k \\ \hat{b}_k \end{pmatrix} = \begin{bmatrix} \hat{a}_{k-1} \\ \hat{b}_{k-1} \end{bmatrix} - \begin{bmatrix} f_{11.k-1} & f_{12.k-1} \\ f_{12.k-1} & f_{22.k-1} \end{bmatrix}^{-1} \begin{bmatrix} B_{1.k-1} \\ B_{2.k-1} \end{bmatrix}$$

$$\begin{pmatrix} \hat{a}_k \\ \hat{b}_k \end{pmatrix} = \begin{bmatrix} 3.6121 \\ 13.6 \end{bmatrix} - \begin{bmatrix} 9873.4 & 18179.5 \\ 18179.5 & 49141.4 \end{bmatrix} \begin{bmatrix} -148.21 \\ -147.42 \end{bmatrix}$$

$$\hat{a}_k = 45.532 - \frac{(-148.21)(49141.4) - (-147.42)(18179.5)}{(-9873.4)(-49141.4) - (18179.5)^2}$$

$$\hat{a}_k = 45.532 + \frac{4603225}{3973596010.3} = 45.533$$

$$\hat{b}_k = 6.2013 - \frac{(-147.42)(9873.4) - (-148.21)(18179.5)}{(-9873.4)(-49141.4) - (18179.5)^2} = 6.102$$

The least square estimators and the maximum likelihood estimators did not converge, for this reason, we need a second iteration. In the second iteration 45.533 and 6.102 are used as estimators.

Second iteration

B_1	B_2	f_{11}	f_{22}	f_{12}	$\hat{b}_k$	$\hat{a}_k$
-147.67	-147.91	-9873.46	-49141.47	-18179.59	6.102	45.533

$$\hat{a}_{k+1} = 45.5312 - \frac{(-147.67)(49141.47)-(-147.91)(18179.59)}{(-9873.46)(-49141.47)-(18179.55)^2} = 45.530$$

$$\hat{b}_{k+1} = 6.023 - \frac{(-147.91)(9873.46)-(-147.67)(18179.59)}{(-9873.46)(-49141.47)-(18179.55)^2} = 6.023$$

Further iterations cannot change the estimates, hence 45.530 and 6.023 are the true maximum likelihood estimates for $\hat{a}$ and $\hat{b}$.

For large samples, the variance –covariance matrix of the estimators $\hat{a}$ and $\hat{b}$ is given by inverting the matrix of the second partial derivatives. This means that the approximate values $Var\hat{a}$, $Var\hat{b}$ and $Cov(\hat{a},\hat{b})$ is the elements of the matrix

$$-\begin{bmatrix} E(\frac{\partial^2 \text{Log} f(t)}{\partial a^2}) & E(\frac{\partial^2 \text{Log} f(t)}{\partial a \partial b}) \\ E(\frac{\partial^2 \text{Log} f(t)}{\partial a \partial b}) & E(\frac{\partial^2 \text{Log} f(t)}{\partial b^2}) \end{bmatrix}^{-1} = \begin{bmatrix} (9879.46) & 18179.59 \\ 18179.59 & 49147.47 \end{bmatrix}$$

$$\begin{bmatrix} Var(\hat{a}) & Cov(\hat{a},\hat{b}) \\ Cov(\hat{a},\hat{b}) & Var(\hat{b}) \end{bmatrix} = \begin{bmatrix} (9879.46) & 18179.59 \\ 18179.59 & 49147.47 \end{bmatrix}$$

From the second iteration estimate

$\hat{a} = 45.530$ this means that the patients have no tumor in their breast and have average survival time of 46 months. From the study, the presence of tumor in the breast cancer contributes to six times the death of the cancer patients

Simulation with covariates

The method used to simulate the data without covariates is similar to the method used to simulate covariate data. The only difference is the addition of a covariate vector to the simulation method discussed in Section 4.4. The only difference is that, data that contains covariates variables needs a covariate vector to be introduced into the simulation process. In the covariate simulation, we used uniform distribution as possible distribution for the covariates.

Table 1: Simulated Parameters with covariates

No of subjects at risk	No of events	Proportion of subjects with event	Total follow-up time	Median follow-up time	Density of incidence
2000	666	0.333	8796.176	4.17874	0.07571472
10000	5588	0.5588	55002.15	5.37774	0.101596
30000	16732	0.5577333	164435	5.362376	0.1017545
50000	27802	0.55604	274169.8	5.366777	0.1014043
100000	19181	0.19181	449228.4	4.039394	0.04269765
150000	28982	0.1932133	674962.8	4.040854	0.04293866
200000	38533	0.192665	899924.4	4.044289	0.04281804
500000	499994	0.199988	961884.53	4.043159	0.04322151

When the data was simulated to 2000, the number of patients at risk of cancer also increased to 666 where the total length of follow-up is 8796.176 with a mean follow-up time of 0.333. The median follow-up time and density of incidence are 4.17874 and 0.07571472 respectively. This means that when the data was simulated from 1011 to 2000, the event proportion became 0.333.

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