



Trends in cancer mortality among people with vs without diabetes in the USA, 1988–2015

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Abstract

Aims/hypothesis Cancer-related death is higher among people with vs without diabetes. However, it is not known if this excess risk has changed over time or what types of cancer may be driving these changes.

Methods To estimate rates of site-specific cancer mortality in adults with vs without self-reported diagnosed diabetes, we used data from adults aged ≥ 18 years at the time of the interview who participated in the 1985–2012 National Health Interview Survey. Participants' data were linked to the National Death Index by the National Center for Health Statistics to determine vital status and cause of death through to the end of 2015. Cancer deaths were classified according to underlying cause of death. Death rates for five time periods (1988–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2015) were estimated using discrete Poisson regression models adjusted for age, sex and race/ethnicity with p for linear trend reported (p_{trend}). Site-specific cancer mortality rates were stratified by diabetes status and period, and total cancer mortality rates were additionally stratified by sex, race/ethnicity, education and BMI status.

Results Among adults with diabetes, age-adjusted cancer mortality rates (per 10,000 person-years) declined 25.5% from 39.1 (95% CI 30.1, 50.8) in 1988–1994 to 29.7 (26.6, 33.1) in 2010–2015, $p_{\text{trend}} < 0.001$. Among adults without diabetes, rates declined 25.2% from 30.9 (28.6, 33.4) in 1988–1994 to 23.2 (22.1, 24.2) in 2010–2015, $p_{\text{trend}} < 0.01$. Adults with diabetes remained approximately 30% more likely to die from cancer than people without diabetes, and this excess risk did not improve over time. In adults with diabetes, cancer mortality rates did not decline in some population subgroups (including black people, people with lower levels of education and obese people), and the excess risk increased for obese adults with vs without diabetes. Declines in total cancer mortality rates in adults with diabetes appear to be driven by large relative declines in cancers of the pancreas (55%) and breast (65%), while for lung cancer, declines are modest (7%).

Conclusions/interpretation Declines in cancer mortality rates were observed in adults with and without diabetes. However, adults with diabetes continue to be more likely to die from cancer than people without diabetes. This study highlights the continued need for greater cancer risk-factor mitigation, especially in adults with diabetes.

Keywords Cancer · Diabetes · Epidemiology · Mortality · Trends

Abbreviations

NCHS National Center for Health Statistics
NDI National Death Index
NHIS National Health Interview Survey

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Introduction

Diabetes is associated with an approximately 75% increase in mortality risk in the US population and the typical adult diagnosed with diabetes at age 60 loses 5 years of their life to the disease [1, 2]. Cardiovascular diseases have historically accounted for the largest number of those deaths. However,

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Research in context

What is already known about this subject?

- It is well known that people with diabetes have an increased risk for death from several cancer types, compared with people without diabetes
- It is not known if this excess risk has changed over time or what types of cancer may be driving these changes

What is the key question?

- Has the excess risk of site-specific cancer mortality in people with vs without diabetes changed in the USA between 1988 and 2015?

What are the new findings?

- Between 1988 and 2015, adults both with and without diabetes experienced a decline in cancer mortality rates. However, during the 2010–2015 time period, adults with diabetes remained approximately 30% more likely to die from cancer than people without diabetes, and this excess risk did not improve over time
- Cancer mortality rates did not decline in some of the population subgroups of people with diabetes (including black people, people with lower levels of education and obese people), and the excess risk increased for obese adults with vs without diabetes
- Declines in total cancer mortality rates in adults with diabetes appear to be driven by large relative declines in cancers of the pancreas and breast, while for lung cancer declines are modest

How might this impact on clinical practice in the foreseeable future?

- This study highlights the continued need for greater cancer risk-factor mitigation in adults with diabetes to prevent premature death from cancer

some population studies have suggested there may be shifts underway in the epidemiology of diabetes-related complications and deaths [3, 4]. In the USA, rates of vascular disease mortality have declined more than other types of morbidities leading to a change in proportional mortality [5].

Rates of cancer-related deaths among the diabetic population could be affected by a decreasing competing risk of deaths from vascular disease. However, diabetes has been independently associated with the incidence of several types of cancer, particularly of the liver, breast, endometrium, pancreas, colon and kidney [6], as well as with cancer-related mortality [7, 8]. In addition, insulin treatment and oral glucose-lowering medications have been associated with increased cancer risk, although the causal association of this connection remains unclear [9, 10].

Despite the growing awareness and apparent complexity of the association of diabetes with cancer, no nationally representative studies in the USA have examined trends in cancer-related mortality rates among adults with diabetes. Therefore, to address this knowledge gap, we used nationally representative data from the USA to estimate trends in mortality rates of common cancer types among adults with and without self-reported diagnosed diabetes between 1988 and 2015.

Methods

Data sources Data came from the 1985–2012 National Health Interview Surveys (NHIS) data linked to the National Death

Index (NDI) by the National Center for Health Statistics (NCHS) data linkage program [11]. The NHIS is a nationally representative household survey of the civilian non-institutionalised US population. The NHIS sample is drawn from each state and the District of Columbia using a multi-stage probability design to select an average of 35,000 households containing approximately 87,500 persons per year [12]. NHIS data are used to monitor the health of the nation, the prevalence and incidence of disease, the extent of disability and the use of healthcare services. Self-reported data on diagnosed diabetes status, age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), education (below high school, high school, above high school), family income (defined as income poverty ratio <2.0 [low income], 2.0–4.9 [moderate income], ≥5.0 [high income]), smoking (current smoker/not current smoker), insulin use (yes/no), and BMI (normal [<25 kg/m²], overweight [25–29.9 kg/m²], and obese [>30 kg/m²]) among adults aged 18 and over were used for this analysis.

Vital status and cause of death was ascertained through to the end of 2015 via linkage of the NHIS data to the NDI. Cancer deaths were classified according to underlying cause of death using International Classification of Diseases (ICD-9 [www.icd9data.com/2007/Volume1] for deaths prior to 1999, and ICD-10 [http://apps.who.int/classifications/icd10/browse/2016/en] for deaths occurring from 1999 onwards) (electronic supplementary material [ESM] Table 1).

Statistical analyses To determine whether changes in cancer mortality rates over time differed in diabetes vs non-diabetes populations, we used weighted discrete Poisson regression to predict average marginal death rates according to baseline diabetes status and time period of follow-up (1988–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2015). Because cohorts for each annual survey overlap during their follow-up time, we divided the continuous time-to-event survival data into discrete follow-up years. To reduce potential selection bias as a result of people with acute and life-threatening illness being less likely to be interviewed at baseline, we excluded all follow-up time of participants up to the end of the 2nd year of follow-up [5, 13]. We further limited the follow-up period to less than 10 years to reduce misclassification of respondents owing to incident diabetes during the follow-up period. We examined the effect of the time period exclusions with a sensitivity analysis which demonstrated that predicted mortality rates were substantially lower with the exclusions than without, which is consistent with the expected biases (see ESM Table 2).

Sample weights were adjusted for survey respondents who were excluded from analysis because of insufficient identifying data for NDI linkage [14]. In addition, weights in the discrete time-to-event data were calibrated to compensate for overlapping and ageing survey cohorts and to make the sample for each follow-up year nationally representative [15]. For results aggregated by time period, final weights were divided by the number of years in each time period [14].

Poisson regression models adjusted for time-varying age at follow-up, sex and race/ethnicity with robust variance estimation [15]. Hypothesis tests were conducted for differences by diabetes status, and for linear trends over time periods (p_{trend}). We included an interaction effect between diabetes status and time period in the estimated rates based on significant period-by-diabetes status interactions. Annual cancer mortality rates, by diabetes status, were also stratified by sex, race/ethnicity, education and BMI. Site-specific cancer mortality rates were stratified by diabetes only. We used a p value of <0.05 as an indication of statistical significance. We used SAS (version 9.4; https://www.sas.com/en_us/software/sas9.html; accessed 30 July 2019) and SUDAAN (<https://www.rti.org/impact/sudaan-statistical-software-analyzing-correlated-data>; accessed 30 July 2019) to account for the complex multistage sampling design and produce weighted estimates and contrasts, 95% CIs and total case estimates. RRs and their 95% CIs were computed manually using the delta method [16].

Ethics NHIS is approved by the Research Ethics Review Board of the National Center for Health Statistics and the US Office of Management and Budget. All NHIS respondents provided oral consent prior to participation.

Results

Between 1988–1991 and 2007–2012, the total number of adults with reported diagnosed diabetes increased from 6.3 million to 20 million US adults. Among adults with diabetes, the proportion of men, proportion of those who were obese, proportion of Hispanics, proportion with a history of cancer, and proportion with newly diagnosed diabetes (diagnosed within 1 year) increased across time periods (Table 1). In contrast, the proportion of non-Hispanic white people, smokers, insulin users and less than high school educated adults decreased across time periods, while the proportion of adults with low income decreased between 1988–1991 and 2002–2006, and then increased. Similar patterns across time periods in adults without diabetes were observed, however, compared with adults without diabetes, those with diabetes were more likely to be older and non-Hispanic black, and to be obese and have lower levels of education.

Among adults with diabetes, age-adjusted cancer mortality rates (per 10,000 person-years) declined 25.5% from 39.1 (95% CI 30.1, 50.8) in 1988–1994 to 29.7 (26.6, 33.1) in 2010–2015, $p_{\text{trend}} < 0.001$ (Table 2). Among adults without diabetes, cancer mortality rates similarly declined 25.2% from 30.9 (28.6, 33.4) in 1988–1994 to 23.2 (22.1, 24.2) in 2010–15, $p_{\text{trend}} < 0.001$. The RR of cancer mortality remained approximately 30% higher in people with vs without diabetes, and this excess risk did not change over time (from RR 1.3 [1.0, 1.7] in 1988–1994, to 1.3 [1.1, 1.4] in 2010–2015).

By subgroup, in the population with diabetes, total cancer mortality rates declined significantly among men, non-Hispanic white people, people educated to high school level, and overweight adults (Table 2). For all other subgroups, there were no statistically significant differences over time. Among the population without diabetes, statistically significant declines were noted among all subgroups, with the exception of Hispanic/other and non-Hispanic black adults, and adults with less than high school level education, where declines were noted, but linear trends were not significant. The RR between diabetic and non-diabetic populations remained similar over time in all subgroups, excluding adults who were obese, where it increased from 0.8 to 1.2, respectively (Table 2).

By cancer type, for adults with and without diabetes, declines in multivariate adjusted mortality rates were observed for cancers of the lung, colorectal region, pancreas, breast and ‘other’ (Table 3). Between 1988–1994 and 2010–2015, the greatest relative declines among adults with diabetes were observed for pancreas (55%) and breast (65%) cancers, $p_{\text{trend}} < 0.05$. The relative decline in lung cancer mortality rates was 27% for adults without diabetes, and a modest 7% decline for adults with diabetes. For melanoma, although similar relative declines were noted in both adults with and without diabetes, the decline was significant only for adults without

Table 1 Characteristics of the US adult (≥ 18 years) population participating in the 1985–2012 NHIS with and without diabetes, by survey year cohorts

Variable	Diabetes					No diabetes				
	1985–1991	1992–1996	1997–2001	2002–2006	2007–2012	1985–1991	1992–1996	1997–2001	2002–2006	2007–2012
Survey year										
<i>n</i> (unweighted)	3387	2653	9793	10,991	16,055	84,633	57,170	146,491	127,961	147,846
<i>n</i> (weighted, in millions)	6.3	7.6	11.3	15.4	20.0	167.2	176.7	188.0	198.8	208.4
Age, years										
Mean	60.4 (59.8, 61.1)	60.8 (60.1, 61.4)	59.9 (59.5, 60.3)	59.9 (59.5, 60.3)	60.5 (60.2, 60.8)	43.5 (43.2, 43.8)	44.2 (44.0, 44.4)	44.5 (44.3, 44.7)	44.9 (44.7, 45.1)	45.4 (45.2, 45.7)
18–44	17.0 (15.5, 18.6)	16.5 (14.9, 18.2)	16.6 (15.7, 17.6)	15.8 (15.0, 16.7)	13.9 (13.2, 14.7)	59.7 (59.0, 60.3)	58.3 (57.7, 59.0)	56.6 (56.2, 57.1)	54.1 (53.6, 54.6)	51.8 (51.3, 52.3)
45–64	39.9 (38.0, 41.9)	39.7 (37.7, 41.7)	43.1 (41.9, 44.3)	45.5 (44.4, 46.7)	47.8 (46.8, 48.8)	25.1 (24.7, 25.5)	26.2 (25.7, 26.7)	28.6 (28.2, 28.9)	31.6 (31.2, 32.0)	33.4 (33.0, 33.8)
≥ 65	43.1 (41.2, 45.1)	43.8 (41.7, 46.0)	40.3 (39.0, 41.6)	38.6 (37.5, 39.8)	38.3 (37.3, 39.2)	15.2 (14.7, 15.7)	15.5 (15.0, 15.9)	14.8 (14.5, 15.1)	14.3 (14.0, 14.6)	14.8 (14.4, 15.2)
Men	45.0 (43.1, 46.8)	45.2 (43.2, 47.3)	47.7 (46.4, 49.0)	49.4 (48.3, 50.5)	49.6 (48.6, 50.6)	47.6 (47.3, 47.8)	47.9 (47.6, 48.2)	48.0 (47.7, 48.3)	48.0 (47.7, 48.3)	48.2 (47.8, 48.5)
Race/ethnicity										
White, non-Hispanic	73.9 (71.8, 76.0)	69.9 (67.7, 72.1)	68.4 (66.9, 69.8)	68.1 (66.9, 69.2)	64.3 (63.2, 65.4)	78.8 (77.7, 79.9)	75.8 (74.9, 76.7)	74.9 (74.3, 75.5)	72.2 (71.6, 72.7)	69.0 (68.3, 69.6)
Black, non-Hispanic	16.5 (14.7, 18.5)	17.4 (15.6, 19.2)	16.7 (15.4, 17.9)	15.7 (14.8, 16.7)	15.7 (14.8, 16.5)	10.6 (9.8, 11.5)	10.7 (10.1, 11.4)	10.9 (10.5, 11.4)	11.0 (10.6, 11.5)	11.5 (11.0, 11.9)
Hispanic	7.4 (6.0, 8.9)	8.9 (7.6, 10.4)	11.6 (10.7, 12.5)	11.9 (11.1, 12.7)	14.3 (13.5, 15.1)	7.7 (7.0, 8.4)	9.1 (8.5, 9.7)	10.2 (9.8, 10.7)	12.4 (12.0, 12.8)	13.9 (13.5, 14.4)
Other	2.2 (1.6, 3.1)	3.8 (2.9, 5.0)	3.4 (2.9, 4.0)	4.4 (3.8, 5.0)	5.7 (5.2, 6.3)	2.9 (2.4, 3.5)	4.3 (3.9, 4.9)	3.9 (3.7, 4.2)	4.4 (4.2, 4.7)	5.7 (5.4, 5.9)
Education groups										
Less than high school	43.9 (41.9, 45.9)	38.6 (36.4, 40.9)	33.0 (31.8, 34.1)	27.0 (26.0, 28.0)	24.3 (23.4, 25.3)	22.4 (21.7, 23.1)	19.8 (19.2, 20.3)	18.0 (17.6, 18.4)	16.7 (16.3, 17.1)	14.4 (14.1, 14.8)
High school	33.4 (31.8, 35.1)	35.3 (33.4, 37.3)	31.7 (30.6, 32.9)	31.5 (30.4, 32.6)	31.2 (30.2, 32.2)	38.7 (38.1, 39.3)	36.9 (36.4, 37.5)	29.9 (29.5, 30.4)	29.1 (28.7, 29.5)	26.9 (26.5, 27.3)
More than high school	22.6 (21.1, 24.2)	26.0 (24.0, 28.1)	35.3 (34.1, 36.6)	41.5 (40.3, 42.8)	44.5 (43.4, 45.5)	38.9 (38.0, 39.8)	43.3 (42.6, 44.0)	52.1 (51.5, 52.7)	54.2 (53.6, 54.8)	58.7 (58.1, 59.3)
Poverty income ratio										
<2.0 (low)	74.0 (72.2, 75.8)	74.7 (72.6, 76.7)	64.8 (63.6, 65.9)	64.5 (63.3, 65.6)	72.0 (71.0, 72.9)	81.8 (81.0, 82.6)	82.1 (81.4, 82.7)	71.6 (71.0, 72.1)	69.4 (68.9, 70.0)	76.4 (75.9, 76.9)
2.0–4.9 (moderate)	13.3 (12.0, 14.7)	13.4 (11.9, 15.0)	12.3 (11.5, 13.2)	11.2 (10.6, 11.9)	13.9 (13.2, 14.7)	9.5 (9.0, 10.1)	9.6 (9.1, 10.0)	8.7 (8.4, 9.1)	8.5 (8.2, 8.8)	11.7 (11.3, 12.1)
≥ 5.0 (high)	12.7 (11.3, 14.2)	11.9 (10.4, 13.5)	23.0 (21.9, 24.1)	24.3 (23.3, 25.4)	14.1 (13.4, 14.9)	8.7 (8.2, 9.3)	8.4 (7.9, 8.9)	19.7 (19.3, 20.2)	22.0 (21.5, 22.5)	11.8 (11.5, 12.2)
BMI (kg/m^2)										
Mean	27.9 (27.7, 28.1)	28.8 (28.5, 29.1)	30.1 (29.9, 30.2)	31.1 (30.9, 31.3)	31.7 (31.6, 31.9)	24.8 (24.7, 24.8)	25.4 (25.4, 25.5)	26.3 (26.3, 26.4)	26.8 (26.8, 26.8)	27.2 (27.2, 27.2)
<25 (normal)	32.8 (31.1, 34.6)	28.2 (26.4, 30.2)	21.7 (20.7, 22.8)	18.1 (17.2, 19.0)	16.0 (15.4, 16.7)	57.5 (57.0, 58.1)	52.2 (51.6, 52.7)	45.0 (44.6, 45.3)	41.8 (41.4, 42.2)	39.4 (39.0, 39.8)
25–29.9	37.7 (36.0, 39.5)	35.8 (33.9, 37.7)	34.3 (33.2, 35.5)	32.1 (31.0, 33.1)	30.9 (29.9, 31.9)	30.8 (30.4, 31.2)	33.0 (32.6, 33.5)	35.3 (35.0, 35.7)	35.6 (35.2, 35.9)	35.3 (35.0, 35.6)
(overweight)										
≥ 30 (obese)	29.4 (27.7, 31.2)	36.0 (34.1, 37.9)	43.9 (42.7, 45.2)	49.9 (48.7, 51.0)	53.0 (52.0, 54.1)	11.6 (11.3, 12.0)	14.8 (14.4, 15.2)	19.7 (19.4, 20.0)	22.7 (22.3, 23.0)	25.3 (24.9, 25.7)
Years since diabetes diagnosis										
<1	9.9 (8.8, 11.1)	10.0 (8.8, 11.3)	15.8 (15.0, 16.7)	16.4 (15.6, 17.3)	14.3 (13.6, 15.1)	NA	NA	NA	NA	NA
1–5	27.5 (25.9, 29.3)	28.4 (26.5, 30.4)	27.2 (26.3, 28.2)	27.6 (26.7, 28.7)	25.5 (24.7, 26.3)	NA	NA	NA	NA	NA
≥ 5	62.5 (60.5, 64.5)	61.6 (59.4, 63.8)	57.0 (55.9, 58.1)	55.9 (54.8, 57.0)	60.1 (59.2, 61.0)	NA	NA	NA	NA	NA
History of cancer ^a	NA	NA	12.7 (12.0, 13.5)	14.0 (13.3, 14.8)	14.9 (14.2, 15.7)	NA	NA	6.2 (6.1, 6.4)	6.6 (6.4, 6.7)	7.5 (7.3, 7.7)
Current smoker ^a	NA	NA	18.0 (17.0, 19.0)	16.3 (15.5, 17.2)	16.5 (15.7, 17.3)	NA	NA	24.2 (23.9, 24.6)	22.1 (21.8, 22.5)	20.0 (19.6, 20.4)
Insulin use (%) ^a	NA	NA	32.3 (31.2, 33.4)	27.6 (26.6, 28.7)	27.6 (26.7, 28.5)	NA	NA	NA	NA	NA

Characteristics are % and 95% CI unless otherwise specified

^a History of cancer, smoking status and insulin use were first asked in 1997

Note: Table 1 presents participants' characteristics by survey year, while Tables 2 and 3 present cancer mortality rates by follow-up year

NA, not applicable

Table 2 Age-adjusted mortality rates from all cancers (per 10,000 person-years, 95% CI), by period and diabetes status, stratified by sex, race/ethnicity, education level, poverty/income ratio and BMI status, USA 1988–2015

Period	1988–1994	1995–1999	2000–2004	2005–2009	2010–2015	<i>p</i> _{trend}
Total population						
Diabetes	39.1 (30.1, 50.8)	37.4 (30.2, 46.4)	38.3 (32.3, 45.4)	33.0 (29.4, 37.1)	29.7 (26.6, 33.1)	<0.001
No diabetes	30.9 (28.6, 33.4)	28.2 (26.4, 30.0)	27.4 (25.9, 28.9)	26.0 (24.8, 27.3)	23.2 (22.1, 24.3)	<0.001
Excess risk (vs no diabetes)	8.2 (−2.3, 18.7)	9.3 (1.1, 17.5)	10.9 (4.2, 17.6)	7.0 (3.0, 11.0)	6.5 (3.1, 9.9)	
RR (vs no diabetes)	1.3 (1.0, 1.7)	1.3 (1.1, 1.7)	1.4 (1.2, 1.7)	1.3 (1.1, 1.4)	1.3 (1.1, 1.4)	
Sex						
Men						
Diabetes	45.0 (31.9, 63.4)	38.6 (28.5, 52.2)	45.9 (36.3, 58.1)	35.8 (30.6, 41.9)	29.6 (25.4, 34.4)	0.007
No diabetes	35.3 (31.7, 39.4)	33.0 (30.3, 35.9)	32.9 (30.5, 35.6)	29.2 (27.4, 31.1)	25.3 (23.6, 27.0)	<0.001
Excess risk (vs no diabetes)	9.7 (−6.7, 26.0)	5.6 (−6.2, 17.4)	13.0 (1.8, 24.2)	6.6 (0.9, 12.3)	4.3 (−0.5, 9.1)	
RR (vs no diabetes)	1.3 (0.9, 1.8)	1.2 (0.9, 1.6)	1.4 (1.1, 1.8)	1.2 (1.0, 1.5)	1.2 (1.0, 1.4)	
Women						
Diabetes	34.3 (23.5, 49.9)	36.0 (26.9, 48.2)	28.2 (22.3, 35.7)	29.1 (24.4, 34.7)	28.3 (24.3, 33.1)	0.182
No diabetes	27.4 (24.3, 30.9)	24.0 (21.9, 26.3)	22.6 (20.9, 24.5)	23.1 (21.7, 24.6)	21.2 (19.8, 22.7)	<0.001
Excess risk (vs no diabetes)	6.9 (−6.1, 19.8)	12.0 (1.1, 23.0)	5.6 (−1.4, 12.6)	6.0 (0.7, 11.2)	7.2 (2.6, 11.7)	
RR (vs no diabetes)	1.3 (0.8, 1.9)	1.5 (1.1, 2.0)	1.2 (1.0, 1.6)	1.3 (1.0, 1.5)	1.3 (1.1, 1.6)	
Race/Ethnicity						
White, non-Hispanic						
Diabetes	46.9 (34.4, 63.8)	46.6 (36.9, 58.9)	43.5 (35.8, 52.9)	36.7 (31.8, 42.4)	35.9 (31.6, 40.8)	0.020
No diabetes	33.5 (30.8, 36.5)	31.5 (29.2, 33.8)	29.6 (27.8, 31.5)	28.7 (27.3, 30.2)	24.7 (23.4, 26.1)	<0.001
Excess risk (vs no diabetes)	13.3 (−1.6, 28.3)	15.2 (4.0, 26.3)	13.9 (5.3, 22.6)	8.0 (2.6, 13.5)	11.2 (6.4, 16.0)	
RR (vs no diabetes)	1.4 (1.0, 1.9)	1.5 (1.2, 1.9)	1.5 (1.2, 1.8)	1.3 (1.1, 1.5)	1.5 (1.3, 1.7)	
Black, non-Hispanic						
Diabetes	30.2 (16.1, 56.6)	20.7 (12.4, 34.7)	32.2 (22.5, 46.1)	33.0 (25.2, 43.2)	20.2 (15.7, 26.0)	0.472
No diabetes	29.7 (23.3, 38)	27.2 (22.7, 32.5)	30.3 (26, 35.3)	24.1 (20.7, 28.0)	24.1 (21.2, 27.5)	0.076
Excess risk (vs no diabetes)	0.5 (−19.4, 20.4)	−6.4 (−18.6, 5.7)	1.9 (−11.4, 15.3)	8.9 (−1.0, 18.8)	−4.0 (−10.0, 2.1)	
RR (vs no diabetes)	1.0 (0.5, 2.0)	0.8 (0.4, 1.3)	1.1 (0.7, 1.6)	1.4 (1.0, 1.9)	0.8 (0.6, 1.1)	
Hispanic/Other						
Diabetes	S	S	20.2 (11.6, 35.2)	17.1 (12.6, 23.2)	15.6 (11.8, 20.5)	0.562
No diabetes	S	S	15.3 (12.8, 18.4)	15.4 (13.4, 17.8)	15.4 (13.5, 17.6)	0.436
Excess risk (vs no diabetes)	S	S	4.9 (−6.8, 16.5)	1.6 (−3.8, 7.1)	0.1 (−4.5, 4.8)	
RR (vs no diabetes)	S	S	1.3 (0.7, 2.4)	1.1 (0.8, 1.6)	1.0 (0.7, 1.4)	
Education level						
Less than high school						
Diabetes	51.2 (36.1, 72.5)	57.3 (42.7, 76.9)	58.2 (45.7, 74.2)	51.5 (42.5, 62.3)	46.5 (38.2, 56.5)	0.406
No diabetes	51.8 (46.4, 57.8)	45.3 (41.1, 50.0)	46.3 (42.1, 51.1)	46.6 (42.9, 50.6)	44.0 (40.0, 48.3)	0.058
Excess risk (vs no diabetes)	−0.6 (−19.9, 18.7)	12.0 (−5.3, 29.4)	11.9 (−3.1, 26.8)	4.9 (−5.5, 15.2)	2.5 (−7.3, 12.3)	
RR (vs no diabetes)	1.0 (0.7, 1.4)	1.3 (0.9, 1.7)	1.3 (1.0, 1.6)	1.1 (0.9, 1.4)	1.1 (0.9, 1.3)	
High school						
Diabetes	49.1 (32.7, 73.8)	46.0 (32.0, 66.2)	41.8 (31.5, 55.5)	33.3 (26.7, 41.6)	27.5 (22.8, 33.3)	0.002
No diabetes	30.2 (26.4, 34.6)	28.5 (25.7, 31.7)	28.4 (25.9, 31.2)	27.4 (25.3, 29.6)	22.9 (20.9, 25.1)	<0.001
Excess risk (vs no diabetes)	18.9 (−1.5, 39.2)	17.5 (0.4, 34.5)	13.4 (1.2, 25.5)	5.9 (−1.8, 13.6)	4.6 (−1.0, 10.2)	
RR (vs no diabetes)	1.6 (1.1, 2.5)	1.6 (1.1, 2.4)	1.5 (1.1, 2.0)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	
More than high school						
Diabetes	29.7 (18.6, 47.3)	17.7 (10.5, 29.8)	25.8 (18.2, 36.3)	24.2 (19.7, 29.8)	23.4 (19.4, 28.1)	0.787
No diabetes	20.3 (17.3, 23.8)	20.1 (17.7, 23.0)	18.7 (16.9, 20.6)	17.4 (16.1, 18.8)	16.1 (15.0, 17.3)	<0.001
Excess risk (vs no diabetes)	9.4 (−4.8, 23.6)	−2.4 (−12.0, 7.1)	7.1 (−2.0, 16.2)	6.8 (1.7, 12.0)	7.2 (2.8, 11.7)	
RR (vs no diabetes)	1.5 (0.9, 2.4)	0.9 (0.5, 1.5)	1.4 (1.0, 2.0)	1.4 (1.1, 1.7)	1.5 (1.2, 1.8)	

Table 2 (continued)

Period	1988–1994	1995–1999	2000–2004	2005–2009	2010–2015	<i>p</i> _{trend}
BMI status						
<25 kg/m ² (normal)						
Diabetes	31.6 (21.5, 46.3)	41.5 (27.9, 61.7)	33.0 (23.2, 47.0)	34.0 (26.2, 44.1)	26.1 (20.1, 33.8)	0.272
No diabetes	29.2 (26.4, 32.4)	27.1 (24.9, 29.6)	26.0 (24.0, 28.2)	25.4 (23.7, 27.3)	22.0 (20.3, 23.8)	<0.001
Excess risk (vs no diabetes)	2.3 (−10.2, 14.9)	14.3 (−2.4, 31.1)	7.0 (−4.8, 18.8)	8.6 (−0.3, 17.6)	4.1 (−2.8, 11.0)	
RR (vs no diabetes)	1.1 (0.7, 1.6)	1.5 (1.0, 2.3)	1.3 (0.9, 1.8)	1.3 (1.0, 1.8)	1.2 (0.9, 1.6)	
25–29.9 kg/m ² (overweight)						
Diabetes	54.8 (36.5, 82.2)	36.3 (26.0, 50.7)	42.7 (33.2, 54.9)	33.3 (27.5, 40.3)	30.7 (25.4, 37.2)	0.011
No diabetes	32.6 (28.6, 37.2)	30.9 (27.8, 34.3)	29.1 (26.6, 32.0)	28.0 (25.9, 30.3)	24.6 (22.8, 26.6)	<0.001
Excess risk (vs no diabetes)	22.1 (−0.6, 44.8)	5.5 (−7.1, 18.1)	13.5 (2.3, 24.8)	5.2 (−1.4, 11.9)	6.1 (−0.1, 12.2)	
RR (vs no diabetes)	1.7 (1.1, 2.6)	1.2 (0.8, 1.7)	1.5 (1.1, 1.9)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	
≥30 kg/m ² (obesity)						
Diabetes	27.9 (16.7, 46.6)	31.4 (21.2, 46.7)	39.8 (30.0, 52.9)	32.6 (26.9, 39.6)	30.3 (25.9, 35.6)	0.814
No diabetes	34.3 (27.9, 42.2)	25.9 (21.9, 30.6)	28.5 (24.9, 32.8)	24.3 (21.9, 27.0)	24.6 (22.2, 27.2)	0.006
Excess risk (vs no diabetes)	−6.4 (−21.9, 9.0)	5.5 (−7.8, 18.8)	11.3 (−0.6, 23.2)	8.3 (1.7, 14.9)	5.7 (0.3, 11.2)	
RR (vs no diabetes)	0.8 (0.5, 1.4)	1.2 (0.8, 1.9)	1.4 (1.0, 1.9)	1.3 (1.1, 1.7)	1.2 (1.0, 1.5)	

S indicates suppressed cell (if $n < 10$)

Excess risk = rate (diabetes) − rate (no diabetes); RR = rate (diabetes) − rate (no diabetes)/rate (diabetes)

For unweighted counts of total cancer by subgroup, see ESM Table 3

diabetes, $p_{\text{trend}} < 0.001$ due to the larger sample size. The RR in adults with vs without diabetes decreased for pancreatic, breast and ‘all other’ cancers, but did not marginally change for cancers of the lung or colorectal region or for melanoma (Table 3).

Discussion

We report several key findings in the trends in site-specific cancer mortality rates among US adults with and without diabetes. First, declines in cancer mortality rates were observed in both adults with and without diabetes. However, during the 2010–2015 time period, adults with diabetes remain approximately 30% more likely to die from cancer than people without diabetes. Furthermore, this RR has not improved over time. Second, rates of cancer mortality showed no significant change in some population subgroups, and the RR between adults with obesity, with and without diabetes, increased. Third, declines in total cancer mortality rates in adults with diabetes appear to be driven by large relative declines in cancers of the pancreas and breast, while for lung cancer, declines are modest.

In general, adults with diabetes have a 20–80% increased risk for cancer-specific mortality, depending on the cancer site [7]. Positive associations have been shown between baseline diabetes and risk of mortality from cancers of the colon, liver, pancreas and bladder [2, 17, 18], while associations for prostate, breast, endometrial and lung cancers are inconsistent [2,

17, 18]. Some evidence also supports an association between diabetes and risk of all-cause mortality in individuals with cancer [19, 20], but the evidence for cancer-specific mortality is varied [20–23]. Few studies, however, have examined rates of cancer-specific mortality over time, and none have previously examined trends in rates of site-specific cancers in adults with and without diabetes.

In the USA, Gregg et al. [5] reported similar modest declines in rates of total cancer mortality in adults with and without diabetes between 1988 and 2015, but did not examine trends in rates of site-specific cancer mortality. They showed that, while the proportion of deaths as a result of vascular diseases in adults with diabetes declined significantly over time (from 47.8% to 34.1%), the proportion of deaths from cancer remained relatively stable, ranging from 15.9% to 19.9% [5]. In contrast, an Australian national diabetes registry reported an increase in the proportion of cancer deaths between 1997 and 2010, from 19% to 25% in women and from 25% to 34% in men with type 2 diabetes [24], but no change in age-standardised rates of cancer mortality [25]. However, when stratified by age group, declines in cancer mortality rates were noted in older age groups with type 2 diabetes, but a significant increase was observed among those aged <40 years [25]. Increases in rates of cancer mortality among young adults may be attributed to a rise in cancer incidence. In the USA, the risk of developing several obesity-related cancers has increased in younger adults with steeper increases observed in successively younger generations since the 1950s [26]. In the current study, a non-significant increase in rates

Table 3 Trends in multivariate adjusted^a cancer-specific mortality rates (deaths per 10,000 person-years, 95% CI), by period and diabetes status, USA 1988–2015

Site-specific cancer	1988–1994	1995–1999	2000–2004	2005–2009	2010–2015	Relative change (%) ^b	<i>p</i> _{trend}
All cancers							
Diabetes	38.8 (29.9, 50.4)	36.9 (29.8, 45.8)	37.1 (31.3, 44.0)	32.3 (28.7, 36.4)	28.9 (25.9, 32.2)	25.5	<0.001
No diabetes	31.0 (28.7, 33.5)	28.2 (26.5, 30.0)	27.5 (26.0, 29.1)	26.1 (24.9, 27.3)	23.2 (22.2, 24.4)	25.2	<0.001
Excess risk (vs no diabetes)	7.8 (6.7, 8.8)	8.7 (7.9, 9.5)	9.6 (9.0, 10.3)	6.2 (5.8, 6.6)	5.6 (5.3, 6.0)		
RR (vs no diabetes)	1.3 (1.0, 1.6)	1.3 (1.0, 1.6)	1.3 (1.1, 1.6)	1.2 (1.1, 1.4)	1.2 (1.1, 1.4)		
All cancers except prostate							
Diabetes	38.5 (29.6, 50.2)	34.5 (27.6, 43.1)	34.3 (28.8, 40.9)	31.5 (27.9, 35.5)	28.6 (25.6, 32.0)	25.7	<0.001
No diabetes	29.1 (26.9, 31.5)	26.4 (24.8, 28.2)	25.9 (24.4, 27.4)	24.6 (23.5, 25.8)	22.0 (21, 23.1)	24.4	<0.001
Excess risk (vs no diabetes)	9.4 (8.3, 10.4)	8.1 (7.3, 8.8)	8.4 (7.8, 9.1)	6.8 (6.5, 7.2)	6.5 (6.2, 6.9)		
RR (vs no diabetes)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.3 (1.1, 1.6)	1.3 (1.1, 1.5)	1.3 (1.2, 1.5)		
Lung							
Diabetes	8.5 (5.1, 14.2)	11 (7.3, 16.7)	11.2 (8.2, 15.4)	8.2 (6.4, 10.5)	7.9 (6.5, 9.6)	7.1	<0.001
No diabetes	8.9 (7.7, 10.4)	7.9 (7.0, 8.9)	7.6 (6.8, 8.4)	7.8 (7.1, 8.4)	6.5 (5.9, 7.2)	27.0	<0.001
Excess risk (vs no diabetes)	−0.5 (−0.9, 0.0)	3.1 (2.6, 3.6)	3.6 (3.3, 4.0)	0.5 (0.2, 0.7)	1.4 (1.2, 1.5)		
RR (vs no diabetes)	1.0 (0.6, 1.6)	1.4 (0.9, 2.1)	1.5 (1.1, 2.1)	1.1 (0.8, 1.4)	1.2 (1.0, 1.5)		
Colorectal							
Diabetes	3.7 (1.8, 7.7)	3.7 (2.1, 6.8)	5.0 (3.1, 8.2)	2.3 (1.5, 3.4)	2.0 (1.3, 3.0)	45.9	0.059
No diabetes	3.7 (2.9, 4.7)	2.9 (2.4, 3.4)	2.7 (2.3, 3.3)	2.2 (1.9, 2.6)	2.0 (1.7, 2.4)	45.9	<0.001
Excess risk (vs no diabetes)	0.1 (−0.2, 0.4)	0.9 (0.6, 1.1)	2.3 (2.0, 2.5)	0.0 (−0.1, 0.1)	0.0 (−0.1, 0.1)		
RR (vs no diabetes)	1.0 (0.5, 2.2)	1.3 (0.7, 2.4)	1.9 (1.1, 3.1)	1.0 (0.7, 1.7)	1.0 (0.6, 1.6)		
Pancreas							
Diabetes	4.9 (2.5, 9.5)	2.9 (1.4, 5.8)	1.5 (0.7, 3.5)	3.0 (2.0, 4.3)	2.2 (1.5, 3.2)	55.1	0.028
No diabetes	1.7 (1.2, 2.4)	1.5 (1.1, 2.0)	1.5 (1.2, 2.0)	1.5 (1.3, 1.8)	1.4 (1.2, 1.8)	17.6	<0.001
Excess risk (vs no diabetes)	3.2 (2.8, 3.5)	1.4 (1.2, 1.6)	0.0 (−0.1, 0.1)	1.5 (1.4, 1.6)	0.8 (0.7, 0.8)		
RR (vs no diabetes)	2.9 (1.3, 6.2)	1.9 (0.9, 4.0)	1.0 (0.4, 2.6)	2.0 (1.3, 3.0)	1.6 (1.0, 2.5)		
Melanoma							
Diabetes	5.5 (3.2, 9.5)	3.6 (2.0, 6.6)	2.1 (1.3, 3.5)	4.4 (3.2, 6.2)	4.2 (3.0, 6.0)	23.6	0.117
No diabetes	3.4 (2.8, 4.2)	3.4 (2.9, 4.0)	3.2 (2.7, 3.8)	3.0 (2.6, 3.4)	2.4 (2.1, 2.7)	29.4	<0.001
Excess risk (vs no diabetes)	2.1 (1.8, 2.4)	0.2 (0.0, 0.4)	−1.1 (−1.2, 1.0)	1.5 (1.3, 1.6)	1.8 (1.7, 2.0)		
RR (vs no diabetes)	1.6 (0.9, 2.9)	1.1 (0.6, 2.0)	0.7 (0.4, 1.1)	1.5 (1.0, 2.1)	1.8 (1.2, 2.6)		
Breast^c							
Diabetes	10.1 (4.8, 21.5)	4.4 (2.1, 8.9)	4.3 (2.3, 7.9)	4.4 (2.9, 6.6)	3.5 (2.5, 5.0)	65.3	0.047
No diabetes	4.4 (3.5, 5.6)	4.1 (3.4, 4.9)	3.5 (2.9, 4.2)	2.8 (2.4, 3.3)	3.1 (2.6, 3.7)	29.5	<0.001
Excess risk (vs no diabetes)	5.7 (4.9, 6.4)	0.3 (0.0, 0.6)	0.8 (0.5, 1.1)	1.6 (1.4, 1.8)	0.4 (0.3, 0.5)		
RR (vs no diabetes)	2.3 (1.0, 5.1)	1.1 (0.5, 2.2)	1.2 (0.7, 2.3)	1.6 (1.0, 2.4)	1.1 (0.8, 1.7)		
All other cancers							
Diabetes	6.1 (3.3, 11.3)	3.3 (1.7, 6.5)	4.0 (2.3, 6.7)	3.5 (2.5, 5.0)	3.4 (2.4, 4.7)	44.3	0.017
No diabetes	3.7 (2.9, 4.8)	3.3 (2.8, 4.0)	3.2 (2.8, 3.7)	3.4 (3.0, 3.8)	2.8 (2.5, 3.2)	24.3	<0.001
Excess risk (vs no diabetes)	2.4 (2.0, 2.8)	0.0 (−0.2, 0.3)	0.7 (0.5, 1.0)	0.1 (0.0, 0.3)	0.6 (0.5, 0.7)		
RR (vs no diabetes)	1.6 (0.8, 3.2)	1.0 (0.5, 2.0)	1.3 (0.7, 2.2)	1.0 (0.7, 1.5)	1.2 (0.8, 1.8)		

^a Adjusted for age at follow-up time, sex, race/ethnicity^b Relative change = rate (1988–1994) – rate (2010–2015)/rate (1988–1994) × 100^c Women only, adjusted for age at follow-up time, race/ethnicity

Excess risk = rate (diabetes) – rate (no diabetes); RR = rate (diabetes) – rate (no diabetes)/rate (diabetes)

For unweighted counts of site-specific cancers, see ESM Table 4

of cancer mortality was observed among adults who were both obese and had diabetes. Unfortunately, because of small numbers, we were unable to explore this trend by age group. However, given the high prevalence of both diabetes and obesity in the USA, and the increased number of years living with these conditions, there may be important implications for future cancer incidence and subsequent mortality, particularly among young adults [27].

Relative mortality reductions in total cancer, colorectal cancer and melanoma were similar in adults with and without diabetes. This finding may reflect population-wide reductions in exposure to risk factors such as smoking [28] and ultraviolet light [29], as well as the impact of national screening programmes [30] and therapeutic advances [31]. For pancreas and breast cancers, relative declines were greater for adults with than without diabetes. This may suggest more aggressive treatment among adults with diabetes, though this is, generally, not supported in the literature [32, 33]. Alternatively, use of diabetes medications, namely metformin, as well as the adoption of low fat diets may lead to reductions in cancer risk, though current evidence to support this is conflicting [34–37]. It may be more likely, for breast cancer, that adults with diabetes had a higher mortality rate from these cancers to begin with, and thus population-wide uptake of screening programmes may have caused greater absolute and relative reductions among adults with than without diabetes. In contrast, the relative reductions for lung cancer were considerably less for adults with than without diabetes. In the USA it has previously been reported that tobacco use between 1999 and 2010 declined in people without but not with diabetes [38]. It is therefore plausible that the smaller reduction in rates of lung cancer mortality may be due to a lack of decline in smoking rates in the diabetes population.

There are several mechanisms by which diabetes may increase the risk for cancer-specific mortality among people with cancer. There is considerable evidence that cancer patients with diabetes are treated less aggressively or receive modified anti-cancer treatment as compared with cancer patients without diabetes [20, 32, 33]. Studies also report that people with diabetes have a more advanced stage at cancer diagnosis [20, 33, 39], poorer response to treatment [40] and increased risk of treatment-related adverse effects [40–45] and short-term mortality [41, 45, 46] compared with cancer patients without diabetes. The current study is unable to differentiate the impact of diabetes on cancer incidence, vs treatment outcomes, on cancer-specific mortality.

This is the largest, nationally representative study to explore rates in site-specific cancer mortality rates over time in adults with vs without diabetes. Nonetheless, there are limitations to be considered. First, cause-of-death reporting is affected by medical opinion and subjective judgement that could

shift over time or by the transition from ICD-9 to ICD-10. However, in a US study, the overall sensitivity between death certificate data and cancer registry diagnoses was 82.8% and 85.0% for ICD-10 and ICD-9, respectively, with confirmation rates 95% or greater for more commonly diagnosed cancers (e.g. prostate, breast and lung) [47]. We are not aware of research about the comparability of ICD reporting by diabetes status nor of studies that have validated cause-of-death reporting against adjudicated medical records over time to determine whether reporting is changing.

Second, diabetes was self-reported and changes in diabetes definitions could have affected the population with diagnosed diabetes, leading to detection of diabetes at earlier stages and lower mortality rates. In the current study, we showed an increase in the proportion of adults with diabetes with less than 1 year of disease duration. However, other national data show that there has been no change in the average age at diagnosis nationally [48]. In addition, both the content and structure of the NHIS changed in 1997. As such, the way information pertaining to diabetes was collected changed before and after this time. For example, between 1980 and 1996, only a subsample of participants (one of every six) was asked ‘During the past 12 months, did you have diabetes?’ From 1997 onwards, all sampled adults were asked ‘Has a health professional ever told you that you have diabetes?’ Third, all types of diabetes are included in the current analysis with the assumption that the vast majority (~90–95%) have type 2 diabetes [49]. Fourth, the NHIS does not include undiagnosed diabetes or incident cases of diabetes post-baseline and thus misclassification may have occurred for a small number of participants. Fifth, small case numbers may have led to an increased risk of a type I statistical error for several tests of linear trends among subgroups of the population. Last, our analyses did not adjust for multiple comparisons, and some of the trends in specific cancer deaths over time are based on fairly large CIs and warrant replication and continued monitoring.

Conclusions In the USA, between 1988–1994 and 2010–2015, rates of cancer mortality declined but remained approximately 30% higher in adults with vs without diabetes. While declines in rates were noted across most subgroups of the population, adults who were both obese and had diabetes did not experience a decline in cancer mortality rates over time. In addition, relative declines were not consistent across site-specific cancers, with considerable reductions in cancers of the pancreas and breast among adults with diabetes, but modest declines for lung cancer. This study highlights the continued need for greater cancer risk-factor mitigation in adults with diabetes to prevent premature death from cancer.

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Data availability The data that support the findings of this study are available from the National Center for Health Statistics but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the National Center for Health Statistics.

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