Differences in cancer rates among adults born between 1920 and 1990 in the USA: an analysis of population-based cancer registry data

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Summary

Background Trends in cancer incidence in recent birth cohorts largely reflect changes in exposures during early life and foreshadow the future disease burden. Herein, we examined cancer incidence and mortality trends, by birth cohort, for 34 types of cancer in the USA.

Methods In this analysis, we obtained incidence data for 34 types of cancer and mortality data for 25 types of cancer for individuals aged 25–84 years for the period Jan 1, 2000, to Dec 31, 2019 from the North American Association of Central Cancer Registries and the US National Center for Health Statistics, respectively. We calculated birth cohort-specific incidence rate ratios (IRRs) and mortality rate ratios (MRRs), adjusted for age and period effects, by nominal birth cohort, separated by 5 year intervals, from 1920 to 1990.

Findings We extracted data for 23 654 000 patients diagnosed with 34 types of cancer and 7 348 137 deaths from 25 cancers for the period Jan 1, 2000, to Dec 31, 2019. We found that IRRs increased with each successive birth cohort born since approximately 1920 for eight of 34 cancers ($p_{cohort}<0.050$). Notably, the incidence rate was approximately two-to-three times higher in the 1990 birth cohort than in the 1955 birth cohort for small intestine (IRR 3.56 [95% CI 2.96–4.27]), kidney and renal pelvis (2.92 [2.50–3.42]), and pancreatic (2.61 [2.22–3.07]) cancers in both male and female individuals; and for liver and intrahepatic bile duct cancer in female individuals (2.05 [1.23–3.44]). Additionally, the IRRs increased in younger cohorts, after a decline in older birth cohorts, for nine of the remaining cancers ($p_{cohort}<0.050$): oestrogen-receptor-positive breast cancer, uterine corpus cancer, colorectal cancer, non-cardia gastric cancer, gallbladder and other biliary cancer, ovarian cancer, testicular cancer, anal cancer in male individuals, and Kaposi sarcoma in male individuals. Across cancer types, the incidence rate in the 1990 birth cohort ranged from 12% ($IRR_{1990\ vs\ 1975}$ 1.12 [95% CI 1.03–1.21] for ovarian cancer) to 169% ($IRR_{1990\ vs\ 1930}$ 2.69 [2.34–3.08] for uterine corpus cancer) higher than the rate in the birth cohort with the lowest incidence rate. The MRRs increased in successively younger birth cohorts alongside IRRs for liver and intrahepatic bile duct cancer in female individuals, uterine corpus, gallbladder and other biliary, testicular, and colorectal cancers, while MRRs declined or stabilised in younger birth cohorts for most cancers types.

Interpretation 17 of 34 cancers had an increasing incidence in younger birth cohorts, including nine that previously had declining incidence in older birth cohorts. These findings add to growing evidence of increased cancer risk in younger generations, highlighting the need to identify and tackle underlying risk factors.

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Introduction

We previously reported that incidence rates increased in successively younger birth cohorts for eight cancer types—six of which are obesity-related—alongside steeper or exclusive increases in young adults (age 25–49 years) over time in the USA.[1] Some studies have since reported increases in cancer incidence among young adults (usually defined as diagnosis age <50 years) in the USA and elsewhere.[2–5] A recent analysis of data from 13 registries in the USA suggested that individuals born between 1965 and 1980 (also known as Generation X) might have higher incidence rates of some cancers (eg, thyroid, colorectal, kidney, uterine corpus, and

leukaemia) as well as an increased risk of all leading cancers combined.[6] However, a comprehensive analysis that examines both cancer incidence and mortality trends by birth cohort or year of birth in contemporary generations has yet to be done. Trends in cancer incidence in young generations or young adults (age <50 years) largely reflect increased exposure to carcinogenic factors during early life or young adulthood compared with previous generations,[7] and foreshadow future disease burden as these young cohorts carry their increased risk into older age, when cancers most frequently occur.[7] To quantify cancer risk among younger generations of adults compared with their older

counterparts, we aimed to examine trends in incidence rates of 34 cancers and mortality rates of 25 cancers for 2000 to 2019 by birth cohort spanning from 1920 to 1990 in the USA using nationally representative high-quality data.

Methods

Study design and data sources

In this analysis of population-based registry data, we obtained incidence data for the period Jan 1, 2000 to Dec 31, 2019, for the 34 most common cancer types diagnosed at ages 25–84 years (ie, diagnosed in at least 200000 individuals during the study period) from the North American Association of Central Cancer Registries (known as NAACCR); these data covered 94% of the US population, with six states and the District of Columbia excluded due to incompleteness of data (appendix p 7). For female breast cancer, we obtained incidence data from 17 Surveillance, Epidemiology, and End Results (SEER) Program registries to enable subtype-specific analysis.

Cases were classified per the International Classification of Disease Oncology, third edition, and further into anatomical, histological, and molecular subtypes (ie, oestrogen receptor-positive and oestrogen receptor-negative for breast cancer; cardia and non-cardia for gastric cancer; adenocarcinoma and squamous cell carcinoma for oesophageal cancer; and HPV-related and non-HPV-related for oral cavity and pharynx cancers;[8,9] appendix p 8). Nationwide mortality data were obtained from the US National Center for Health Statistics. Mortality analyses were restricted to 25 cancer types, classified by ICD-10, with exclusion of Kaposi sarcoma because of a low number of deaths, and breast, oesophagus, oral cavity and pharynx, and gastric cancers because of the absence of subtype classification (appendix pp 3–4). The population estimates (denominators used to calculate rates) were provided by the US Census Bureau for each study year. Sex and age information were extracted from all databases. Data on race and ethnicity were available but were not analysed.

This study used de-identified publicly available data, which is considered non-human participants research under the Common Rule (US federal regulation 45 CFR §46); thus, institutional review board approval and informed consent were not needed.

Statistical analysis

To evaluate birth cohort trends in cancer rates, adjusted for age and period effects, we fitted age-period-cohort models to the incidence or mortality rates of each cancer type using weighted least squares, assuming Poisson-distributed counts and including overdispersion parameters for potential extra-Poisson variation.[10] A change in the birth cohort trend usually indicates changes in exposure prevalence, leading to varying risks of developing cancers for individuals of the same generation. By contrast, a period effect reflects systematic changes in cancer ascertainment or the influence of newly introduced or improved medical interventions, affecting all age groups simultaneously during the same period.

To obtain stable parameter estimates across all cancer types, 5-year intervals were used to categorise age groups (age 25–29 years up to age 80–84 years) and period of cancer diagnosis or death (2000–04, 2005–09, 2010–14, and 2015–19). Nominal birth cohorts (eg, 1990 birth cohort) were constructed by subtracting the mid-year age (eg, 27 for 25–29 years) from the mid-year period (eg, 2017 for 2015–19), resulting in 15 partially overlapping birth cohorts, referenced by mid-year of birth and spaced by 5 years (from 1920 up to 1990). Such that, for instance, the 1990 birth cohort largely represents the experiences of those born in approximately 1990, with 80% of cases or deaths in this cohort involving individuals born between 1987 and 1993 (appendix pp 3–4).[10] First, we generated cohort rate ratio curves, which are composite curves that include backward projections for older cohorts and forward projections for younger cohorts.[10] A ratio of the net incidence or mortality rate in each cohort relative to the reference cohort, also known as incidence rate ratio (IRR) and mortality rate ratio (MRR), respectively, was computed for each birth cohort.[10] We first analysed cancer types for which IRRs increased with each successive birth cohort, and for these analyses we chose the 1955 birth cohort as the reference because it is midway among the birth cohorts examined. We then analysed cancers for which there was a reversal in IRR trend between older and younger cohorts (such that decreasing trends in IRR for older cohorts began to increase for younger cohorts), and for these analyses, the birth cohort with the lowest incidence rate of all cohorts was selected as an alternative reference, with the most recent reversal birth year being selected as the reference if there was more than one change in trend. Next, we calculated the average annual percentage changes (AAPCs) from 2000 to 2019 in model-based estimates of incidence or mortality rates that were specific to each age group.[10] We used a Wald test to assess the significance of the non-linear components of the cohort rate ratio curves

(birth cohort deviation) and the heterogeneity in AAPCs across age groups. Finally, we visualised trends in observed age-specific incidence or mortality rates by birth cohort (canonical plots) to inspect so-called non-parallelism, which is indicative of the birth cohort effect. All age-period-cohort analyses were conducted overall and by sex.

Two-sided p values of less than 0·05 were considered to be statistically significant. Not adjusting for multiple comparisons was preferred because the analyses were exploratory rather than testing hypotheses, and the data under evaluation (cancer incidence and mortality) were actual observations in nature rather than random numbers.[11] Correcting for multiple comparisons could increase the type 2 errors, potentially causing important findings (eg, subtle trends or those based on a relatively small number of cases or deaths) to be overlooked. We tabulated the number of cancer cases and deaths along with population estimates using SEER*Stat (version 8.4.2) and an established web tool for age-period-cohort analysis[10] to obtain estimable functions of the age-period-cohort model.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit for publication.

Results

We extracted data for 23 654 000 patients diagnosed with 34 types of cancer and 7 348 137 deaths from 25 cancers for the period Jan 1, 2000, to Dec 31, 2019 (frequencies by cancer type are in the appendix [pp 5–6]).

Birth cohort trends in cancer incidence and mortality rates for 11 of 34 cancers for which IRRs increased with each successive birth cohort born since approximately 1920 and across the 1950 to 1990 birth cohorts are shown in figure 1 (all estimates and 95% CIs are in the appendix [pp 9–17]). Data for male and female individuals combined were presented if IRRs increased in both sexes; otherwise, sex-specific IRRs with increasing trends were provided (all sex-specific data are in the appendix [p 28]). Compared with individuals in the 1955 birth cohort, the incidence rate was approximately two-to-three times higher in the 1990 birth cohort for cancers of the small intestine (IRR 3·56 [95% CI 2·96–4·27]), thyroid (3·29 [2·91–3·73]), kidney and renal pelvis (2·92 [2·50–3·42]), and pancreas (2·61 [2·22–3·07]). Additionally, female individuals in the 1990 birth cohort had higher incidence of liver and intrahepatic bile duct (IRR 2·05 [1·23–3·44]) and those in the 1985 birth cohort had a higher incidence of non-HPV-associated oral or pharyngeal (1·26 [1·14–2·61]) cancers than did those in the 1955 birth cohort. The birth cohort effect on the incidence trends, tested for deviations in IRRs from linear trends, was significant for eight of 11 cancers (p_{cohort}<0·050), and was non-significant for thyroid, soft tissue including heart, and female oesophageal adenocarcinoma (appendix pp 25–26).
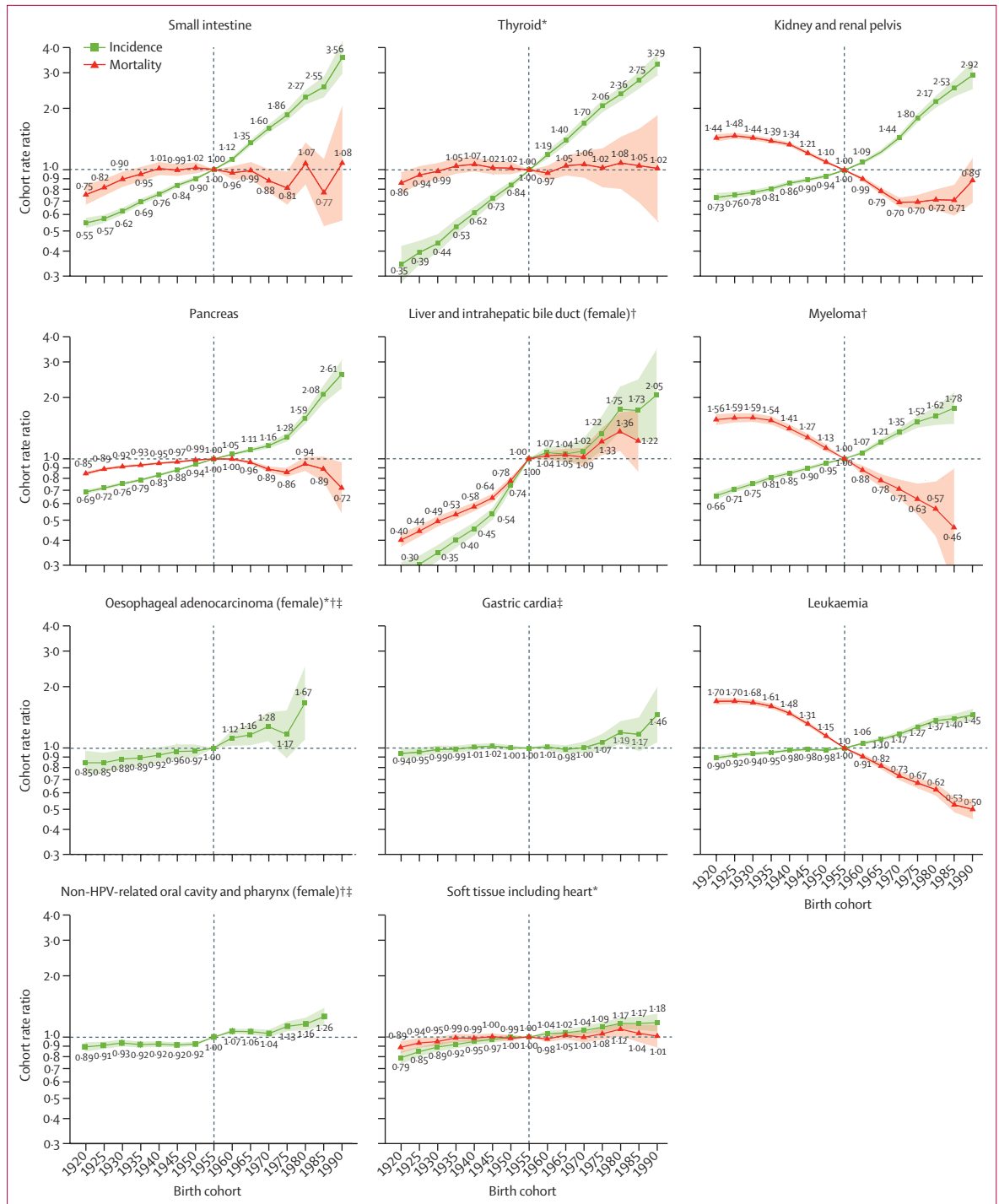
Figure 1: Birth cohort incidence and mortality rate ratio trends from 1920 to 1990 for 11 cancers with a consistent increase in incidence across birth cohorts in the USA, 2000–19
The shaded areas indicate 95% CIs. Data are for both male and female individuals combined, unless otherwise stated. The rate in the 1955 birth cohort was used as the reference to calculate the relative risk. The panels are sorted by the magnitudes of the IRR for the latest birth cohort. IRR=incidence rate ratio. *The test for non-linear components of the IRR curves (birth cohort deviation) is not significant (p_{cohort}>0·050). †Due to the relatively small number of cases or deaths, the youngest birth cohorts were truncated. ‡Mortality data were not available.

Among these 11 cancers, mortality data were available for eight cancers, and, by contrast with the incidence trends, birth cohort trends in mortality rates decreased (eg, myeloma and leukaemia), plateaued (eg, small intestine and thyroid), or fluctuated (eg, pancreas and kidney and renal pelvis) in the 1955 to 1990 birth cohorts
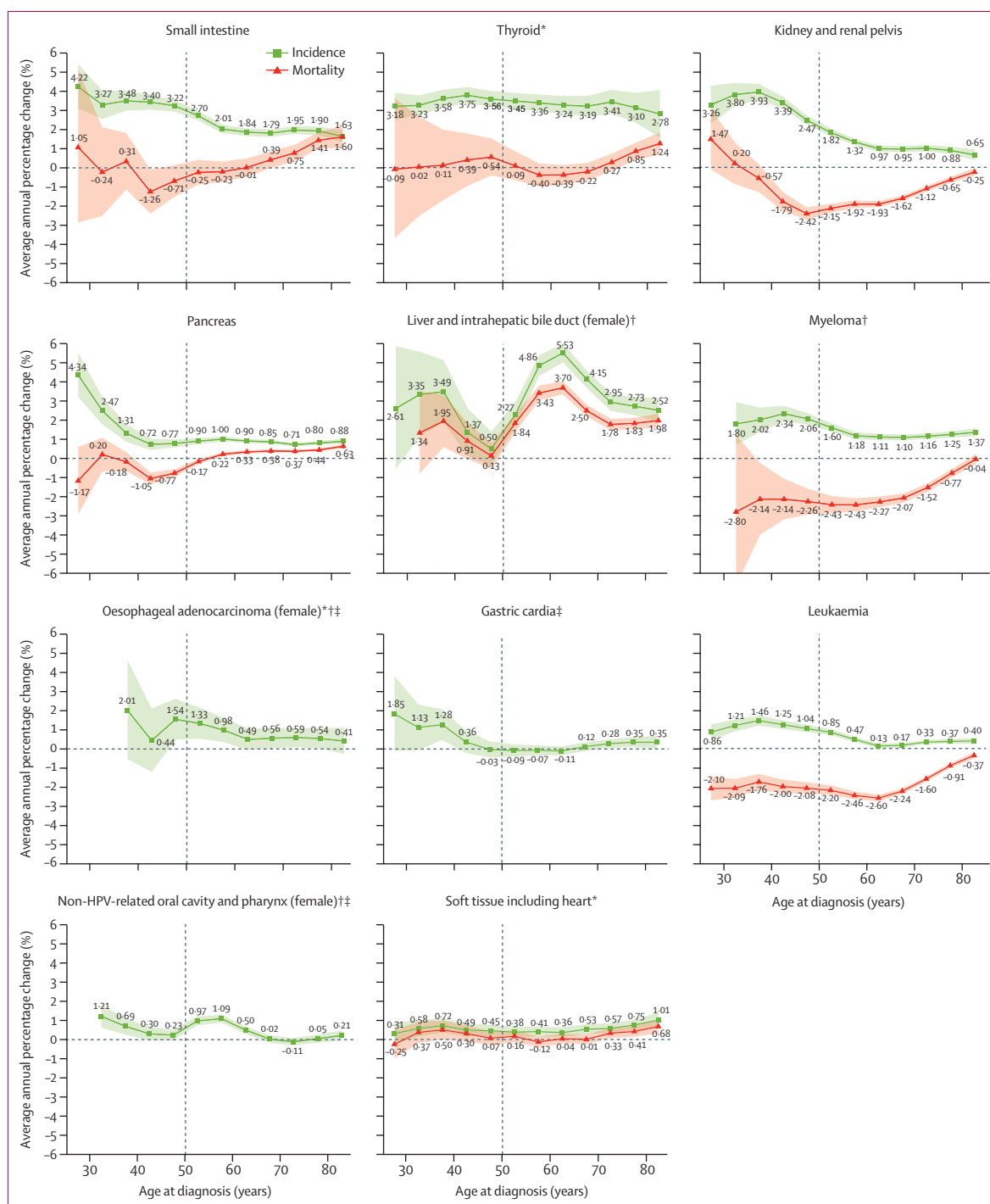
Figure 2: Age-specific average annual percentage changes in incidence or mortality rates from 2000 to 2019 for 11 cancers with a consistent increase in incidence in the USA across birth cohorts from 1920 to 1990

The shaded areas indicate 95% CIs. Data are for both male and female individuals combined, unless otherwise stated. The vertical line at 50 years is indicative of the cutoff for young adults, defined as individuals younger than 50 years. Average annual percentage changes were derived from the slope (derivative) of the cohort rate ratio curve and are estimated trends in fitted rates over time specific to each age group. *The test for heterogeneity in average annual percentage changes (age deviation) is not significant ($p_{age} > 0.05$). †Due to the relatively small number of cases or deaths, the youngest age groups were truncated. ‡Mortality data were not available.

for all cancers, except for female liver and intrahepatic bile duct cancer, for which, compared with those in the 1955 birth cohort, the 1980 birth cohort had an MRR of 1·36 (95% CI 1·09–1·69; all MRR estimates and 95% CIs are in the appendix [pp 18–24]).

Age-specific AAPCs in incidence or mortality rates from 2000 to 2019 for the 11 identified cancers are shown in figure 2 (sex-specific results are shown in the appendix [p 29]). Among young adults (aged 25–49 years), the most rapid annual increases in incidence rates were seen for pancreatic (4·34%, age 25–29 years), small intestine (4·22%, age 25–29 years), and kidney and renal pelvis (3·93%, age 35–39 years) cancers. In female individuals, bimodal patterns were observed for liver

and intrahepatic bile duct and non-HPV-associated oral and pharyngeal cancers, with rapid increases in incidence among individuals aged 30–39 years and 55–64 years. By contrast, increases in incidence rates did not vary significantly across age groups for thyroid cancer, female oesophageal adenocarcinoma, and soft tissue including heart cancer (p_{age}>0·050), consistent with the age invariant period effect (p_{period}<0·050; all test results are in the appendix [pp 25–26]). Mortality rates either decreased or stabilised in young adults (aged 25–49 years), except for female liver and intrahepatic bile duct cancer, which increased by 1·95% (95% CI 0·59–3·34) annually among those aged 35–39 years (p_{age}<0·050; all test results are in the appendix [p 27];
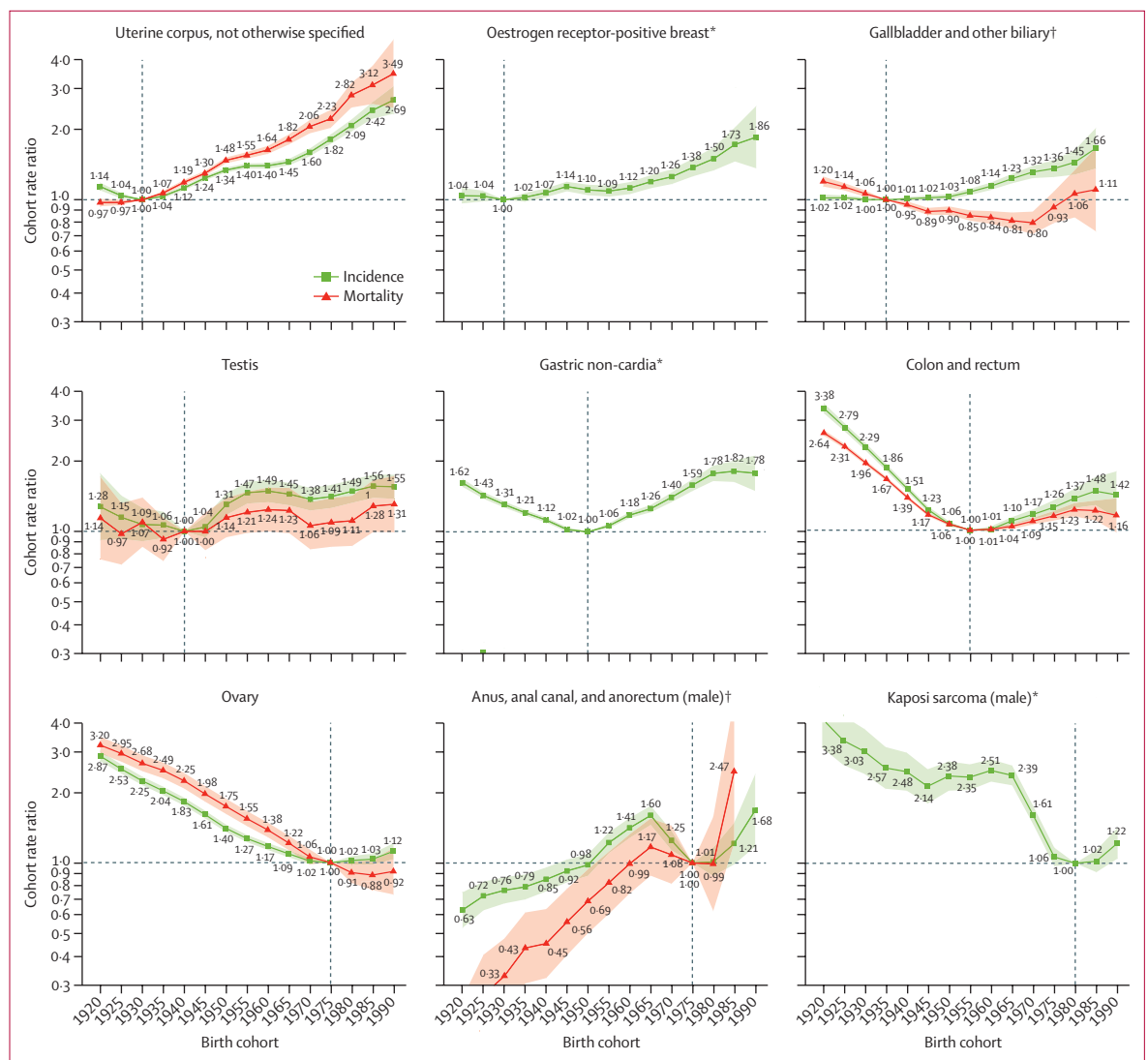
Figure 3: **Birth cohort incidence and mortality rate ratios trends from 1920 to 1990 for nine cancers with reversing trends in incidence compared with older birth cohorts in the USA, 2000–19**
The shaded areas indicate 95% CIs. Data are for both male and female individuals combined, unless cancer is sex-specific or otherwise stated. The birth cohort with the lowest incidence rate was used as the reference to calculate the relative risk. The panels are sorted by the magnitudes of the IRR for the latest birth cohort. IRR=incidence rate ratio. *Mortality data were not available. †Due to the relatively small number of cases or deaths, the youngest birth cohorts were truncated.

age-specific mortality estimates are shown in the appendix [pp 18–24]).

Birth cohort trends for the nine of 34 cancers for which IRRs increased in younger birth cohorts after previous short-term or long-term declines in older birth cohorts are shown in figure 3. Data for male and female individuals combined were presented if IRRs increased after a previous decrease in both sexes, otherwise, sex-specific IRRs were provided (sex-specific results are in the appendix [p 28]). The reversal in IRRs occurred in the 1930 to 1935 birth cohorts for uterine corpus, oestrogen receptor-positive breast, and gallbladder and other biliary cancers; in the 1940 birth cohort for testicular cancer; in the 1950 to 1955 birth cohorts for non-cardia gastric and

colorectal cancers; and in the 1975 to 1980 birth cohorts for ovarian cancer, anus, anal canal and anorectum cancer (hereon referred to as anal cancer) in male individuals, and Kaposi sarcoma in male individuals (all p_{cohort}<0·050; appendix pp 25–26). Compared with the birth cohort with the lowest incidence rate, incidence rates in the 1990 birth cohort were 12% (IRR$_{1990\ vs\ 1975}$ 1·12 [95% CI 1·03–1·21] for ovarian cancer) to 169% (IRR$_{1990\ vs\ 1930}$ 2·69 [2·34–3·08] for uterine corpus cancer) higher (appendix pp 9–17). Among these nine cancers, mortality data were available for six cancers. The birth cohort trends in mortality rates generally mirrored those of the incidence rates (sex-specific results are in the appendix [pp 18–24]) with the steepest increase in MRR estimated for uterine corpus cancer

Figure 4: Age-specific average annual percentage changes in incidence or mortality rates from 2000 to 2019 for nine cancers with reversing trends in incidence compared with older birth cohorts in the USA
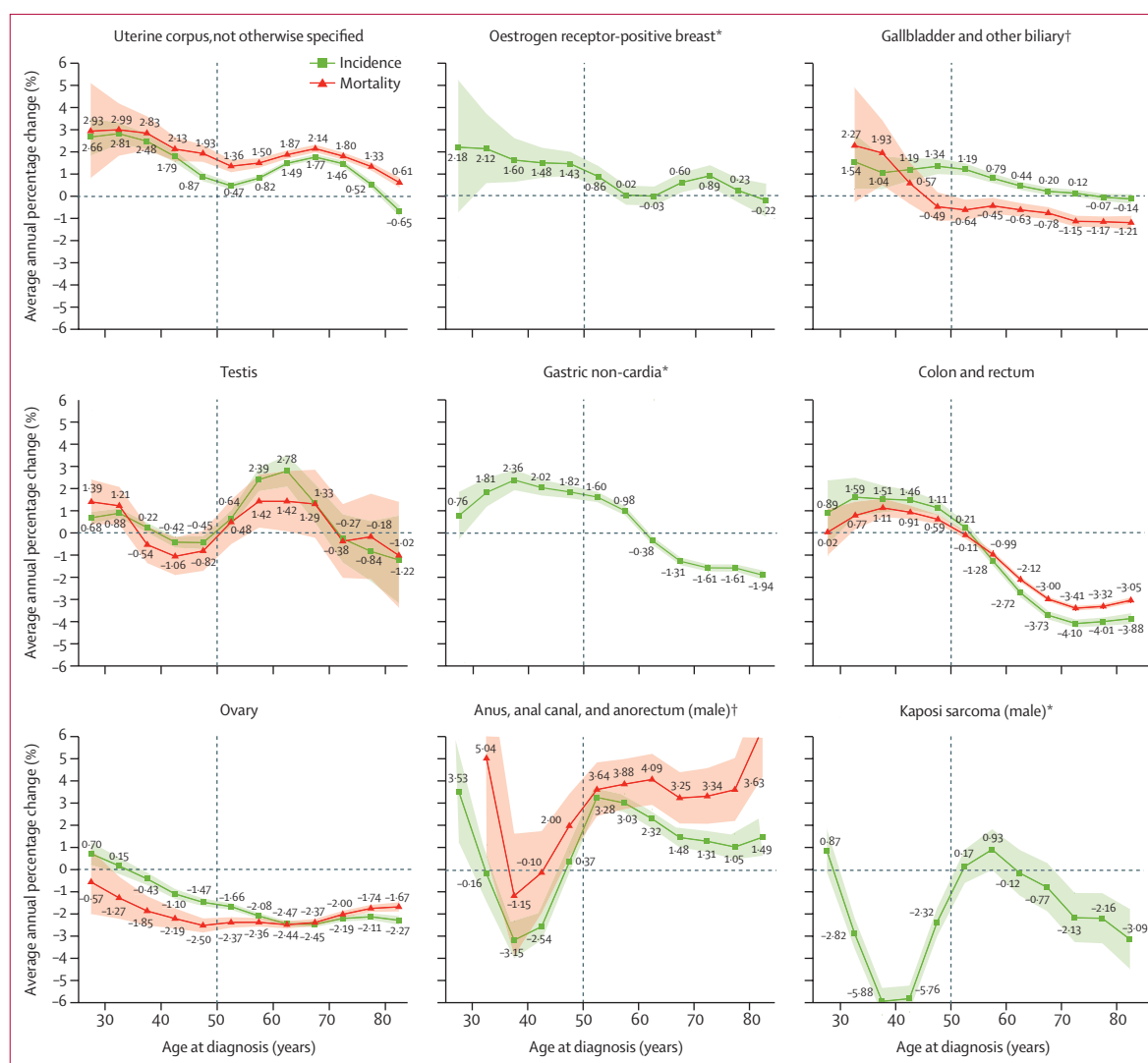
The shaded areas indicate 95% CIs. Data are for both male and female individuals combined, unless cancer is sex-specific or otherwise stated. The vertical line at 50 years is indicative of the cutoff for young adults, defined as individuals younger than 50 years. Average annual percentage changes were derived from the slope (derivative) of the cohort rate ratio curve and represent estimated trends in fitted rates over time specific to each age group. *Mortality data were not available. †Due to the relatively small number of cases or deaths, the youngest age groups were truncated.

(MRR$_{1990 \, vs \, 1930}$ 3·49 [95% CI 2·49–4·88; appendix pp 18–24]). The birth cohort effect on the mortality trends, tested for deviations in MRRs from linear trends, was significant for all six cancers (p$_{cohort}$<0·050; appendix 27).

Age-specific AAPCs in incidence or mortality rates from 2000 to 2019 for these nine cancers are shown in figure 4 (sex-specific AAPC incidence and mortality results are in the appendix [pp 9–24]). For uterine corpus, oestrogen receptor-positive breast, and gallbladder and other biliary cancers, incidence rates increased across almost all age groups, with younger age groups having faster increases than older age groups. For non-cardia gastric and colorectal cancers, increases in incidence were confined to younger age groups (age 30–59 years for non-cardia gastric and 30–54 years for colorectal cancer). Male individuals aged 25–29 years had a 3·53% (95% CI 1·25 to 5·87) annual increase in anal cancer and a non-significant 0·87% (–0·09 to 1·84) annual increase for Kaposi sarcoma, contrasting with adjacent older age groups (30–49 years) who had rapid declines in incidence. A similar pattern was found for testicular cancer with male individuals aged 25–34 years having a 0·68% (95% CI 0·42 to 0·94) to 0·88% (0·66 to 1·09) annual increase in incidence. For ovarian cancer, the decreasing incidence trends lessened with progressively younger age groups; and the incidence rate increased in those aged 25–29 years by 0·70% per year (95% CI 0·19–1·21). Age-specific mortality rates increased in some young adult age groups (25–49 years) for cancers of the gallbladder and other biliary and colorectum. Uterine corpus cancer increased in age-specific mortality across all age groups, with greater increases in younger groups, and testicular cancer and anal cancer in male individuals had a bimodal increase in age-specific mortality, one among younger adults (age 25–34 years for testicular and age 30–34 years for anal cancer in male individuals) and another among older cohorts (age 55–64 years for testicular and age 45–84 years for anal cancer in male individuals).

Birth cohort trends for the remaining 14 cancers decreased or were relatively stable over successive birth cohorts from approximately 1955 to 1990 (appendix p 30). Unlike other cancers, the IRRs for vulva and HPV-related oral and pharyngeal cancers decreased after the 1960 birth cohort and for melanoma decreased after the 1980 birth cohort, after having shown a steady increase in incidence across older birth cohorts. Other notable observations are the sharp downturn in IRRs for cervical cancer between the 1985 and 1990 birth cohorts and the decelerations of long-term declines in IRRs for smoking-related cancers (eg, lung, larynx, and oesophageal squamous cell carcinoma) for birth cohorts born around 1975. Sex-specific patterns were similar to each other except for the aforementioned smoking-associated cancers and melanoma, with a lag of 10 to 30 years in the female birth cohorts exhibiting these trends compared with male birth cohorts (appendix p 32).

The corresponding age-specific AAPCs across 2000 to 2019 for the 14 cancers with decreasing or stable birth cohort trends are in the appendix (p 31). In young adults (age 25–49 years), incidence rates for all these cancers generally decreased or stabilised, with mortality rates often declining more sharply than incidence rates (eg, lung cancer and lymphomas). A sharp decline in the incidence of cervical cancer was seen in females aged 25–29 years (–1·45% per year), which was steeper than declines among those aged 30–39 years (–0·49% to –0·63% per year).

Consistent with the trends based on the fitted rates (ie, the modelled rates), trends in observed age-specific incidence increased in some age groups among young adults (age 25–49 years) for the 20 cancers with increasing IRRs (appendix p 34; corresponding mortality data are in the appendix [p 35]), showing that the birth cohort findings were not an artifact of modelling. Age-specific incidence rates for the 14 cancers with decreasing or stable IRRs are shown in the appendix (p 36; corresponding mortality trends are in the appendix [p 37]).

Discussion

Based on a comprehensive model-based cohort analysis of nationwide, high-quality, cancer incidence and mortality data, we found that incidence rates for 17 of the 34 cancer types studied increased in progressively younger birth cohorts in the USA, after adjusting for age and period effect (p$_{cohort}$<0·050). These findings expand on our previous research,[1] adding eight cancer types (cardia gastric, small intestine, oestrogen receptor-positive breast, ovary, liver and intrahepatic bile duct and non-HPV-associated oral and pharynx in female individuals, and anus and Kaposi sarcoma in male individuals) to the list of cancers previously identified (colorectum, uterine corpus, gallbladder and other biliary, kidney and renal pelvis, pancreas, myeloma, non-cardia gastric, testis, and leukaemia). For liver and intrahepatic bile duct in female individuals, uterine corpus, gallbladder and other biliary, testicular, and colorectal cancers, mortality trends mirrored incidence trends, suggesting the increase in incidence in younger generations is substantial enough to outweigh improvements in cancer survival. The increasing cancer incidence rates over the successive younger generations up to those born around 1990 suggest there have been increases in the prevalence of carcinogenic exposures during early life or young adulthood in this generation, which have yet to be elucidated.

Ten of 17 cancers with increasing incidence in younger birth cohorts are obesity-related cancers (colorectum, kidney and renal pelvis, gallbladder and other biliary, uterine corpus, pancreas, cardia gastric, oestrogen receptor-positive breast, ovary, myeloma, and liver and intrahepatic bile duct),[12] suggesting a potential role of obesity in emerging cancer trends in recent generations. Since the late 1970s, the obesity epidemic in the USA has affected individuals across all age groups; however, the

most rapid rise has been seen among individuals aged 2–19 years,[13] indicative of birth cohort effects. This hypothesis is supported by analyses of nationally representative survey data from the USA indicating increasing odds of developing obesity, type 2 diabetes, and metabolic syndrome among generations born after those born in 1946–64 (known as the Baby Boomer generation),[14–17] and that has also been linked to the increase in premature cardiometabolic mortality since 2011[18] and the decrease in life expectancy since 2014.[19] Accumulating evidence underscores the substantial influence of bodyweight in early life, as highlighted by a recent study associating excess bodyweight during early adulthood (ages 18–40 years) with up to 18 cancers.[20]

The effect of exposures to other suspected risk factors (eg, unhealthy diet, sedentary lifestyle, altered sleep patterns, and environmental chemicals) during early life and young adulthood on cancer risk,[3,21] as well as birth cohort trends in the prevalence of these factors, remain poorly understood. Some dietary patterns (eg, high in saturated fats, refined grain, ultra-processed foods, and sugar, as well as meat *vs* plant diets) and sedentary behaviours during adolescence and young adulthood have been associated with increased risk of some cancers, most consistently for colorectal and breast cancers.[3,21] The constellation of gastrointestinal tract cancers (including those not necessarily associated with obesity—eg, small intestine and non-cardia gastric cancers) that are increasing in incidence in recent birth cohorts highlight the potential involvement of an altered microbiome, given substantial changes in dietary patterns and antibiotics use in particular over the past few decades.[22,23] Evidence from multiple sources, ranging from murine models to prospective cohort studies, has linked specific microbes or associated dietary patterns to oral and gastrointestinal tract cancer carcinogenesis.[24–26] Microbial dysbiosis via various exposures, leading to heightened oxidative stress and inflammation, is thought to promote epigenetic alterations and somatic mutations via interactions with host genetics and the immune system.[24,25]

Historical changes in reproductive patterns probably had at least a small role in shaping birth cohort trends for cancers in female individuals. In particular, the nadir of the IRR curves for oestrogen receptor-positive breast and uterine cancers among women born in approximately 1930 corresponds to the peak fertility rate during 1946–64 (ie, the birth of the Baby Boomer generation). The subsequent increase (in the 1930–50 birth cohorts) and deceleration, and then increase in IRRs align with trends in fertility rates, which reduced (1957–76), stabilised, and then decreased. Reasons for the reversal in the birth cohort trend observed for ovarian cancer since 1975 are unclear; however, it might in part reflect the decline in oral contraceptive use from the early 1970s to the mid-1990s, considering the inverse association of oral contraceptive use and ovarian cancer risk.[27]

For liver and non-HPV-associated oral and pharyngeal cancers, incidence rates increased in women in successive birth cohorts born since approximately 1970, whereas rates decreased or stabilised in men. Increasing birth cohort trends in women are consistent with lifetime trajectories in alcohol-related behaviours among those born in the late 1970s and early 1980s, as well as acceleration in binge drinking from 1990 to 2010, when individuals in this birth cohort would have been aged 30–49 years.[28] Conversely, the stabilisation of liver and intrahepatic bile duct cancer incidence and the decline in the incidence of oral and pharyngeal cancer among recent male birth cohorts might be attributable, at least in part, to decreased alcohol consumption and smoking among male individuals aged 18–25 years.[28] The effect of the increase in the prevalence of hepatitis C virus infection since approximately 2010, which disproportionately affects young adults,[29] on trends in liver cancer remains to be determined, given the latency from viral exposure to the onset of hepatocellular carcinoma.

The rising incidence rate of anal cancer and Kaposi sarcoma in recent male birth cohorts is a reversal from previous trends. The partially similar patterns of both malignancies might indicate the influence of shared risk factors, such as HIV infection.[30] The escalating incidence rate in the 1945–65 birth cohorts in men is probably indicative of the AIDS epidemic during the 1980s, and its peak in 1993, when these birth cohorts were aged 20–49 years.[31] The subsequent sharp decrease in the birth cohort incidence of these two cancers aligns with the swift decline in AIDS incidence, reflecting major advances in antiviral therapies during the mid-1990s.[32] Such treatment advances probably manifested as a period effect, affecting incidence rates across all age groups. The increase in incidence of anal cancer and Kaposi sarcoma in male individuals among birth cohorts born since 1975–80 is somewhat unexpected and highlights the need for further investigation, especially considering the increase in the number of men with HIV aged 25–34 years, contrasting with a continued decrease in older adults[33] and increased screening (for anal cancer) in high-risk individuals.[34]

The accelerated downturn in the birth cohort trend of cervical cancer incidence shows the effectiveness of HPV vaccination, particularly in women born in approximately 1990, who were approximately age 16 years when HPV vaccination was first approved in the USA for women and girls aged 9–26 years in 2006.[35] The strong downward birth cohort trends for mainly smoking-associated cancers (eg, lung, larynx, and oesophageal squamous cell carcinoma) probably reflect the rapid decline in the prevalence of smoking among younger birth cohorts; however, signs of slowed progress in the youngest birth cohorts (approximately from 1975 birth cohort onward) warrant continuous monitoring with additional years of data.

Declines in birth cohort trends for mortality rates, observed for many cancers that showed increases in the

birth cohort trends for incidence, should be interpreted with caution. The seemingly contradictory pattern of increasing incidence and decreasing mortality could be because of early detection or treatment advancements, or a combination of both, which improves cancer survival. For example, for pancreatic cancer, the improvement in 5-year survival among young adults (aged <50 years; from 16·5% in 2000 to 37·2% in 2016 in the USA[36]) might have outpaced the effect of increasing incidence. For cancers with decreasing birth cohort trends for both incidence and mortality, mortality often declined more sharply than incidence, reflecting both successful primary prevention efforts and treatment breakthroughs during the past few decades (eg, lung cancer).[37,38] Additionally, the increased use of diagnostic testing and overdiagnosis probably contributed to the rise in incidence rates of cancers that are highly sensitive to diagnostic scrutiny (eg, thyroid and kidney cancers), without increasing mortality trends.

The findings of increased cancer incidence in recent birth cohorts for 17 cancer types have important public health implications. The heightened cancer risk in recent birth cohorts has already translated into an increasing cancer morbidity and mortality burden in young adults, posing unique challenges to the health-care system and community. Improving awareness among health-care providers and the general public about the signs and symptoms of cancer among young adults is crucial for early detection and treatment. Because most existing cancer care systems in the USA are not tailored to the unique needs of young adults with cancer, targeted programmes and services are needed. Additionally, our findings should prompt a more vigorous application of the life course framework in epidemiological studies to fill significant gaps in understanding birth-cohort-specific exposures and the trajectories of cancer risk, beginning as early as adolescence, childhood, infancy, and even prenatal stages,[39] prioritising modifiable exposures. Funding should also support research on the development of interventions that align with the influential social and cultural context, values, and preferences of younger generations. Without effective population-level interventions, the maturation of younger generations could lead to an overall increase in cancer burden in the future, halting or reversing decades of progress against cancer.

The strengths of this study include the use of high-quality representative population-based data; an analysis of both incidence and mortality trends; the use of age-period-cohort modelling; and a comprehensive and systematic examination of various cancers.

The major limitation of this study stems from the so-called identifiability issue that is inherent to all age-period-cohort modelling studies, where changes in disease incidence cannot be separately attributed to each element because of their co-linear nature.[40] Nevertheless, statistical testing of cohort deviations, adjusted for age

and period effects, uniquely captured changes in cancer incidence attributable to the birth cohort effect and signifies generational differences in cancer risk. Furthermore, all interpretations were based on model-derived quantities; the cohort rate ratio curve is a composite curve, integrating observed data with projected rates under the assumption that the age-period-cohort model provides an adequate description of the data.[6,10] Partly because of the absence of data in cancer registries, we were unable to assess the contribution of secular changes in plausible risk factors or diagnostic practices to changes in cancer incidences in younger generations. Assessing incidence trends by cancer stage and method of detection (eg, patient symptoms or signs, screening, or incidental findings) could help differentiate the effect on incidence trends of diagnostic changes versus generational population risk changes. Additionally, some cancers are likely to have been misclassified. In particular, the classification of HPV-associated versus non-HPV-associated oral and pharyngeal cancers was solely determined by histology without information on risk factors such as HPV infection and smoking status.[8,9] Furthermore, the accuracy of cancer mortality statistics based on death certificates varies by cancer type, although the concordance with population-based cancer registry data is generally high for common cancers.[41] Additionally, the fact that our study focused specifically on US adult populations might limit the generalisability of our findings. Finally, aggregated data obscures health disparities among diverse socioeconomic and demographic groups, including by race and ethnicity, warranting future studies to identify high-risk populations and intervention priorities.

In conclusion, controlling for age and period effects on cancer incidence rates, each successive generation born during the second half of the 20th century has had increased incidences of many common cancer types of heterogeneous aetiologies compared with preceding generations in the USA. Our findings highlight the importance of early lifetime exposures and highlight crucial opportunities to prevent a substantial fraction of cancer occurrence through modification of environmental and lifestyle risk factors. Extensive efforts are needed to identify underlying risk factors responsible for these trends to inform prevention strategies.

References
1 Sung H, Siegel RL, Rosenberg PS, Jemal A. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. *Lancet Public Health* 2019; **4:** e137–47.
2 Koh B, Tan DJH, Ng CH, et al. Patterns in cancer incidence among people younger than 50 years in the US, 2010 to 2019. *JAMA Netw Open* 2023; **6:** e2328171.
3 Ugai T, Sasamoto N, Lee HY, et al. Is early-onset cancer an emerging global epidemic? Current evidence and future implications. *Nat Rev Clin Oncol* 2022; **19:** 656–73.
4 di Martino E, Smith L, Bradley SH, et al. Incidence trends for twelve cancers in younger adults—a rapid review. *Br J Cancer* 2022; **126:** 1374–86.
5 Heer EV, Harper AS, Sung H, Jemal A, Fidler-Benaoudia MM. Emerging cancer incidence trends in Canada: the growing burden of young adult cancers. *Cancer* 2020; **126:** 4553–62.
6 Rosenberg PS, Miranda-Filho A. Cancer incidence trends in successive social generations in the US. *JAMA Netw Open* 2024; **7:** e2415731.
7 Doll R. Progress against cancer: an epidemiologic assessment. The 1991 John C. Cassel Memorial Lecture. *Am J Epidemiol* 1991; **134:** 675–88.
8 Kreimer AR, Chaturvedi AK, Alemany L, et al. Summary from an international cancer seminar focused on human papillomavirus (HPV)-positive oropharynx cancer, convened by scientists at IARC and NCI. *Oral Oncol* 2020; **108:** 104736.
9 Tota JE, Best AF, Zumsteg ZS, Gillison ML, Rosenberg PS, Chaturvedi AK. Evolution of the oropharynx cancer epidemic in the United States: moderation of increasing incidence in younger individuals and shift in the burden to older individuals. *J Clin Oncol* 2019; **37:** 1538–46.
10 Rosenberg PS, Check DP, Anderson WF. A web tool for age-period-cohort analysis of cancer incidence and mortality rates. *Cancer Epidemiol Biomarkers Prev* 2014; **23:** 2296–302.
11 Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990; **1:** 43–46.
12 Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—viewpoint of the IARC Working Group. *N Engl J Med* 2016; **375:** 794–98.
13 Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–2018. NCHS Health E-Stats, 2020. https://www.cdc.gov/nchs/data/hestat/obesity-child-17-18/obesity-child.htm (accessed May 24, 2024).
14 Reither EN, Hauser RM, Yang Y. Do birth cohorts matter? Age-period-cohort analyses of the obesity epidemic in the United States. *Soc Sci Med* 2009; **69:** 1439–48.
15 Robinson WR, Keyes KM, Utz RL, Martin CL, Yang Y. Birth cohort effects among US-born adults born in the 1980s: foreshadowing future trends in US obesity prevalence. *Int J Obes (Lond)* 2013; **37:** 448–54.
16 Fishman EI, Stokes A, Preston SH. The dynamics of diabetes among birth cohorts in the U.S. *Diabetes Care* 2014; **37:** 1052–59.
17 Zheng H, Echave P. Are recent cohorts getting worse? Trends in US adult physiological status, mental health, and health behaviors across a century of birth cohorts. *Am J Epidemiol* 2021; **190:** 2242–55.
18 Shah NS, Lloyd-Jones DM, Kandula NR, et al. Adverse trends in premature cardiometabolic mortality in the United States, 1999 to 2018. *J Am Heart Assoc* 2020; **9:** e018213.
19 Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med* 2005; **352:** 1138–45.
20 Recalde M, Pistillo A, Davila-Batista V, et al. Longitudinal body mass index and cancer risk: a cohort study of 2.6 million Catalan adults. *Nat Commun* 2023; **14:** 3816.
21 Murphy CC, Zaki TA. Changing epidemiology of colorectal cancer—birth cohort effects and emerging risk factors. *Nat Rev Gastroenterol Hepatol* 2024; **21:** 25–34.
22 Browne AJ, Chipeta MG, Haines-Woodhouse G, et al. Global antibiotic consumption and usage in humans, 2000–18: a spatial modelling study. *Lancet Planet Health* 2021; **5:** e893–904.
23 Whelan K, Bancil AS, Lindsay JO, Chassaing B. Ultra-processed foods and food additives in gut health and disease. *Nat Rev Gastroenterol Hepatol* 2024; **21:** 406–27.
24 Zepeda-Rivera M, Minot SS, Bouzek H, et al. A distinct *Fusobacterium nucleatum* clade dominates the colorectal cancer niche. *Nature* 2024; **628:** 424–32.
25 Nguyen LH, Cao Y, Hur J, et al. The sulfur microbial diet is associated with increased risk of early-onset colorectal cancer precursors. *Gastroenterology* 2021; **161:** 1423–32.e4.
26 Mima K, Kosumi K, Baba Y, Hamada T, Baba H, Ogino S. The microbiome, genetics, and gastrointestinal neoplasms: the evolving field of molecular pathological epidemiology to analyze the tumor-immune-microbiome interaction. *Hum Genet* 2021; **140:** 725–46.
27 Webb PM, Green AC, Jordan SJ. Trends in hormone use and ovarian cancer incidence in US White and Australian women: implications for the future. *Cancer Causes Control* 2017; **28:** 365–70.
28 Keyes KM, Jager J, Mal-Sarkar T, Patrick ME, Rutherford C, Hasin D. Is there a recent epidemic of women's drinking? A critical review of national studies. *Alcohol Clin Exp Res* 2019; **43:** 1344–59.
29 Ryerson AB, Schillie S, Barker LK, Kupronis BA, Wester C. Vital signs: newly reported acute and chronic hepatitis C cases - United States, 2009–2018. *MMWR Morb Mortal Wkly Rep* 2020; **69:** 399–404.
30 Zhang ER, Pfeiffer RM, Austin A, et al. Impact of HIV on anal squamous cell carcinoma rates in the United States, 2001–2015. *J Natl Cancer Inst* 2022; **114:** 1246–52.
31 Centers for Disease Control and Prevention (CDC). HIV and AIDS—United States, 1981-2000. *MMWR Morb Mortal Wkly Rep* 2001; **50:** 430–34.
32 National Institute of Allergy and Infectious Diseases. Antiretroviral drug discovery and development. https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development#:~:text=In%20March%201987%2C%20AZT%20became,reverse%20transcriptase%20inhibitors%2C%20or%20NRTIs (accessed May 24, 2024).
33 US Centers for Disease Control and prevention. HIV surveillance report. HIV diagnoses; 2008–2023; 25–34; all races/ethnicities; both sexes; all transmission categories; United States. https://gis.cdc.gov/grasp/nchhstpatlas/charts.html (accessed May 24, 2024).
34 Haas CB, Engels EA, Palefsky JM, et al. Severe anal intraepithelial neoplasia trends and subsequent invasive anal cancer in the United States. *J Natl Cancer Inst* 2024; **116:** 97–104.
35 Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2007; **56:** 1–24.
36 SEER*Explorer: An interactive website for SEER cancer statistics. Surveillance, Epidemiology, and End Results Program, National Cancer Institute, 2024. https://seer.cancer.gov/statistics-network/explorer/ (accessed June 2, 2024).
37 Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; **389:** 255–65.
38 Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med* 2020; **383:** 640–49.
39 Wagner C, Carmeli C, Jackisch J, et al. Life course epidemiology and public health. *Lancet Public Health* 2024; **9:** e261–69.
40 Holford TR. Understanding the effects of age, period, and cohort on incidence and mortality rates. *Annu Rev Public Health* 1991; **12:** 425–57.
41 German RR, Fink AK, Heron M, et al. The accuracy of cancer mortality statistics based on death certificates in the United States. *Cancer Epidemiol* 2011; **35:** 126–31.