Age-Period-Cohort Analysis of Primary Bone Cancer Incidence Rates in the United States (1976 – 2005)

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Running head: APC analysis of primary bone cancer
MS contains 3646 words, 1 table, 4 figures, 1 supplementary figure
Abstract

Background: Primary bone cancer comprises three major histological types: osteosarcoma (OS), Ewing sarcoma (ES) and chondrosarcoma (CS). Given the limited knowledge about the etiology of primary bone cancer, we undertook an age-period-cohort (APC) analysis to determine whether incidence varied by birth cohort or calendar period. The purpose was to examine the temporal development of each bone cancer type and generate etiologic hypotheses via the observed birth cohort-related changes.

Methods: An APC model was fitted to incidence data for U.S. whites for OS, ES and CS obtained from nine registries of the Surveillance, Epidemiology, and End Results (SEER) program, which covers about 10% of the U.S. population, 1976-2005.

Results: The incidence of OS decreased between 1976 and 2005 among those aged 60+ years, a decline that occurred among patients with OS as their primary malignancy only. From 1986-95 to 1996-2005, the incidence rate of CS among females 20-69 years rose by about 50%, with rates increasing among consecutive cohorts born 1935-75. CS rates among males were stable, as were rates of ES.

Conclusion: The risk reduction in OS as a primary malignancy at older ages could possibly be related to diminished exposure over time to bone-seeking radionuclides. The CS increase among females corresponds to birth cohorts with rising exposures to oral contraceptives and menopausal hormonal therapy.

Impact: As the estrogen signaling pathway has been shown to stimulate proliferation of normal and malignant chondrocytes, estrogen exposure may increase the risk for CS. Further studies are warranted to clarify its possible etiological significance.
Introduction

Osteosarcoma (OS), Ewing sarcoma (ES) and chondrosarcoma (CS) are the three major histological types of primary bone cancer. The three groups combined represent less than 1% of all cancers diagnosed in the U.S., with OS historically being the most frequent. Although multi-agent chemotherapy has greatly improved the survival rate, mortality is still high, with overall five-year survival ranging from about 15 to 60 percent for OS patients with and without visible metastases, respectively, at the time of diagnosis (1-4). Although the majority of OS cases occur in adolescence, there is a second peak in incidence in the seventh and eighth decades of life. OS in elderly patients is often considered as a secondary neoplasm attributed to sarcomatous transformation of Paget's disease of the bone or a late effect of previous radiotherapy or chemotherapy (5, 6). At all ages after the first decade of life, males are affected more frequently than females.

There are few established risk factors for OS apart from early exposure to radiation, Paget's disease, hereditary retinoblastoma, and Li-Fraumeni syndrome (7-11). The bimodal age-incidence curve with peak rates occurring both in adolescence and in older age suggests two separate etiologies. Enhanced carcinogenic susceptibility during the adolescent growth period is implicated by higher radiogenic bone cancer risk among children than adults and the characteristic development of childhood tumors in the long bone epiphyses of the lower limbs. Higher male than female incidence rates in puberty and the early age at which OS incidence first peaks, at ages 10–14 and 15–19 for girls and boys respectively, may indicate the importance of accelerated growth and hormonal differences. Very early-in-life characteristics including high birth weight have also been implicated in the etiology of OS (12).
The age distribution of ES resembles that of OS in early life, albeit with its peak incidence among even younger patients (13). This indicates a similar link between the onset of puberty and this type of bone cancer (6). ES rarely develops later in life (13) and differs from OS in that it is not induced by radiation. In general, there is a paucity of studies examining putative risk factors for this disease. ES is more common among Caucasians than African-Americans and Asians, suggesting a genetic predisposition (14, 15). A translocation between chromosomes 11 and 22 is found in almost all cases (16).

CS is rare in childhood and incidence rates, unlike those of OS and ES, increase fairly uniformly with age. Risk factors for this subtype are largely unknown, although there is some evidence that ionizing radiation may play a role (6, 17). Secondary CS may arise in a benign precursor, either an osteochondroma or enchondroma. CS is less common in African-Americans than Caucasians, as is the case for ES (14).

In this paper we fit age-period-cohort (APC) models to U.S. incidence data for OS, ES and CS cases diagnosed during the period 1976-2005, as obtained from the nine, longstanding registries of the Surveillance, Epidemiology, and End Results (SEER) program covering about 10% of the U.S. population. The aims of this study were to examine the temporal trends of each bone cancer type and to generate possible etiologic hypotheses implicated in the observed birth cohort-related changes.
Material and Methods

Incident cases of bone cancer diagnosed among white residents of the nine Surveillance, Epidemiology, and End Results (SEER) registries during 1976-2005, were categorized by sex, age (0-4, 5-9, ..., 80-84, 85+) and morphology code (18). Corresponding population data were available from the same source. Incidence rates were grouped for the major types of bone cancer: osteosarcoma (ICD-O-3 9180-9200), Ewing sarcoma (ICD-O-3 9260) and chondrosarcoma (ICD-O-3 9220-9243) (19). Bone cancers with all other or unspecified morphologies were categorized as ‘other’ (ICD-O-3 9210; 9250-9252; 9261-9342).

Age-specific and age-standardized (world) incidence rates per 100,000 person-years were computed by morphologic type and sex, overall and in 10-year calendar periods (1976-85, 1986-95, and 1996-2005) and plotted according to age, year of diagnosis, or birth cohort. Age was categorized using five-year intervals in adjusted rates and 10-year intervals for age-specific rates and the models. Birth cohorts were estimated by subtracting the midpoints of 10-year age groups from the corresponding midyears of 10-year calendar time. Figures 1-3 were plotted using a uniform log(rate) scale of 0.1:2.0 for the vertical axis and an arithmetic (year) scale for the horizontal axis such that an annual rate of change of 1% was portrayed by an angle of 10 degrees, i.e., 1 log cycle is the same length as 40 years (20). Rates based on fewer than 10 cases or single data points were not shown.

Observed age-specific trends are presented as rates for calendar periods (herein referred to as “periods”) and rates for birth cohorts (herein referred to as “cohorts”), with parallelism of the curves an indication of their respective cohort or period influence on the temporal pattern. Cohort effects may be established by environmental determinants acting
prenatally or early in life, or they may reflect factors that exert influences shared by members of the same group as they age together. Period effects are characterized by an immediate or fixed-delayed change in the incidence rates for all age groups (regardless of their birth cohort), and thus may reflect events that quickly change rates with the same order of magnitude across all affected age groups. Commonly they transpire from changes in classification criteria, the availability of new diagnostic tests, or specific interventions that affect rates similarly across all age groups. Comparison of the shapes, slopes, and alignments of the age-specific curves may reveal the roles of period versus cohort effects.

Given the limitation of age-period-cohort (APC) analyses, i.e., the inherent inability to identify the individual slopes of age, period and cohort simultaneously due to the linear dependency between the time components (20), the estimated effects are presented here with an \textit{a priori} focus on describing and interpreting the cohort effects obtained from the full APC model. The allocation of drift (the identifiable sum of period and cohort slopes) to birth cohort was used to obtain a unique solution, according to the method of Holford (21, 22). By constraining the period effect to zero on average and with a slope of zero, we assume the changes in rates (and specifically the underlying linear trends) may be attributed to birth cohort influences. Other interpretations and solutions are possible, and the model-based results should be interpreted with caution.

APC analysis was performed using the functions available in the library \textit{Epi} (version 1.0.8) in R (23), and specifically the \textit{apc.fit} command. Synthetic two-year birth cohorts, each overlapping one year, were derived from 1-year period and 1-year age groups. Given specific concerns regarding the data quality in the elderly for Ewing sarcoma and because of low
numbers of cases, we restricted the modeling analyses to ages 0-64 years at diagnosis for this type; for the other histological types, the age range was 0-84 years.

The necessary smoothing was obtained using a natural splines function, with the number of parameters set to five for the age, period and cohort effects. The knots were set so that the number of events was the same between them. The cohort and period effects are presented as rate ratios with the reference cohort 1930. Stata 10 (24) was used for data management and plotting of the observed trends.

Results

Age-specific Patterns

The age-specific rates of OS during 1976-2005 exhibited a bimodal distribution with the highest incidence rate occurring in the second decade of life, with a decline to the lowest incidence between 30 and 50 years of age, followed by a second peak in those 75-79 years of age (Figure 1). After the age of 15, females had a lower incidence of OS than males, and the highest incidence rate in females was observed at a slightly younger age (10-14 years) than in males (15-19 years). The age and sex distribution of ES incidence rates was similar to that for OS until the age of 40, after which very few cases of ES were diagnosed. An increasing incidence by age was noted for CS, reaching a plateau around the age of 65. A male predominance was generally apparent at the older ages and at ages <30 years, in contrast to modest and inconsistent sex differences among the middle age groups.

Overall Incidence Rates and Trends 1976-2005
In males, the incidence rates were highest for OS and CS throughout the period 1976-2005 and were also quite stable (Table 1). Among females, this was also the case for the first two 10-year periods, albeit at a level some 30% lower than in males. During the most recent years (1996-2005), however, the incidence rate for CS in females was comparable to that of OS, rising by almost 70% from 0.16 in 1976-85 to 0.27 in 1996-2005. This increase in the incidence rate of CS among females was statistically significant (P < 0.05), with the estimated change reaching almost 3% per year. An overall rise in the rate of bone cancer among females (0.8% per year) was mainly due to the increasing CS incidence. Rates of CS among males were basically unaltered over time, as were the ES rates for both males and females. The estimated annual percentage change was based on data for the individual years. The male to female ratio was largely between 1.2 and 1.6 for all types throughout the three 10-year periods, except for CS, which had dropped to unity in the last period.

The presentation of trends from 1976 to 2005 graphically further demonstrates that age-standardized incidence rates for primary bone cancer and its major subtypes have been relatively stable (Figure 2), with the exception of that for CS in females which has been rising since the late 1990s, exceeding rates of OS during the last decade. Despite a slight increase in the rate of OS among females, CS accounted for most of the overall increase in bone cancer within this group.

**Age-specific Trends by Period and by Cohort**

Figure 3 shows the incidence rates of OS and ES related to period of diagnosis and to birth cohort by 10-year age groups for both sexes combined (A and B). Males and females were combined since their patterns were similar. Sex-specific incidence rates for OS and CS are
presented as supplementary material. No consistent patterns in incidence trends by period were observed for OS. However, cohort-specific declines in OS were seen in successive generations born 1905-34, while there were some indications of an increasing trend among recent birth cohorts, born after the mid 1950s. A further analysis of the SEER data showed that the OS decline at ages 60-69 and 70-79 clearly occurred among those patients with only one primary malignancy, or who had OS as the first of multiple primaries. There was no indication of declining rates for patients with OS following another primary malignancy (data not shown). For ES, no patterns in incidence trends by period or cohort were apparent.

For CS (Figure 3, C and D), there was no consistent pattern in the trends among males. In females, however, increases were apparent over the entire study period 1976-2005; among older women ages 50+, rates rose during the latter half of the study period. Splitting by cohorts, revealed increasing incidence rates for consecutive cohorts born since the early 1900s. The earliest and steepest increases occurred among women aged 40-49 years, born during the 1930s-1950s; rates among younger women, born more recently, also have been rising rapidly.

**APC Modeled Trends**

Assuming a period slope of zero and, hence, drift attributed entirely to birth cohort, Figure 4 presents age-period-cohort graphs depicting the fitted age-specific rates (left part) and relative changes in incidence rates of OS, ES and CS among subsequent cohorts compared to those born circa 1930 (middle part) and over period of diagnosis (right part). The rates are given relative to the respective reference cohort of each cancer type, which explains why the highest age-specific rates are not always comparable to those presented in Figures 1-3.
With respect to goodness-of-fit, two-factor models fitted the data adequately for the three subtypes, possibly due to underdispersion, although for most subtype/sex combinations, non-linear period and/or cohort effects contributed to significant improvements in the model fit.

A decline in OS was seen in both sexes for cohorts born from 1890 to 1925, with a slight increase thereafter. An increase, followed by a leveling off and decrease (in women), in rate ratio of ES in successive birth cohorts was observed. These apparently striking ES effects are based on relatively few cases, and thus subject to random variation to a larger extent than OS and CS. The CS incidence rate ratio increased in successive cohorts born between 1925 and 1955 in females, but not males. For the subsequent cohorts, CS rate ratios remained clearly higher in women than men.

**Discussion**

The epidemiology of primary bone cancer has been the subject of several reports over the past years, emphasizing incidence and survival rates across tumor subgroups (13, 25-27). To our knowledge, APC modeling has not yet been undertaken for these cancer types. Given the limited number of established risk factors for primary bone cancers, APC modeling is a reasonable approach to attempt to identify testable hypotheses, in particular those pertaining to birth cohort or calendar period. The presence of cohort patterns may support the notion that exogenous factors are important in the carcinogenesis of the disease under study. For other cancers, such as testis and breast, the identification of cohort patterns has generated new hypotheses regarding external risk factors (28, 29).
The present study has revealed some hitherto unrecognized changes in the secular trends of the two major types of primary bone cancer, OS and CS. Incidence rates of OS decreased between 1976 and 2005 among those 60 years and older, corresponding to cohorts born from 1905 to 1934. This represents the second peak of the bimodal age-incidence curve of OS, around 70 years of age, where OS is often attributed to late effects of cancer radiotherapy or chemotherapy (5), or sarcomatous transformation of Paget’s disease (6). Based on recently published SEER data, OS as a second or later cancer comprises about one fourth of all OS cases in this age group (26). It turned out, however, that the OS decline at ages 60-79 in the present study occurred among patients with only one primary malignancy, or who had OS as the first of multiple primaries. There was no indication of declining rates for patients with OS following another primary malignancy. Thus, developments in cancer therapy over the past decades are not relevant in this context. The risk reduction in OS as a primary malignancy at older ages could possibly be related to diminished exposure over time to the fall-out of Strontium and other bone-seeking radionuclides in the 1950s and 1960s, which has been implicated in the etiology of OS (30).

OS with Paget’s disease among those older than 60 years of age comprises about one tenth of all OS cases in the SEER database, and this proportion has been quite stable throughout the study period (26). Although we did not analyze OS with Paget’s disease separately in our data, it is reasonable to assume that changes pertaining to this subgroup of cases do not explain the observed decline in incidence rates.

There appears to be an increased incidence rate of CS for females over the study period, whereas that of males seems largely unaltered. This applies to females 20-69 years of age, for cohorts born between 1935 and 1975, and corresponds roughly to the
introduction of estrogens, both in terms of oral contraceptives and hormone therapy. Oral contraceptives were introduced in the U.S. in 1960, and among women using contraception, 25-30% have used the pill fairly consistently since that time. The proportion of women aged 15-44 currently using an oral contraceptive increased from 56% in 1982 to 64% in 1995, and then declined slightly to 62% in 2002 (31).

In the first place, oral contraception was used by parous women to end their reproductive period. Later, use became prevalent among younger women. This seems to be reflected in our data in two ways. Firstly, the earliest and steepest increase, i.e., the first period (1975-85), took place among those aged 40-49 years. Secondly, in the second period (1985-95), a similar increase was observed among those aged 20-29 and 30-39 years. In this period, however, a corresponding increase was seen also among those aged 50-59 and 60-69 years, which is possibly attributable to those being exposed to hormone therapy some years earlier.

Use of menopausal hormone therapy became widespread in the U.S. during the 1960s (32). When the use of estrogen monotherapy was linked with endometrial cancer in the 1970s, combined estrogen/progestin use, introduced in the 1980s, increased among women who were not hysterectomized. The proportion of women undergoing natural menopause who ever used hormone therapy increased from about 10% in the 1950s to about 50% in the 1990s (32). Use of hormone therapy further rose throughout the 1990s, as it was thought to prevent chronic diseases. Use has decreased dramatically following the Women’s Health Initiative (WHI) trial results published in 2002 showing that the overall health risks actually exceeded benefits from use of combined estrogen plus progestin among healthy postmenopausal women (33). A substantial part of the U.S. female population has
thus been exposed to estrogens in a period coinciding with an unequivocal rise in the incidence of CS. This ecological correlation is supported by insight gained during the past 10-15 years pertaining to the role of estrogen in the molecular cell biology of CS.

Estrogen is involved in cartilage metabolism in both male and female chondrocytes and plays an important role in the human growth plate by regulation of longitudinal skeletal growth mediated by chondrocyte proliferation and differentiation (34). At the cellular level, the estrogen effect is mediated by the estrogen receptor (ER), since mRNA expression and nuclear immunoreactivity for ER have been demonstrated in chondrocytes as well as CS cells (35, 36). Furthermore, the expression of CYP19 mRNA, the gene encoding aromatase, which converts androstenedione to estrogen, has been demonstrated in both normal and neoplastic cartilaginous tissue (37). In vitro studies have shown that the estrogen signaling pathway stimulates proliferation of chondrocyte cell cultures and CS cell lines. This growth promoting role of estrogen in normal and malignant chondrocytes is apparently similar to the well-established late-acting role of estrogen action in cancer promotion in the female breast as well as in other estrogen sensitive organs. It is also of interest that estrogen has been shown to stimulate vascular endothelial growth factor, and thus neovascularization, which is a characteristic trait of progression of CS (17).

It is of note that estrogen receptors have also been demonstrated in human OS tissue as well as in OS cell lines. There is conflicting evidence, however, as to whether estrogen signaling has a proliferative or an anti-proliferative effect on OS (38, 39). This inconsistency in cellular response to estrogen in OS makes it plausible that a possible stimulatory effect of estrogen is observed for CS, but not for OS, although both malignancies have the ability to respond to estrogen.
Against this background it seems fair to conclude that there is a biological rationale for estrogens promoting the development of CS. To our knowledge, exposure to estrogens has not previously been proposed as a risk factor for CS, and as such, needs to be assessed in analytic studies, e.g., in a case-control study design. Given the large drop in the use of hormone therapy after 2002 when the WHI trial results showed its adverse effects, future studies may be expected to observe a corresponding decrease in the incidence in CS over time. Although this is a very rare cancer form, an association eventually being demonstrated between estrogen exposure and CS might have implications in terms of a raised awareness for primary bone cancer among those who have been exposed.

In conclusion, the risk reduction in OS as a primary malignancy at older ages is possibly related to diminished exposure over time to bone-seeking radionuclides. The increase in CS among females corresponds to birth cohorts who were increasingly exposed to estrogens, both in terms of oral contraceptives and hormone therapy. Supporting our hypothesis of estrogens being involved in the increased rate of CS among women over time, in vitro studies show that the estrogen signaling pathway stimulates proliferation of both normal and malignant chondrocytes. Further studies are warranted to clarify the possible etiological significance of estrogen exposure in CS risk.

Acknowledgments

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References


25. Stata Statistical Software, College Station. StataCorp, editor. TX, StataCorp LP; 2009.


**Table 1.** Incidence counts, rates* and the estimated annual percentage change 1976-2005 by histological type and sex, SEER 9

<table>
<thead>
<tr>
<th></th>
<th>Incidence count</th>
<th>Rate</th>
<th>Estimated Annual Percentage Change</th>
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<tbody>
<tr>
<td><strong>Males</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>298</td>
<td>306</td>
<td>325</td>
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<tr>
<td>Ewing sarcoma</td>
<td>169</td>
<td>160</td>
<td>163</td>
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<tr>
<td>Chondrosarcoma</td>
<td>235</td>
<td>289</td>
<td>332</td>
</tr>
<tr>
<td>Other bone cancers</td>
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<td>225</td>
<td>236</td>
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<tr>
<td>Total bone cancer</td>
<td>905</td>
<td>980</td>
<td>1056</td>
</tr>
<tr>
<td><strong>Females</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
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<td>259</td>
<td>250</td>
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<td>Ewing sarcoma</td>
<td>112</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>197</td>
<td>209</td>
<td>364</td>
</tr>
<tr>
<td>Other bone cancers</td>
<td>158</td>
<td>170</td>
<td>193</td>
</tr>
<tr>
<td>Total bone cancer</td>
<td>689</td>
<td>735</td>
<td>902</td>
</tr>
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</table>

Total person-years at risk (1976-2005) = 102 287 400 (males) and 103 835 595 (females)

*Rate per 100,000 person-years, age-adjusted using the World standard
Figure Legends

**Figure 1.** Age-specific incidence rates of bone cancer during the period 1976-2005 for the three major types by sex among U.S. whites (SEER 9).

**Figure 2.** Trends in age-standardized (World) incidence rates of bone cancer for the major types by sex among U.S. whites (SEER 9) during the 10-year aggregates 1976-85, 1986-95, 1996-2005.

**Figure 3.** Observed trends in the incidence of (A) osteosarcoma (both sexes combined) and (B) Ewing sarcoma (both sexes combined), and (C) chondrosarcoma (males) and (D) chondrosarcoma (females) among U.S. whites 1976-2005 (SEER 9). Age-specific rates for 10-year age groups ages 0-79 are presented by calendar period of diagnosis and by birth cohort. Rates below 0.1 per 100,000 person-years or based on fewer than 10 cases are not shown.

**Figure 4.** Age, period and cohort effects, based on Holford’s approach for the three major types of bone cancer by sex among U.S. whites (SEER 9). Estimates are based on the APC model assuming a linear slope of zero for period. The rate (left y axis) corresponds to the left part, whereas the rate ratio (right y axis) applies to the middle and right part of the graphs. The rate ratios relate to the reference cohort (1950) and the reference period (1990), which are marked with a circle. Solid and stippled lines are for males and females, respectively.
![Graph showing age-standardised rates per 100,000 person-years for bone cancer subtypes.](attachment:graph.png)

**Males**

**Females**

Legend:
- Total bone cancer
- Osteosarcoma
- Chondrosarcoma
- Ewing sarcoma
- Other

Period of diagnosis:
- 1980
- 1990
- 2000

Age-standardised rates per 100,000 person-years (world)
Cancer Epidemiology, Biomarkers & Prevention

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