ORIGINAL ARTICLE

Trends in breast cancer incidence rates by age and tumor characteristics of women in the city of Isfahan for the period 2001-2010: An application of joinpoint analysis

Mehdi Tazhibi, Zahra Fazeli Dehkordi, Shadi Babazadeh[1]

Department of Biostatistics and Epidemiology, Faculty of Health, [1]Department of Radiation Oncology of Breast Cancer of Seyed-al-Shohada, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Cancer incidence trends use by health officials in order to program evaluations and development of cancer control strategies. The trends of cancer incidence have used to evaluate programs and develop the cancer control strategies. The aim of this study is to analyze changes of breast cancer incidence trends in Isfahan city using joinpoint regression models. **Materials and Methods:** The study was based on all cases of breast cancer reported among women residing in the city of Isfahan for the period 2001-2010. Age-standardized rates were calculated for each tumor characteristics, using the direct method. Joinpoint regression was used to provide estimated annual percentage change. **Results:** A plot of the age-specific rates of breast cancer showed an increase in all age groups from 30 to 69 years and sharp increase in the incidence of breast cancer confined to estrogen receptor-positive and progesterone receptor-positive tumors and the significant change (2003) by progesterone receptor$^-$ tumors. The analysis by tumor size and grade, incidence rates decreased for tumors >5 cm by 10.6% since 2006.7 and for poorly differentiated tumor by 26.1% since 2007.8. No decrease in incidence was observed for group of proportion of positive lymph nodes to lymph node surgery ≥25%. The proportion of positive lymph node to surgery node ≤25% (nonsignificant) was upward. **Conclusion:** The trend of incidence rates with tumor size ≤2, well-differentiated tumor grade, moderately differentiated tumor grade, positive estrogen and progesterone hormone receptors was upward. The pattern of breast cancer can help to cancer prevention and prognosis, selecting the best type of surgery.

Key words: Age trend, breast cancer, incidence, joinpoint regression, tumor characteristics

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INTRODUCTION

Cancer incidence trends uses by health officials in order to program evaluations and development of cancer control strategies. Incidence rate is the most important in cancer registry. Trend analysis is a technique that aims to identify a pattern of changes, or trend, in a series of observations. It is therefore, important to evaluate trends in incidence within various time segments, to identify changes in trends, and to determine the most recent trends in rates and counts.[1]

Breast cancer is an adenocarcinoma that starts in the breast cells.[2] Women make up more than 99% of patients in this cancer. Breast cancer is less prevalent in the age of 30,[3] among white women in developed countries, and urban communities is more than other regions.[4] This cancer, after lung cancer is the second leading cause of cancer deaths. The risk of developing breast cancer in women life time is 12.5% (that is one of eight) and risk of dying from breast cancer is 3.6% (that is one of 28).[5]

Breast cancer incidence is about 22/100000 and its prevalence is 120/100000 in Iran.[6] Isfahan is located in the first ranking of cancer in the country, and the breast cancer among women has been assigned the first place to itself. Based on the statistics of 2004, about 10% of breast cancer cases in the country have been reported in Isfahan.[7]

Joinpoint regression is composed of a few continuous linear phases, which are often useful to describe changes in incidence and mortality rate trends. Joinpoint regression due to the assess of the response variable (breast cancer incidence) behavior at different intervals explanatory variables (time) is used in abundance in cancer data analysis.[8] In a study conducted in 2010

Address for correspondence: Ms. Zahra Fazeli Dehkordi, Department of Biostatistics and Epidemiology, Faculty of Health, Isfahan University of Medical Sciences, Hezarjarib Street, Isfahan, Iran. E-mail: z_fazeli_d@yahoo.com

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by Burrows, *et al*. in the field of incidence of treatment for end the last stage renal disease among individuals with diabetes in the US continues to decline was used a joinpoint regression to estimate the model parameters, and the value of parameter regression were estimated for each piece.[9] Leslie, *et al*. applied joinpoint regression to describe changes in hip fracture rates in Canada.[10] La Torre, *et al*. considered a joinpoint analysis in the field an assessment of the effect of hepatitis B vaccine in decreasing the amount of hepatitis B disease in Italy.[11] Silva, *et al*. used a joinpoint regression to evaluation trends in the epidemiologic paradox of low birth weight in Brazil.[12]

Women are an important part of community and their health is deeply linked with the health of others; hence, considering the high prevalence of breast cancer in Iran and given the fact that Iranian women compared with developed countries at least a decade earlier the disease can be caught,[5] the present study was conducted to determine the pattern of breast cancer incidence rates by age and tumor characteristics in women using joinpoint regression model.

MATERIALS AND METHODS

This research was a descriptive-analytical of the type cross-sectional time series study. Data on breast cancer incidence for the years 2001 through 2010 were obtained among women residing in the city of Isfahan, referring to cancer treatment centers; The study was based on 3640 patients and restricted to women in the age of 30-69.

This information includes personal details and all information related to the tumor cancer including such as age at diagnosis categorized in 5-year intervals groups, tumor size (≤2 cm, 2.1-5 cm, and >5 cm), grade (well-differentiated, moderately differentiated, and poorly differentiated), estrogen/progesterone receptor status (positive vs. negative) and proportion of positive lymph nodes to lymph node surgery (<25% vs. ≥25%).

Age-specific and age-standardized incidence rates were calculated. Standardization was performed using the direct method (Isfahan province female population of the census in 2006 as a standard population).

The joinpoint regression analysis was used to identify points where a statistically significant change over time in linear slope of the trend occurred.[8] The analysis starts with the minimum number of joinpoints, and tests, whether one or more joinpoints are statistically significant and should be added to the model. The tests of significance use a Monte Carlo permutation tests method with 4499 replicates. In the final model, each joinpoint indicates a statistically significant change in trend, and estimated annual percentage change and estimated average annual percentage change are computed for each of those trends by means of least squares method assuming a normal distribution (the dependent variable was the age-standardized rate). A maximum number of one joinpoint was allowed for estimations because the number of years of available data was 10. We used Hudson method for estimating joinpoints because it is more realistic that the joinpoints take any value within the observed data range [Appendix]. Joinpoint software, version 3.5.2[13] and statistical analysis in social science (SPSS) software, version 18 were used.

RESULTS

Age-specific breast cancer incidence rates are shown in Figure 1. Statistically significant changes in breast cancer incidence rates were associated with increasing in the age groups 40-44, 45-49, and 55-59 years from 2001 to 2010. The annual percentage change in this period for the above categories was estimated 6.2%, 5.3%, and 3.5%, respectively. Breast cancer incidence rates in the age group of 40-44 years changed during the study from 17.6/100000 to 25/100000 in 2010. Joinpoint analysis of trends by age at diagnosis didn't indicate any break during the whole period [Table 1].

Results of the joinpoint analysis of trends by hormone receptors status (estrogen receptor [ER] and progesterone receptor [PR]) are shown in [Table 2]. The largest increase in the incidence of breast cancer by ER and PR status was in positive group and the statistically significant change was seen in the year 2003 by PR^- tumors. The average annual percentage change for recent five, 6.9% and for 10 years, 11% was estimated.

The largest increase of breast cancer by tumor size was in size of ≤2 cm with an estimated annual increase of 18.2%. Furthermore in 2006.7, a statistically significant change was seen in the breast cancer increase by tumor size of >5 cm [Table 2]. The joinpoint analysis in the two periods

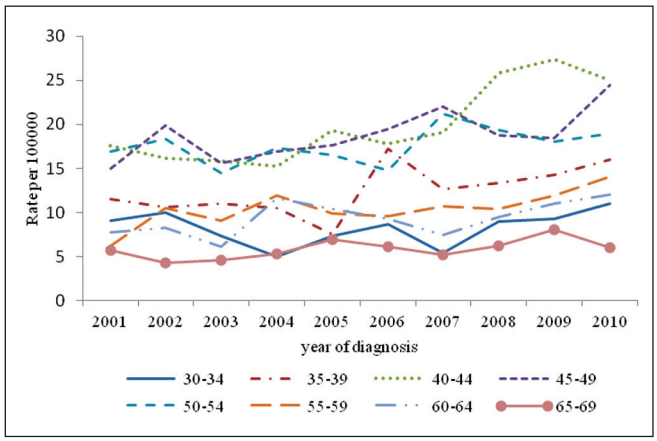

Figure 1: Age-specific breast cancer incidence rates in Esfahan city, 2001-2010

Table 1: Breast cancer incidence rates and joinpoint analysis by age (2001-2010)

Age	2001		2010		EAPC 2000-2010	Trend 1		Trend 2	
	Number	Rate	Number	Rate		Year	EAPC	Year	EAPC
30-34	28	9.1	45	11	1.6	2001-2010			
35-39	35	11.5	57	15.9	4.6	2001-2010			
40-44	56	17.6	96	25	6.2*	2001-2010			
45-49	45	14.9	100	24.4	3.5*	2001-2010			
50-54	45	16.9	84	18.9	1.7	2001-2010			
55-59	18	6.2	69	14	5.3*	2001-2010			
60-64	21	7.8	51	12	4.1	2001-2010			
65-69	17	5.7	23	6.1	3.9	2001-2010			

*The EAPC is significantly different from 0 ($P < 0.05$); EAPC = Estimated annual percent change

Table 2: Breast cancer incidence rates and joinpoint analysis by tumor characteristic (2001-2010)

Tumor characteristic	2001		2010		EAPC 2000-2010	Trend 1		Trend 2	
	Number	Rate	Number	Rate		Year	EAPC	Year	EAPC
Size									
≤2 cm	19	6.4	84	20.1	18.2*	2001-2010	18.2*		
2.1-5 cm	167	56.8	271	65.7	2.4*	2001-2010	2.4*		
>5 cm	68	22.9	93	22.7	0.2	2001-2006.7	6.3	2006.7-2010	−10.6
Grade									
Well-difference	26	8.8	37	8.9	8*	2001–2010	8*		
Moderately difference	49	16.5	132	32	10.2*	2001-2007.7	16.6*	2007.7-2010	−15.1
Poorly difference	20	6.8	54	12.9	7.3*	2001-2007.8	17*	2007.8-2010	−26.1
ER status									
Negative	55	18.5	150	36.7	5.1*	2001-2010	5.1*		
Positive	63	21.3	264	63.9	10.5*	2001-2010	10.5*		
PR status									
Negative	48	16.1	168	40.9	7.2*	2001-2010	7.2*		
Positive	69	23.5	241	58.4	8.8*	2001-2003	26.5*	2003-2010	6.9*
Lymph+nodes/lymph node surgery									
<25%	137	46.2	180	43.4	1.7	2001-2010	1.7		
≥25%	109	37.2	102	24.8	0.6	2001-2010	0.6		

*The EAPC is significantly different from 0 ($P < 0.05$); EAPC = Estimated annual percent change; ER = Estrogen receptor; PR = Progesterone receptor

showed an increase by 6.3% per year in the first period and a nonsignificant decline in the second period [Figure 2].

Results of the joinpoint analysis of trends by grade of tumor are shown in Table 2. In the well-differentiated grade, a steady increase was observed over the whole period (8%). In the moderately differentiated grade, incidence increased by 16.6% per year from 2001 to 2007.7 then declined by 15.1% per year from 2007.7 to 2010. In the poorly differentiated grade, incidence increased by 17% per year from 2001 to 2007.8 then declined by 26.1% per year from 2007.8 to 2010 [Figure 3].

The highest increase in the incidence of breast cancer by proportion of positive lymph nodes to lymph node surgery was showed in group of ≤25%, although this increase was not significant and joinpoint analysis of trends by this tumor characteristic didn't indicate any break during the whole period [Table 2].

DISCUSSION

Recent reports have documented sudden, unprecedented declines in the incidence of breast cancer, particularly for invasive, ER-positive tumors diagnosis in women 50 years and older. Thus far, substantial drops have been observed in the US, New Zealand, and Canada but not in the Netherlands, Norway, and Sweden. In population reporting a decrease, gradual incidence declines began as early as 1999 but accelerated in 2002 after the early and widely publicized termination of the Women's Health Initiative.[23]

Jemal, *et al*. study (2003-1975) on 4,54,728 patient data in United States showed the largest percentage decreases from 2002 to 2003 that occurred in women 55-59 years old (11.3%), 60-64 years old (10.6%), and 65-69 years old (14.3%). The downturn in incidence rate from 2002 to 2003 in women 50-69 years old may reflect early consequences of the reduced use of hormone replacement therapy (HRT).[15]

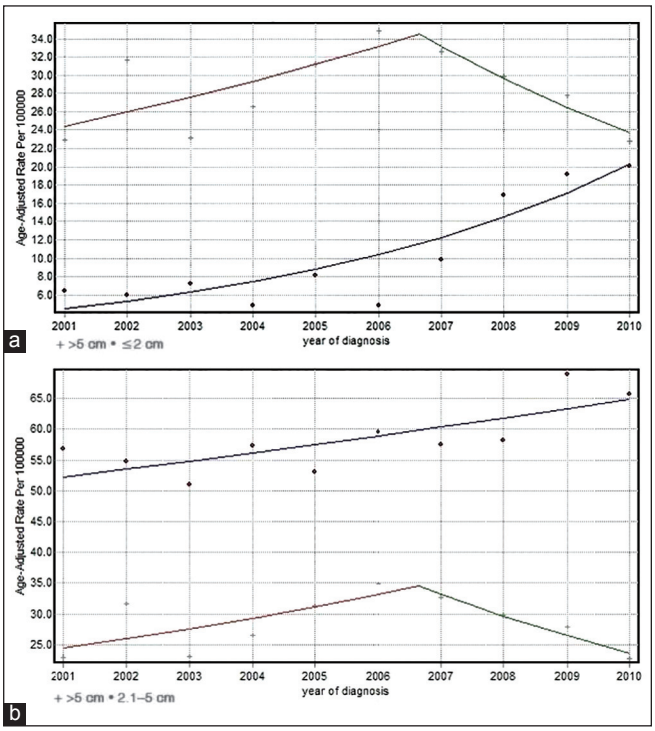

Figure 2: Age-standardized (per 100000) breast cancer incidence rates by tumor size in Esfahan city, 2001-2010

Daubisse-Marliac, *et al*. study (2007-1990) on 19,239 patient data in French showed an increase in incidence rates in the 20-49 and the ≥75 age groups, with a mean annual increase of 1.6% and 0.9%, respectively. In the age group of 50-74 years, incidence increased by 1.5% per year from 1990 to 1999 and by 6% per year from 1999 to 2003. From 2003, there was a 3.4% annual drop in incidence. The reduction in HRT prescription may explain this decrease.[16] Francoise Renard, *et al*. study (2006-1999) in Belgium showed a stable incidence rate in the group of 35-49 years in Flemish Region, an increase from 1999 to 2003 (5.4%) and then a sharp decrease from 2003 to 2006 (−4%). In the oldest age group, a steady increase was observed over the whole period (1.5%). This phenomenon was interpreted as resulting from a drastic decline in HRT use.[17] Carsten Rusner, *et al*. study (2007-1998) among women aged from 50 to 69 years in Germany showed the age-standardized incidence rates in breast cancer virtually constant were over the entire period in all regions and no substantial changes over time occurred within the age analyses. The lack of temporal changes in breast cancer incidence may be explained by introduction of opportunistic and organized mammography screening and low absolute levels of HRT prescription in Germany.[18]

Brinton, *et al*. study (1992-2004) on 3,87,231 patient data in US showed the number of breast cancers increased among younger women during 1992-2004, but this increase largely reflected population growth rather than rising rates of invasive disease.[19]

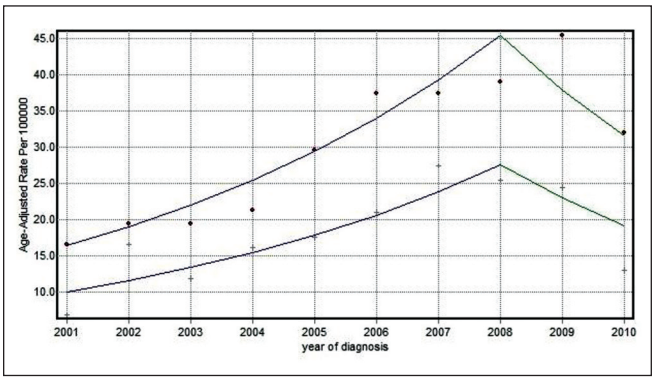

Figure 3: Age-standardized (per 100000) breast cancer incidence rates by tumor size in Esfahan city, 2001-2010. +: poorly difference, •: moderately difference

Shin, *et al*. study (1993-2002) on 1,61,800 patient data among Eastern and Southeastern Asian women more than 20 years old showed the incidence rates increased gradually in all countries. Incidence rates increased significantly in Korea during the 10-year period in all age groups except the >70 group. The Philippines had the lowest annual percentage change (APC) in most age groups. Women aged 50-69 years had significantly higher APC in most countries and registries, but not in Japan, rural China, or the Philippines.[20] The number and mean age of breast cancer cases is expected to increase as the female Asian population ages, the prevalence of certain risk factors change (early menarche, late menopause, low parity, late age at first live birth, and low prevalence of breastfeeding), and as Asian countries introduce mass screening programs.

Unfortunately, the incidence of breast cancer in Iranian women occurs 10-15 years lower than western countries and the average age of the most cases at age 40-49 are reported.[6]

The incidence of cancer in women 55 years and older is high and power of the immune system in this age is low; The results of this study showed that breast cancer incidence has increased in all age categories. The increase in incidence rates were in the 40-44, 45-49, and 55-59 age groups, with a mean annual increase of categories 6.2%, 3.5%, and 5.3%, respectively. The results of this study were consistent with the incidence in East Asia.

Jemal, *et al*. study by 5-year age interval showed that the decrease in the incidence rates from 2002 to 2003 was much larger in women 50-69 years old for ER^+ and PR^+ than for ER^- and PR^- tumors from 2002 to 2003, the incidence rate in women 65-69 years old decreased by 20% for ER^+ and PR^+ tumors compared to an increase of 2% for ER^- tumors and a decrease of 9% for PR^- tumors.[15] Kerlikowske, *et al*. prospectively collected data from 1997 to 2003 for 6,03,411 screening mammography examinations performed on women aged 50-69 years in US of these women, 3238 were diagnosed with breast cancer within 12 months of a

screening examination. Between 2001 and 2003, annual rates of ER^+ invasive breast cancer declined by 13% while this rates were stable during until 2001. In the first quarter of 2003 increased slightly (not significant) was observed in patients with ER^- tumors.[21] Hausauer, *et al*. study (1992-2004) among women aged more than 20 years in Asian/Pacific Islander, Hispanic, and African-American women in the US showed in Asian/Pacific Islander women, perceptible, but statistically nonsignificant decreases were observed for hormone receptor-positive. Rates of hormone receptor-negative tumors increased among African-Americans (26.1%) and Hispanics (26.9%) during 2001-2004. The data presented in these analyses provide further evidence that population-level Hormone Therapy (HT) use is a major influence on population-level rates of particular breast cancer subtypes, especially receptor-positive tumors.[14]

Brinton, *et al*. study showed that despite the declining use of hormone therapy, from 1999 to 2004, the age-standardized incidence of breast cancer was stable in the all-time interval by hormone receptors and the highest incidence (21.7) was observed at the age of 30-39 years.[19]

Since about 60% breast cancer cases of ER is positive and the role of estrogen and progesterone can't be separated in breast carcinogenesis; hence, the prognosis of patients in this regard will be very important. Results showed the highest increase in the incidence of breast cancer according to ER and PR status was positive. Significant change in 2003 was seen in the incidence of breast cancer with PR^+. The average annual percentage change for recent five, 6.9% and for 10 years, 11% was estimated.

Jemal *et al*. and Hausauer, *et al*. studies showed breast cancer incidence rates was confined to small tumors (≤2 cm) in joinpoint analysis by tumor size. Saturation in mammographic screening would theoretically maximum lead time so as to increase the diagnosis of small and *in situ* tumors.[14,15] Brinton, *et al*. study showed the highest incidence rate by tumor size occurred in small tumors (≤2 cm).[19]

Results of this study showed the largest increase of breast cancer by tumor size was in size of ≤2 cm. Furthermore, a significant change-point was seen in the breast cancer tumor size >5 cm in 2006.7. The joinpoint analysis in the two periods showed a significant increase in the first period and an insignificant decline in the second period.

Brinton, *et al*. study showed the highest incidence rate by grade occurred in high grade (24.8).[19]

Results of this study showed according effect of exact tumor size and histological cancer cells at diagnosis on choice of surgery and complementary therapies, awareness preaching classes of women with symptoms of cancer, screening and identifying patients in 2008 caused significant changes in the trend of reducing the incidence of breast cancer this year with the grade of poorly differentiated.

Brinton, *et al*. study showed the highest incidence rate by lymph nodes status occurred in negative lymph node (21.6).[19] Since the probability of relapse in patients with lymph nodes in cancer patients is 75% more than the other, the results of this study showed the highest increase in the incidence of breast cancer by proportion of positive lymph nodes to lymph node surgery was in <25%, group, although this increase was not significant.

CONCLUSION

Awareness preaching classes of women with symptoms of cancer, screening and identifying patients in 2008 caused significant changes in the trend of reducing the incidence of breast cancer this year with the grade of poorly differentiated. Increase of breast cancer by tumor size of <2 cm and decline the incidence of >5 cm, reduce proportion of positive lymph nodes to lymph node surgery in 25% can be attributed mainly to enhance women's awareness regarding breast self-examination and physical examination, and greater use of mammography. Definitely, women's knowledge regarding the breast cancer symptoms and screening behaviors is a significant factor to detection of less advanced stage.

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APPENDIX

The joinpoint regression model, which is composed of a few continuous linear phases, is often useful to describe changes in trend data. Suppose that for the observations, $\{(x_1, y_1),...(x_n, y_n)\}$ $x_1 \le x_2 \le \ldots \le x_n$, the responses $y_i = E(y|x) + e_i$, $i = 1,\ldots,n$, with $E(e_i) = 0$ and $V(e_i) = \sigma^2_i$ for random errors e_i. The joinpoint regression models assume that, in each segment, the $E(y|x)$ follows a linear model

$$E(y|x) = \beta_{k,0} + \beta_{k,1}x, \text{ if } \tau_{k-1} < x \le \tau_k,\ k = 1,\ldots, K+1 \quad (1)$$

where $\tau_0 = -\infty$, $\tau_{k+1} = \infty$ and $E(y|x)$ is continuous throughout $[X_0, X_n)$, such that

$$\beta_{k,0} + \beta_{k,1}\tau_k = \beta_{k+1,0} + \beta_{k+1,1}\tau_k \text{ for } k = 1,\ldots,K+1 \quad (2)$$

As the response is continuous at the change points, we call model (1) the joinpoint model and the τ_ks joinpoints (JPs). An alternative parameterization of the JP model (1) is

$$E(y|x) = \beta_{10} + \beta_{11}x + \sum_{i=1}^{k}\delta_k(x-\tau_k)^+, \quad (3)$$

where $\delta_k = \beta_{k+1,1} - \beta_{k,1}$ and $(x-\tau_k)^+ = x - \tau_k$ if $x \ge \tau_k$ and 0 otherwise. This parameterization implicitly satisfies the continuity of $E(y|x)$ at τ_k

Estimation of multiple JP model in continuous scale (Hudson's method)

τ and β are unknown parameters in the model and must be estimated. One of the methods for estimation in joinpoint regression is the Hudson method. This method for a model with a change-point was introduced in 1961 by Hadson

and for multiple change-point models introduced in 2007 by Yu, *et al*. that assumes the joinpoints take any value within the observed data range.

For a *K*-JP model, there are $K+1$ segments, $S_1,\ldots, S_{k+1}$ and K JPs. The k^{th} JP $\tau_K \in [x_{i_k}, x_{i_k+1}]$ divides segments S_k and S_{k+1}. The number of possible trials for a *K*-JP model is given by

$$M = \sum_{r=0}^{k} 2^r \binom{K}{r} \binom{n-K-2}{r}$$

Then, for each of the M state estimates τ, β and the sum of squared errors are calculated and state that has the lowest sum of squared errors is selected as the final model and the estimates of the model parameters are chosen. We do the following steps for all of the M possible states:

First, regression coefficients using weighted least squares method obtains for each segment

$$\underline{\hat{\beta}} = (\underline{\hat{\beta}}_1,\ldots, \underline{\beta}_{k+1})' = (X'\Sigma^{-1}X)^{-1} X'\Sigma^{-1}\underline{Y}$$

When the e'_is are independent, hence Σ are diagonal matrices and as a result:

$$(X'\Sigma^{-1}X)^{-1} = \begin{pmatrix} (X_1'\Sigma_1^{-1}X_1)^{-1} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & (X'_{K+1}\Sigma_{K+1}^{-1}X_{K+1})^{-1} \end{pmatrix}$$

$$(X'\Sigma^{-1}Y) = \begin{pmatrix} X_1'\Sigma_1^{-1}Y_1 \\ \vdots \\ X'_{K+1}\Sigma_{K+1}^{-1}Y_{K+1} \end{pmatrix}$$

Thus we have for each segment separately:

$$\hat{\beta}_i = (X_i'\Sigma_i^{-1}X_i)^{-1} X_i'\Sigma_i^{-1}Y_i$$

The k^{th} JP $\hat{\tau}_k$ is obtained by solving equation $\hat{\beta}_{k,0} + \hat{\beta}_{k,1}\tau_k = \hat{\beta}_{k+1,0} + \hat{\beta}_{k+1,1}\tau_k$. Let T_k denote the location of $\hat{\tau}_k$ If the estimated JP $\hat{\tau}_k$ is in the "right" place, i.e., $x_{i_k} < \hat{\tau}_k < x_{i_{k+1}}$, then $T_k = 1$; otherwise $T_k = 2$ and further adjustment is needed.[22]