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Original Article

A comparative analysis of premature heart disease- and cancer-related mortality in women in the USA, 1999–2018

Safi U. Khan [1], Siva H. Yedlapati[2], Ahmad N. Lone[1], Muhammad Shahzeb Khan[3], Nanette K. Wenger[4], Karol E. Watson[5], Martha Gulati[6], Allison G. Hays[7], and Erin D. Michos [7,8]*

[1]Department of Medicine, West Virginia University, Morgantown, WV, USA; [2]Department of Medicine, Erie County Medical Center, Buffalo, NY, USA; [3]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; [4]Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA; [5]Department of Medicine, Division of Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [6]Department of Medicine, Division of Cardiology, University of Arizona, Phoenix, AZ, USA; [7]Department of Medicine, Division of Cardiology, Johns Hopkins School of Medicine, Baltimore, MD, USA; and [8]Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins School of Medicine, Blalock 524-B, 600 N. Wolfe Street, Baltimore, MD 21287, USA

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Aims To compare premature heart disease- and cancer-related deaths in women in the USA.

Methods and results We analysed the US national database of death certificates of women aged <65 from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database between 1999 and 2018. We measured annual percentage changes (APCs) in age-adjusted mortality rates (AAMRs) and years of potential life lost per 100 000 persons due to heart disease and cancer. Overall, cancer was a more prevalent cause of premature death compared with heart disease. Between 1999 and 2018, the AAMRs decreased for both cancer (61.9/100 000 to 45.6/100 000) and heart disease (29.2/100 000 to 22.6/100 000). However, while APC in AAMR for cancer declined consistently over time, after an initial decline, APC in AAMR for heart disease increased between 2010 and 2018 [0.53 95% confidence interval (0.18–0.89)], with a significant rise in Midwest, medium/small metros, and rural areas after 2008. Compared with cancer, APC in AAMR for heart disease increased in women aged 25–34 years [2.24 (0.30–4.22); 2013–18) and 55–64 years [0.46 (0.13–0.80); 2009–13], as well as Non-Hispanic (NH) Whites [APC, 0.79 (0.46–1.13); 2009–18] and NH American Indian/Alaskan Native [2.71 (0.59–4.87); 2011–2018]. Consequently, the mortality gap between cancer and heart disease has narrowed from an AAMR of 32.7/100 000 to 23.0/100 000.

Conclusions The mortality gap between cancer and heart disease is decreasing among women <65 years. Intensive cardiovascular health interventions are required focusing on vulnerable young demographic subgroups and underserved regional areas to meet the American Heart Association's Impact Goal and Million Hearts Initiative.

Keywords Women • Premature mortality • Heart disease • Cancer

Introduction

Premature mortality (<65 years) is increasing in the USA, primarily driven by drug abuse, accidental deaths, and organ system diseases.[1,2] Cancer and heart disease are the two major causes of death in women.[3] While, heart disease is the leading cause of death overall, cancer is the major contributor to premature mortality in the USA.[3,4] Since about one-third of cardiovascular events occur in women before the age of 65,[5] a particular emphasis has been given in the American Heart Association (AHA)'s strategic 2030 Impact Goal

* Corresponding author. Tel: +410-502-6813; Email: edonnell@jhmi.edu

blueprints to mitigate the progression of heart disease in younger adults, with a focus on vulnerable demographic subgroups.[6,7] Similarly, the United Nations Sustainable Development Goal is a global public health initiative to reduce premature deaths from non-communicable diseases by 40% between 2015 and 2030.[8] However, recent statistics signal that the decline in heart disease mortality rates has slowed since 2011.[9,10] Similarly, because stagnation of mortality was only limited to heart disease and did not influence cancer mortality, a reduction in heart disease and cancer mortality gap was noticed through 2014.[6] Cardiometabolic risk factors are on the rise in young women, and young women with heart disease have a greater relative risk of mortality compared to men.[2,11] Thus, we compared premature mortality attributed to heart disease and cancer in women to assess contemporary trends in the mortality gap between both disease entities, stratified by demographic subsets and regional groups.

Methods

Data source

This study did not require institutional review board approval because we analysed government-issued public use data without individually identifiable information. We analysed death certificate records from the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) database. This national database contains the assigned cause of mortality from all death certificates in the USA filed in the 50 states and the District of Columbia. We identified natural deaths as defined by the World Health Organization (WHO) (*the disease or injury that initiated the events leading directly to death as entered by the physician on the death certificate*),[12] attributed to heart disease and cancer. *International Classification of the Diseases, 10th Revision* codes were used to identify women decedents aged <65 years at the time of death from heart disease (I00–I09, I11, I13, I20–I51) and cancer (C00–C97).

Data extraction

We defined premature mortality as death that occurred in those younger than 65 years.[1] The number of cause-specific premature deaths and population size were abstracted from 1999 to 2018. The data were abstracted heart disease and cancer subtypes (Supplementary material online, *Table S1*), age, ethnicity/race, census region (Northeast, Midwest, South, and West), 2013 county-level urbanization (*urban*: large central metro, large fringe metro, medium metro, small metro; *rural*: micropolitan, NonCore).[13] We stratified age-specific mortality data into <25 years and then 10-year age groups between 25 and 64 years. Ethnicity/race was defined as non-Hispanic (NH) White, NH Black, NH American Indian/Alaskan Native (AI/AN: North, Central, and South American Indians, Eskimos, and Aleuts), NH Asian/Pacific Islander (Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islanders), and Hispanics.

Statistical analysis

We calculated the crude death rates for individual years by dividing the number of cause-specific deaths by the total corresponding population. We calculated the annual cause-specific mortality rates per 100 000 population. Years of potential life lost (YPLL: the number of years of potential life lost by each death occurring before 65 years) was calculated using the previously described standard method using age-specific death rates for heart disease and cancer.[14,15] The mortality rates and YPLL were age-standardized to the 2000 US standard population. The rates were suppressed for data representing zero to nine (0–9) deaths. Corresponding denominator population figures were also suppressed when the population represents fewer than 10 persons. Rates were marked as 'unreliable' when the death count was less than 20. Rates were marked as 'not applicable' when the denominator population figure was unavailable, such as 'not stated' or unknown age or ethnicity. Deaths of persons with 'not stated' or unknown age were not included in calculating age-adjusted rates.

We estimated age-adjusted mortality rates (AAMRs) and YPLL per 100 000 for all demographic subgroups. Additional analyses were restricted to AAMRs for premature deaths in women according to census region and 2013 county-level urbanization. The absolute mortality gap between cancer and heart disease was calculated by subtracting AAMRs of heart disease from cancer.[6] Temporal trends were analysed by fitting log-linear regression models using the Joinpoint Regression Program version 4.7.0.0. We substituted the Monte Carlo permutation tests with a modification of the program's Bayesian Information Criteria (BIC) method, i.e., BIC3, to reduce computation time.[1] We calculated annual percent rate change (APC) with 95% confidence intervals (CIs) in AAMRs and YPLL for the line segments linking joinpoints.[16] The weighted average of the APCs was estimated to calculate the average annual percent change (AAPC) for the entire study period—with the weights equal to the length of the APC interval.[16] Slopes were considered increasing or decreasing if the estimated slope differed significantly from zero.[1,17] The statistical significance was set at 0.05.

Results

Between 1999 and 2018, cancer was the more prevalent cause of premature death in women than heart disease (*Table 1*). A total of 741 397 heart disease-related, and 1 628 641 cancer-related premature deaths occurred in women (2 628 383 388 person-years), corresponding to AAMRs of 24.0 (95% CI 23.9–24.1) per 100 000 and 52.6 (52.5–52.7) per 100 000, respectively. Ischaemic heart disease was the most prevalent cause of heart disease mortality (*Figure 1A*), whereas respiratory tract/lung cancer was the leading cause of cancer-related mortality (*Figure 1B*). Irrespective of aetiology, more premature deaths occurred in South and rural areas; the age-specific mortality rates increased exponentially with age, and NH Black women had higher AAMRs than other ethnicities/races.

Comparative trends between cancer and heart disease

Age-adjusted years of potential life lost

Age-adjusted YPLL from cancer and heart disease were 699.2 years per 100 000 and 321.8 years per 100 000, respectively. Overall, age-adjusted YPLL were higher for NH Blacks compared with other race/ethnicities (*Figure 2*). During the study period, the age-adjusted YPLL decreased due to cancer- (753.4 years per 100 000 to 553.4 years per 100 000) and heart disease- (345.8 years per 100 000 to 286.5 years per 100 000) mortality (*Figure 3A*). The APC in age-adjusted YPLLs due to heart disease mortality decreased between 1999 and 2011 [-1.68 (-2.00 to -1.36)], followed by a stagnation in the subsequent years [0.38 (-0.31 to 1.08)]—owing to an increase in NH White [0.83 (0.30–1.37); 2010–18] and stalling across all other ethnicities/races (Supplementary material online, *Table S2*). The APC in age-adjusted YPLL due to cancer mortality consistently declined between 1999 and 2008 [-1.87 (-2.08 to -1.67)], and 2008 and 2018 [-1.39 (-1.56 to -1.21)]. The APC in age-adjusted YPLL due to cancer

Table 1. Mortality data in women (<65 years) due to heart disease and cancer between 1999 and 2018 in the USA

		Heart Disease		Cancer	
	Person-years	No. of deaths	Mortality rate (95% CI) per 100 000	No. of deaths	Mortality rate (95% CI) per 100 000
Overall	2 628 383 388	741 397	24.0 (23.9–24.1)	1 628 641	52.6 (52.5–52.7)
Age					
<25	1 008 889 670	13 895	1.4 (1.3–1.5)	25 229	2.5 (2.4–2.6)
25–34	410 724 778	21 622	5.3 (5.2–5.4)	37 985	9.2 (9.1–9.3)
35–44	425 750 347	71 255	16.7 (16.6–16.9)	149,402	35.1 (34.9–35.3)
45–54	429 924 668	206 060	47.9 (47.7–48.1)	471 400	109.6 (109.3–110.0)
55–64	353 093 925	428 565	121.4 (121.0–121.7)	944 625	267.5 (267.0–268.1)
Race					
NH White	1 657 917 914	482 563	21.9 (21.8–22.0)	1 184 831	53.5 (53.4–53.6)
NH Black	363 648 655	191 476	51.9 (51.7–52.1)	259 675	70.3 (70.0–70.5)
NH AI/AN	23 505 402	678	28.0 (27.3–28.7)	10 250	43.3 (42.5–44.1)
NH Asian/Pacific Islander	145 833 061	12 355	7.9 (7.8–8.1)	50 524	32.5 (32.3–32.8)
Hispanic	437 478 356	45 733	13.6 (13.4–13.7)	119 804	35.2 (35.0–35.4)
Region					
Northeast	473 292 254	116 121	19.7 (19.6–19.9)	301 437	51.4 (51.2–51.6)
Midwest	570 069 990	166 398	24.7 (24.5–24.8)	370 046	54.5 (54.3–54.7)
South	973 621 359	337 449	29.7 (29.6–29.8)	634 766	55.6 (55.4–55.7)
West	611 399 785	121 429	17.5 (17.4–17.6)	322 392	46.8 (46.6–47.0)
2013 county-level urbanization					
Urban					
Large central metro	822 891 821	220 173	24.2 (24.0–24.3)	466 976	51.4 (51.3–51.6)
Large fringe metro	650 177 725	148 284	18.9 (18.8–19.0)	389 093	49.6 (49.4–49.7)
Medium metro	543 081 840	152 962	24.0 (23.9–24.2)	337 568	52.8 (52.6–53.0)
Small metro	237 025 101	73 788	26.4 (26.2–26.5)	154 199	54.6 (54.3–54.9)
Rural					
Micropolitan (non-metro)	222 695 247	80 677	29.5 (29.3–29.7)	159 051	57.5 (57.2–57.8)
Non-Core	152 511 654	65 513	32.9 (32.7–33.2)	121 754	60.2 (59.9–60.6)

Age-specific and age-adjusted premature mortality rates are reported.
AI/AN, American Indian/Alaskan Native.

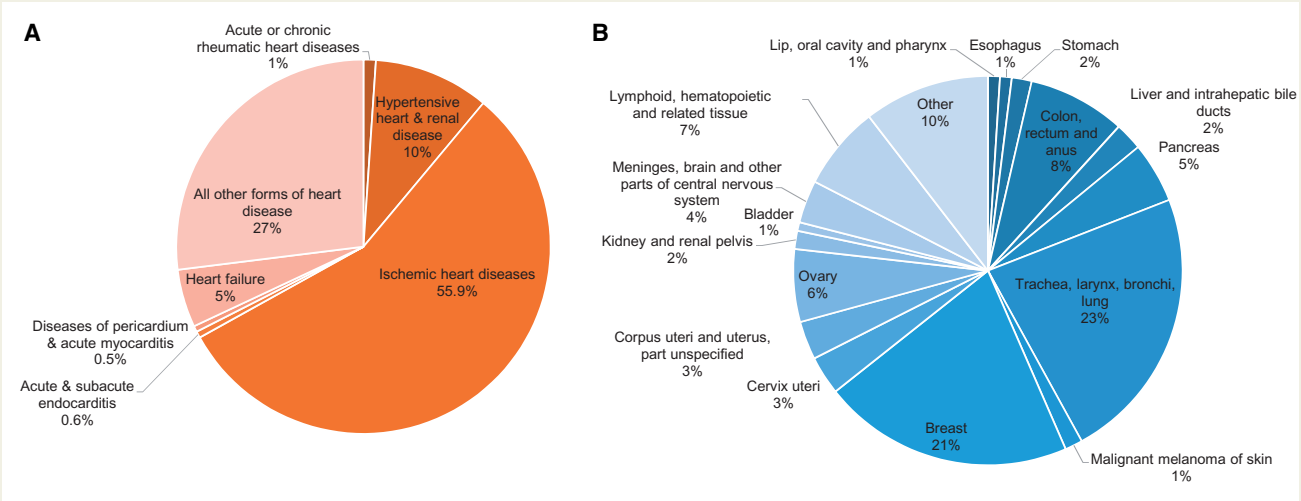

Figure 1. Components of (*A*) heart disease mortality, and (*B*) cancer mortality in women (<65 years) in the USA, 1999–2018.

mortality declined in NH Whites and NH Blacks but stalled for other ethnicities/races after joinpoints (Supplementary material online, *Table S3*).

Age-adjusted mortality rates

Between 1999 and 2018, the AAMRs decreased in both cancer [61.9 (61.5–62.4) per 100 000 to 45.6 (45.3–46.0) per 100 000] and heart disease [29.2 (28.9–29.5) per 100 000 to 22.6 (22.3–22.8) per 100 000; *Figure 3B*]. However, this decline was not consistently uniform for both diseases. While the APC in AAMR for cancer declined significantly throughout the period, the APC in AAMR for heart disease initially declined [-2.55 (-2.76 to -2.34)], and then increased between 2010 and 2018 [0.53 (0.18–0.89); Supplementary material online, *Tables S4* and *S5*).

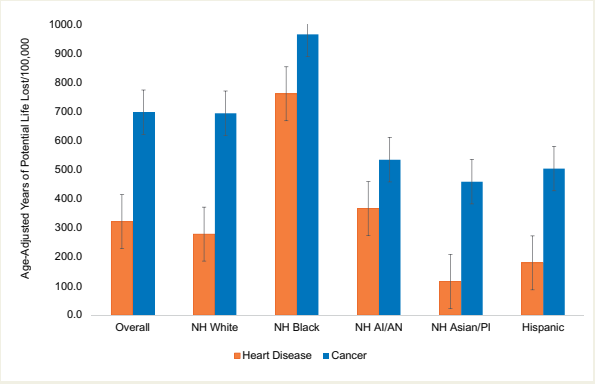

Figure 2. Age-adjusted years of potential life lost in women (<65 years) who died of cancer and heart disease in the USA, 1999–2018. Error bars represent standard errors across point estimates. NH, Non-Hispanic; AI/AN, American Indian/Alaskan Native; PI, Pacific Islander.

The APC in AAMR for heart disease increased in women aged 25–34 years [2.24 (0.30–4.22)] and 55–64 years [0.46 (0.13–0.80)] since 2013 and 2009, respectively (*Figure 4*). Whereas the APC in AAMR for cancer reduced/slowed down consistently across all age groups. With respect to ethnicity/race, the APC in AAMR for heart disease increased in NH Whites [0.79 (0.46–1.13); 2009–18], and NH AI/AN [2.71 (0.59–4.87); 2011–18), stalled in NH Black [0.27 (-0.50 to 1.04); 2011–18], and declined in Hispanic [-0.78 (-1.41 to -0.14); 2010–18) women (*Figure 5*). The APC in AAMR for cancer declined in all ethnicities/races but slowed in Hispanic women.

Regions

In contrast with cancer, the APC in AAMR for heart disease either increased in Midwest [0.59 (0.28–0.89); 2009–18) or became stagnant during the second half of the study in all other regions (Supplementary material online, *Table S6*). *Figure 6* illustrates the corresponding region-wise YPLL for both cancer and heart disease mortality. The APC in AAMR for heart disease increased in medium/small metros and rural areas since 2008 and 2009, respectively (Supplementary material online, *Table S7*). Conversely, the APC in AAMR for cancer demonstrated a consistent decline throughout urban and rural areas (Supplementary material online, *Table S8*).

Cancer and heart disease mortality gap

Between 1999 and 2018, the absolute mortality gap between cancer and heart disease has significantly decreased from 32.7 per 1000/year to 23.0 per 100 000/year (Supplementary material online, *Table S9*). The APC in the mortality gap was -1.40 (-1.67 to -1.14) between 1999 and 2012, and -3.10 (-3.94 to -2.25) between 2012 and 2018.

Discussion

This study utilizing over 19 years of US data showed that while cancer remains the more prevalent cause of premature death in women, premature heart disease mortality has increased since 2010. This national rise in heart disease mortality reflects accelerated mortality in

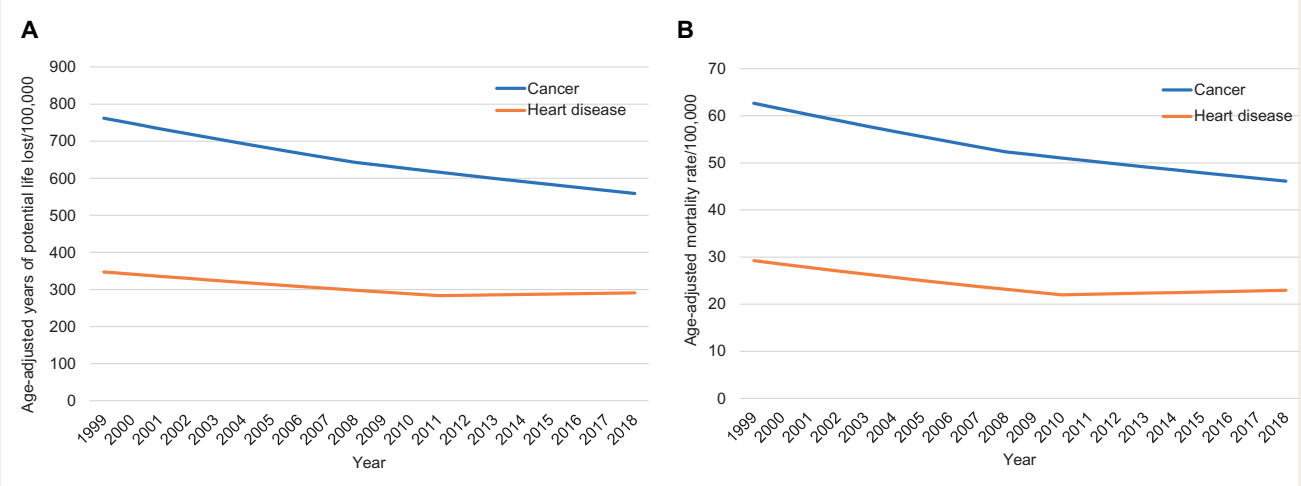

Figure 3. Trends of age-adjusted years of potential life lost (*A*) and age-adjusted mortality rates (*B*) in women (<65 years) due to heart disease and cancer in the USA, 1999–2018.

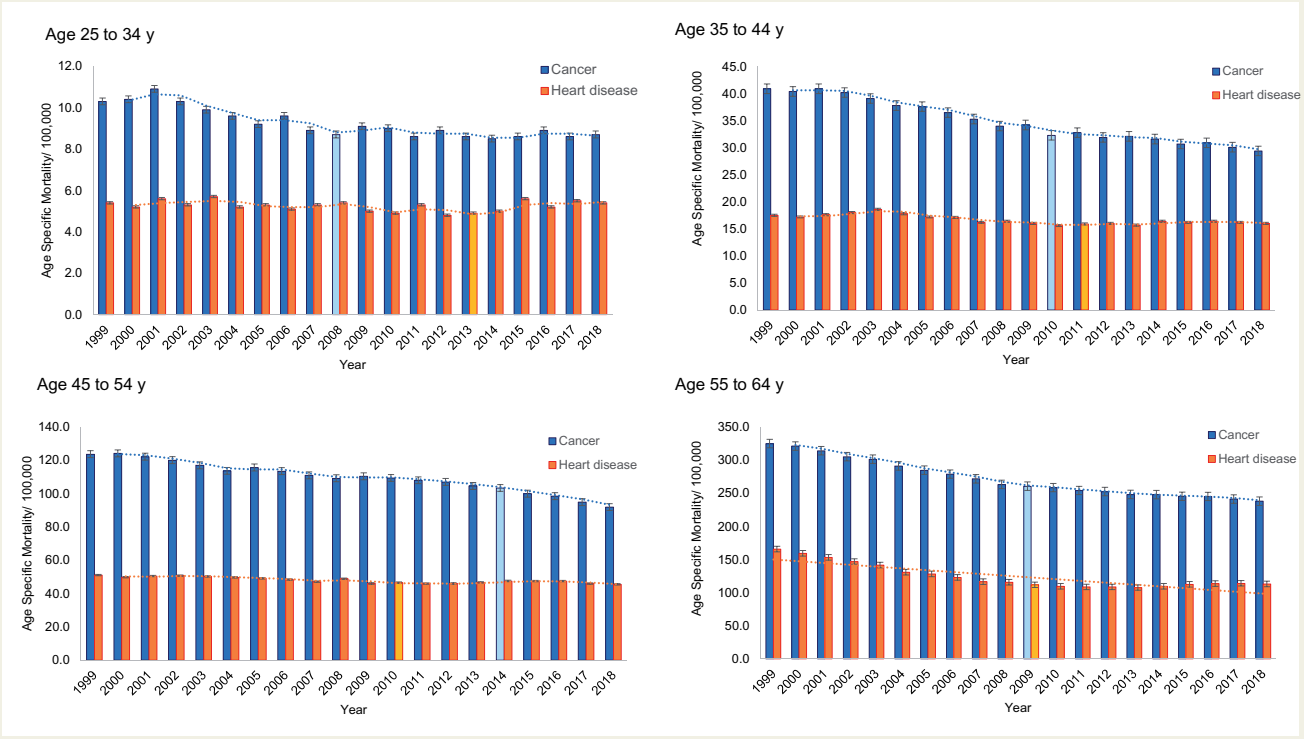

Figure 4. Age-specific mortality rates in women (25–64 years) due to heart disease and cancer in the USA, 1999–2018. Dashed lines represent trends. Error bars represented standard errors. Yellow bars represent inflection year in heart disease mortality; light blue bars represent inflection year in cancer mortality.

Midwest, medium/small metros, and rural areas. Demographically, the upsurge in heart disease mortality was noted in women aged 25–34 years and 55–64 years, NH Whites and NH AI/AN compared with women who died of cancer. Consequently, the mortality gap between cancer and heart disease is narrowing at an accelerated rate since 2012.

A 2019 AHA National Survey reported that awareness among women considering heart disease as the leading cause of death has declined from 65% in 2009 to 44% in 2019.[18] The awareness decline was consistent across all ethnicities/races and ages except women ≥65 years. Women aged 25–34 years and ethnic/racial minorities (NH Blacks and Hispanic women) faced the most significant decline in awareness. Interestingly, the odds of women identifying breast cancer as the leading cause of death had increased almost three-fold in 2019 from 2009, with a stronger association observed in young women. Moreover, awareness about symptoms of heart disease has declined in women as well. A previous report showed a consistent decline in cancer mortality between 2000 and 2014 and a deceleration in heart disease mortality decline between 2011 and 2014; however, women-focused analyses were not performed.[6] Moreover, premature mortality in the USA is higher than comparable Organisation for Economic Co-operation and Development (OECD) countries (4721 vs. 2723 YPLLs per 100 000 in 2015).[19] Another report showed that in 2016, premature mortality in women due to cancer and ischaemic heart disease was 47% and 5.1%, respectively, in European countries.[20] In comparison, a lesser proportion of women (30%) died due to cancer, and a higher proportion of women died due to ischaemic heart disease (7%) in 2016 in the USA. In this context, we examined the most contemporary nationwide mortality data attributed to heart disease and cancer in women aged <65 years—stratified by age, ethnicity/race, and geographic subgroups to investigate patterns of disparities in vulnerable populations.

Cancer-related death rates have decreased since the early 1990s secondary to multi-layer efforts focusing on promoting healthy behaviours and screening/vaccination strategies for early detection, prevention, and treatment.[21,22] Since nearly one-third of all cancers and one-fourth of heart diseases are attributable to smoking, the decline in smoking from 25.5% in 1999 to 16.8% in 2014 likely contributed significantly to these trends in a reduction in premature deaths for both diseases.[23–25] However, there is an emerging rise in the use of e-cigarettes and combustible cigarettes, with higher odds of adverse cardiovascular outcomes among young adults.[26–28] Moreover, shifting trends in modifiable cardiovascular risk factors affecting young adults have influenced heart disease mortality.[2,17] About 56 million US adults aged 18–64 have uncontrolled hypertension per the 2017 guideline criteria, and hypertension control has plateaued during the past decade.[29–31] During 2013–14, only 50% of eligible US adults aged 35–64 were taking statins,[32] with eligible women even less likely to be treated.[33] Additionally, an increasing prevalence of obesity is found among US adults aged 20–74.[34,35] Growing rates of chronic kidney disease, low diet quality, and physical inactivity were also on

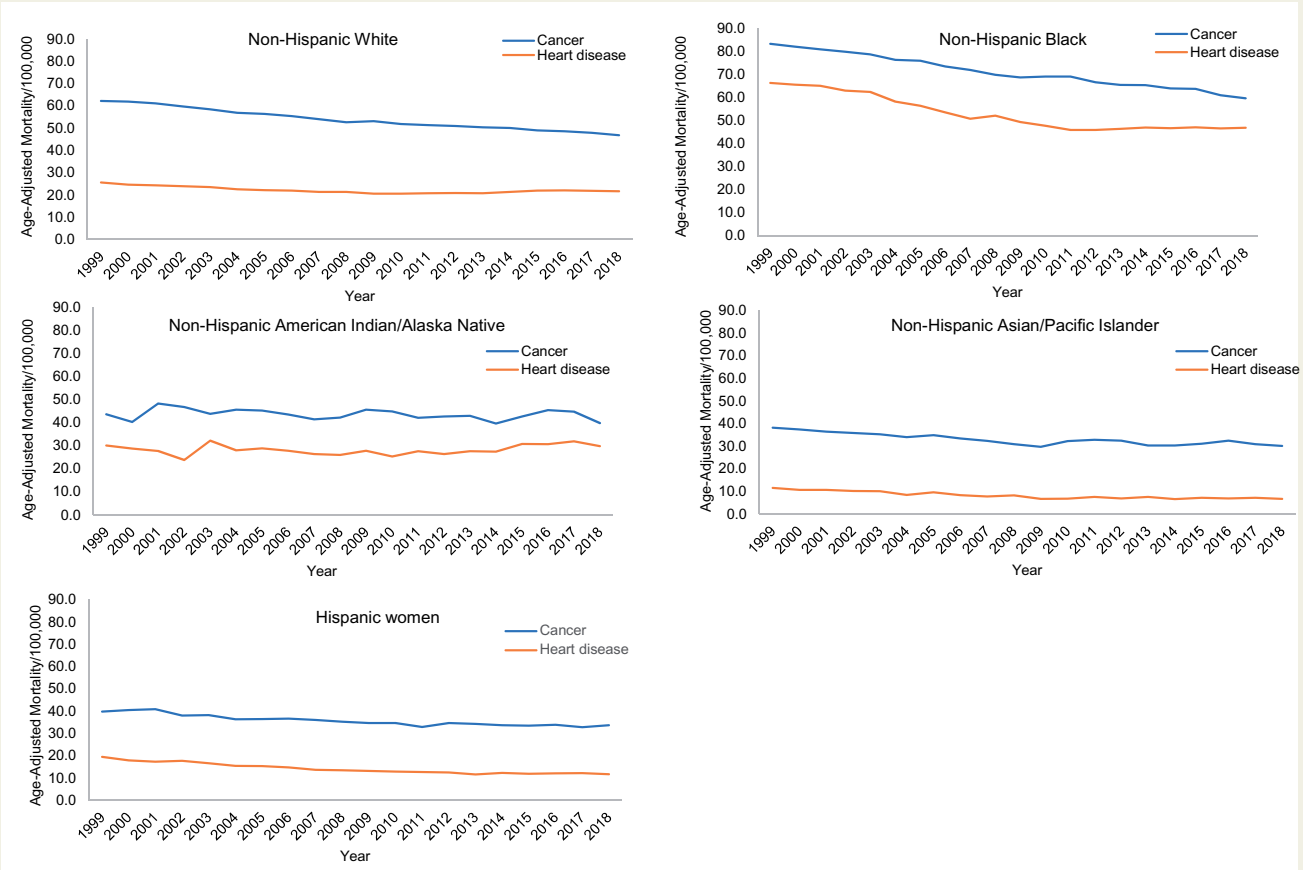

Figure 5. Trends of age-adjusted mortality rates in women stratified by ethnicities/race due to heart disease and cancer in the USA, 1999–2018.

the rise among young adults.[32,36] These factors combined have resulted in a tapering of the premature mortality gap between cancer and heart disease. A recent CDC report on middle-aged adults aged 45–64 years showed similar dynamic mortality patterns between cancer and heart disease through 2017.[4] We now show that these patterns have extended in women, even in the younger age groups.

The following is a summary of potential explanations for the rise in premature heart disease mortality in women during the last decade. Ischaemic heart disease (IHD) and heart failure (HF) are significant causes of heart disease mortality, and both entities disproportionally contribute to mortality in women.[11] A larger number of women with IHD remain underdiagnosed and are more likely to have missed or delayed management due to atypical presentation for acute myocardial infarction (AMI) compared with men.[2,11,37] Between 1995 and 2014, younger women (<55 years) had a higher proportion of hospitalization rates for AMI compared with men.[2] This trend was in conjunction with a higher comorbidity burden among younger women vs. younger men.[2] Similarly, women had a higher proportion of HF episodes than men,[2,7,11] most likely owing to higher prevalence of HF with preserved ejection fraction (for which no therapies have yet altered outcomes or mortality),[38] or suboptimal treatment of HF.[37,39] Younger adults (25–44 years) showed a significant increase in APC in AAMRs of HF between 1999 and 2018, which was consistent for both sexes. The racial disparities among women further influence cardiovascular outcomes.[37] For instance, Black women with HF had higher AAMRs than White women,[15] which were more pronounced among women <65 years.[40] Between 2011 and 2018, HF mortality increased at an annual rate of 5.8% in Black women compared with 3.9% in White women.[15] Another critical component of premature heart disease mortality is a rise in infective endocarditis owing to the drug abuse epidemic among younger adults.[1,17,41] A nationwide analysis showed younger women (15–34 years) were more likely to be hospitalized (53%) with drug-use-related infective endocarditis than men.[41] Rates of infective endocarditis mortality increased in women aged 25–44 years between 2010 and 2018.[17]

Cardiovascular risk burden has accumulated in women vs. men over time.[10] Compared with men, young women admitted with AMI were more likely to have hypertension, diabetes, chronic kidney insufficiency, and prior cerebrovascular events in a US-based community surveillance study.[2] The obesity epidemic has affected women more than men, and diabetes in middle-aged women increases their risk of IHD by five-fold compared to men and women without diabetes.[42,43] Furthermore, systolic hypertension, diabetes, smoking, and obesity had higher hazards for AMI in women than men.[2,11,44] In concordance, data suggest that women were less likely to receive evidence-based cardiovascular therapy compared with men.[2,45,46]

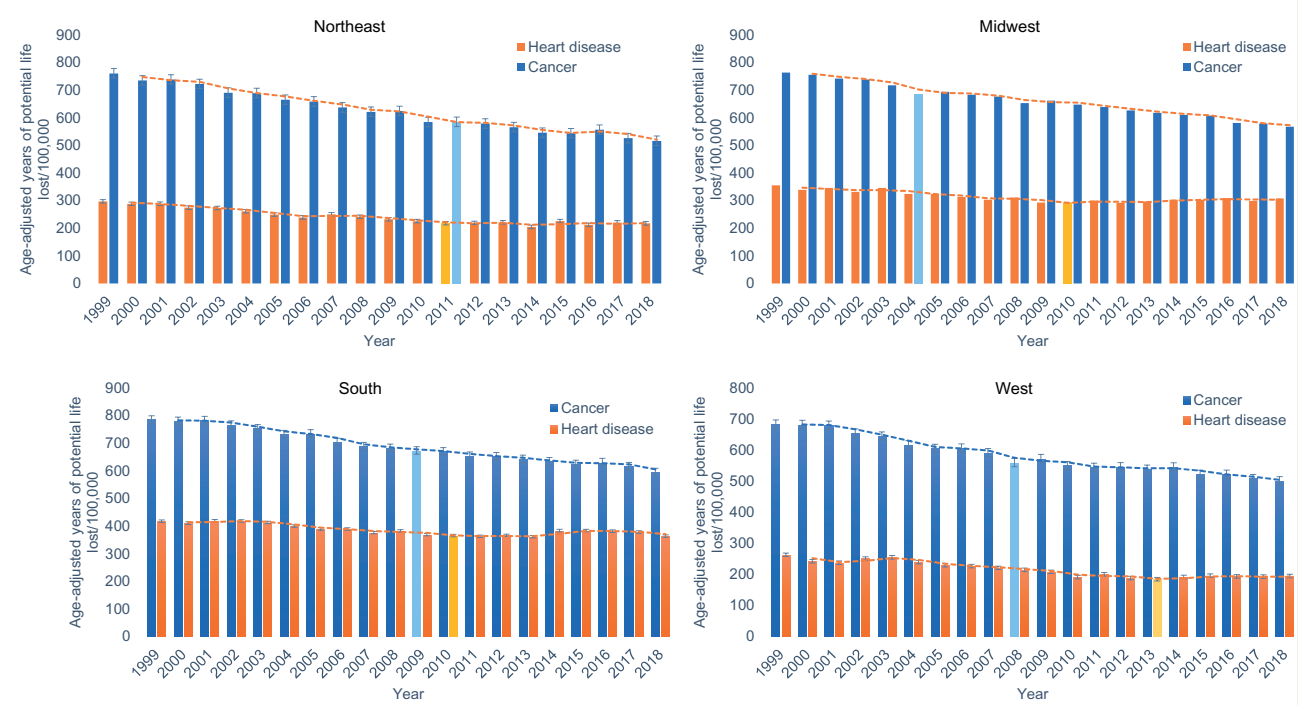

Figure 6. Age-adjusted years of potential life lost stratified by regions in the USA, 1999 and 2018. Dashed lines represent trends. Error bars represented standard errors. Yellow bars represent inflection year in heart disease mortality; light blue bars represent inflection year in cancer mortality.

Under-enrollment of women in cardiovascular clinical trials can contribute to sex-based disparities.[47] For example, in a systematic review of lipid-lowering therapy trials, only 28.5% of participants were women.[47] Compared with men, younger women with AMI had a lesser likelihood of receiving invasive or medical treatments.[2,45,46] Women with atherosclerotic cardiovascular disease were less likely to receive aspirin or statins.[48] In a recent meta-analysis of 43 studies (28% women), 41% of women with high risk or established cardiovascular disease were prescribed aspirin by primary care physicians vs. 56% of men and were less likely to receive angiotensin-converting enzyme inhibitors.[49]

Finally, gender bias in recognizing and managing heart disease has been shown to influence survival in women.[50] A study of patients with AMI admitted to Florida hospital between 1991 and 2010 showed higher mortality among women treated by male physicians, and male physicians achieved better outcomes for women patients when they worked with female colleagues.[50] Fewer women are listed for or received heart transplantation than men, highlighting a potential referral bias.[11,51]

While the reduction in cancer mortality occurred at a slower rate in rural areas than urban areas, the upsurge in mortality was limited to heart disease in women. About 20% of the US population residing in the rural communities,[52] experience upstream disparity in the prevalence of cardiovascular risk factors compared with urban areas.[53,54] Women living in the rural USA experienced an increase in premature coronary artery disease (CAD) mortality in contrast to their counterparts in metropolitan areas which have seen a continued reduction in premature CAD mortality.[52] Our findings are consistent with general trends showing a widening urban-rural gap in mortality, driven by combinations of economic challenges (such as witnessed in industrial Midwest), a higher burden of cardiovascular risk factors, change in demographic profile, and limited access to health care.[1,13] The rise in premature heart disease mortality among NH AI/AN women, who historically face socioeconomic disadvantages, also reflects the influence of suboptimal education, low levels of income, higher levels of unemployment, etc. on the heart health of these demographic groups.[55,56] Understanding and addressing these social determinants will have significant implications in allocating healthcare resources and prevention programs in medically and economically underserved populations.

This study has several limitations. Vital statistics and census population data rely on death certificates, which are subject to miscoding[57] and misclassification.[1] We did not examine the trends in subtypes of heart disease or cancer. That said, the heterogeneities in the burden of heart disease mortality by subtypes have been reported recently and would not have added significant additional information in the current analysis.[15] The data should not be interpreted as the clinical progression of heart disease or cancer.[15] Finally, a major limitation of this dataset is that we lacked assessment on pertinent clinical and socioeconomic risk factors and treatment modalities that could influence mortality.

Conclusion

This report suggests that the mortality gap between cancer and heart disease is tapering among US women <65 years. AHA's Strategic

Impact Goal and Million Hearts Initiative have prioritized taking action to address modifiable cardiac risk factors among younger adults.[32,58] If extreme public health measures are not taken to mitigate cardiovascular risk factors, focusing on high-risk groups, heart disease mortality may supersede cancer to become the leading cause of death in young women.

Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

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Data availability

The data underlying this article are available in the Centers for Disease Control and Prevention Wide- Ranging OnLine Data for Epidemiologic Research (WONDER) database (https://wonder.cdc.gov/ucd-icd10.html).

Conflict of interest: none declared.

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