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Use of age-period-cohort analysis in cancer epidemiology research

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Abstract

Purpose of review: Age-period-cohort (APC) models simultaneously estimate the effects of age – biological process of aging; time period – secular trends that occur in all ages simultaneously; and birth cohort – variation among those born around the same year or from one generation to the next. APC models inform understanding of cancer etiology, natural history, and disparities. We reviewed findings from recent studies (published 2008–2018) examining age, period, and cohort effects and summarized trends in age-standardized rates and age-specific rates by birth cohort. We also described prevalence of cancer risk factors by time period and birth cohort, including obesity, current smoking, human papilloma virus (HPV), and hepatitis C virus (HCV).

Recent findings: Studies (n=29) used a variety of descriptive analyses and statistical models to document age, period, and cohort trends in cancer-related outcomes. Cohort effects predominated, particularly in breast, bladder, and colorectal cancers, whereas period effects were more variable. No effect of time period was observed in studies of breast, bladder, and oral cavity cancers. Age-specific prevalence of obesity, current smoking, HPV, and HCV also varied by birth cohort, which generally paralleled cancer incidence and mortality rates.

Summary: We observed strong cohort effects across multiple cancer types and less consistent evidence supporting the effect of time period. Birth cohort effects point to exposures early in life – or accumulated across the life course – that increase risk of cancer. Birth cohort effects also illustrate the importance of reconsidering the timing and duration of well-established risk factors to identify periods of exposure conferring the greatest risk.

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Compliance with Ethical Standards

Conflict of Interest

Caitlin C. Murphy and Yang Claire Yang each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Incidence; time factors; SEER program; risk factors; age factors

Introduction

Cancer registries across the world monitor incidence and mortality rates to assess the distribution of disease, often informing our understanding of cancer etiology, natural history, and disparities. Age-period-cohort (APC) models provide additional and useful insight by documenting change in cancer incidence and mortality over time that may be attributable to age, time period of observation, and birth cohort.[1] Models simultaneously estimate the effects of age – biological process of aging; time period – secular trends that occur in all ages simultaneously; and birth cohort – variation among those born in or around the same year or from one generation to the next. Epidemiologic studies using APC models have improved our understanding of the burden and etiology of several cancers. For example, birth cohort effects evidenced in lung cancer[2,3] point to younger age at smoking initiation and longer duration of smoking as important risk factors.

Although linear APC models have been limited by the identification problem (i.e., age, period, and cohort variables may be perfectly collinear), methodologic advances have provided several new APC models useful in cancer research, and that extend beyond the conventional, linear approach. We review recent studies estimating the differential contributions of age, period, and cohort to cancer incidence and mortality. We also estimated prevalence of cancer risk factors by time period and birth cohort.

Methods

We reviewed findings from studies examining age, period, and cohort effects published between 2008 and 2018. For each study, we described cancer type, geographic location, data source, and statistical methods. We also summarized temporal trends in age-standardized rates and age-specific rates by birth cohort.

Prevalence of Cancer Risk Factors

We described trends in the prevalence of cancer risk factors by time period and birth cohort, including obesity, current smoking, human papilloma virus (HPV), and hepatitis C virus (HCV). We obtained prevalence estimates from the National Health and Nutrition Examination Survey (NHANES) from 1999 through 2016 (approximately 45,000 adults age ≥18 years). NHANES includes a standardized physical examination, where trained health technicians collect a complete set of anthropometric and laboratory measures from survey participants.

Obesity.—Body weight and height were measured in mobile examination centers using standardized procedures and equipment. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2), and then rounded to one decimal place. Consistent with national guidelines, we defined obesity as BMI ≥ 30 kg/m^2.

Current smoking.—We defined current smoking by combining responses to two survey questions: 1) “Have you smoked at least 100 cigarettes in your entire life?”; and 2) “Do you now smoke cigarettes?” Interview questions are asked in the home by trained interviewers using the Computer-Assisted Personal Interviewing (CAPI) system. Participants who replied “yes” to the first question and reported now smoking “every day” or “some days” were considered current smokers.

Hepatitis C virus.—NHANES participants’ serum specimens are tested for antibodies to HCV (anti-HCV) using VITROS Anti-HCV chemiluminescence assay (CIA). Supplemental recombinant immunoblot assays (RIBA) (Chiron RIBA 3.0 Strip Immunoblot Assay) are performed on all repeatedly positive specimens by CIA testing. Specimens with a positive RIBA results are reported as confirmed positive for antibody to HCV. Because the confirmed anti-HCV test was discontinued by the manufacturer in 2012, and subsequently no longer used in NHANES, we estimated prevalence of anti-HCV through 2012 only.

Human papilloma virus.—Women (ages 18–59 years) participating in NHANES provide self-collected vaginal swabs, which are then analyzed for 37 HPV genotypes using the Roche Linear Array Assay. We estimated prevalence of all high-risk HPV (ref) genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), as well as prevalence of genotypes 16 and 18 (targeted in all vaccines).

For each risk factor, we report temporal trends in prevalence, as well as age-specific prevalence by birth cohort, separately for men and women. All prevalence estimates are weighted to account for survey sampling and nonresponse.

Results

Age, period, and cohort effects and cancer incidence and mortality

Table 1 summarizes findings from 29 studies of cancer incidence and/or mortality of breast, liver, gastric, bladder, bone, esophageal, oral cavity, lung, colorectal, pancreatic, and prostate cancers and leukemia. Most studies were conducted in the U.S., although about one-third were conducted internationally, including Canada, Norway, China, Argentina, Mexico, France, Japan, and Spain. A variety of statistical methods were used across studies (Table 2). Findings relevant to each cancer type are described below.

Breast.—In studies of breast cancer, we noted variable period and cohort effects across studies by geographic region. For example, age-standardized incidence rates declined from 1980 through to 2010 in the U.S.[4] but increased in other countries during the same period.[5,6] Despite these differences, most studies of breast cancer show a stronger cohort effect than period effect, which may be due to estrogen-related or reproductive risk factors (e.g., age at menarche, breastfeeding patterns, number and age childbirth).[7]

Liver.—Worldwide, age-standardized incidence of liver cancer has increased dramatically since the late 1970s,[8–11] primarily driven by increases in hepatocellular carcinoma. Age-specific incidence has also increased across successive birth cohorts through the 1960 birth cohort[8] and subsequently declined.[9] Chronic HCV infection, a common blood-borne

infection, increases risk of liver cancer,[12,13] and about 75% of adults infected with HCV in the U.S. are baby boomers (born between 1945 and 1965). Baby boomers likely became infected from contaminated blood and blood products before widespread screening began in the early 1990s.[14]

Colorectal.—Age-standardized incidence and mortality rates of colorectal cancer have decreased in the U.S. since the mid-1980s,[15] with particularly dramatic declines among older adults (age ≥50 years). In contrast, incidence increased in Spain[16] and the Netherlands[17] during the same period. Mortality rates decreased in all three geographic regions starting around 1990. Notably, age-specific incidence rates have increased among U.S. birth cohorts after 1950.[15]

Lung.—Two U.S. studies of lung cancer incidence show age-specific incidence and mortality rates declined starting in the 1990s.[18,19] Incidence and mortality rates have also declined across successive birth cohorts after about the 1930 birth cohort, which parallels dramatic declines in the prevalence of smoking by cohort.[20,21] However, incidence increased among women born in 1950 to 1960, and in certain age groups, incidence rates in women have surpassed those of men.[19] Because the prevalence of smoking has decreased among women born in the 1950s and 60s, this increase in incidence is likely not due to smoking patterns or tobacco exposure.

Bladder.—Bladder cancer incidence and mortality varied by period and cohort, and across geographic region. For example, age-standardized incidence rates increased in Norway in the 1980s and then stabilized,[22] but incidence increased in China from 1973 to 2005.[23] Mortality rates in Argentina declined among men after 1986 and among women after 1996.[24] Cohort trends appeared more consistent, and age-specific rates were generally higher among birth cohorts born in the early 1900s.[22,23] Smoking causes about half of all bladder cancers,[25,26] and the consistent declines across birth cohorts may be due to simultaneous declines in smoking prevalence by birth cohort.[20,21]

Oral cavity.—In the U.S.[27] and economically developed countries,[28,29] age-standardized incidence rates of HPV-related oral cancers (e.g., oropharyngeal cancers – tonsils, tonsillar crypt, base of tongue) increased from the early 1980s through to the most recent time period, particularly among men. Age-specific incidence generally increased across successive birth cohorts starting with persons born in 1930. HPV is the most common sexually transmitted infection and the leading cause of oropharyngeal cancers (thought to cause 70% in U.S. [30,31]). Oral HPV is transmitted via oral sex, and changes in sexual behavior[32,33] in the 1960s may explain rising incidence in more recent birth cohorts.

Gastric.—Across all racial/ethnic groups in the U.S., age-standardized incidence rates of gastric cancer declined starting in the late 1970s.[34] Age-specific incidence rates declined among whites through about the 1950 birth cohort and then subsequently increased among more recent cohorts. The majority of gastric cancers are attributable to chronic infection with *Helicobacter pylori,*[35] commonly acquired in childhood. In the U.S., prevalence of *H. pylori* has decreased dramatically across birth cohorts,[36] likely due to improvements in sanitation and increased antibiotic use.[37] Lower gastric cancer incidence rates among older

birth cohorts may reflect decreased *H. pylori* infection in their childhood, but reasons for increasing rates in younger birth cohorts remain unclear.

Esophagus.—Starting in about 1985, age-standardized incidence rates of esophageal adenocarcinoma exceeded rates of squamous cell carcinoma worldwide.[38] Rates of squamous cell carcinoma steadily declined during this same period.[39] In the U.S., age-specific incidence rates increased from about 1990 to 2012 and across successive birth cohorts born from 1885 to 1950.[40] Increasing rates of esophageal adenocarcinoma have been attributed to increasing prevalence of risk factors, such as obesity[41] and gastroesophageal reflux disease.[42,43] Our prior work shows a stronger period effect than cohort effect, largely explained by temporal trends in obesity.[40] Although the increase in esophageal adenocarcinoma has slowed in recent years, it remains one of the few cancers in the U.S. with a rising incidence.[44]

Pancreas.—Age-standardized mortality rates of pancreatic cancer in the U.S. have varied by race/ethnicity and sex.[45] For example, among white men, rates decreased from 1970 to 1995 but increased among white women during the same period. Rates also increased among black men and women from 1970 to 1989, and then subsequently declined through to 2009. Cohort effects appeared stronger in men than women, and age-specific mortality rates decreased among white and black men after the birth cohort born in 1910. Racial differences in the prevalence of risk factors, such as smoking, diabetes, and obesity,[46,47] which also differ by sex, may contribute to these observed trends.

Leukemia.—Because leukemia comprises a heterogeneous group of cancer, period and cohort trends differ according to subtype. Age-standardized incidence rates of chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) decreased from 1992 to 2009.[48] However, rates of acute lymphoblastic leukemia (ALL), most common among children and older adults, increased during the same period. Age-specific incidence rates of ALL have also increased across successive birth cohorts, starting with persons born in the mid-1940s.

Bone.—Similarly, bone cancer comprises a diverse group of cancers, including osteosarcoma, Ewing sarcoma, and chondrosarcoma. Age-standardized incidence rates of bone cancer have been generally stable since the late 1970s.[49] Notably, age-specific incidence rates of osteosarcoma declined in successive birth cohorts born between 1905 and 1934.

In studies of common cancer types (Table 3), period and cohort effects were assessed descriptively and in statistical models. Most studies described trends in one dimension (e.g., period changes in rates for all ages combined) or two dimensions (e.g., cohort changes in age- specific rates). Fewer studies reported results of statistical models estimating the independent effects of age, period, and cohort. In these studies, cohort effects predominated, particularly in breast, bladder, and colorectal cancers, whereas period effects were more variable. No effect of time period was observed in studies of breast, bladder, and oral cavity cancers.

Prevalence of cancer risk factors by period and cohort

Obesity.—Prevalence of obesity (BMI ≥ 30 kg/m^2) increased from 1999 to 2016, and prevalence was higher among women than men in all survey years (Figure 1). Among men, prevalence ranged from 27 to 32%, and among women, from 32 to 39%. Age-specific prevalence across birth cohorts also differed by sex. Except for the youngest age group (18–29 years), obesity increased among men in all age groups and across successive birth cohorts, with particularly steep increases from the 1930 though 1955 birth cohorts. Prevalence was highest among men age 60–69 years. In contrast, age-specific prevalence of obesity generally declined across successive birth cohorts among women. Obesity increased slightly among women born in 1915 through 1935, and subsequently remained stable or decreased.

Current smoking.—As shown in Figure 2, prevalence of smoking declined slowly from 1999 through 2016 and remained consistently higher among men (range 21 – 29%) than women (range 16 – 22%). Age-specific prevalence of smoking was highest among 18–29 year-old men born in the 1970s. Prevalence remained stable in all age groups for birth cohorts born from 1915 to 1940 but then decreased across successive birth cohorts. Among women, starting with the 1955 birth cohort, there were sharp declines in smoking in all age groups through the 1995 birth cohort.

Hepatitis C virus.—After an increase in prevalence from 1999 to 2002, anti-HCV remained stable through 2012 (Figure 3). Prevalence was consistently higher among men than women, and in both groups remained low, around 2%. Cohort trends in anti-HCV appeared much more prominent. In men and women, there were sharp increases in age-specific prevalence across the 1945 to 1960 birth cohorts. Prevalence was highest among 40- and 50-year olds born in 1955. Starting with persons born around 1960, prevalence declined in all age groups.

Human papillomavirus (women only, ages 18–59 years).—Prevalence of high-risk HPV hovered around 20% from 2003 to 2010 and then declined slightly to 17% in 2013–14 (Figure 4). We observed a similar pattern, although of smaller magnitude, for HPV genotypes 16 and 18 (not shown). Age-specific prevalence decreased among 40- and 50-years olds born in 1940 to 1960. Subsequently, and starting with women born around 1965, prevalence increased through to the 1980 birth cohort. There were hints of declines among women born in the 1980s, and prevalence decreased dramatically among the youngest birth cohort. Across all birth cohorts, high-risk HPV was highest in 18–29 year olds.

Conclusion

APC methods identify and quantify variation in cancer incidence and mortality associated with age, time period, and birth cohort. Across 29 studies of multiple cancer types, we observed stronger birth cohort effects than period effects. Birth cohort effects point to exposures early in life – or accumulated across the life course – that increase risk of cancer. Birth cohort effects also illustrate the importance of reconsidering the timing and duration of well-established risk factors to identify periods of exposure conferring the greatest risk. For

example, obesity, associated with increased risk of several cancers,[50] may contribute to some of the observed increases in incidence. Measuring obesity during windows of growth and development (e.g., birthweight[51] or childhood obesity[52]) may advance our understanding of its role in carcinogenesis and identify vulnerable periods of exposure that matter most.

We found less consistent evidence supporting the effect of time period, which also differed by geographic region (i.e., temporal trends were not consistent across the globe). These regional differences may point to the influence of screening or diagnostic practices, such as mammography screening. Indeed, studies of breast cancer incidence and mortality showed the greatest variations in period effects, and in some regions, there was no period effect. Economically developed countries have adopted screening mammography guidelines at various time points (e.g., early 1980s in the U.S.,[53] early 1990s in the U.K.[54,55]), and the U.S. was among the early adopters. This may explain why mortality rates declined in earlier time periods in the U.S. but not in other regions. Differences in period effects or temporal trends across geographic region may also underscore differences in the timing of risk factor prevalence. For example, HCV became prevalent in Asian countries before it did in the U.S., which parallels trends in liver cancer incidence between the two regions.

Trends in cancer incidence and mortality generally paralleled prevalence of risk factors. For example, prevalence of anti-HCV was highest among birth cohorts born between 1945 and 1960, and incidence rates of liver cancer were highest among these cohorts.[8,9,11] Declines in the prevalence of smoking by birth cohort also mirrored age-specific rates of lung,[18,19,29] bladder,[22–24] and pancreatic[45] cancer incidence and mortality. Although there were some exceptions, rates of these cancers often declined in birth cohorts with lower prevalence of smoking. Meanwhile, prevalence of obesity has increased by time period and birth cohort, which may contribute to recent observations that the incidence of gastric[34] and colorectal[15] cancer has increased among younger adults.

Studies used a variety of descriptive analyses and statistical models to track age, period, and cohort effects. Nearly all included one-dimensional or summary indices to describe period variation in overall incidence or mortality rates. Although useful for understanding cancer burden, these indices may be less relevant to APC analysis because they: 1) only describe variation in rates attributable to factors during the period of cancer diagnosis or death, ignoring different trends at different ages; and 2) are sensitive to the choice of standard population (i.e., for age-standardizing), which may not capture recent changes in population structure due to aging. Other studies used two-dimensional graphical displays, which improve upon summary indices by providing information on age-specific change. For example, many studies described or displayed age-specific trends across birth cohorts. Two-dimensional trends are helpful for *qualitative* impressions about patterns for each age group but not for *quantitative* assessment of the source of change.

Fewer studies reported results of statistical models, and of those that did, most used linear models and an estimable function approach. Estimable functions, such as deviation, curvature, and drift, are used to derive estimates.[56–59] For example, many ascribe net drift (annual percent change of the expected age-standardized rates) to overall log-linear trends by time period and birth cohort. These approaches generally use constraints to resolve the

identification problem inevitable in linear models, raising two important limitations. First, different constraints yield different estimates but identical or similar model fit. Second, effect estimates are sensitive to the choice of the identifying constraints and require *a priori* information, which rarely exists. These limitations also make it challenging to compare findings across studies. While we recommend researchers present results of linear models in conjunction with a detailed descriptive analysis[1] and use caution in interpretation of these results, we also suggest using hierarchical APC models. Hierarchical models not only address the problems inherent in linear models, but they also offer the additional advantage of including covariates or risk factors to test explanatory hypothesis about the underlying mechanisms for observed age, period, and cohort trends.

In summary, APC models track changes in cancer incidence and mortality over time that may be attributable to age, time period of observation, and birth cohort. We observed strong cohort effects across 29 studies of various cancer types, highlighting the importance of early life exposures that may promote biological pathways initiating carcinogenesis in adulthood. We also observed variations in cancer risk factors (e.g., obesity, smoking) by time period and birth cohort, which paralleled trends in cancer incidence and mortality.

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Oncology 2014;23(11):2296–2302.Publicly available web tool that allows researchers to upload a dataset and derive estimates for age, period, and cohort effects

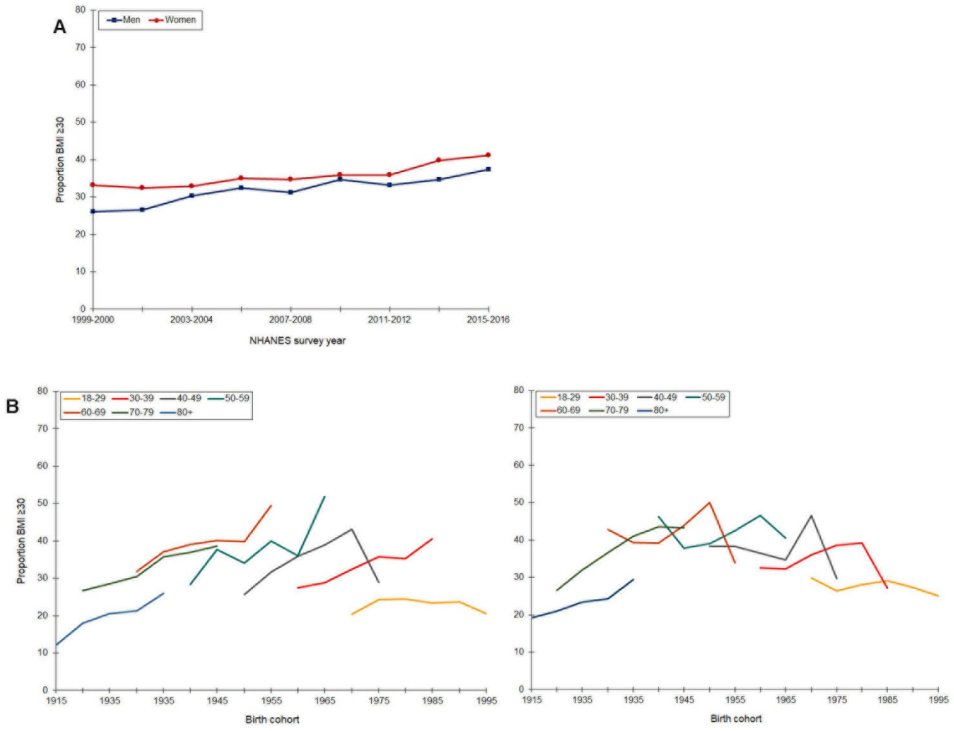

Figure 1.

Prevalence of obesity by time period (A) and age-specific prevalence by birth cohort (B, men; C, women), National Health and Nutrition Examination Survey, Continuous Cycles, 1999 – 2016

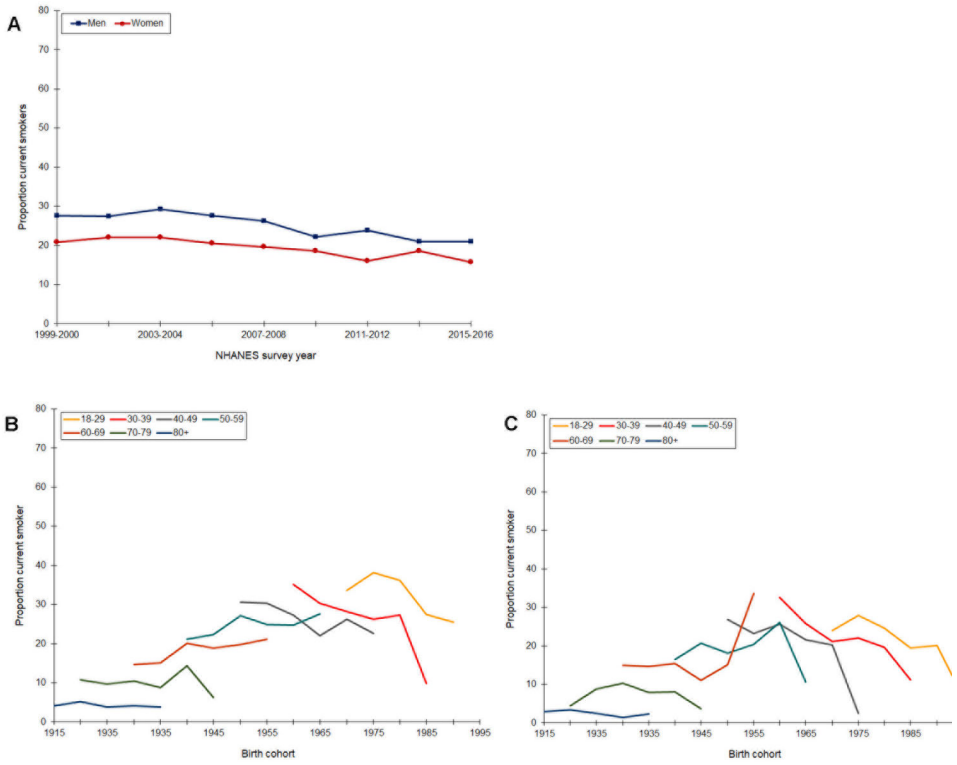

Figure 2.

Prevalence of current smoking by time period (A) and age-specific prevalence by birth cohort (B, men; C, women), National Health and Nutrition Examination Survey, Continuous Cycles, 1999 – 2016

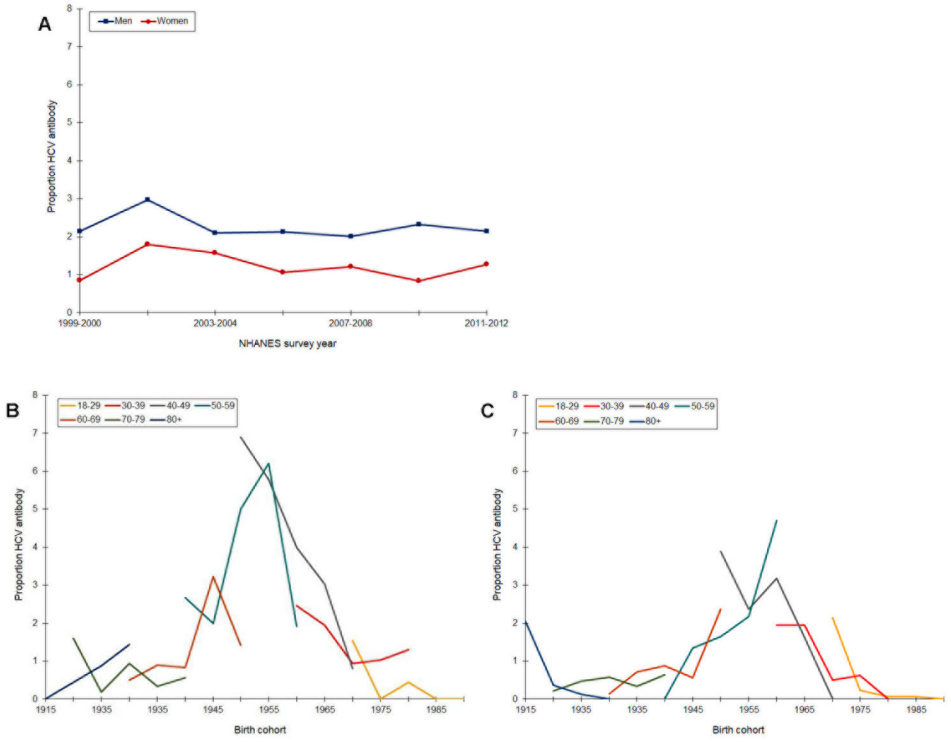

Figure 3.

Prevalence of Hepatitis C antibody by time period (A) and age-specific prevalence by birth cohort (B, men; C, women), National Health and Nutrition Examination Survey, Continuous Cycles, 1999 – 2012

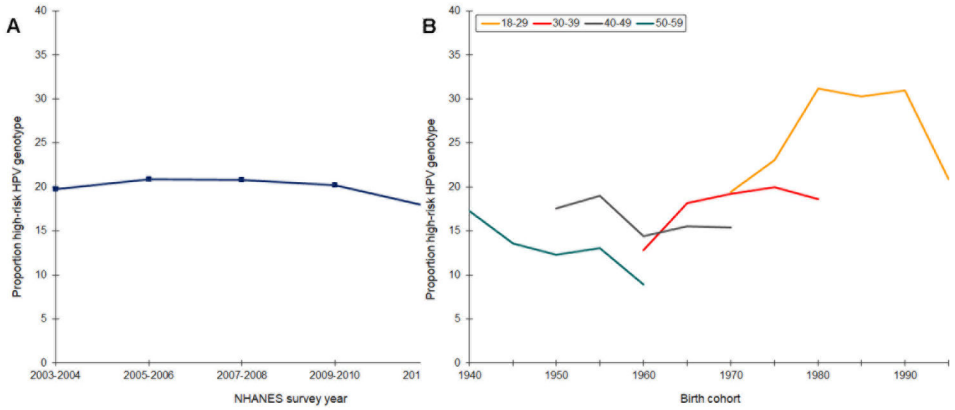

Figure 4.

Prevalence of high-risk HPV genotypes among women (ages 18–39 years) by time period (A) and age-specific prevalence by birth cohort (B), National Health and Nutrition Examination Survey, Continuous Cycles, 2003 – 2014

Table 1.

Characteristics of and relevant findings from studies examining age, period, and cohort effects in cancer incidence and mortality

Author (year)	Cancer type	Geographic location	Data source, years	Method	Relevant findings
Altekruse (2009)	Liver	U.S.	SEER 9, 1975–2015; SEER 13, 1992–2015	Not reported	• Age-adjusted incidence rates tripled between 1975 and 2005 • Age-specific incidence rates increased in successive birth cohorts born between 1900 and 1959
Anderson (2010)	Gastric	U.S.	SEER 9, 1973–1991; SEER 13, 1992–1999; SEER 17, 2000–2006	Estimable function approach	• Across all racial/ethnic groups, age-standardized incidence rates declined from 1977–81 to 2002–06 • Among whites, age-specific incidence rates declined through the 1947 birth cohort, then increased across successive cohorts
Andreassen (2016)	Bladder	Norway	Cancer Registry of Norway, 1981–2014	Estimable function approach	• Among men, age-standardized incidence rates increased from 1981 to 1989 and remained stable from 1990 to 2014 • Age-specific incidence rates increased among birth cohorts born after 1910
Anfinsen (2011)	Bone[1]	U.S.	SEER 9, 1976–2005	Estimable function approach	• Age-standardized incidence rates stabilized from 1976 to 2005, with the exception of chondrosarcoma among women • Age-specific incidence rates of osteosarcoma declined in successive birth cohorts born between 1905 and 1934
Arnold (2017)	Esophagus	Multiple[2]	Cancer Incidence in Five Continents, 1988–2007	Not reported	• After 1985, age-standardized incidence rates of adenocarcinoma exceeded rates of squamous cell carcinoma • Cohort trends not described
Bao (2016)	All	China (Shanghai)	Shanghai Cancer Registry, 1973–2010	Estimable function approach	• Among men, age-standardized incidence rates (all cancer combined) declined from 1973 to 1996, stabilized from 1996 to 2001, and declined from 2001 to 2010; among women, rates declined from 1973 to 1980, stabilized from 1980 to 1996, increased from 1996 to 2001, and stabilized from 2001 to 2010 • Starting with persons born around 1930, age-specific incidence rates declined across successive birth cohorts for colorectal (men only), prostate,

Author (year)	Cancer type	Geographic location	Data source, years	Method	Relevant findings
					kidney, lymphoma, thyroid, breast (women only), ovarian, and uterine cancers
Chaturvedi (2008)	Oral cavity	U.S.	SEER 9, 1973–2004	Estimable function approach	• Age-adjusted incidence rates of HPV-related cancers increased from 1973 to 1982, stabilized from 1983 to 1999, and increased from 2000 to 2004 • Age-specific incidence rates of HPV-related cancers increased among birth cohorts born after 1930
Chaturvedi (2013)	Oral cavity	Multiple[3]	Cancer Incidence in Five Continents, 1983–2002	Estimable function approach	• Among men, age-standardized incidence rates increased from 1983 to 2002 in economically developed countries • Cohort trends not described by country
Franco-Marina (2009)	Breast	Mexico	National Institute of Geography and Statistics, 1980–2005	Estimable function approach	• Age-standardized mortality rates increased from 1982 to 1987 and declined between 1987 and 2005 • Age-specific mortality rates increased among birth cohorts born between 1935 and 1950, and more slowly after 1950
Franco-Marina (2015)	Breast	Multiple[4]	Cancer Incidence in Five Continents, 1988–2007	Estimable function approach	• Age-standardized incidence rates fluctuated from 1988 to 2008, and changes were not significantly different • In most countries, age-specific incidence rates increased across successive birth cohorts born after 1940
Gangnon (2015)	Breast	U.S.	SEER 9, 1975–2010	Estimable function approach	• Age-adjusted incidence rates increased from 1940 to 1980 and then declined through to 2010 • Age-specific incidence rates of premenopausal breast cancer increased among birth cohorts born from 1890 to 1900, except for slight declines among those born in 1930 to 1950
Gilhodes (2015)	Lung, oral cavity, esophagus[5]	France	Regional cancer registries, 1982–2010	Estimable function approach	• Among men and women, age-standardized incidence rates of lung cancer declined from 1982 to 2012; among men only, rates of oral cavity and esophageal cancer declined from 1982 to 2012 • Among men, age-standardized incidence rates (all cancers) declined across successive birth cohorts from 1940 to 1970

Author (year)	Cancer type	Geographic location	Data source, years	Method	Relevant findings
Ito (2011)	All	Japan	Osaka Cancer Registry, 1968–2007	Estimable function approach	• Among men, age-standardized incidence and mortality rates (all cancers combined) increased from 1968 to 1985, stabilized from 1985 to 1998, then declined through to 2007; among women, incidence rates increased from 1971 to 1985 and stabilized after 1998; mortality rates among women declined in the same period
Jemal (2012)	Lung[6]	U.S.	National Center for Health Statistics, 1973–2007	Estimable function approach	• Starting in the 1990s, age-specific mortality rates declined among women ≤70 years • In Alabama, age-specific mortality increased among birth cohorts born from 1983 to 1933, plateaued, and then increased from the 1950 birth cohort forward
Jemal (2018)	Lung	U.S.	NAACCR, 1995–2014	Estimable function approach	• Age-specific incidence rates declined from 1995 to 2014 • Age-specific incidence rates declined across successive birth cohorts; among women, rates increased among birth cohorts born from 1950 to 1960 and subsequently declined
Lopez-Abente (2010)	Colorectal	Spain	European Network of Cancer Registries, 1975–2004	Estimable function approach	• Age-adjusted incidence rates increased from 1975–79 to 2000–04; age adjusted mortality rates increased from 1975–79 to about 1998, then subsequently declined • Age-specific incidence and mortality rates increased across successive birth cohorts born from to 1900 to 1950, then subsequently declined
Ma (2013)	Pancreas	U.S.	National Center for Health Statistics, 1970–2009	Estimable function approach	• Among white men, age-adjusted mortality rates declined from 1970 to 1995 and then increased through 2009; among white women, rates increased from 1970 to 1984, stabilized from 1984 to 1988, and then increased through 2009; among black men and women, rates increased from 1970 to 1989, then declined to 2009 • For white and black men, age-specific mortality rates declined after the birth cohort born in 1910
Murphy (2017)	Esophagus	U.S.	SEER 9, 1973–2012	Hierarchical model	• Age-specific incidence rates increased from about 1990 to 2012 • Age-specific incidence rates increased across successive birth cohorts born from 1885 to 1950

Author (year)	Cancer type	Geographic location	Data source, years	Method	Relevant findings
Niclis (2011)	Prostate	Argentina	Cordoba Ministry of Health, 1986–2006	Estimable function approach	• Age-standardized mortality rates increased from 1986 to 1996 and declined through to 2005 • Cohort trends not described
Petrick (2016)	Liver[7]	U.S.	SEER 18, 1992–2012	Estimable function approach	• Age-specific incidence rates increased across successive birth cohorts born from 1895 to 1959 and declined after the 1960 cohort
Pocobelli (2008)	Liver	Canada	Canadian Cancer Registry, 1976–2000	Estimable function approach	• Among both men and women, age-adjusted incidence rates increased from 1976 to 2000 • Among men, age-specific incidence rates increased across successive birth cohorts born from 1985 to 1955; among women, rates increased across successive birth cohorts from 1895 to 1935, stabilized from 1935 to 1950, and increased after the 1955 cohort
Pou (2011)	Bladder	Argentina	Cordoba Ministry of Health, 1986–2006	Estimable function approach	• Among men, age-standardized mortality rates declined from 1986 to 2006; among women, rates increased from 1986 to 1996 and declined from 1996 to 2006 • Starting in persons born after 1931, age-specific mortality rates declined across successive birth cohorts
Rosenberg (2012)	Leukemia[8]	U.S.	SEER 13, 1992–2009; SEER 18, 2000–2009	Estimable function approach	• Age-standardized incidence rates of CML and CLL declined from 1992 to 2009; rates of ALL increased during the same period • Starting with persons born around 1946, age-specific incidence rates of ALL increased across successive birth cohorts
Siegel (2017)	Colorectal	U.S.	SEER 9, 1974–2013	NCI web tool	• Age-specific incidence rates declined among adults ≥55 from the mid-1980s to 2013; among adults <55, rates increased starting in the mid-1990s through to 2013 • Age-specific incidence rates declined across successive birth cohorts born from the late 1880s to 1940, then increased for subsequent cohorts
van Steenbergen (2009)	Colorectal	Netherlands	Eindhoven Cancer Registry, 1970–2006	Estimable function approach	• Age-standardized incidence rates of colon cancer increased from 1975 to 2004, and rectal cancer rates remained stable

Author (year)	Cancer type	Geographic location	Data source, years	Method	Relevant findings
					• Age-standardized mortality rates increased from 1970 to 1975 and subsequently declined through to 2006 • Starting with persons born after 1920, age-specific incidence rates increased, and mortality rates declined, across successive cohorts
Viel (2011)	Breast	France	Doubs Cancer Registry, 1987–2003	Estimable function approach	• Age-standardized incidence rates increased from 1978 to 2003 • Age-specific incidence rates increased across successive birth cohorts born from 1920 to 1940, declined from 1940 to about 1960, and subsequently increased after the 1960 birth cohort
Wang (2015)	Breast	Multiple[9]	WHO Mortality Database and Cancer Statistic Registries, 1953–2012	Intrinsic estimator	• Age-standardized mortality rates increased in East Asian countries (except urban China) from 1955 to 2010; rates in the U.S. stabilized before 1990 and then declined through 2010. • Starting with persons born after 1950, age-specific mortality rates declined across successive birth cohorts in all regions
Yan (2015)	Liver	U.S.	SEER 18, 2003–2011	Not reported	• Period trends not described • Among baby boomers (1945–1965), pre-baby boomer, and post- baby boomer cohorts, incidence increased from 2003 to 2011
Yang (2013)	Bladder, kidney	China (Shanghai)	Shanghai Cancer Registry, 1973–2005	Intrinsic estimator	• Age-standardized incidence rates of bladder cancer increased from 1973 to 2005; rates of kidney cancer increased from 1973 to 2005 • Age-specific incidence rates of bladder cancer peaked among persons

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; NR, not reported; HPV, human papillomavirus; WHO, World Health Organization; NAACCR, North American Association of Central

women, rates of kidney cancer Cancer Registries; IE, Intrinsic Estimator; CML, chronic myeloid leukemia; CLL, chronic lymphocytic declined among birth cohorts before leukemia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia

[1] Bone cancer includes osteosarcoma, Ewing sarcoma, and chondrosarcoma

[2] U.S., Canada, Japan, Australia, Denmark, U.K., France, Netherlands, Croatia, Italy, Spain, Slovakia

[3] India, Japan, Philippines, Singapore, Thailand, Australia, Austria, Denmark, Estonia, France, Italy, Netherlands, Poland, Slovakia, Spain, Switzerland, U.K., Canada, U.S., Brazil, Colombia, Costa Rica, Ecuador

[4] Brazil, Colombia, Ecuador, Costa Rica, Manitoba, Canada, U.S.

[5] Gilhodes (2011) only included young adults age 20–44 years

[6] Jemal (2012) estimated trends among women only

[7] Petrick (2016) reported projected (vs. observed) incidence rates by time period

[8] Leukemia included chronic myeloid leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, and acute lymphoblastic leukemia

[9] China, South Korea, Japan, U.S.

Table 2.

Methods used to estimate age, period, and cohort effect

Method	Description
Linear model[60]	• Generalized linear model; log or logit transformation of age-period-cohort specific rates are modeled as a linear function of additive effects of age, period, and cohort
	• Suffers from "identification problem" induced by linear dependency between age, period, and cohort
	• Design matrix is less than full rank, leading to multiple rather than unique estimators of the three effects[1,61]
Coefficient-constraints approach[60]	• Placing one or more identifying constrain on the parameter vector to just-identify or over-identify the model
	• Model coefficients are sensitive to choice of constraint
Estimable function approach[57–59]	• Focuses on non-linear (vs. linear) components and uses deviations, curvatures, and drift to derive unique estimates
Intrinsic estimator[62,63]	• Estimates the unique estimable function of linear and non-linear components of the age-period-cohort model
	• Determined by the Moore-Penrose generalized inverse function using principal component regression
Hierarchical model	• Mixed-effect models estimate fixed effects of age at the individual level and random effects of period and cohort at a higher level
	• Capture contextual effects of cohort membership and historical time relevant in disease processes
	• Allows researchers to include additional covariates at different levels to test explanatory hypotheses about specific risk factors (e.g., obesity, smoking) contributing to observed trends
NCI web tool[64]	• Publically available web tool for researchers, providing a panel of estimable functions and corresponding Wald test

NOTE: Coefficient-constraints and estimable function approaches are two approaches within the linear model framework; intrinsic estimator is a specific example of an estimable function

Table 3.

Analytic methods and findings across studies of common cancers

	Analytic method					
	Descriptive analysis			Statistical models		
	Period	Age x Period	Age x Cohort	Age	Period	Cohort
Breast (n=5)	++	++	++	++	++*	++
Lung (n=3)		++	+			+
Liver (n=4)	+	+	++		+	+
Bladder (n=3)	++	+	+	++	+*	++
Oral cavity (n=3)	++	+	++		*	+
Esophageal (n=3)	+	+	+	+	++	++
Colorectal (n=3)	+	+	++	++	++	++

+ reported association in at least one study;

++ reported association in two or more studies;

* null findings in at least one study

NOTE: Cancer types for which we identified only one study in our review are not included in the table