# Cancer Incidence in the Oldest Old: Disentangling Age, Period, and Cohort Effects

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Abstract: *The rapid growth of the 85+ population makes it an important age group to study morbidity trends. Cancer incidence in this age group is understudied because data are not easily accessible. This study uses data from the Utah Cancer Registry (UCR), US Census, and National Center for Health Statistics (NCHS) to generate age-specific estimates of cancer incidence for the oldest old (85+) from 1973 to 2002 for Utah. Age-period-cohort (APC) analyses are used to describe the simultaneous effects of age, period and cohort on cancer incidence rates. We find that there is a general trend of increased cancer incidence rates at younger ages for more recent cohorts. Our results also show that cancer incidence rates increase up to the 85 – 89 age group and are followed by slight declines for ages 90 -99 net of period and cohort effects. We also find evidence of period and cohort effects, suggesting that biological mechanisms are not the only factors contributing to declining cancer incidence rates between the ages of 85 and 100.*

## INTRODUCTION

The demographic profile of the United States is changing with an increasing proportion of the population falling into the 65+ age category[1]. More individuals are surviving to very old ages, making the oldest old (85+) the fastest growing segment of this population. The oldest old population is projected to more than triple from its current estimate of 5.7 million to 24 million by 2050[1]. This substantial increase in the number and proportion of Americans reaching age 85 makes the study of morbidity and mortality for this age group increasingly important.

Cancer is one of the leading causes of death for the population over age 65. It is estimated that 70% of all cancer deaths and 57% of incident cancers occur to those in the 65+ age category[2]. Individuals aged 65 or older have a risk of cancer that is 11 times greater than those under the age of 65[2]. In 2000, the oldest old age group accounted for 8% of all incident cancer cases. This number is projected to rise to 17% by 2050 assuming current incidence rates[3]. This projected growth will make it the fastest growing age sector with regards to cancer incidence trends.

The National Cancer Institute's Surveillance epidemiology and End Results (SEER) program aggregates cancer incidence information for the 85+ age group making it difficult to

study cancer trends in the oldest old. There is sparse literature analyzing disaggregated cancer incidence trends for the oldest old population and more work needs to be done to understand the morbidity and disability profiles for this sub-population. The main focus of this paper will be to examine cancer incidence trends for the population ages 65 – 99, in order to assess risk across the complete spectrum of ages in this population.

The few studies that examine cancer incidence trends past the age of 85 present evidence that supports hypotheses explaining a deceleration and decline in cancer at the oldest ages, however they do not control for period and cohort effects [4-6]. These studies show a general pattern of increased cancer incidence, prevalence, and mortality with age followed by a deceleration and decline in rates for the oldest old. Similar patterns of slowing and decline in cancer incidence and prevalence are seen across gender and over several time periods. While patterns for different time periods are presented, the literature is limited with regard to analyzing change in the trends over time for the oldest old population. Cohort and period specific trends may confound the true age trajectory of cancer in this population. Studies that do not account for changes in the environment, diet, health behaviors, and screening and diagnostic practices are ignoring the multifaceted determinants of cancer. It is important to consider sex-specific trends in both all-cause and site-specific cancer because there may be different biological and social determinants of cancer for men and women that vary by site[7]. Decomposing rates into their component parts of age, period, and cohort will lead to better understanding of cancer trends for the full continuum of the old age population. This study aims to contribute to the current literature by examining age, period, and cohort trends of cancer incidence from 1973 to 2002 for ages 65 to 99 using data from the Utah Cancer Registry (UCR), SEER database, and decennial Census data.

BACKGROUND

## Disentangling Age, Period, and Cohort Effects

Examining the age, period, and cohort trends of cancer incidence in the oldest old will provide crucial insight into the factors that drive decreasing cancer incidence at advance ages. Studies have shown that age patterns of cancer vary by time and geographic region suggesting that these differences may reflect period and cohort differences in exposure to carcinogens[8]. It is possible that incidence rates reflect underlying risks, diagnostic practices including screening recommendations, and differential environmental exposures to carcinogens. Separating the temporal and age trends that contribute to differential rates of cancer incidence with age will allow for a better understanding of the pathology of cancer in the oldest old.

In theory, disentangling these trends will allow the separation of social, medical, and environmental changes that affect cancer incidence. Age effects are the biological characteristics of an individual that affect cancer trends. The age related decline in the cell proliferation rate (the time between two cellular doublings) is an example of an age effect. Cross-sectional studies of all-site cancer incidence and death rates show that rates generally increase with age, peak sometime between ages 75 and 85, and then reach a plateau before declining in advanced ages[4, 6, 9-11]. However, many of these studies can only offer limited conclusions about cancer trends in the oldest old because they are for a single period or they are aggregated for ages 85+.

Period effects are temporal effects that modify risk for all individuals in a population. For example, the introduction of new diagnostic tools into the health care market, changes in screening policies, and changes in medical practices. Mammography screening became widespread during the 1980s, leading to an increase in breast cancer cases for females over the

age of 65[12]. Colon cancer cases increased during the 1990s as a result of changes in colorectal screening[12]. There was a steep increase in prostate cancer cases for males over the age of 65 between 1988 and 1992 due to the introduction of a prostate screening test, Prostate-Specific Antigen (PSA)[12]. These changes may not affect the oldest old, leading to an observed decline at these ages. For example, the Agency for Healthcare Research and Quality does not recommend routine colonoscopies after the age of 75[13] and questions about the efficacy of cancer screening for the oldest old have also been raised[14, 15]. In addition to the bias created by cancer screening recommendations, cancer incidence rates for these ages may be subject to detection bias because screening is difficult for frail individuals and individuals with multiple morbidities [16].

Cohort effects are temporal changes in the social or ecological environment unique to a group of individuals born in the same group of years. Cohort effects arise when a temporal exposure is dependent upon the age of the individual. Cohort effects may also describe variations in length of time exposed to certain risk factors. There is evidence of a shift in relative proportions of cancer in the oldest ages. Several studies show that there has been an increase in the proportion of colorectal and prostate cancers in the oldest old age groups[6, 11]. A more comprehensive understanding of the age, period, and cohort factors contributing to cancer incidence rates in the oldest old is imperative to effective screening and treatment recommendations for this population.

Results from previous studies examining cancer incidence in the oldest-old show that the shape, height, and peak of the curves describing cancer incidence with age are sensitive to both temporal period and cancer site [4-6]. The fluctuation in rates is evidence of period and cohort factors that contribute cancer rates. The assumption that rates of decline are equal across birth

cohorts greatly simplifies estimates and ignores evidence that there may be cohort differences in exposure to carcinogens [17]. Treating the pattern of decline as an effect of aging neglects evidence of period and cohort effects that may alter trends for this age group [5, 11]. Examining temporal changes in cancer rates may better describe social and environmental factors that affect risk for these age groups. Using a comprehensive approach that studies cancer trends over time and accounts for period and cohort effects will provide clues the mechanisms that drive cancer rates in the oldest old.

**Aging and Cancer**

Several studies have evaluated cancer incidence in the oldest old and have documented a deceleration and decline in all-site cancer incidence and prevalence between the ages of 75 and 84[4, 6, 11, 18] and a decline in cancer mortality after age 90[19]. Studies observing gender specific trends found that the observed decline in all-cause cancer incidence and mortality with age was similar for males and females [4, 6, 19]. While there is general consensus between studies that cancer incidence and prevalence rates decrease at old ages, there is variation in the estimated time of the decline. Harding *et al*. show steady increases in cancer incidence for those age 65 and over up to age 80, followed by a deceleration and decline in all-cause cancer incidence cases for the 85 - 89 age group and found that the general pattern of decreased cancer incidence with age was consistent across periods for both males and females [4]. However, Saltztein el al. estimates that incidence rates for this age group peak at age 85 and show a deceleration and decline in incidence rates beginning at age 90[6]. A close examination of the period specific plots published by Harding *et al*. show that the inflection points, height, and the shape of the curves were sensitive to the time period of study [4]. Stanta noted that prevalence rates were much higher in their study compared to historical studies. The study cited a four fold

increase in prevalence for individuals aged 75 to 90 and a two fold increase for those aged 90 and above compared to studies done 30 to 60 years prior[11].

There is still debate over theories explaining the relationship between cancer and aging and the observed decline in incidence beginning at age 85[16, 20]. Several theories predict both increases and decreases in cancer incidence with age and the theories are not necessarily mutually exclusive. Table 1 summarizes the arguments for the relationship between cancer and aging and suggests period and cohort factors that may modify the relationship.

Table 1 Here

**Theories supporting an increase in cancer incidence with age**

The multi-stage theory predicts that cancer incidence rates should increase with age because the neoplastic transformation of cells occurs through several successive carcinogenic steps [20-22]. This framework describes cancer incidence as a power function of exposure time and not age. The neoplastic transformation of cells is caused by the dose and duration of carcinogenic exposure over a person's lifetime regardless of any effects of aging[16, 20]. According to this theory, cancer incidence should steadily increase with length of exposure and therefore age.

Physiological changes that occur in the aging organism may also contribute to an increase in cancer incidence with age. The probability of the neoplastic transformation of a cell may be dependent upon the age of an individual because physiological changes with age may create a more conducive environment for neoplastic transformations. As an individual ages, there is a decline in the rate of cellular proliferation[16, 23]. Because cancer cells do not "age", their metabolic, proliferative, growth, and signaling profiles may give them a survival advantage [16,

20, 23]. There are other changes in the cellular environment that may influence the relationship between carcinogenesis and age. The longevity-cancer tradeoff hypothesis posits that cellular mechanisms that reduce cancer risk also increase rates of aging. Telomere dysfunction, a decline in immune surveillance, loss in tumor suppressor function, and mutation accumulation are all factors that have been cited as possible mechanisms leading to the increasing rates of cancer incidence with age[16, 20, 23]. These changes may be modified by environmental exposures such as diet, smoking, and exposure to infectious disease[16].

**Theories that explain a flattening or decline in cancer incidence with age**

It has been suggested that the multi-stage theory is correct and leveling off or decline in cancer rates at old ages may reflect period and cohort trends[24]. If exposure to different carcinogens fluctuates over time, such as tobacco smoke, changes in diet, or other environmental carcinogens, the deceleration in incidence rates at the oldest ages may reflect these changes rather than somatic aging. A decline or deceleration in cancer trends in old ages may be a function of cohort experiences or screening practices for this age group.

Detection bias can potentially alter trends in cancer incidence for the oldest old. Routine cancer screening has increased in the general population[12]. However, studies have suggested that there is a decrease in surveillance for the oldest old. Cancer trends periodically shift due to changes in screening procedures and recommendations. Han et al. used SEER data from the National Cancer Institute to summarize trends in the generational risk of cancer for individuals age 20 to 84. They found that there was a steady increase in screening-detectable cancers from 1975 to 2004[25]. A separate study shows that tumors are misdiagnosed or unreported in a high percentage of older persons and that the prevalence of these errors increases with age. They

estimate that 50% of cancer cases in the oldest old may go undiagnosed and approximately 40% are misdiagnosed[11]. Kaplan et. al find that there is a systematic decline in the use of mammography beginning at age 75 and that this decline parallels the number of incidence breast carcinoma in-situ (CIS)[5].

Physiological changes can also contribute to the decline in incidence in the oldest old. Age related declines in rates of cellular metabolism, information processing, suppression of tumor generation, and increased cellular doubling time have all been suggested reasons for cancer declines at advanced ages[16]. Non-proliferating cells have low or no probability of malignant transformation. Cancer incidence may decline in the oldest old because the number of non-proliferating cells increases with age. These physiological changes may favor slower growing tumors or suppress tumor generation[16, 20].

The force of mortality may decrease at advanced ages[26], leading researchers to use a selection or genetic advantage hypothesis to explain the decline. In a study of nonagenarians and centenarians from the New England Centenarian Study, Anderson *et al*. showed on average the oldest old had a delayed onset of non-skin cancer and some evaded the disease entirely. Members of the oldest old age group may have genetic variations that are protective or lack variations that predispose them to cancer [9]. Studies have shown that there may be strong genetic components to exceptional longevity and possibly influence the susceptibility to age related illnesses such as cancer[27]. For example, individuals with deleterious BRCA1 mutations have elevated mortality rates compared to the general population making them less likely to survive to advanced ages[28]. According to these hypotheses, there is differential selection in a heterogeneous population with the frail being selected out of the population at earlier ages. Individuals who are selected out of the population may have a genetic or

environmental predisposition to cancer, and their robust counterparts who survive to the oldest ages may have a survival advantage that protects them from cancer.

Cancer trends for the oldest old population have historically been understudied, with cancer incidence rates being combined for all 85+ individuals[29]. The projected increase in the sheer size of the oldest old population will lead to increases in cancer incidence cases in the oldest age categories. This study aims to improve upon current literature by examining temporal trends of cancer incidence from 1973 to 2002 for ages 65 to 99 using data from the Utah Cancer Registry (UCR), SEER database, and decennial Census data.

## METHODS

### Data

Sex and site specific cancer incidence trends for ages 65 to 99 between the years of 1973 to 2002 for the state of Utah were selected for the analysis. While the main purpose of this study is to assess cancer trends for ages 85 and over, it was necessary to view the rates in relation to the young old and old populations. This study relies on data for the state of Utah from 1973 to 2002 collected from three sources. Cancer incidence counts and US Census Bureau's Population Estimates for the state of Utah for ages 65 to 84 were obtained from the SEER*Stat software[30, 31]. State-wide cancer data are collected by the Utah Cancer Registry (UCR) as part of routine cancer surveillance for the National Cancer Institute's SEER Program. Cancer cases are identified through health service units and death certificates on which cancer is listed as a cause of death. Site and histology are coded according to the International Classification of Diseases for Oncology (ICD-O) edition at the time of diagnosis and converted to the Third Edition coding[32].

Age-specific incidence counts for ages 85 to 99 are not reported by the SEER program. Age misstatement at these ages is a widely recognized problem making population estimates less reliable[29]. Tabulated incidence data by year and age for these ages were provided by the UCR. Intercensal population estimates were calculated via the cohort-component and extinct cohort methods using decennial data from the US Census Bureau and mortality data from the National Center for Health Statistics. Use of decennial census and death certificate data have been criticized because age-misstatement can lead to a downward bias of incidence rates for this population, however age misstatement has been shown to be a relatively rare occurrence with error rates improving over time[29, 33, 34]. Data collection issues have also caused error in population estimates for the oldest-old, for example a flawed questionnaire design of the 1970 census led to an overestimate of individuals age 100 and over[35]. The extinct cohort and survivor ratio methods are alternative methods of calculating population counts that rely on death certificate data and are thought to be more reliable when cohorts are close to extinction because they are less subject to bias caused may age misreporting. Rates from both methods were compared and we found that when cohorts are farther from extinction a larger fraction of the estimates using the survivor ratio method become less reliable. The cohort component method was selected as the basis for the final models. A detailed description of the methodology and comparison between rates will be provided in a forthcoming article by Rudy *et al.* and can be provided upon request. The final data set consisted of population level cancer incidence numerators and cohort-component denominators for the 65 – 99 year old population in Utah from 1973 to 2002.

**Analytic Methods**

Cancer incidence rates were calculated as the ratio of incidence cases to person years of exposure. Age-specific incidence rates were tabulated in an age *a* by calendar year period *p* array with diagonal elements of the matrix corresponding to the birth cohorts *c* ($c = p + a - 1$), where the oldest cohort is observed for the oldest age interval during the earliest calendar period and the youngest cohort is observed for the youngest age interval during the latest calendar period. Seven five-year age groups, ranging from 65 – 69 to 95 – 99, and six five-year time periods, from 1973 – 1977 to 1998 – 2002 were used in the analysis. This yielded 12 successive ten year birth cohorts with midpoints ranging from 1878 to 1933. There is some ambiguity in the measurement of cohort because data are tabulated into five year age and period groupings. For example, an individual age 69 in 1973 would have a birth year of 1904 while an individual age 65 in 1978 would have a birth year of 1913.

Traditional age, period, and cohort (APC) analyses suffer from an "identification problem" resulting from the linear dependency between age, period and cohort ($c=a+p$) and a unique solution cannot be determined. This problem can be solved by imposing constraints to the model to allow for an identifiable solution [36-39]. However, selection of the constraint requires some a priori knowledge of the disease under investigation and models are sensitive to the constraint selected. Another approach specific to cancer incidence rates is to assume that the rate of aging decreases with age and use a modified Strehler and Mildvan model to explain the decrease in cancer incidence with age[8, 10]. Constraining age to a non-linear functional form eliminates the linear relationship between the three variables and allows for the estimation of all three effects. Other authors have suggested using a proxy characteristic for cohort [40-42]. However, cohort characteristics may not entirely explain cohort effects and the residuals may still be confounded in the model estimates with age and period effects.

The Intrinsic Estimator (IE) proposed by Yang *et al* [39, 43] can also be viewed as a constrained approach; however it does not require that an a priori assumption about the constrained factor be made. The IE estimates the effects of age, period, and cohort effects through a form of principle components analysis that removes the null space from the design matrix *X* on the estimator. Other studies have shown that the IE produces substantively meaningful and empirically valid results[43]. . After initial estimations, we selected the IE to estimate the APC effects of cancer incidence.

Descriptive plots were produced by age and sex for all-cause, breast, colon, lung, and prostate cancers to assess the age, period, and cohort cancer incidence trends for each site. A similar approach to that used by Yang *et al*.[39, 43] was used to identify an appropriate model to analyze the temporal trends in all-site and site-specific cancer incidence rates. A series of Poisson log-linear models were estimated for each site and sex.

$$\ln(\text{rate}_{ijk}) = \ln(\text{case}_{ijk}/n_{ijk}) = \mu + \alpha_i + \beta_j + \gamma_k$$

where $\text{rate}_{ijk}$ indexes the expected cancer incidence rate in cell $(i, j, k)$; $\text{case}_{ijk}$ indexed the expected number of cancer incidence cases; $n_{ijk}$ indexes the number of person years; μ indexes the intercept of age adjusted mean rate; $\alpha_i$ indexes the $i$th row age effect for $i = 1, \ldots, a$ age groups; $\beta_j$ represents the $j$th column period effect for $j = 1, \ldots, p$ periods; and $\gamma_k$ represents the $k$th diagonal cohort effect for $k = 1, \ldots, (a + p - 1)$ cohorts.

One factor models (*a*, *p*, or *c*), two factor models (*ap*, *pc*, ca) and IE models were compared. Both descriptive analyses and model fit, based on the Akaike Information Criterion (AIC), were used to select the final models presented in the paper. Full analyses are available upon request. The log-linear regression coefficients, standard errors, and model fit were

computed using Stata 11. 2. Estimates of the full APC models using the IE approach used the apc_ie.ado downloaded from the Stata command line.

## RESULTS

To assess the variation in age-specific incidence by period a series of age-period plots were created. Figure 1 shows the sex-specific age and period all-cause cancer incidence rate plots. Each panel shows the age-specific incidence trends by calendar period, ranging from 1973 to 1978 on the far left to 1998 to 2002 on the far right. The solid lines show the disaggregated rates and the dashed lines display the trend when cancer rates are aggregated at age 85. These plots show that when rates are aggregated for the 85 plus age group, specious conclusions about age at which incidence rates peak may be drawn. These plots show that for the vast majority of the periods, the age group with the highest incidence rates can be found in the 85 to 89 age groups. The peak is then followed by a leveling off or decline for the 90 to 94 and 95 to 99 age groups. These plots also show that the trends are not stable over time. If the only factor influencing cancer incidence trends were age, you would expect to see the period specific curves following the same age trajectory and stacked on top of one another. The plots show both variation in the intercept (age 65 to 69), slope, and shape of the curve. It appears that there has been a steady increase in the level of cancer incidence over time, with the most recent periods sitting highest on the y-axis for most, but not all, of the age groups.

Figure 1 here

Figure 2 here

Age-cohort plots were created to assess the variation in the age trends by birth cohort and gender. Figure 2 displays the variation in shape, slope, and point of inflection in all-cause cancer

incidence age trends by cohort for both males and females. We are unable to observe a single cohort for the entire age range because we only have data for a 30 year window, from 1973 to 2002. Age trends for the 1903 and 1908 have the most data points, with incidence calculated for ages 70 to 99 and 65 to 94 respectively. There is less variation in the trend in age specific incidence rates between cohorts for the females compared to the males. The plots suggest that the peak in incidence is moving to younger ages for more recent birth cohorts for the males; however these peaks coincide with the expected rise in incidence that resulted from the PSA testing for male prostate cancer. There is a general trend of increased cancer incidence rates at younger ages for more recent cohorts for both males and females. For both females and males, the largest differences in cancer incidence occur at ages 90 – 99. The increased noise at advanced ages is partially of function of decreased sample sizes. The addition or deletion of a single case at these ages will lead to larger changes in the incidence rates compared to ages with larger denominators. The age-period and age-cohort plots indicate period and cohort factors may confound observed trends in age specific cancer incidence.

Table 2 here

A series of Poisson log-linear and IE models were used to further investigate the age, period, and cohort effects. Table 2 shows the goodness-of-fit statistics for the log linear models. The IE model provided the best fit for both male and female all-cause cancer, breast cancer and prostate cancer incidence. The fit statistics suggest weak cohort effects for the women, with the IE model only providing a slightly better fit than the age-period models for both all-cause and breast cancer incidence. The age-period model provided the best fit for both male and female colon cancer incidence models.

The results for the best fitting models are presented here. Figure 3 shows the IE results for all-cause cancer incidence by gender. The figure shows an increase in cancer incidence with age up to age 85. This is consistent with Saltztein's[6] observed peak in age-specific incidence rates for males and higher than the limit estimated by Harding for both sexes[4]. All-cause cancer incidence rates are the highest for the 85 to 89 age group net of period and cohort effects for both males and females. Female all-cause incidence rates for ages 90 and above appear to level off and the estimated coefficients are not statistically significant. There is a steeper decline in the all-cause incidence rate for the males after age 85; however it is interesting to note that the estimated coefficient for rates at age 90 ($p=0.06$) is still higher than the estimated rates for both the 60 to 64 and 65 to 69 age groups.

The period specific trends show that there has been a gradual increase in cancer incidence over time. While this gradual increase in cancer incidence with time may be indicative of changes in screening behaviors or environmental exposures, it may also be an artifact of changes in SEER data collection methods. The quality of SEER's data has increased with time, with more cases being properly recorded over time. The period effects for the males are as expected based on the descriptive analyses and the known increase in cancer incidence for males between 1988 and 1992 that resulted from the changes in prostate screening practices. The rates drop to pre-1988 levels in the next period and continue their decline into the 1998 – 2002 period.

The results show that there are moderate cohort effects for females. All-cause cancer incidence was significantly higher for the 1888 and 1893 birth cohorts and lower for the 1928 birth cohort. This is a slightly different conclusion than what may have been drawn if only analyzing the age-cohort plots. The preliminary plots of the more recent cohorts had higher incidence rates, suggesting that cancer incidence was higher for more recent cohorts. The cohort

effects for males resemble a trough, with slightly elevated risk (albeit insignificant) for early cohorts, followed by a decline and leveling off for the 1903 to 1917 birth cohorts, and ending with an increase that almost reaches the height of the 1883 birth cohort. The increases in cancer incidence in the 1917 birth cohort corresponds with increased rates of tobacco use in the United States after WWI[44]. The increase in the prevalence parents who smoke and a greater likelihood of tobacco use during adulthood are important factors contributing to cancer incidence for the post WWI birth cohorts. The gender difference in cohort trends is not unexpected because female tobacco use did not reach its highest levels until the 1930s[45].

Figure 3 here

Figure 4 displays the IE estimates for breast and prostate cancer. The age effects for the site specific cancers are somewhat different than the all-case trends. For females, the highest level of breast cancer incidence, and the only estimate significantly different from zero, is between the ages of 75 to 79 ($p=0.03$) which is consistent with previously reported trends in breast cancer [4-6]. The age effect for males steadily increases up to age 75 where it reaches a plateau, followed by a decline at age 90. The period effects are similar to those observed in the all-cause rates. There is a gradual increase with time in female breast cancer incidence. This increase may be partially due to increased detection by mammographic screening[12] and improvements in data collection and classification(ref). Male prostate cancer incidence steadily increases up to 1988 and then sharply declines over time, again for reasons of PSA testing. Cohort plays a small role in determining female breast cancer incidence over age 65 The decline in breast cancer incidence for the 1928 birth cohort is somewhat consistent with previous findings showing a decline in breast cancer incidence for the 1924 to 1938 birth cohorts[46].

Cohorts between 1898 and 1918 have slightly lower rates of prostate cancer incidence and a steady rise in rates is seen in subsequent cohorts.

Figure 4 here

Figure 5 shows the estimated coefficients for the log-linear AP models of colon cancer incidence. Model fit statistics showed that the two-factor model provided the best fit for colon cancer incidence, meaning that cohort effects can be constrained to zero. A study of colon cancer incidence and mortality in Connecticut reported downward sloping birth cohort trends of colon cancer mortality net age and period effects[47], however cancer mortality trends may reflect improvements in detection and treatment that prevent colon cancer mortality but not necessarily modify the risk of colon cancer incidence. The study did not report cohort specific trends of colon cancer incidence. Figure shows that there is a steady increase in colon cancer incidence with age up to age 85, followed by a slight decline (albeit still significantly higher than the referent category of 65 – 69) at the advanced ages. This finding is in accordance with previous estimates of colon cancer incidence rates reaching their maximum ages 85 and over[4, 6]. The period trends show a slight elevation in colon cancer incidence in between 1983 and 1987 for females and between 1983 and 1992 for males compared to the incidence rates in 1973 – 1977.

Figure 5 here

## DISCUSSION

This study found evidence supporting hypotheses of increased all-cause cancer incidence rates with age up to ages 85-89 net period and cohort effects, followed by modest decline in rates up to age 99. Incidence appears to drop after age 90, the rates up to age 99 are still higher than

rates for the young old. This finding is supported by other studies and highlights the importance of disaggregating cancer incidence rates for the oldest old [4, 19]. We also found evidence of period and cohort effects influencing cancer trends, which highlights the importance of considering these factors when studying cancer trends in the population age 65 and over. We conclude that the age, period, and cohort effects of site specific cancer incidence varied by site and gender. Cohort played a larger role for males than females and did not affect colon cancer incidence rates. The cohort results may indicate age-specific screening differences. For example, there were strong period effects associated with the introduction of PSA for the males. The birth cohorts that would have been in the oldest age categories at the time PSA was introduced on the market, the highest peak in incidence, have decreased cancer incidence rates relative to those cohorts that would have been below the age of 85. As more people begin to reach these advance ages, it will become increasingly important to understand the mechanisms driving cancer trends in the oldest old. These results emphasize the importance of Boscoe *et al.*'s call for greater specificity in age-specific data for the oldest-old[29].

Our findings suggest that the peak in all-cause cancer incidence is between the ages of 85 and 89 net period and cohort effects, which is higher than Harding *et al.'s* estimates of 80[4]. Our findings are consistent with Saltztein *et al.*'s observed peak in age-specific incidence rates for males but not females[6]. There could be several reasons for the variation in the estimated peaks in age-specific incidence rates. First, previous studies of age-specific cancer incidence in the oldest old age group have not considered the role of period and cohort effects. Ignoring the exogenous factors that may contribute to cancer incidence over simplifies the problem and leads to the age-specific incidence rates that are confounded by period and cohort differences in cancer incidence. Changes in cancer screening and diagnosis and cohort specific experiences modify

cancer incidence rates for the population over 65 and should be considered when studying the relationship between cancer and aging. APC analyses of cancer incidence may provide less biased estimates of the true relationship between cancer and aging.

Second, the differences may be caused by error in the estimated denominators. Preston *et al*. show that the difference between the correct population distribution and one estimated with age overstatement increases with time[34]. Any difference between the estimated peak cancer incidence and true peak cancer incidence should be negative. If age-misstatement led us to overestimate the size of the oldest old population, then our estimate of a peak in incidence between the ages of 85 and 89 is conservative. In a related study, we also compared the results to rates constructed with extinct cohort denominators and linked CMS denominators and found little variation between the denominators up to age 94 (Rull *et al. forthcoming*) and no difference in substantive conclusions when the extinct cohort component denominators were used. Also, because other studies have also used decennial census data to construct their denominators[4, 18], we argue that this is not the reason for the observed differences in peak age-specific incidence rates.

Third, geographic variation in trends should be considered when studying aging and cancer. While not directly assessed, our findings are suggestive of geographic variation, given the difference in the estimated peak of cancer incidence between our study and other studies of overlapping time periods in the US[4, 6, 18]. Other studies have shown that there is between state variation in cancer incidence [46, 48, 49]and we have shown that period and cohort effects play a significant role in determining cancer incidence rates. These effects may vary by geographic location within as well as between countries.

This study showed that all-cause cancer incidence peaked between the ages of 85 and 89 and were followed by a modest decline and leveling off between the ages of 90 and 99 for both males and females. There is not widespread consensus in the cause of the decline in cancer rates at advanced ages because it has been largely understudied. Several studies have provided evidence supporting the four mechanisms leading to cancer decline in the oldest old presented in Table 1. Smith supports the mortality selection argument, proposing that the oldest old confer a genetic or environmental advantage that decreases their risk for cancer[19]. According to this argument, individuals surviving to these advance ages are a select group of robust survivors. If this theory is correct then it is important to consider this argument within the context of increases in cohort life-expectancy. Carnes has argued that as life expectancy increases the oldest-old population will become more heterogeneous and new or infrequently observed morbidity profiles will be observed [50]. This argument applied to cancer incidence would imply that frail individuals with a higher susceptibility to cancer have historically been selected out of the population due to other causes of death. Declines in the force of mortality at all ages may lead to increased population heterogeneity at old ages, thus possibly cohorts of individuals with more susceptibility to cancer. At what age will the robust survivor argument be appropriate if life-expectancy continues to rise and higher proportions of cohorts reach the oldest-old age group? The gradual uptick of cancer incidence for males during more recent birth cohorts is evidence of changing cohort susceptibility to cancer. While it is difficult to separate the environmental factors from the changes it population heterogeneity, this finding emphasizes the importance of both improved surveillance in cancer trends for the oldest old and the consideration of cohort effects when studying cancer trends for this age group.

Two factors likely play a small role in the deceleration and decline in cancer incidence above age 90. However, these findings do not suggest that they are the main reason. Stanta suggests a possible differential exposure to environmental carcinogens in addition to a biological explanation of less aggressive tumors and cancer decline in the oldest old [11]. Our results show variation in cohort tends of cancer incidence over time that coincide with known changes in environmental exposure to tobacco products. However, these factors are not the driving force in the decline because the decline in cancer incidence beginning at age 90 still remains after controlling for cohort and period effects. Other authors have suggested that screening bias may cause the decrease in cancer incidence for the oldest old. Kaplan notes parallel trends downward sloping trends between breast cancer screening and prevalence in the elderly[5]. However other studies not subject to screening bias show that the prevalence of cancer decreases with age[11]. This study also suggests that screening bias may not be the reason for decreases in cancer incidence with age. SEER data collection processes include checking death certificate information. Any cancer occurrence that contributes to the COD for an individual is reported to the SEER registries. Only cancers not determined to be an underlying factor in the death would be missed by the system. This suggests that detection bias is not a likely cause in the observed decrease in cancer at advanced ages.

Harding *et al*. propose a simple senescence theory, claiming that increasing senescence reduces the ability for cells to divide and drives the decline[4, 18]. However their period specific graphs show variation in both the peak and shape of the age trends by period. Reasons for decline that are solely biological in nature should not vary over short periods of time. We are not arguing against biological determinants of cancer decline, but we do advocate a more inclusive theory that considers social and environmental factors that may influence the age-specific trends.

This study suggests that the peak cancer incidence rates in Utah may differ from those at the national level[4, 18]. Regional differences in cancer incidence trends may be attributable to differences in sociodemographic characteristics, health beliefs, access to resources, reproductive characteristics, and exposure to environmental carcinogens. There may be geographical variation in both the shape of the age specific incidence trends and the magnitude of period and cohort effects. Utah has one of the lowest cancer incidence and mortality rates in the Nation, however age-adjusted prostate cancer incidence rates are higher than the national averages[32]. Utah has the lowest rates of lung cancer incidence and mortality for both males and females in the United States[45]. Failing to consider the temporal influences of cancer incidence may lead to erroneous conclusions about the behavior of cancer in the oldest old. Comparing age, period, and cohort trends across different geographical regions may give more insight into the biological, social, and environmental characteristics that affect cancer incidence rates.

There are several limitations to studying cancer trends in the oldest old age groups, many of which were present in the selected studies. Use of clinical and death certificate diagnoses may lead to an underreporting of trends in the oldest old [5, 11]. Trends calculated using cancer registry and census data are subject to error because the reliability of age estimates for individuals over the age of 85 is questionable[1, 12]. However, we used several different methods to create measures of the population size and found no substantive differences in the age, period, and cohort trends in all-cause cancer incidence.

This study contributes to the current literature by providing estimates of cancer incidence for the 85+ population. We also analyze age-specific trends of cancer incidence within the broader context of age and period effects. We show that cohort and period effects are important predictors of all-cause, breast and prostate cancer incidence and should be considered when

studying trends in cancer incidence. Studies utilizing an APC approach to the analysis of cancer trends may provide less biased estimates of the relationship between cancer and aging. The existence of cohort and period effects also justifies the use of direct measures of the exogenous factors contributing to cancer incidence. Future studies should evaluate the proportion of variation in cancer incidence explained by direct measures of period influences and cohort characteristics. We also show that there is variation in cancer incidence trends in the oldest old population and reiterate the importance of treating this population as heterogeneous. In order to gain a more comprehensive understanding of morbidity and mortality patterns for this rapidly growing segment of the population, cancer incidence and US Census population estimates need to be disaggregated for the oldest-old population.

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**Table 1. Explanation of Rising and Falling Cancer Rates with Age**

| | |
|---|---|
| **Increasing cancer rates in the oldest old** | |
| Multi-Stage Theory of Carcinogenesis | Probabilistic events are required for the somatic evolution of cancer. Several sequential 'hits' are required for the neoplastic transformation of cells. The neoplastic transformation of cells is caused by the dose and duration of carcinogenic exposure over a person's lifetime regardless of any effects of aging. |
| Somatic Aging | Age related changes create a more conducive environment for cancer. Senescent cells lose ability to undergo apoptosis. There is a decline in immune surveillance with age . Change in the tissue microenvironment may arise for age-associated exposure, such as infectious agents.<br><br>Telomere shortening and reactivation of telomerase are also important components of aging and carcinogenesis<br><br>Age accumulation of senescent cells. Increasing proportions of damaged proliferating cells in an organism with age . Because cancer cells do not "age", their metabolic, proliferative, growth, and signaling profiles may give them a survival advantage. |
| **Decreasing cancer rates in the oldest old** | |
| Exposure to carcinogens has increased over time | Older cohorts may have had less exposure to carcinogens, making their cancer rates lower. It is not physiological aging driving the decrease with age, but differences in exposure. |
| Selection | Cancer and aging trends are similar. The force of mortality decreases at these old ages possibly. The survivors at this age may be robust and have a genetic advantage, in other words, selection favors those less prone to cancer. |
| Detection Bias | Screening recommendations are different for older populations. It is difficult to screen and/or detect symptoms of cancer in the frail and individuals with multiple comorbidities. |
| Physiological factors that reduce the probability of carcinogenesis | Physiological changes may favor slow growing tumors or suppress tumor generation.<br><br>Age-related decline in rates of metabolism, information processing, and cell proliferation may increase tumor doubling time<br><br>Cellular mechanisms that reduce cancer risk also increase rates of aging. |

Table 2. Goodness-of-fit Statistics for APC log-linear models of Utah Cancer Incidence

| | Female | | | | Male | | | |
|---|---|---|---|---|---|---|---|---|
| | Age | Age Period | Age Cohort | IE | Age | Age Period | Age Cohort | IE |
| All -Cause | | | | | | | | |
| Deviance | 503.81 | 376.44 | 365.77 | 355.99 | 866.36 | 532.55 | 653.49 | 358.24 |
| AIC | 517.81 | 400.44 | 401.77 | 399.99 | 852.36 | 556.55 | 689.49 | 402.24 |
| Breast | | | | | | | | |
| Deviance | 488.38 | 317.36 | 312.16 | 295.81 | | | | |
| AIC | 502.38 | 341.36 | 348.16 | 339.81 | | | | |
| Prostate | | | | | | | | |
| Deviance | | | | | 1356.96 | 775.87 | 279.60 | 254.33 |
| AIC | | | | | 1370.96 | 799.87 | 315.60 | 298.33 |
| Colon | | | | | | | | |
| Deviance | 314.68 | 280.45 | 280.11 | 269.47 | 329.01 | 264.91 | 304.23 | 261.04 |
| AIC | 328.68 | 304.45 | 316.11 | 313.47 | 343.01 | 288.91 | 340.23 | 305.04 |

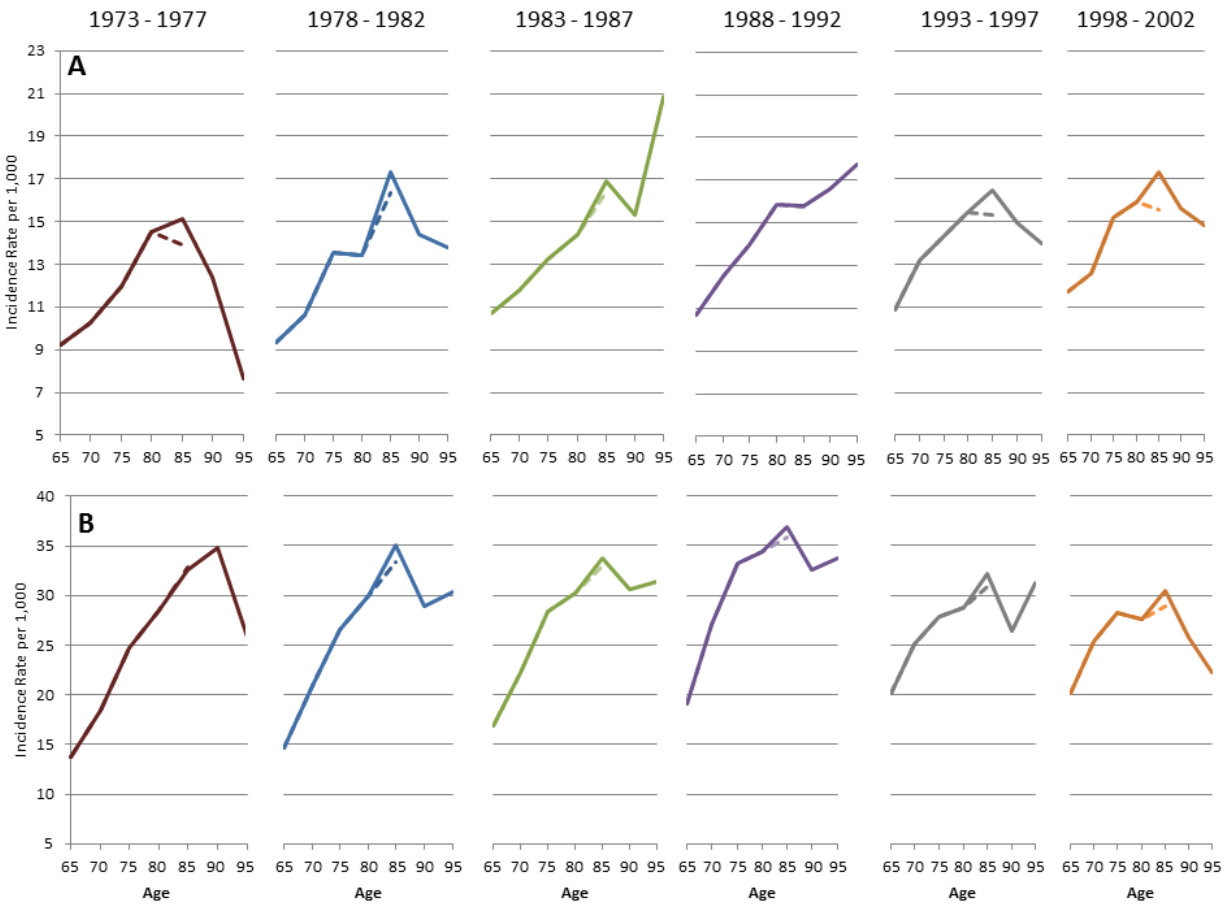


**Figure 1. Panel A: Utah Female All-Cause Cancer Incidence Rates by Age and Period. The dashed lines show the trend when cancer incidence is aggregated for individuals 85 years and above and the solid lines show trends up to age 99. Panel B: Utah Male All-Cause Cancer Incidence Rates by Age and Period.**

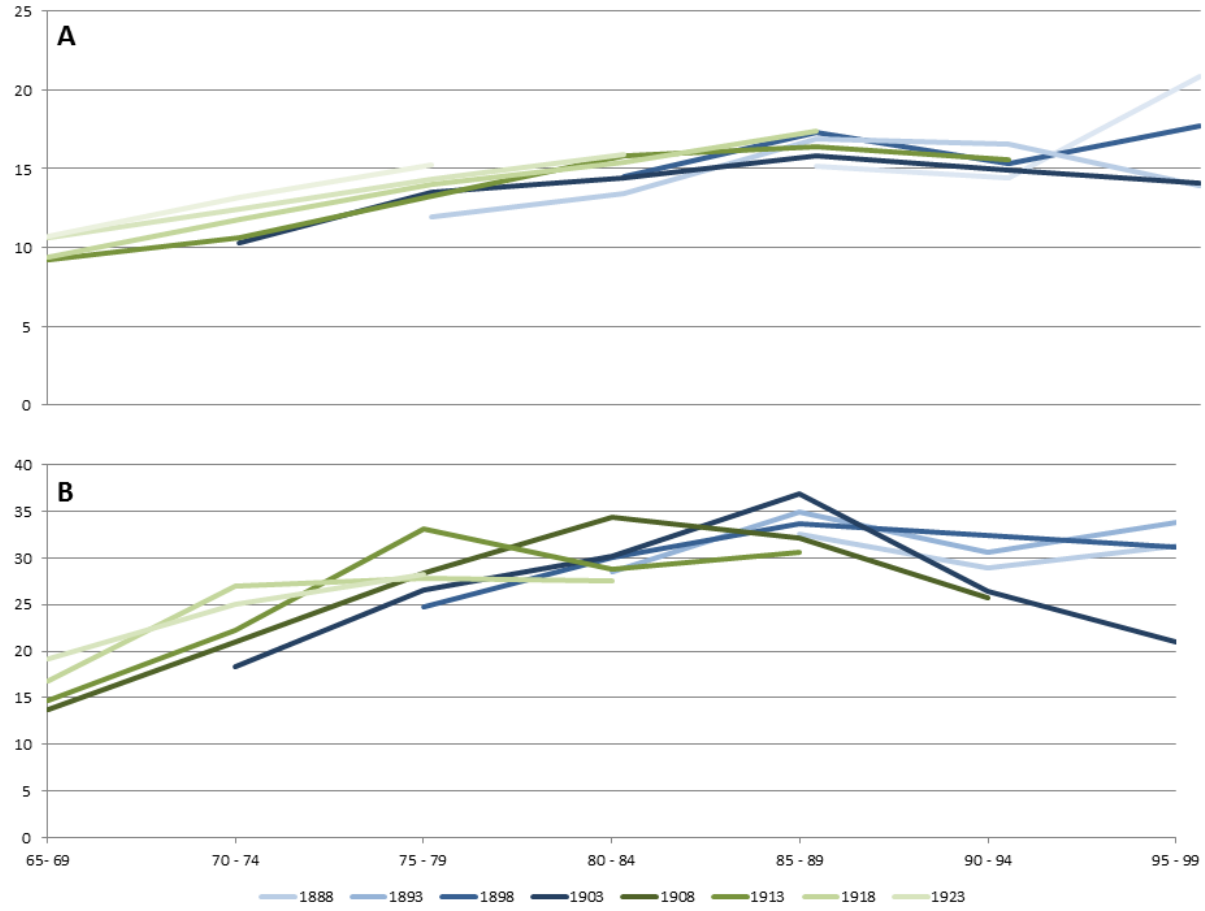


**Figure 2. Panel A: Utah female all-site cancer incidence by birth cohort. The scale of the y-axis is smaller than the scale for the male graphs to allow for the visibility of the variation. Female incidence rates are lower than male incidence rates and increase with age at a slower rate. Panel B: Utah male all-cause cancer incidence by birth cohort.**

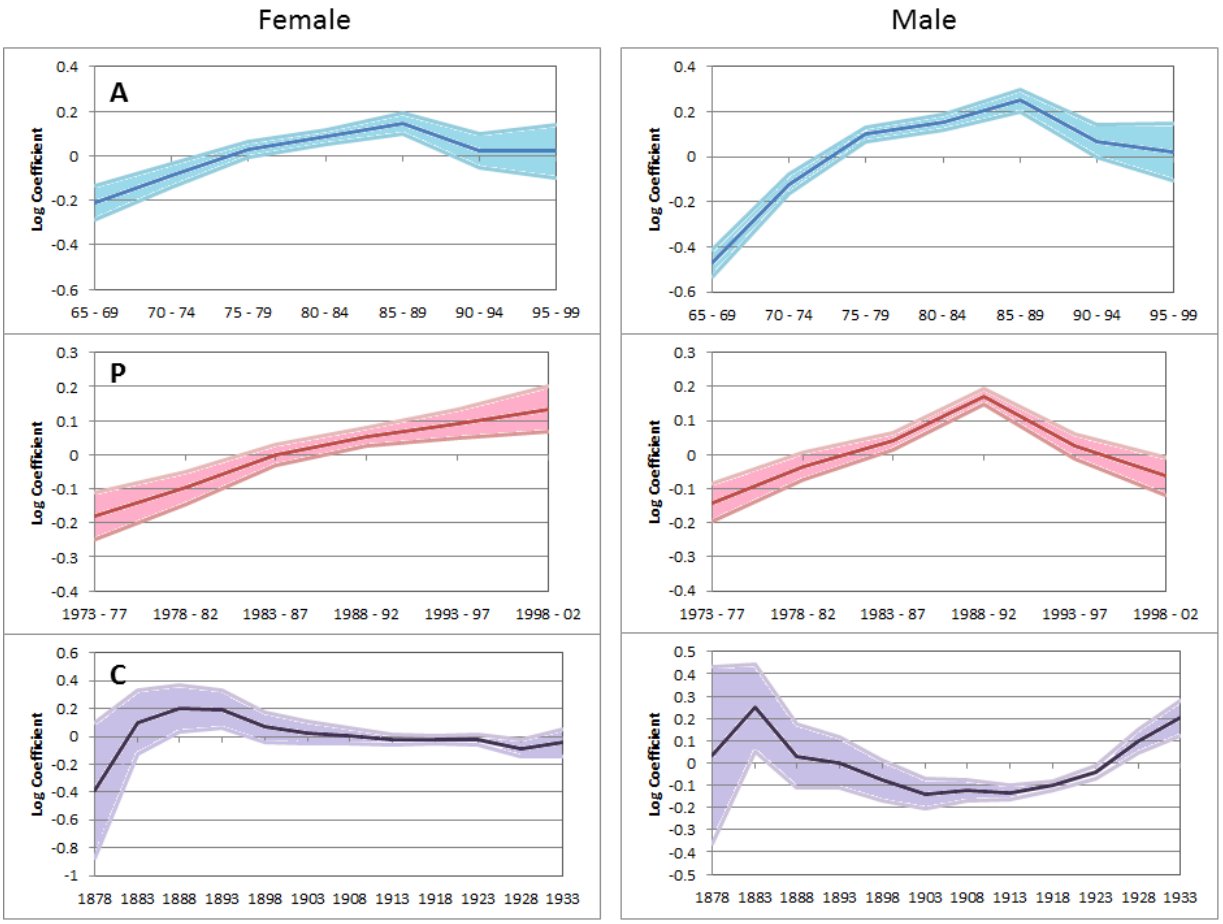


**Figure 3. APC IE estimated trends of all-cause cancer incidence rates for ages 65 to 99 in the state of Utah are illustrated with 95% confidence intervals. Panel A: Age effects net period and cohort. Panel B: Period effects net age and cohort. Panel C: Cohort effects net age and period.**

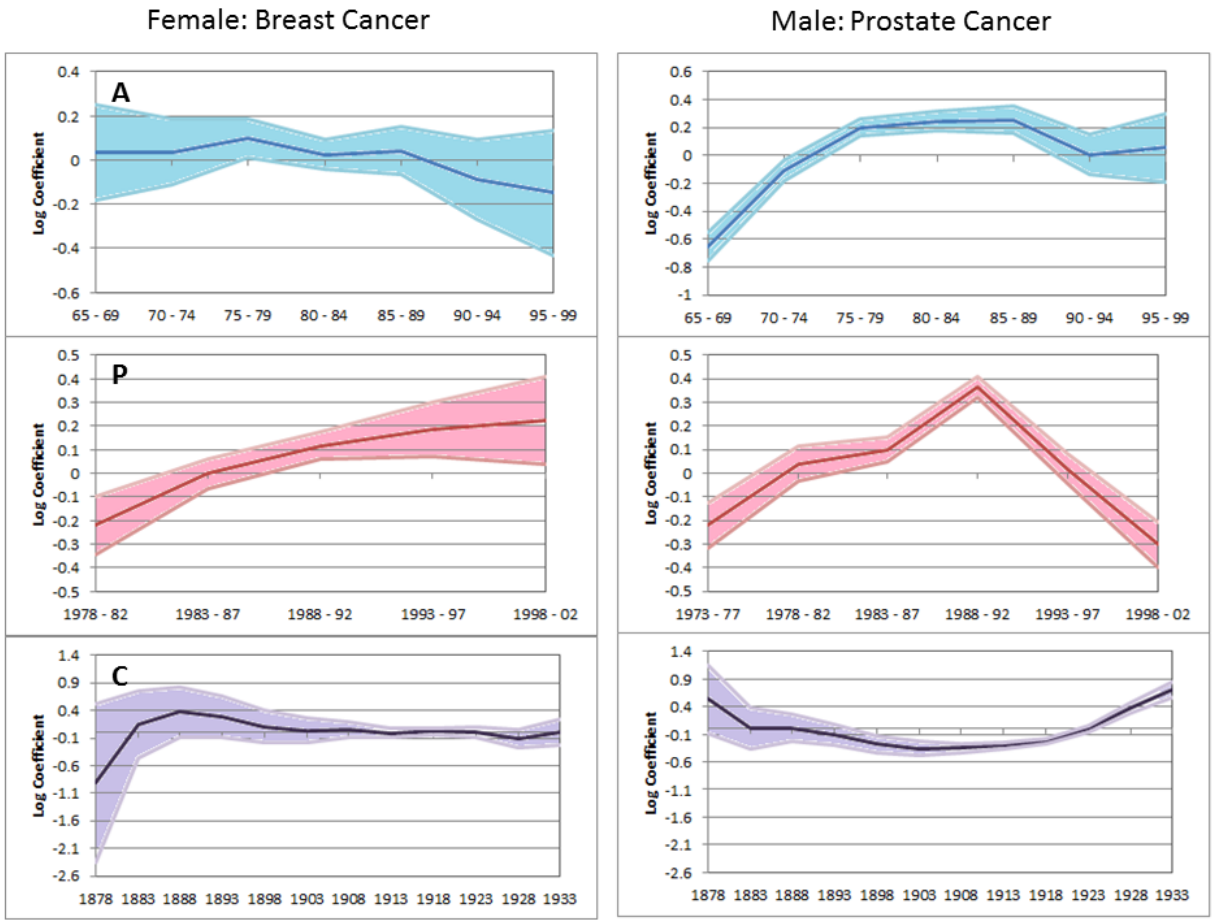


**Figure 4. APC IE estimates female breast and male prostate cancer incidence rates for ages 65 to 99 in the state of Utah are illustrated with 95% confidence intervals. Panel A: Age effects net period and cohort. Panel B: Period effects net age and cohort. Panel C: Cohort effects net age and period.**

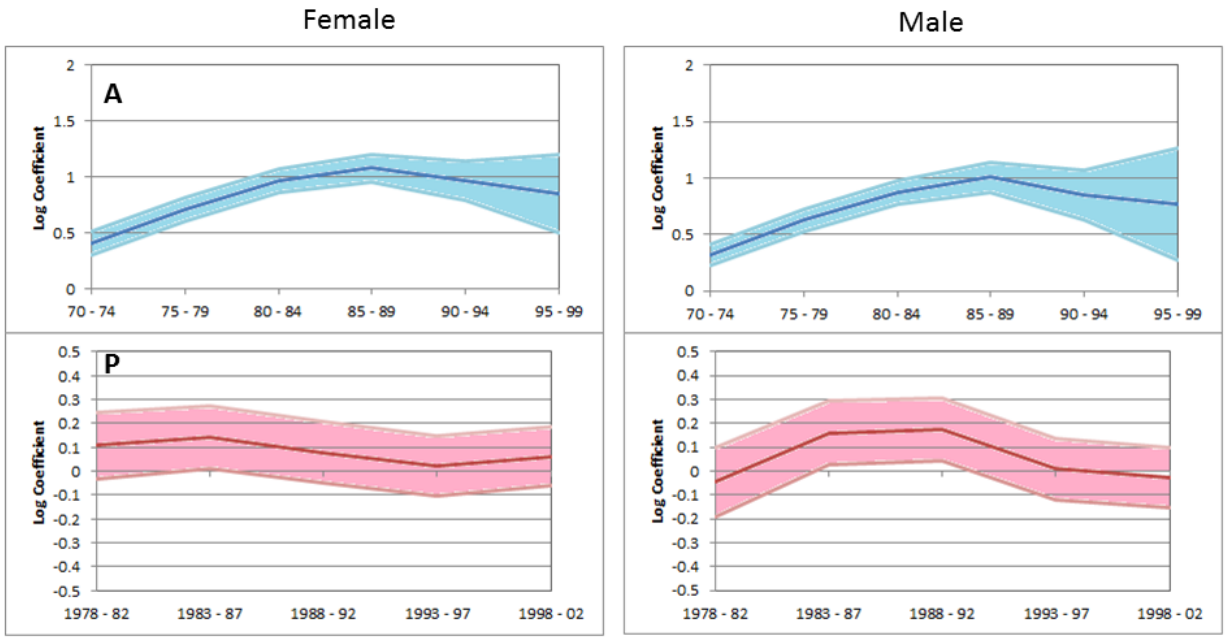


**Figure 5. Poisson log-linear estimates of age and period effects on colon cancer incidence with 95% confidence intervals. Panel A: Age effects net period and cohort. Panel B: Period effects net age and cohort.**