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Comparing Trends in Cancer Rates Across Overlapping Regions

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Abstract

Monitoring and comparing trends in cancer rates across geographic regions or over different time periods has been one main task of the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program as it profiles health care quality as well as decides health care resource allocations within a spatial-temporal framework. A fundamental difficulty, however, arises when such comparisons have to be made for regions or time intervals that overlap, e.g. comparing the change in trends of mortality rates in a local area (e.g. the mortality rate of Breast Cancer in California) with a more global level (i.e. the national mortality rate of Breast Cancer). In view of sparsity of available methodologies, this paper develops a simple corrected Z-test that accounts for such overlapping. The performance of the proposed test over the two-sample "pooled" t-test that assumes independence across comparison groups is assessed via the Pittman asymptotic relative efficiency as well as Monte Carlo simulations and applications to the SEER cancer data. The proposed test will be important for the SEER*STAT software, maintained by the NCI, for the analysis of the SEER data.

Key words: Age-adjusted cancer rates; Annual percent change (APC); Surveillance; Trends; Hypothesis testing; Pittman asymptotic relative efficiency (ARE).

1 Introduction

Cancer continues to be a major epidemic concern in the United States, contributing the second most deaths each year in the United States. For instance, cancer resulted in approximately 570,280 deaths in year 2005 (American Cancer Society 2005), while the overall cost of cancer, including the costs of diagnosis, treatment, lost person-hours, and education and research, tallied as much as $189.8 billion for 2004 (Ghosh and Tiwari, 2007).

Many public and private agencies dealing with cancer and related problems depend on the rates of cancer deaths or new cases as an estimate of cancer burden for planning and resource allocation. Among these agencies, the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is the most authoritative and comprehensive source of information on cancer incidence and deaths in the United States, which currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately over a quarter of the entire US population. One main task of the SEER program is to routinely monitor and compare trends in cancer mortality and incidence rates across geographic regions or over different time periods. The data are analyzed by SEER*STAT software, which is maintained by the NCI, with the results periodically published at http://seer.cancer.gov/csr/. Indeed, this surveillance task has important social and economic ramifications, ranging from deciding which cancer programs get funded to deciding how the funds are allocated among various regions. Having reliable and accurate comparisons of trends of cancer rates is thus of tremendous importance.

However, a fundamental statistical difficulty arises when such comparisons, largely for policy making purposes, have to be made for regions or time intervals that overlap, e.g. comparing the most recent changes in trends of cancer rates in a local area (e.g. the mortality rate of breast cancer in California) with a more global level (i.e. the

national mortality rate) over two overlapping time periods, because of availability of the data. For example, as detailed in the data analysis section, it is of substantial interest to compare the changes in California cancer mortality rates with the national cancer mortality rates in the last 15 years. However, for a 15-year block, the California cancer rates were available for 1990-2004, while the national data were available for 1988-2002.

As the current SEER*STAT software utilizes the two-sample pooled t-test (Kleinbaum et al., 1988) that assumes independence across comparison groups, it is not appropriate for the aforementioned settings. In this paper, we develop a simple corrected Z-test that accounts for the overlap and that will be available for the NCI SEER program.

The rest of this article is structured as follows. In Section 2, we introduce the cancer rate regression model that has been used in the SEER analysis, followed by the classical t-test, employed by the current SEER*STAT software for comparing the trends between two independent regressions in Section 3. In Section 4, we propose a corrected Z-test that properly accounts for correlation when the comparison has to be made across two overlapping regions or time intervals. The performance of the proposed test is assessed via applications to the SEER cancer data, with its validity confirmed by simulations in Section 5. We conclude with a short summary in Section 6. The technical detail is relegated to the Appendix.

2 Age-adjusted Cancer Rate Regression Model and Annual Percent Change

Let n_{ji} and d_{ji} be the mid-year population at risk and counts of deaths or incidents for age group j $(j = 1, \ldots, J)$ at time $t_i, i = 1, \ldots, I$. The age-adjusted rate, at time t_i, is

typically computed as

$$\tilde{r}_i = \sum_{j=1}^{J} w_j \frac{d_{ji}}{n_{ji}}, \tag{1}$$

where $w_j > 0, j = 1, \ldots, J$, are the known standards for the age group j so that $\sum_{j=1}^{J} w_j = 1$. In the SEER program, there are $J = 19$ standard age-groups consisting of 0-1, 1-4, 5-9, $\ldots$, 85+.

To describe the trend in mortality or incidence, we often use a logarithm transformation of $\tilde{r}_i$ and fit a linear regression on the calendar time. However, for rare cancers, $\tilde{r}_i$ defined in (1) can be zero, making its logarithm transformation undefined. To avoid this situation, we introduce a correction factor, which amounts to distributing a count of 1 uniformly to all J categories, and hence adding $1/J$ to d_{ji}, yielding a zero-corrected rate (Tiwari et al., 2006)

$$r_i = \sum_{j=1}^{J} w_j \frac{d_{ji} + 1/J}{n_{ji}}. \tag{2}$$

Numerically, the difference between (1) and (2) is negligible; however, the logarithm of the latter is always well defined. A simple linear regression has been established by a number of authors (Kim et al. 2000; Tiwari et al., 2005; Fay et al., 2006) to link the logarithm transformation of mortality or incidence rate r_i, say, $y_i = \log(r_i)$, to the calendar time t_i, via

$$y_i = \beta_0 + \beta_1 t_i + e_i, \tag{3}$$

where the e_i are i.i.d. normal with mean 0 and variance σ^2, which measures the fluctuation of rates over years.

Model (3) is commonly referred to as the (transformed) Cancer Rate Regression Model in the SEER analysis (see e.g. Kim et al. 2000; Tiwari et al., 2005; Fay et al., 2006), which can be conveniently fitted for observed data $(t_i, y_i), i = 1, \ldots, I$, using the least squares or the maximum likelihood estimation methodologies. The resulting estimates of $\beta = (\beta_0, \beta_1)$ are denoted by $\hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1)$.

Regression coefficient β_1 in (3) has been of main interest, as it transcribes the trends of mortality or incidence. Indeed, the annual percent change (APC), defined as $APC = 100(e^{\beta_1} - 1)$, has been used by the NCI (see e.g. Fay et al., 2006) for describing the trends of cancer incidence and mortality. Its estimate, $\widehat{APC} = 100(e^{\hat{\beta}_1} - 1)$, along with its variance, obtained via the delta method (Ries et al., 2003; Fay et al., 2006), $\hat{V} = 10^4 e^{2\hat{\beta}_1}\hat{\sigma}^2_{\hat{\beta}_1}$, constitutes the basis of drawing inference on the trend, e.g. constructing confidence intervals or testing hypothesis. Here, $\hat{\sigma}^2_{\hat{\beta}_1} = \hat{\sigma}^2 / \sum_{i=1}^{I}(t_i - \bar{t})^2$ and the unbiased estimator $\hat{\sigma}^2 = \sum_{i=1}^{I}(y_i - \hat{y}_i)^2/(I-2)$, where $\bar{t} = \sum_{i=1}^{I} t_i/I$ and $\hat{y}_i$ is a prediction of y_i based on (3), namely, $\hat{y}_i = \hat{\beta}_0 + \hat{\beta}_1 t_i$.

For the purpose of health-care evaluations, it is of substantial interest to compare the APC of one region (e.g., county or state level) to that of another region, or to a more global level (e.g. state or national level). One may also be interested in comparing the APCs over two overlapping intervals. In the following, we derive the tests for comparing APCs of two overlapping regions within two overlapping time intervals, which includes the aforementioned local-vs-global comparison as a special case.

3 Test for Equality of APCs for Two Independent Regressions

To start, we briefly review the test for comparing APCs for two independent comparison groups, e.g. for two non-overlapping regions or time intervals. That is, we consider two independent linear regressions

$$y_{ki} = \beta_{k0} + \beta_{k1} t_{ki} + e_{ki}, i = 1, \ldots, I_k, \tag{4}$$

for $k = 1, 2$, flagging groups 1 and 2, respectively.

Let APC_1 and APC_2 be the corresponding APC values for these two regressions. Often, we wish to test the null hypothesis $H_0 : APC_1 = APC_2$ versus the alternative

hypothesis $H_1 : APC_1 \neq APC_2$, which is equivalent to testing $H_0' : \beta_{11} = \beta_{21}$ versus $H_1' : \beta_{11} \neq \beta_{21}$. Under the assumption that error variances for the two groups are equal, a test for the latter is given by Kleinbaum et al. (1988):

$$t = \frac{\hat{\beta}_{11} - \hat{\beta}_{21}}{\sqrt{S_p^2 \left((\sum_{i=1}^{I_1} (t_{1i} - \bar{t}_1)^2)^{-1} + (\sum_{i=1}^{I_2} (t_{2i} - \bar{t}_2)^2)^{-1} \right)}} \sim t_{(I_1 + I_2 - 4)}, \tag{5}$$

where

$$\bar{t}_k = \sum_{i=1}^{I_k} t_{ki} / I_k$$

for $k = 1, 2$, and S_p^2 is the "pooled" unbiased estimate of σ^2 given by

$$S_p^2 = \frac{\sum_{i=1}^{I_1} (y_{1i} - \hat{y}_{1i})^2 + \sum_{i=1}^{I_2} (y_{2i} - \hat{y}_{2i})^2}{I_1 + I_2 - 4},$$

where $\hat{y}_{ki} = \hat{\beta}_{k0} + \hat{\beta}_{k1} t_{1i}$ are the predictions for $k = 1, 2$. Test (5) is currently employed by the NCI SEER*STAT software (http://seer.cancer.gov/seerstat).

4 A Corrected Z-test for Two Dependent Regressions

Much difficulty arises as (5) is no longer valid if the independence assumption is violated. Suppose we are interested in comparing the APCs of two overlapping regions, say, Region 1 and Region 2, with data collected over two time intervals $[t_1, t_m]$ and $[t_{s+1}, t_{s+I}]$, which possibly overlap. That is, $t_1 \leq t_{s+1} < t_m \leq t_{s+I}$. We modify (4) to accommodate this situation

$$y_{1i} = \beta_{10} + \beta_{11} t_i + e_{1i}, i = 1, \ldots, m, \tag{6}$$

for Region 1, and

$$y_{2i} = \beta_{20} + \beta_{21} t_i + e_{2i}, i = s + 1, \ldots, s + I, \tag{7}$$

for Region 2. Let $\hat{\beta}_{11}$ and $\hat{\beta}_{21}$ be the estimates of the slope parameters of the regression lines for these two regions respectively. In particular,

$$\hat{\beta}_{11} = \frac{\sum_{i=1}^{m}(t_i - \bar{t}_1)(y_{1i} - \bar{y}_1)}{\sum_{i=1}^{m}(t_i - \bar{t}_1)^2}, \ \hat{\beta}_{21} = \frac{\sum_{s+1}^{s+I}(t_i - \bar{t}_2)(y_{2i} - \bar{y}_2)}{\sum_{s+1}^{s+I}(t_i - \bar{t}_2)^2}.$$

where $\bar{y}_1 = \sum_{i=1}^{m} y_{1i}/m$, $\bar{t}_1 = \sum_{i=1}^{m} t_i/m$, $\bar{y}_2 = \sum_{i=s+1}^{s+I} y_{2i}/I$ and $\bar{t}_2 = \sum_{i=s+1}^{s+I} t_i/I$.

When Regions 1 and 2 are overlapping, the two regressions may not be independent and, hence, (5) will not be valid as it fails to account for the correlation between $\hat{\beta}_{11}$ and $\hat{\beta}_{21}$. Indeed, under the assumption that, errors e_{1i} and e_{2i} are i.i.d. normal with mean 0 and equal variance σ^2 for the two regions,

$$(\hat{\beta}_{11} - \hat{\beta}_{21}) \sim N\left(\beta_{11} - \beta_{21}, \sigma^2\left(\frac{1}{\sigma_{1t}^2} + \frac{1}{\sigma_{2t}^2}\right) - 2Cov(\hat{\beta}_{11}, \hat{\beta}_{21})\right),$$

where $\sigma_{1t}^2 = \sum_{i=1}^{m}(t_i - \bar{t}_1)^2$, $\sigma_{2t}^2 = \sum_{s+1}^{s+I}(t_i - \bar{t}_2)^2$. It turns out that the derivation of $Cov(\hat{\beta}_{11}, \hat{\beta}_{21})$, when the two time intervals $[t_1, t_m]$ and $[t_{s+1}, t_{s+I}]$ under consideration are overlapping, is nontrivial as it requires a careful consideration of the overlapping of two regions. The detailed derivation is given in the Appendix, which shows

$$Cov(\hat{\beta}_{11}, \hat{\beta}_{21}) \doteq \frac{\sigma^2 \sigma_{12t}}{\sigma_{1t}^2 \sigma_{2t}^2} \frac{(n^{(O)})^2}{n_1 n_2}, \tag{8}$$

where $n_k = \sum_{i=s+1}^{m} \sum_{j=1}^{J} n_{kji}$ for $k = 1, 2$, $n^{(O)} = \sum_{i=s+1}^{m} \sum_{j=1}^{J} n_{ji}^{(O)}$. Here, we have used superscript 'O' to denote the intersection of Regions 1 and 2, and denoted by n_{kji} and $n_{ji}^{(O)}$ the numbers of underlying population at risk for age group j at time t_i in Region $k(k = 1, 2)$, and in the overlapping subregion, respectively.

The cross term in (8)

$$\sigma_{12t} = \sum_{s+1}^{m}(t_i - \bar{t}_1)(t_i - \bar{t}_2),$$

merits attention as it determines the sign of (8) and is completely decided by how $[t_1, t_m]$ overlaps with $[t_{s+1}, t_{s+I}]$. For example, when $[t_1, t_m]$ coincides with $[t_{s+1}, t_{s+I}]$ (i.e. $s = 0, m = I$), then $\bar{t}_1 = \bar{t}_2$, and hence, $\sigma_{12t} = \sum_{1}^{m}(t_i - \bar{t}_1)^2 > 0$. On the other

hand, when $[t_1, t_m]$ only partially overlaps with $[t_{s+1}, t_{s+I}]$ σ_{12t} can be negative, causing a negative covariance in (8). For example, when s is close to m such that $t_{s+1} > \bar{t}_1$ and $t_m < \bar{t}_2$, then $t_i - \bar{t}_1 > 0$ and $t_i - \bar{t}_2 < 0$ for any $i \in [s+1, m]$, leading to $\sigma_{12t} < 0$.

Note that when the overlapping region is an empty set, $n^{(O)} = 0$, and $Cov(\hat{\beta}_1, \hat{\beta}_2) = 0$. When $s + 1 > m$ (i.e. the time intervals are non-overlapping), $\sigma_{12t} = 0$ and, hence, $Cov(\hat{\beta}_{11}, \hat{\beta}_{21}) = 0$ as well. On the other hand, if, for example, Region 1 is completely contained in Region 2, then $n_1 = n^{(O)}$, and

$$Cov(\hat{\beta}_{11}, \hat{\beta}_{21}) = \frac{\sigma^2 \sigma_{12t}}{\sigma_{1t}^2 \sigma_{2t}^2} \frac{n_1}{n_2}.$$

So, in summary, if the two regions are non-overlapping (or time intervals are non-overlapping),

$$\hat{\beta}_{11} - \hat{\beta}_{21} \sim N\left(\beta_{11} - \beta_{21}, \sigma^2\left(\sigma_{1t}^{-2} + \sigma_{2t}^{-2}\right)\right) \tag{9}$$

and if Region 1 is completely contained in Region 2,

$$\hat{\beta}_{11} - \hat{\beta}_{21} \sim N\Big(\beta_{11} - \beta_{21}, \sigma^2\Big(\sigma_{1t}^{-2} + \sigma_{2t}^{-2} - 2\sigma_{12t}\sigma_{1t}^{-2}\sigma_{2t}^{-2}\frac{n_1}{n_2}\Big)\Big),$$

where n_1/n_2 is typically termed as the *overlapping ratio*. In general, for two regions that overlap partially,

$$\hat{\beta}_{11} - \hat{\beta}_{21} \sim N\Big(\beta_{11} - \beta_{21}, \sigma^2\Big(\sigma_{1t}^{-2} + \sigma_{2t}^{-2} - 2\sigma_{12t}\sigma_{1t}^{-2}\sigma_{2t}^{-2}\frac{(n^{(O)})^2}{n_1 n_2}\Big)\Big). \tag{10}$$

Eq. (10) reveals that its asymptotic efficacy (AE), defined by its noncentrality, is

$$\frac{(\beta_{11} - \beta_{21})^2}{\sigma^2\Big(\sigma_{1t}^{-2} + \sigma_{2t}^{-2} - 2\sigma_{12t}\sigma_{1t}^{-2}\sigma_{2t}^{-2}\frac{(n^{(O)})^2}{n_1 n_2}\Big)\Big)}, \tag{11}$$

compared to the AE of the naive test that ignores overlapping [cf. (9) or (5)]

$$\frac{(\beta_{11} - \beta_{21})^2}{\sigma^2\Big(\sigma_{1t}^{-2} + \sigma_{2t}^{-2}\Big)}. \tag{12}$$

Hence, the Pittman Asymptotic Relative Efficiency (ARE), which is the ratio of (11) and (12), and measures the gain of efficiency by accounting for overlapping, is

$$\text{ARE} \;=\; \frac{\sigma_{1t}^{-2}+\sigma_{2t}^{-2}}{\sigma_{1t}^{-2}+\sigma_{2t}^{-2}-2\sigma_{12t}\sigma_{1t}^{-2}\sigma_{2t}^{-2}\frac{(n^{(O)})^2}{n_1n_2}}.$$

Several points are worth mentioning. First, when $n^{(O)}=0$ (corresponding to disjoint regions) or $t_{s+1}>t_m$ (corresponding to disjoint time intervals), the Pittman ARE is 1, justifying the use of the classical test (as used in the current SEER*STAT software). Secondly (and interestingly), depending on the sign of σ_{12t}, i.e the mixing of the time intervals, the ARE can be greater or less than 1. Specifically, when $\sigma_{12t}>0$, then $ARE>1$, indicating the naive test will be too conservative; otherwise, $ARE<1$, hinting that the naive test will be too aggressive and will not maintain the nominal type I error, all of which calls for a new test that accounts for overlapping. Finally, as a simple example, when $s=0, m=I$ (i.e. two time intervals are identical), then $\sigma_{12t}=\sigma_{1t}^2=\sigma_{2t}^2$, and, hence, $ARE=\left\{1-\frac{(n^{(O)})^2}{n_1n_2}\right\}^{-1}$, indicating that the naive test will always be too conservative and the efficiency loss will become more severe as the overlapping population $n^{(O)}$ becomes larger.

In practice, as σ^2 is unknown, we have to replace it with a consistent estimate, leading to the following Z-test,

$$Z=\frac{\hat{\beta}_{11}-\hat{\beta}_{21}}{\left\{\hat{\sigma}^2\left(\sigma_{1t}^{-2}+\sigma_{2t}^{-2}-2\sigma_{12t}\sigma_{1t}^{-2}\sigma_{2t}^{-2}\frac{(n^{(O)})^2}{n_1n_2}\right)\right\}^{1/2}}. \tag{13}$$

Under the null hypothesis, Z in (13) approximately follows a normal distribution, where an unbiased estimate for σ^2 is given by

$$\hat{\sigma}^2=\frac{\sum_{i=1}^{m}(y_{1i}-\hat{y}_{1i})^2+\sum_{i=s+1}^{s+I}(y_{2i}-\hat{y}_{2i})^2}{m+I-4}.$$

5 Analysis of SEER Mortality Data and Simulation Studies

It is of substantial interest to compare the changes in cancer mortality rates in California with the national levels as a California law (Health and Safety Code, Section 103885) was passed in late 1980's that mandated the reporting of malignancies diagnosed throughout the state. For this purpose, we applied the proposed methodology to compare the annual percent change (APC) in the age-adjusted mortality rates for the United States (US) for the period from 1988-2002 to that of California (CA)for the period from 1990 to 2004. We fitted the simple linear models (4) to the logarithms of the age-adjusted mortality rates for both male and female for a number of cancer sites from the *Cancer Facts & Figures* (American Cancer Society, 2007). The mortality data for the United States are compiled by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (www.cdc.gov/nchs) and are available from the National Cancer Institute's Surveillance, Epidemiology, and End Results SEER) Program (http://www.seer.cancer.gov). The ratio of the total population for all age-groups combined for CA to that for the US for the overlapping years (i.e. n_1/n_2) was around 11% for females, and 11.5% for males. The results are summarized in Tables 1a and 1b. The tables give the estimates of the slope parameters for CA and US and their standard errors, along with the p-values for the comparisons based on the naive t- and the corrected Z- tests. The estimate of common residual variance σ^2 is also provided. We also calculated the residual variances for all the cancer sites for CA and the US separately (not reported in the tables), and found that they were close, confirming our common variance assumption.

The table shows that the corrected Z-test has higher power to detect the difference between the two APCs than the t-test, yielding smaller p-values for all the cancer sites. For example, the corrected Z-test detected a significant difference in the APC between

CA and the US on the site of Stomach in men (meaning CA has a more rapid decrease of Stomach cancer mortality rate compared to the US), while the naive t-test failed to detect such a difference at 5% type I error rate level.

We also compared annual percent change (APC) in the recent 15 years' age-adjusted mortality rates for California (1990 to 2004) to the national mortality rates during eighties and early nineties (1980-1994). Indeed, it was a common practice for policy-makers to evaluate the progress made at a state level by comparing with the historical national trends (see e.g. http://statecancerprofiles.cancer.gov/historicaltrend). Statistically, this comparison is also of interest. In particular, as $\sigma_{12t} < 0$ in this case, the theoretical results in Section 4 hinted that the naive t-test would be too aggressive, and, hence, might 'exaggerate' the progress made in California. The ratio of the total population for all age-groups combined for CA to that for the US for the overlapping years (1990-1994) (i.e. n_1/n_2) was around 11.1% for females, and 11.4% for males. The results are summarized in Tables 2a and 2b. These tables show that the naive t-test was a bit more aggressive than the corrected Z-test, yielding slightly smaller p-values for all the cancer sites. This confirmed our theoretical results.

To further confirm our analysis results, simulation studies were performed to compare the characteristics of the naive t-test, based on (5), with the corrected Z-test (13) that properly accounts for overlapping. We generated the data based on models (6) and (7), where $t_i = i$ and $m = I = 15$ mimicking the number of SEER followup years in Tables 1 and 2. We varied σ^2 from $\sigma^2 = 0.001$ (common cancer sites), to $\sigma^2 = 0.01$ (moderate cancer sites) to $\sigma^2 = 0.3$ (rare cancer sites). The choices of σ^2 mimicked those reported in Tables 1 and 2, and those reported in Kim et al. (2000). We let Region 1 be completely contained in Region 2 and chose the overlapping ratio $n_1/n_2 = 0.1$. This setup mimics a comparison between the local rate (e.g. California) and the global rate (national level), a main endpoint of the aforementioned SEER mortality study.

For the overlapping of two time intervals, we considered 2 scenarios. In Scenario 1, we chose $s = 0$ and $m = I = 15$. That is, we were comparing two overlapping regions over the same intervals $[t_1, t_{30}] = [1, 15]$, in which case, $\sigma_{12t} = 280 > 0$, meaning the naive test is expected to be conservative. In Scenario 2, we chose $s = 10$ and $m = I = 15$, reflecting that we were comparing two overlapping regions over two partially overlapping time intervals, namely, $[1, 15]$ and $[11, 25]$. In this case, $\sigma_{12t} = -115 < 0$ and hence, the naive test was expected to be too aggressive.

Tables 3 and 4 display the powers of the corrected Z-test and the naive Kleinbaum's t-test (5) as a function of the absolute difference between APCs, $\Delta = |APC_1 - APC_2| = 100|\exp(\beta_{11}) - \exp(\beta_{21})|$, under these two scenarios and based on 10000 simulations for each parameter set-up. Indeed, for small values of β_{11} and β_{21}, $\Delta \doteq 100|\beta_{11} - \beta_{21}|$. The results clearly showed that corrected test maintained the nominal type I error under both scenarios and had good power, which approached 1 quickly as the Δ valued increased. On the contrary, the naive test did not maintain the nominal type I error. It was too conservative in Scenario 1 (as in Table 3), with the type I error being around 0.028, almost half less than the nominal level, and its power was obviously less than the corrected test, while in Scenario 2 (as in Table 4), its type I error rate was around 0.060, almost 20% more than the nominal level. Hence, our simulation results verified the theoretical results.

6 Discussion

In this paper, we have considered an important problem where comparisons have to be made for regions or time intervals that overlap. We have shown that the existing methodology, which does not properly account for such overlapping, will be be inappropriate as it will not maintain the type I error. We have proposed a simple test that solves this fundamental difficulty and correctly accounts for overlapping. Simulations

have indicated good performance of the proposed methodology. We have applied the developed methodology to the analysis of the major cancer sites from the SEER Program and have found that the corrected Z-test renders more power than the naive t-test. Hence, the proposed Z-test will be an important addition to the SEER*STAT software, which only handles independent comparisons at this time.

We have focused on the local linearity for the cancer rates by considering time periods of short or moderate length. Indeed, linearity assumption for the cancer rates is a debatable issue in cancer surveillance, which is likely to be violated over a longer period (e.g. $\geq$ 30 years). A detailed discussion on this issue has been made in Fay et al. (2006), which proposed a joinpoint linear regression for long-term cancer rate analysis. In a similar context, we plan to pursue APC comparisons for longer periods by considering joinpoint linear regressions, and will report the results in a subsequent communication.

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Appendix: Derivation of Equation (8)

To proceed, we assume that $t_1 \leq t_{s+1} < t_m \leq t_{s+I}$ and note that

$$\begin{aligned} Cov(\hat{\beta}_{11}, \hat{\beta}_{21}) &= \frac{1}{\sigma_{1t}^2 \sigma_{2t}^2} Cov\left(\sum_{i=1}^{m} (t_i - \bar{t}_1) y_{1i}, \sum_{s+1}^{s+I} (t_i - \bar{t}_2) y_{2i} \right) \\ &= \frac{1}{\sigma_{1t}^2 \sigma_{2t}^2} \sum_{s+1}^{m} (t_i - \bar{t}_1)(t_i - \bar{t}_2) Cov(y_{1i}, y_{2i}). \end{aligned} \tag{14}$$

Recall that we use superscript 'O' to denote the intersection of Regions 1 and 2 and 'NO' the non-overlapping subset. We further introduce the following notation. Let n_{kji}, $n_{kji}^{(O)}$ and $n_{kji}^{(NO)}$ be the numbers of underlying population at risk for age group j at time t_i in Region $k(k = 1, 2)$, in the overlapping subregion and in the non-overlapping subregions, respectively. Similarly, define d_{kji}, $d_{kji}^{(O)}$ and $d_{kji}^{(NO)}$ the corresponding numbers of events (e.g. deaths or cancer cases). Denote by $n_{ki} = \sum_{j=1}^{J} n_{kji}, n_{ki}^{(O)} = \sum_{j=1}^{J} n_{kji}^{(O)}, n_{ki}^{(NO)} = \sum_{j=1}^{J} n_{kji}^{(NO)}$. Also define $d_{ki}, d_{ki}^{(O)}$ and $d_{kji}^{(NO)}$ in the similar fashion. In fact, $d_{kji}^{(O)}$ and $n_{kj}^{(O)}$ are independent of index k (for region) as they correspond to the same common subregion for $k = 1, 2$.

Let $y_i^{(O)} = \log(r_i^{(O)}) = \log\left(\sum_{j=1}^{J} w_j \frac{d_{ji}^{(O)} + 1/J}{n_{ji}^{(O)}} \right)$ be the logarithm of the (zero corrected) age-adjusted rate $r_i^{(O)}$ at time t_i for the overlapping region, and let $y_{1i}^{(NO)}$ and $y_{2i}^{(NO)}$ be defined similarly based on $r_{1i}^{(NO)}$ and $r_{2i}^{(NO)}$, respectively, for the non-overlapping regions/intervals for the two groups.

Dropping the subscript i (for time), we assume the age groups have the same distribution across the overlapping and non-overlapping regions, that is,

$$\frac{n_{k1}^{(O)}}{n_{k1}} = \frac{n_{k2}^{(O)}}{n_{k2}} = \ldots = \frac{n_{kJ}^{(O)}}{n_{kJ}} = p_k^{(O)}, \text{ and } \frac{n_{k1}^{(NO)}}{n_{k1}} = \frac{n_{k2}^{(NO)}}{n_{k2}} = \ldots = \frac{n_{kJ}^{(NO)}}{n_{kJ}} = p_k^{(NO)}, \tag{15}$$

for k=1,2. This assumption is common in comparing the age-adjusted rates across different geographical areas (see, e.g., Pickle and White, 1995), under which, we have

$$r_k = \sum_{j=1}^{J} w_j \frac{d_{kj}}{n_{kj}} = \sum_{j=1}^{J} w_j \frac{d_{kj}^{(O)} + d_{kj}^{(NO)}}{n_{kj}}$$

$$
\begin{aligned}
&= \sum_{j=1}^{J} w_j \frac{n_{kj}^{(O)}}{n_{kj}} \frac{d_{kj}^{(O)} + 1/J}{n_{kj}^{(O)}} + \sum_{j=1}^{J} w_j \frac{n_{kj}^{(NO)}}{n_{kj}} \frac{d_{kj}^{(NO)} + 1/J}{n_{kj}^{(NO)}} + c_k \\
&= p_k^{(O)} r_k^{(O)} + p_k^{(NO)} r_k^{(NO)} + c_k,
\end{aligned}
$$

where $c_k = -\frac{1}{J}\sum_{j=1}^{J} \frac{w_j}{n_{kj}}$, a negligible constant. Again, since $r_1^{(O)} = r_2^{(O)}$, let $r^{(O)}$ denote this common value, and let $y^{(O)} = \log(r^{(O)})$. Now, since $Cov(r_1^{(NO)}, r_2^{(NO)}) = 0$ and $Cov(r^{(O)}, r_k^{(NO)}) = 0, k = 1, 2$, using the delta method, we have,

$$
\begin{aligned}
Cov(y_1, y_2) &= Cov(\log(r_1), \log(r_2)) \\
&\approx \frac{1}{E(r_1)E(r_2)} Cov(r_1, r_2) \\
&= \frac{1}{E(r_1)E(r_2)} p_1^{(O)} p_2^{(O)} Var(r^{(O)}) \\
&= \frac{1}{E(r_1)E(r_2)} p_1^{(O)} p_2^{(O)} Var(e^{y^{(O)}}).
\end{aligned}
$$

Let $y^{(O)}$ satisfy the regression model (3), and let $\mu^{(O)} = E(y^{(O)})$. Since $y^{(O)} \sim N(\mu^{(O)}, \sigma^2)$, using the properties of that log normal distribution, we have that

$$
\begin{aligned}
E(r^{(O)}) &= E(e^{y^{(O)}}) = e^{\mu^{(O)}} e^{\sigma^2/2}, \\
Var(e^{y^{(O)}}) &= e^{2\mu^{(O)}} e^{\sigma^2} \left(e^{\sigma^2} - 1\right).
\end{aligned}
$$

Furthermore, the null hypothesis implies that $E(y_1) = E(y_2) = E(y^{(O)})$. Hence, adding back the time index i, we will have

$$
\begin{aligned}
Cov(y_{1i}, y_{2i}) &= \left(e^{\sigma^2} - 1\right) p_{1i}^{(O)} p_{2i}^{(O)} \\
&\approx \sigma^2 p_{1i}^{(O)} p_{2i}^{(O)},
\end{aligned}
$$

when σ^2 is small. For the US population, $p_{1i}^{(O)}$ and $p_{2i}^{(O)}$ were found to be constant over years (as confirmed by the SEER population data base). We then write $p_{ki}^{(O)} \equiv p_k^{(O)}$ for $i = s+1, \ldots, m$, an estimate of which is given by $\hat{p}_k^{(O)} = \frac{n^{(O)}}{n_k}$, where $n_k = \sum_{i=s+1}^{m} \sum_{j=1}^{J} n_{kji}$ and $n^{(O)} = \sum_{i=s+1}^{m} \sum_{j=1}^{J} n_{ji}^{(O)}$. Hence, $Cov(y_{1i}, y_{2i}) \approx \sigma^2 \frac{(n^{(O)})^2}{n_1 n_2}$ for $i = s+1, \ldots, m$. Inserting it back to (14) yields (8).

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Table 1a: Comparison of Changes in Age-adjusted cancer mortality rates between California (1990-2004) and the US (1988-2002) for males. APC_{us} and APC_{ca} are the annual percent changes for the US and California respectively. σ^2 is the common (residual) variance in the Cancer Rate Regression Models (6) and (7).

sites	APC_{us} (SE)	APC_{ca} (SE)	σ^2	p-value (Z-test)	p-value (t-test)
1 All Malignant Cancers	-1.14529 (0.08562)	-1.69304 (0.05924)	0.01323	0.00000	0.00000
2 Oral Cavity and Pharynx	-2.54187 (0.14183)	-2.36549 (0.30387)	0.04262	0.61088	0.62439
3 Lip	-5.04715 (0.93868)	-2.89026 (2.28470)	0.31393	0.39824	0.41626
4 Tongue	-2.30819 (0.17872)	-1.55945 (0.48771)	0.06602	0.16317	0.17961
5 Salivary Gland	-1.21958 (0.39018)	-2.69678 (0.88342)	0.12274	0.13895	0.15445
6 Floor of Mouth	-8.74256 (0.54619)	-4.60891 (1.60742)	0.21577	0.01850	0.02341
7 Gum and Other Mouth	-3.59892 (0.31909)	-4.57622 (0.45483)	0.07062	0.08882	0.10152
8 Nasopharynx	-2.60014 (0.26453)	-2.52804 (0.67281)	0.09188	0.92313	0.92602
9 Tonsil	-1.62000 (0.39344)	-0.51149 (0.97421)	0.13354	0.30741	0.32600
10 Oropharynx	-1.02095 (0.33416)	-0.57017 (0.97536)	0.13104	0.67232	0.68399
11 Hypopharynx	-5.54162 (0.33743)	-3.08101 (0.99334)	0.13334	0.02327	0.02900
12 Other Oral Cavity and Pha	-1.57741 (0.31890)	-2.39696 (0.72259)	0.10039	0.31547	0.33405
13 Digestive System	-1.00699 (0.03420)	-1.03053 (0.06669)	0.00953	0.76122	0.76996
14 Esophagus	0.74199 (0.04981)	0.03682 (0.26946)	0.03483	0.01279	0.01659
15 Stomach	-3.18066 (0.14032)	-2.74636 (0.15274)	0.02636	0.04280	0.05126
16 Small Intestine	-0.71617 (0.35911)	-2.28962 (0.82727)	0.11462	0.09145	0.10433
17 Colon and Rectum	-1.98524 (0.04743)	-2.30563 (0.10036)	0.01411	0.00523	0.00721
18 Colon excluding Rectum	-2.18078 (0.05359)	-2.36600 (0.11226)	0.01581	0.14974	0.16569
19 Rectum and Rectosigmoid J	-0.88380 (0.07602)	-2.00738 (0.31554)	0.04125	0.00081	0.00127
20 Liver and Intrahepatic Bi	2.70060 (0.16143)	2.85857 (0.19285)	0.03196	0.54342	0.55871
21 Liver	2.31905 (0.13813)	2.71266 (0.22187)	0.03322	0.14513	0.16090
22 Intrahepatic Bile Duct	4.89523 (0.40718)	3.73589 (0.51502)	0.08344	0.08758	0.10019
23 Gallbladder	-2.10738 (0.22285)	-1.53995 (0.48949)	0.06836	0.30742	0.32600
24 Other Biliary	-3.39084 (0.23329)	-3.65275 (0.53714)	0.07443	0.66526	0.67715
25 Pancreas	-0.29431 (0.05214)	-0.39426 (0.19401)	0.02553	0.63031	0.64325
26 Retroperitoneum	-4.12158 (0.58644)	-2.68420 (1.11387)	0.15999	0.26932	0.28778
27 Peritoneum, Omentum and M	-0.90453 (0.66323)	4.60791 (1.42707)	0.20001	0.00070	0.00111
28 Other Digestive Organs	3.32072 (1.36339)	3.54776 (2.10751)	0.31902	0.93027	0.93289
29 Respiratory System	-1.60133 (0.08997)	-2.54261 (0.08343)	0.01559	0.00000	0.00000
30 Nose, Nasal Cavity and Mi	-2.45896 (0.36930)	-3.71470 (1.15055)	0.15358	0.31473	0.33332
31 Larynx	-1.89041 (0.15676)	-2.21785 (0.41215)	0.05604	0.47254	0.48938
32 Lung and Bronchus	-1.57318 (0.08800)	-2.53538 (0.08350)	0.01542	0.00000	0.00000
33 Pleura	-4.76359 (0.69374)	-5.63373 (0.83073)	0.13756	0.43671	0.45418
34 Trachea, Mediastinum and	-4.38175 (0.56495)	-4.21490 (1.43052)	0.19548	0.91642	0.91956
35 Bones and Joints	-0.63050 (0.22877)	0.50710 (0.56841)	0.07787	0.07247	0.08391
36 Soft Tissue including Hea	-0.19405 (0.32414)	-1.86636 (0.56160)	0.08241	0.01260	0.01635
37 Skin excluding Basal and	-0.20217 (0.08928)	-0.92676 (0.29656)	0.03936	0.02362	0.02940
38 Melanoma of the Skin	0.22384 (0.14864)	-1.14511 (0.35312)	0.04870	0.00055	0.00088
39 Other Non-Epithelial Skin	-1.28166 (0.33594)	-0.34737 (0.61161)	0.08869	0.19523	0.21260
40 Breast	0.67233 (0.44829)	-0.35521 (1.08577)	0.14930	0.39743	0.41545
41 Male Genital System	-2.17218 (0.34136)	-3.35652 (0.22018)	0.05163	0.00479	0.00664
42 Prostate	-2.18583 (0.34814)	-3.40124 (0.21988)	0.05233	0.00430	0.00600
43 Testis	-1.32447 (0.42559)	-1.31581 (0.90241)	0.12681	0.99330	0.99355
44 Penis	-1.45769 (0.29383)	0.44102 (1.74277)	0.22463	0.29867	0.31724
45 Urinary System	-0.15872 (0.06568)	-0.46994 (0.10662)	0.01592	0.01621	0.02069
46 Urinary Bladder	-0.39827 (0.07156)	-0.66431 (0.19502)	0.02640	0.21539	0.23318
47 Kidney and Renal Pelvis	0.09973 (0.10326)	-0.20732 (0.16686)	0.02494	0.13010	0.14520
48 Ureter	-1.81235 (0.36063)	-3.05155 (1.85441)	0.24011	0.52571	0.54142
49 Other Urinary Organs	4.67508 (1.32642)	4.13840 (2.59886)	0.37084	0.85877	0.86404
50 Eye and Orbit	-2.59686 (0.51488)	2.06275 (1.37227)	0.18629	0.00210	0.00308
51 Brain and Other Nervous S	-0.59408 (0.07447)	-0.76199 (0.27160)	0.03579	0.56409	0.57886
52 Endocrine System	0.46159 (0.22153)	0.94815 (0.49324)	0.06872	0.38402	0.40219
53 Thyroid	1.31809 (0.32622)	2.55398 (0.66252)	0.09386	0.10545	0.11923
54 Other Endocrine including	-0.51444 (0.26401)	-0.90111 (0.73065)	0.09874	0.63017	0.64311
55 Lymphoma	0.04612 (0.25417)	-0.90577 (0.31011)	0.05096	0.02164	0.02710
56 Hodgkin Lymphoma	-3.77024 (0.29593)	-2.91687 (0.50752)	0.07467	0.15996	0.17630
57 Non-Hodgkin Lymphoma	0.32123 (0.28472)	-0.76903 (0.33308)	0.05569	0.01608	0.02054
58 Myeloma	0.00492 (0.15560)	-0.63384 (0.28698)	0.04149	0.05837	0.06852
59 Leukemia	-0.41114 (0.07777)	-1.16978 (0.18611)	0.02564	0.00027	0.00046
60 Lymphocytic Leukemia	-0.80381 (0.18393)	-1.43414 (0.38148)	0.05383	0.14991	0.16587
61 Acute Lymphocytic Leukemi	-1.88621 (0.15635)	-0.61542 (0.70555)	0.09185	0.08891	0.10162
62 Chronic Lymphocytic Leuke	-0.22980 (0.25973)	-1.58381 (0.39517)	0.06010	0.00561	0.00769
63 Other Lymphocytic Leukemi	-3.11597 (0.26524)	-2.84172 (1.08602)	0.14209	0.81241	0.81935
64 Myeloid and Monocytic Leu	0.38178 (0.10812)	-0.34155 (0.26334)	0.03618	0.01397	0.01801
65 Acute Myeloid Leukemia	1.85239 (0.13780)	1.27926 (0.25779)	0.03715	0.05786	0.06795
66 Acute Monocytic Leukemia	-5.87966 (0.33270)	-5.81060 (1.38431)	0.18095	0.96258	0.96398
67 Chronic Myeloid Leukemia	-4.54161 (0.69213)	-7.48499 (0.97162)	0.15162	0.01699	0.02162
68 Other Myeloid/Monocytic L	3.25551 (1.82360)	4.63431 (2.02953)	0.34678	0.62494	0.63804
69 Other Leukemia	-1.26579 (0.15121)	-2.35890 (0.35968)	0.04959	0.00672	0.00910
70 Other Acute Leukemia	-2.69076 (0.21664)	-4.26489 (0.44006)	0.06234	0.00191	0.00281
71 Aleukemic, Subleukemic an	0.19461 (0.25052)	-0.13660 (0.44085)	0.06445	0.52745	0.54313
72 Miscellaneous Malignant C	-0.06793 (0.38400)	-0.04692 (0.33004)	0.06435	0.96798	0.96919

Table 1b: Comparison of Changes in Age-adjusted cancer mortality rates between California (1990-2004) and the US (1988-2002) for females.

sites	APC_{us} (SE)	APC_{ca} (SE)	σ^2	p-value (Z-test)	p-value (t-test)
1 All Malignant Cancers	-0.4967 (0.06367)	-1.1995 (0.07756)	0.01275	0.00000	0.00000
2 Oral Cavity and Pharynx	-2.3100 (0.09949)	-2.6478 (0.32027)	0.04262	0.33065	0.34845
3 Tongue	-1.7552 (0.20731)	-1.9406 (0.56414)	0.07639	0.76566	0.77390
4 Salivary Gland	-1.5547 (0.28108)	-1.6580 (1.53080)	0.19781	0.94885	0.95070
5 Floor of Mouth	-8.5738 (0.59746)	-10.3092 (1.46769)	0.20140	0.29016	0.30797
6 Gum and Other Mouth	-2.4059 (0.33005)	-3.5480 (0.89911)	0.12173	0.24941	0.26696
7 Nasopharynx	-1.8134 (0.28784)	-1.7402 (1.07235)	0.14112	0.94922	0.95105
8 Tonsil	-2.7779 (0.45408)	-3.0276 (1.09826)	0.15105	0.83921	0.84495
9 Oropharynx	-0.5663 (0.55131)	-1.4113 (1.74661)	0.23279	0.65585	0.66754
10 Hypopharynx	-5.0032 (0.69969)	-2.0945 (2.10828)	0.28233	0.20595	0.22284
11 Other Oral Cavity and Pha	-2.4089 (0.33467)	-2.6857 (0.96831)	0.13021	0.79414	0.80143
12 Digestive System	-0.9999 (0.03521)	-1.0174 (0.08568)	0.01177	0.85554	0.86071
13 Esophagus	-0.1298 (0.09611)	-0.4936 (0.44040)	0.05729	0.43558	0.45237
14 Stomach	-2.4744 (0.08503)	-2.2361 (0.26341)	0.03518	0.40560	0.42281
15 Small Intestine	-0.5498 (0.28495)	-1.1258 (0.59587)	0.08395	0.39957	0.41685
16 Colon and Rectum	-1.7837 (0.03854)	-2.1068 (0.12624)	0.01678	0.01804	0.02266
17 Colon excluding Rectum	-1.9450 (0.04393)	-2.0724 (0.12469)	0.01680	0.35203	0.36973
18 Rectum and Rectosigmoid J	-0.6662 (0.09959)	-2.3023 (0.35657)	0.04705	0.00002	0.00004
19 Anus, Anal Canal and Anor	0.9835 (0.36923)	1.4404 (0.50560)	0.07957	0.48091	0.49693
20 Liver and Intrahepatic Bi	2.1121 (0.22646)	2.8416 (0.25130)	0.04299	0.03727	0.04471
21 Liver	1.0356 (0.23798)	2.2415 (0.30421)	0.04909	0.00256	0.00366
22 Intrahepatic Bile Duct	5.3993 (0.32153)	4.6627 (0.45037)	0.07033	0.19849	0.21523
23 Gallbladder	-2.3486 (0.12983)	-1.7201 (0.32906)	0.04496	0.08616	0.09815
24 Other Biliary	-3.3533 (0.27122)	-3.2242 (0.98554)	0.12992	0.90295	0.90645
25 Pancreas	0.0459 (0.06003)	-0.3244 (0.14192)	0.01958	0.02029	0.02529
26 Retroperitoneum	-3.4767 (0.42605)	-2.4084 (2.15884)	0.27968	0.63910	0.65128
27 Peritoneum, Omentum and M	10.6773 (0.50603)	11.5268 (1.02266)	0.14502	0.47208	0.48827
28 Other Digestive Organs	2.9486 (1.25248)	4.0027 (1.31273)	0.23060	0.57471	0.58863
29 Respiratory System	1.1074 (0.14308)	-0.8987 (0.13886)	0.02534	0.00000	0.00000
30 Nose, Nasal Cavity and Mi	-2.7924 (0.50534)	-1.6394 (0.87092)	0.12798	0.26870	0.28641
31 Larynx	-0.9160 (0.31894)	-3.1695 (0.99551)	0.13286	0.03732	0.04476
32 Lung and Bronchus	1.1684 (0.14263)	-0.8594 (0.13851)	0.02527	0.00000	0.00000
33 Trachea, Mediastinum and	-4.1474 (0.51934)	-3.7029 (1.76282)	0.23357	0.81526	0.82183
34 Bones and Joints	-0.3413 (0.23101)	-0.0312 (0.59852)	0.08154	0.64064	0.65278
35 Soft Tissue including Hea	-0.3137 (0.50341)	-2.3136 (0.59262)	0.09883	0.01298	0.01665
36 Skin excluding Basal and	-0.6894 (0.10824)	-1.7968 (0.25599)	0.03532	0.00012	0.00021
37 Melanoma of the Skin	-0.6677 (0.13053)	-2.2282 (0.27928)	0.03918	0.00000	0.00000
38 Other Non-Epithelial Skin	-0.7827 (0.28864)	0.1701 (0.86128)	0.11545	0.31098	0.32882
39 Breast	-2.1080 (0.09911)	-2.4052 (0.12810)	0.02059	0.07627	0.08752
40 Female Genital System	-0.7757 (0.06950)	-0.8266 (0.13887)	0.01974	0.75116	0.75988
41 Cervix Uteri	-2.5485 (0.16808)	-2.7864 (0.30711)	0.04450	0.51164	0.52704
42 Corpus and Uterus, NOS	-0.3500 (0.08836)	-0.4197 (0.22008)	0.03014	0.77630	0.78419
43 Corpus Uteri	-0.9847 (0.10858)	-1.6515 (0.29045)	0.03941	0.03779	0.04529
44 Uterus, NOS	0.2709 (0.20775)	0.6246 (0.30305)	0.04670	0.35242	0.37012
45 Ovary	-0.4497 (0.10827)	-0.3897 (0.19006)	0.02780	0.79108	0.79847
46 Vagina	-1.4893 (0.30881)	-0.0450 (1.12439)	0.14820	0.23152	0.24885
47 Vulva	0.3715 (0.21886)	-0.4401 (0.74207)	0.09833	0.31091	0.32875
48 Other Female Genital Orga	1.0285 (0.89011)	-2.8798 (1.05902)	0.17583	0.00636	0.00854
49 Urinary System	-0.1898 (0.10186)	-0.3737 (0.25074)	0.03440	0.51161	0.52701
50 Urinary Bladder	-0.3297 (0.12862)	-0.2421 (0.36919)	0.04969	0.82869	0.83480
51 Kidney and Renal Pelvis	-0.0759 (0.17167)	-0.5114 (0.23849)	0.03735	0.15231	0.16770
52 Ureter	-1.1593 (0.53854)	-0.4319 (1.29441)	0.17819	0.61627	0.62909
53 Other Urinary Organs	0.97551 (0.98382)	0.51241 (1.65580)	0.24479	0.81634	0.82288
54 Eye and Orbit	-2.29495 (0.51385)	-1.09212 (1.83285)	0.24193	0.54163	0.55636
55 Brain and Other Nervous S	-0.60288 (0.15861)	-0.78950 (0.24186)	0.03676	0.53314	0.54807
56 Endocrine System	-0.03612 (0.17458)	-0.82845 (0.57794)	0.07673	0.20493	0.22180
57 Thyroid	0.19503 (0.22603)	-0.11015 (0.52083)	0.07216	0.60363	0.61680
58 Other Endocrine including	-0.40304 (0.20725)	-2.21315 (0.99215)	0.12882	0.08453	0.09640
59 Lymphoma	0.01028 (0.29109)	-1.31900 (0.40750)	0.06365	0.01035	0.01347
60 Hodgkin Lymphoma	-2.55202 (0.28254)	-1.53544 (0.79565)	0.10731	0.24484	0.26234
61 Non-Hodgkin Lymphoma	0.18531 (0.30940)	-1.29605 (0.41882)	0.06618	0.00600	0.00809
62 Myeloma	0.19767 (0.15648)	-0.87526 (0.33092)	0.04652	0.00464	0.00636
63 Leukemia	-0.47456 (0.09093)	-1.19624 (0.15836)	0.02321	0.00013	0.00023
64 Lymphocytic Leukemia	-0.71969 (0.22034)	-1.55322 (0.35934)	0.05357	0.05613	0.06563
65 Acute Lymphocytic Leukemi	-1.33321 (0.27870)	-0.40742 (0.54511)	0.07781	0.14412	0.15920
66 Chronic Lymphocytic Leuke	-0.11289 (0.28829)	-1.78207 (0.46202)	0.06922	0.00307	0.00433
67 Other Lymphocytic Leukemi	-4.18929 (0.22281)	-5.55778 (1.60359)	0.20577	0.41424	0.43134
68 Myeloid and Monocytic Leu	0.19180 (0.09133)	-0.37999 (0.29947)	0.03979	0.07772	0.08909
69 Acute Myeloid Leukemia	1.60735 (0.11928)	1.22486 (0.30773)	0.04195	0.26296	0.28063
70 Acute Monocytic Leukemia	-7.75354 (0.82563)	-9.06558 (3.75654)	0.48884	0.74178	0.75081
71 Chronic Myeloid Leukemia	-4.29532 (0.63553)	-7.22987 (0.99391)	0.14994	0.01628	0.02057
72 Other Myeloid/Monocytic L	1.78219 (1.33592)	5.14116 (1.49323)	0.25465	0.10538	0.11859
73 Other Leukemia	-1.37872 (0.11477)	-2.39493 (0.25479)	0.03552	0.00044	0.00071
74 Other Acute Leukemia	-3.25827 (0.25236)	-4.90300 (0.39909)	0.06001	0.00077	0.00118
75 Aleukemic, Subleukemic an	0.67118 (0.13108)	0.46868 (0.40711)	0.05436	0.64745	0.65939
76 Miscellaneous Malignant C	-0.11415 (0.29840)	-0.54259 (0.28608)	0.05254	0.31678	0.33461

Table 2a: Comparison of Changes in Age-adjusted cancer mortality rates between California (1990-2004) and the US (1980-1994) for males. APC_{us} and APC_{ca} are the annual percent changes for the US and California respectively. σ^2 is the common (residual) variance in the Cancer Rate Regression Models (6) and (7).

sites	APC_{us} (SE)	APC_{ca} (SE)	σ^2	p-value (Z-test)	p-value (t-test)
1 All Malignant Cancers	0.13395 (0.05004)	-1.69304 (0.05924)	0.00986	0.00000	0.00000
2 Oral Cavity and Pharynx	-2.09739 (0.12845)	-2.36549 (0.30387)	0.04193	0.46045	0.44932
3 Lip	-6.33929 (0.87302)	-2.89026 (2.28470)	0.31086	0.20026	0.18925
4 Tongue	-2.22245 (0.15640)	-1.55945 (0.48771)	0.06510	0.23971	0.22816
5 Salivary Gland	-0.45950 (0.39389)	-2.69678 (0.88342)	0.12294	0.03566	0.03129
6 Floor of Mouth	-6.78522 (0.25603)	-4.60891 (1.60742)	0.20688	0.22460	0.21323
7 Gum and Other Mouth	-3.05074 (0.23408)	-4.57622 (0.45483)	0.06501	0.00676	0.00550
8 Nasopharynx	-1.06262 (0.31636)	-2.52804 (0.67281)	0.09449	0.07342	0.06652
9 Tonsil	-2.82023 (0.38469)	-0.51149 (0.97421)	0.13312	0.04528	0.04017
10 Oropharynx	0.19700 (0.37195)	-0.57017 (0.97536)	0.13267	0.50446	0.49387
11 Hypopharynx	-4.45059 (0.48011)	-3.08101 (0.99334)	0.14022	0.25954	0.24782
12 Other Oral Cavity and Pha	-0.22622 (0.32481)	-2.39696 (0.72259)	0.10069	0.01282	0.01075
13 Digestive System	-0.68619 (0.03274)	-1.03053 (0.06669)	0.00944	0.00003	0.00002
14 Esophagus	1.02825 (0.06092)	0.03682 (0.26946)	0.03511	0.00112	0.00083
15 Stomach	-2.03063 (0.11464)	-2.74636 (0.15274)	0.02427	0.00066	0.00048
16 Small Intestine	0.73969 (0.33065)	-2.28962 (0.82727)	0.11323	0.00201	0.00155
17 Colon and Rectum	-1.24173 (0.08356)	-2.30563 (0.10036)	0.01660	0.00000	0.00000
18 Colon excluding Rectum	-0.98791 (0.12656)	-2.36600 (0.11226)	0.02150	0.00000	0.00000
19 Rectum and Rectosigmoid J	-2.60904 (0.19370)	-2.00738 (0.31554)	0.04706	0.13996	0.13033
20 Liver and Intrahepatic Bi	3.05617 (0.12756)	2.85857 (0.19285)	0.02939	0.43764	0.42628
21 Liver	2.31517 (0.14534)	2.71266 (0.22187)	0.03371	0.17348	0.16298
22 Intrahepatic Bile Duct	9.01465 (0.30636)	3.73589 (0.51502)	0.07616	0.00000	0.00000
23 Gallbladder	-2.64656 (0.24536)	-1.53995 (0.48949)	0.06959	0.06641	0.05990
24 Other Biliary	-2.81449 (0.18682)	-3.65275 (0.53714)	0.07228	0.18065	0.17000
25 Pancreas	-0.40317 (0.05874)	-0.39426 (0.19401)	0.02576	0.96816	0.96737
26 Retroperitoneum	-5.63701 (0.49823)	-2.68420 (1.11387)	0.15509	0.02796	0.02427
27 Peritoneum, Omentum and M	-0.31829 (0.89814)	4.60791 (1.42707)	0.21431	0.00797	0.00653
28 Other Digestive Organs	-4.00785 (0.30807)	3.54776 (2.10751)	0.27071	0.00127	0.00096
29 Respiratory System	0.15618 (0.10760)	-2.54261 (0.08343)	0.01730	0.00000	0.00000
30 Nose, Nasal Cavity and Mi	-2.16152 (0.27623)	-3.71470 (1.15055)	0.15039	0.23318	0.22170
31 Larynx	-0.63743 (0.09716)	-2.21785 (0.41215)	0.05382	0.00070	0.00051
32 Lung and Bronchus	0.20164 (0.11152)	-2.53538 (0.08350)	0.01771	0.00000	0.00000
33 Pleura	0.49245 (0.40844)	-5.63373 (0.83073)	0.11766	0.00000	0.00000
34 Trachea, Mediastinum and	-3.84059 (0.35496)	-4.21490 (1.43052)	0.18733	0.81758	0.81310
35 Bones and Joints	-1.03432 (0.41720)	0.50710 (0.56841)	0.08961	0.04708	0.04183
36 Soft Tissue including Hea	1.03457 (0.10806)	-1.86636 (0.56160)	0.07269	0.00000	0.00000
37 Skin excluding Basal and	1.48499 (0.21683)	-0.92676 (0.29656)	0.04669	0.00000	0.00000
38 Melanoma of the Skin	1.65189 (0.13590)	-1.14511 (0.35312)	0.04809	0.00000	0.00000
39 Other Non-Epithelial Skin	1.10131 (0.47089)	-0.34737 (0.61161)	0.09811	0.08827	0.08060
40 Breast	0.40317 (0.47453)	-0.35521 (1.08577)	0.15060	0.56104	0.55129
41 Male Genital System	1.38340 (0.11120)	-3.35652 (0.22018)	0.03135	0.00000	0.00000
42 Prostate	1.45612 (0.11206)	-3.40124 (0.21988)	0.03137	0.00000	0.00000
43 Testis	-3.17493 (0.29347)	-1.31581 (0.90241)	0.12061	0.07517	0.06817
44 Penis	-2.15477 (0.41309)	0.44102 (1.74277)	0.22764	0.18806	0.17726
45 Urinary System	-0.28045 (0.08727)	-0.46994 (0.10662)	0.01751	0.21163	0.20044
46 Urinary Bladder	-1.12675 (0.16025)	-0.66431 (0.19502)	0.03208	0.09612	0.08809
47 Kidney and Renal Pelvis	1.00260 (0.09281)	-0.20732 (0.16686)	0.02427	0.00000	0.00000
48 Ureter	-1.06126 (0.43471)	-3.05155 (1.85441)	0.24208	0.34258	0.33066
49 Other Urinary Organs	-2.59350 (0.62897)	4.13840 (2.59886)	0.33984	0.02222	0.01909
50 Eye and Orbit	-1.74425 (0.43342)	2.06275 (1.37227)	0.18291	0.01627	0.01379
51 Brain and Other Nervous S	0.85214 (0.10548)	-0.76199 (0.27160)	0.03703	0.00000	0.00000
52 Endocrine System	-0.08767 (0.18546)	0.94815 (0.49324)	0.06698	0.07421	0.06726
53 Thyroid	0.06835 (0.26616)	2.55398 (0.66252)	0.09075	0.00157	0.00119
54 Other Endocrine including	-0.24578 (0.25539)	-0.90111 (0.73065)	0.09837	0.44189	0.43057
55 Lymphoma	2.05381 (0.10812)	-0.90577 (0.31011)	0.04174	0.00000	0.00000
56 Hodgkin Lymphoma	-3.66815 (0.28420)	-2.91687 (0.50752)	0.07393	0.24076	0.22921
57 Non-Hodgkin Lymphoma	2.66716 (0.12986)	-0.76903 (0.33308)	0.04544	0.00000	0.00000
58 Myeloma	1.44945 (0.08579)	-0.63384 (0.28698)	0.03807	0.00000	0.00000
59 Leukemia	-0.31509 (0.08696)	-1.16978 (0.18611)	0.02611	0.00016	0.00011
60 Lymphocytic Leukemia	-0.06745 (0.15905)	-1.43414 (0.38148)	0.05253	0.00267	0.00208
61 Acute Lymphocytic Leukemi	-1.07408 (0.23533)	-0.61542 (0.70555)	0.09453	0.57541	0.56590
62 Chronic Lymphocytic Leuke	0.88433 (0.25397)	-1.58381 (0.39517)	0.05970	0.00000	0.00000
63 Other Lymphocytic Leukemi	-4.22759 (0.26089)	-2.84172 (1.08602)	0.14196	0.25976	0.24804
64 Myeloid and Monocytic Leu	-1.23576 (0.19512)	-0.34155 (0.26334)	0.04166	0.01321	0.01109
65 Acute Myeloid Leukemia	-0.78771 (0.25898)	1.27926 (0.25779)	0.04644	0.00000	0.00000
66 Acute Monocytic Leukemia	-5.35300 (0.52077)	-5.81060 (1.38431)	0.18798	0.77870	0.77332
67 Chronic Myeloid Leukemia	-0.58622 (0.16262)	-7.48499 (0.97162)	0.12521	0.00000	0.00000
68 Other Myeloid/Monocytic L	-7.31063 (0.43678)	4.63431 (2.02953)	0.26385	0.00000	0.00000
69 Other Leukemia	1.00458 (0.22000)	-2.35890 (0.35968)	0.05359	0.00000	0.00000
70 Other Acute Leukemia	1.57263 (0.29680)	-4.26489 (0.44006)	0.06746	0.00000	0.00000
71 Aleukemic, Subleukemic an	0.37945 (0.25853)	-0.13660 (0.44085)	0.06496	0.35908	0.34720
72 Miscellaneous Malignant C	-0.10363 (0.23525)	-0.04692 (0.33004)	0.05151	0.89888	0.89637

Table 2b: Comparison of Changes in Age-adjusted cancer mortality rates between California (1990-2004) and the US (1980-1994) for females.

sites	APC_{us} (SE)	APC_{ca} (SE)	σ^2	p-value (Z-test)	p-value (t-test)
1 All Malignant Cancers	0.40400 (0.03737)	-1.1995 (0.07756)	0.01094	0.00000	0.00000
2 Oral Cavity and Pharynx	-1.35357 (0.09378)	-2.6478 (0.32027)	0.04241	0.00042	0.00031
3 Tongue	-1.33078 (0.19952)	-1.9406 (0.56414)	0.07605	0.35408	0.34273
4 Salivary Gland	-0.79551 (0.27112)	-1.6580 (1.53080)	0.19759	0.61392	0.60550
5 Floor of Mouth	-4.07290 (0.32488)	-10.3092 (1.46769)	0.19106	0.00016	0.00011
6 Gum and Other Mouth	-1.43953 (0.25762)	-3.5480 (0.89911)	0.11887	0.04038	0.03585
7 Nasopharynx	-0.88013 (0.29470)	-1.7402 (1.07235)	0.14135	0.48192	0.47154
8 Tonsil	-3.36049 (0.37876)	-3.0276 (1.09826)	0.14765	0.79443	0.78964
9 Oropharynx	0.53419 (0.70546)	-1.4113 (1.74661)	0.23941	0.34767	0.33631
10 Hypopharynx	-3.84815 (0.54731)	-2.0945 (2.10828)	0.27684	0.46413	0.45355
11 Other Oral Cavity and Pha	-0.08469 (0.37118)	-2.6857 (0.96831)	0.13180	0.02257	0.01954
12 Digestive System	-1.05530 (0.04113)	-1.0174 (0.08568)	0.01208	0.71694	0.71049
13 Esophagus	-0.02695 (0.10507)	-0.4936 (0.44040)	0.05755	0.34862	0.33726
14 Stomach	-2.19679 (0.11168)	-2.2361 (0.26341)	0.03636	0.90055	0.89819
15 Small Intestine	0.49738 (0.23347)	-1.1258 (0.59587)	0.08134	0.02110	0.01822
16 Colon and Rectum	-1.71438 (0.06537)	-2.1068 (0.12624)	0.01807	0.01207	0.01017
17 Colon excluding Rectum	-1.56494 (0.09316)	-2.0724 (0.12469)	0.01978	0.00303	0.00240
18 Rectum and Rectosigmoid J	-2.70471 (0.26231)	-2.3023 (0.35657)	0.05626	0.40840	0.39733
19 Anus, Anal Canal and Anor	1.54210 (0.37044)	1.4404 (0.50560)	0.07966	0.88270	0.87993
20 Liver and Intrahepatic Bi	2.41870 (0.16904)	2.8416 (0.25130)	0.03849	0.20425	0.19367
21 Liver	1.17094 (0.20476)	2.2415 (0.30421)	0.04661	0.00794	0.00657
22 Intrahepatic Bile Duct	8.52092 (0.33496)	4.6627 (0.45037)	0.07134	0.00000	0.00000
23 Gallbladder	-2.94543 (0.15996)	-1.7201 (0.32906)	0.04650	0.00233	0.00182
24 Other Biliary	-3.13665 (0.17143)	-3.2242 (0.98554)	0.12714	0.93656	0.93505
25 Pancreas	0.34744 (0.06179)	-0.3244 (0.14192)	0.01967	0.00008	0.00005
26 Retroperitoneum	-4.32978 (0.40012)	-2.4084 (2.15884)	0.27906	0.42619	0.41525
27 Peritoneum, Omentum and M	4.51348 (0.89926)	11.5268 (1.02266)	0.17308	0.00000	0.00000
28 Other Digestive Organs	-4.25304 (0.33605)	4.0027 (1.31273)	0.17223	0.00000	0.00000
29 Respiratory System	3.61472 (0.13458)	-0.8987 (0.13886)	0.02458	0.00000	0.00000
30 Nose, Nasal Cavity and Mi	-0.70758 (0.43469)	-1.6394 (0.87092)	0.12371	0.38404	0.37282
31 Larynx	1.21371 (0.25728)	-3.1695 (0.99551)	0.13068	0.00011	0.00007
32 Lung and Bronchus	3.71166 (0.13993)	-0.8594 (0.13851)	0.02502	0.00000	0.00000
33 Trachea, Mediastinum and	-2.31106 (0.38885)	-3.7029 (1.76282)	0.22944	0.48327	0.47290
34 Bones and Joints	-0.48883 (0.37556)	-0.0312 (0.59852)	0.08981	0.55596	0.54658
35 Soft Tissue including Hea	1.54851 (0.22162)	-2.3136 (0.59262)	0.08042	0.00000	0.00000
36 Skin excluding Basal and	0.13866 (0.14570)	-1.7968 (0.25599)	0.03744	0.00000	0.00000
37 Melanoma of the Skin	0.17192 (0.15360)	-2.2282 (0.27928)	0.04051	0.00000	0.00000
38 Other Non-Epithelial Skin	0.00164 (0.23994)	0.1701 (0.86128)	0.11363	0.86394	0.86073
39 Breast	-0.08345 (0.12945)	-2.4052 (0.12810)	0.02315	0.00000	0.00000
40 Female Genital System	-0.70389 (0.07288)	-0.8266 (0.13887)	0.01993	0.47665	0.46621
41 Cervix Uteri	-1.81997 (0.12578)	-2.7864 (0.30711)	0.04218	0.00810	0.00671
42 Corpus and Uterus, NOS	-1.45753 (0.09517)	-0.4197 (0.22008)	0.03047	0.00008	0.00006
43 Corpus Uteri	-1.25283 (0.14610)	-1.6515 (0.29045)	0.04132	0.26488	0.25367
44 Uterus, NOS	-1.66602 (0.18009)	0.6246 (0.30305)	0.04480	0.00000	0.00000
45 Ovary	0.12034 (0.07301)	-0.3897 (0.19006)	0.02588	0.02274	0.01969
46 Vagina	-1.52270 (0.33520)	-0.0450 (1.12439)	0.14912	0.25213	0.24101
47 Vulva	-0.19144 (0.26520)	-0.4401 (0.74207)	0.10016	0.77419	0.76896
48 Other Female Genital Orga	-0.51159 (0.45107)	-2.8798 (1.05902)	0.14630	0.06138	0.05545
49 Urinary System	0.12841 (0.07580)	-0.3737 (0.25074)	0.03329	0.08136	0.07437
50 Urinary Bladder	-0.88939 (0.15915)	-0.2421 (0.36919)	0.05110	0.14319	0.13390
51 Kidney and Renal Pelvis	1.17505 (0.15240)	-0.5114 (0.23849)	0.03597	0.00000	0.00000
52 Ureter	-0.86113 (0.44480)	-0.4319 (1.29441)	0.17396	0.77551	0.77031
53 Other Urinary Organs	-1.59386 (0.32699)	0.51241 (1.65580)	0.21451	0.25648	0.24533
54 Eye and Orbit	-2.35049 (0.44521)	-1.09212 (1.83285)	0.23973	0.54409	0.53454
55 Brain and Other Nervous S	0.96806 (0.12100)	-0.78950 (0.24186)	0.03437	0.00000	0.00000
56 Endocrine System	-0.64446 (0.20063)	-0.82845 (0.57794)	0.07776	0.78450	0.77950
57 Thyroid	-1.08132 (0.26928)	-0.11015 (0.52083)	0.07452	0.13204	0.12308
58 Other Endocrine including	0.07706 (0.22568)	-2.21315 (0.99215)	0.12932	0.04069	0.03613
59 Lymphoma	1.61631 (0.06812)	-1.31900 (0.40750)	0.05251	0.00000	0.00000
60 Hodgkin Lymphoma	-3.46456 (0.24364)	-1.53544 (0.79565)	0.10576	0.03503	0.03091
61 Non-Hodgkin Lymphoma	2.11389 (0.06817)	-1.29605 (0.41882)	0.05393	0.00000	0.00000
62 Myeloma	1.31123 (0.08985)	-0.87526 (0.33092)	0.04358	0.00000	0.00000
63 Leukemia	-0.32315 (0.08684)	-1.19624 (0.15836)	0.02295	0.00001	0.00001
64 Lymphocytic Leukemia	-0.11952 (0.19751)	-1.55322 (0.35934)	0.05212	0.00148	0.00113
65 Acute Lymphocytic Leukemi	-0.90026 (0.28043)	-0.40742 (0.54511)	0.07791	0.46476	0.45419
66 Chronic Lymphocytic Leuke	0.91209 (0.23062)	-1.78207 (0.46202)	0.06563	0.00000	0.00000
67 Other Lymphocytic Leukemi	-4.62562 (0.39316)	-5.55778 (1.60359)	0.20985	0.60770	0.59917
68 Myeloid and Monocytic Leu	-1.23508 (0.15510)	-0.37999 (0.29947)	0.04286	0.02114	0.01826
69 Acute Myeloid Leukemia	-0.75770 (0.17158)	1.22486 (0.30773)	0.04478	0.00000	0.00000
70 Acute Monocytic Leukemia	-4.54293 (0.54879)	-9.06558 (3.75654)	0.48252	0.27871	0.26741
71 Chronic Myeloid Leukemia	-0.77315 (0.24368)	-7.22987 (0.99391)	0.13007	0.00000	0.00000
72 Other Myeloid/Monocytic L	-7.61620 (0.54563)	5.14116 (1.49323)	0.20206	0.00000	0.00000
73 Other Leukemia	1.14041 (0.20278)	-2.39493 (0.25479)	0.04139	0.00000	0.00000
74 Other Acute Leukemia	1.45185 (0.30917)	-4.90300 (0.39909)	0.06416	0.00000	0.00000
75 Aleukemic, Subleukemic an	0.75916 (0.16949)	0.46868 (0.40711)	0.05605	0.54922	0.53974
76 Miscellaneous Malignant C	-0.36323 (0.16305)	-0.54259 (0.28608)	0.04185	0.62040	0.61209

Table 3: Comparison of the corrected Z-test and the naive t-test for two overlapping regions over the same time interval.

σ^2	$\lvert APC_1 - APC_2 \rvert$	Z-test	t-test
0.001	0.00	0.04963	0.02808
	0.10	0.06987	0.04235
	0.25	0.18171	0.12579
	0.50	0.55401	0.46102
	0.75	0.88232	0.82877
	1.00	0.98699	0.9772
	3.00	0.99999	0.99998
0.01	0.00	0.05043	0.02822
	0.10	0.05149	0.03001
	0.25	0.06299	0.03738
	0.50	0.10153	0.06527
	0.75	0.167	0.11552
	1.00	0.2634	0.19356
	3.00	0.97777	0.96225
0.3	0.00	0.0504	0.02851
	0.10	0.05079	0.02927
	0.75	0.06158	0.03575
	1.00	0.07147	0.043
	3.00	0.24108	0.1754
	5.00	0.55232	0.45982
	9.00	0.96463	0.94273

Table 4: Comparison of the corrected Z-test and the naive t-test for two overlapping regions over **partially** overlapping intervals.

σ^2	$\lvert APC_1 - APC_2 \rvert$	Z-test	t-test
0.001	0.00	0.05039	0.05968
	0.10	0.0649	0.07668
	0.25	0.14536	0.16357
	0.50	0.43425	0.46561
	0.75	0.76764	0.79023
	1.00	0.94756	0.95542
	3.00	0.99998	0.99999
0.01	0.00	0.04956	0.05914
	0.10	0.05135	0.06114
	0.25	0.05901	0.06966
	0.50	0.08751	0.10042
	0.75	0.13542	0.1524
	1.00	0.20625	0.22884
	3.00	0.92691	0.93676
	5.00	0.99994	0.99996
0.3	0.00	0.04948	0.05951
	0.10	0.0487	0.05833
	0.75	0.05811	0.06841
	1.00	0.06511	0.07635
	3.00	0.1911	0.2136
	5.00	0.4333	0.4624
	9.00	0.89962	0.91292