

Original Contribution

All-Cause, Cardiovascular, and Cancer Mortality Rates in Postmenopausal White, Black, Hispanic, and Asian Women With and Without Diabetes in the United States

The Women's Health Initiative, 1993–2009

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Using data from the Women's Health Initiative (1993–2009; n = 158,833 participants, of whom 84.1% were white, 9.2% were black, 4.1% were Hispanic, and 2.6% were Asian), we compared all-cause, cardiovascular, and cancer mortality rates in white, black, Hispanic, and Asian postmenopausal women with and without diabetes. Cox proportional hazard models were used for the comparison from which hazard ratios and 95% confidence intervals were computed. Within each racial/ethnic subgroup, women with diabetes had an approximately 2–3 times higher risk of all-cause, cardiovascular, and cancer mortality than did those without diabetes. However, the hazard ratios for mortality outcomes were not significantly different between racial/ethnic subgroups. Population attributable risk percentages (PARPs) take into account both the prevalence of diabetes and hazard ratios. For all-cause mortality, whites had the lowest PARP (11.1, 95% confidence interval (CI): 10.1, 12.1), followed by Asians (12.9, 95% CI: 4.7, 20.9), blacks (19.4, 95% CI: 15.0, 23.7), and Hispanics (23.2, 95% CI: 14.8, 31.2). To our knowledge, the present study is the first to show that hazard ratios for mortality outcomes were not significantly different between racial/ethnic subgroups when stratified by diabetes status. Because of the "amplifying" effect of diabetes prevalence, efforts to reduce racial/ethnic disparities in the rate of death from diabetes should focus on prevention of diabetes.

diabetes; health disparities; menopause; mortality; obesity; women's health

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; PARP, population attributable risk percentage; WHI, Women's Health Initiative.

Diabetes is the seventh leading cause of death in the United States. By 2030, an estimated 48 million people older than 64 years of age in developed countries will be living with diabetes (1). Cardiovascular disease (CVD) plays a significant role in the rate of death from diabetes; adults with diabetes are 2–4 times more likely to die of CVD than are those without diabetes (1). Vascular disease is responsible for the vast majority of diabetes-related deaths in North America and Europe.

Women with diabetes are at a higher risk of CVD and experience more adverse outcomes after a vascular event than do women without diabetes (2). Additionally, the increased mortality risk after a myocardial infarction that is associated with diabetes is higher in women than in men with diabetes (3).

In addition to sex, differences in diabetes mortality rates may exist for racial and ethnic groups. Among people with diabetes in the United States, blacks and Hispanics are 2.1 times and 1.5 times more likely than whites to die of all causes, respectively, whereas total mortality among Asians is considerably lower compared with that among whites (1). Death from myocardial infarction has been reported to be significantly lower in blacks with diabetes than in whites (4).

Diabetes and its precursor, the metabolic syndrome, are becoming established as causes of cancers of various anatomic sites, with the strongest evidence for lung cancer (5), colon cancer (6, 7), and breast cancer (8, 9). There is evidence suggesting an elevated risk of colon cancer in blacks with diabetes compared with whites with diabetes (10-12).

To our knowledge, there has been no study that has examined racial/ethnic disparities in mortality outcomes among postmenopausal women with and without diabetes. Data from the Women's Health Initiative (WHI) provide a unique opportunity to examine racial/ethnic disparities on rates of overall, CVD, and cancer mortality among postmenopausal women with and without diabetes. We hypothesized that overall mortality, CVD mortality, and cancer mortality rates will differ by race/ethnicity.

MATERIALS AND METHODS

The WHI participants

The design of the WHI and the baseline characteristics of patients have been described in detail previously (13–15). A total of 161,808 women (68,132 in clinical trials and 93,676 in an observational study) were enrolled in the WHI between 1993 and 1998 with ongoing follow-up. Data used in the present investigation were obtained from women in both the clinical trial and observational study arms at baseline who were followed through August 2009 for an average duration of 10.4 years. The protocol and consent forms were approved by the institutional review boards for all participating institutions.

Identification of diabetes at baseline and follow-up

Diabetes at baseline was defined based on self-report of ever having received a diagnosis of diabetes from a physician when not pregnant. At each annual follow-up visit, participants were asked, "Since the date given on the front of this form, has a doctor prescribed any of the following pills or treatments?" Choices included "pills for diabetes" and "insulin shots for diabetes." Self-report of treatment with oral drugs or insulin was used to define incident diabetes. For the purposes of this analysis, we included both women who reported having prevalent diabetes at baseline and those who reported being treated for diabetes through August 2009. Women who reported prevalent or incident diabetes were characterized as having diabetes. The accuracy of self-reported diabetes in the WHI trials was assessed using self-reported medication and laboratory data, and self-reported diabetes was found to be a valid indicator of diagnosed diabetes (16). This method will not capture cases of undiagnosed diabetes and diabetes managed with dietary intervention only.

Death ascertainment and adjudication

Follow-up for clinical outcomes was performed at 6-month intervals in the clinical trial arm and annually in the observational study arm through August 2009. The participants in clinical trial arm had at least yearly follow-up clinic visits, whereas participants in the observational study arm were followed primarily by mail, with clinic visits at baseline and year 3. Deaths were identified as part of routine participant follow-up that included reports from family/next of kin, obituaries, and National Death Index searches. Death certificates and hospital records were obtained and then centrally adjudicated by reviewers blinded to study component or randomization assignment. Hospitalization records from the time of death and the most recent relevant hospitalization before death, autopsy records, and the death certificate were used by the adjudicators to help determine the cause of death. For many out-of-hospital deaths, documentation consisted only of the death certificate and records from the most recent relevant hospitalization before death. In these cases, the immediate and underlying causes of death were abstracted from the death certificate (17). CVD death was defined as death consistent with CVD as the underlying cause based on a review of medical records and the death certificate. CVD deaths were subclassified as definite coronary heart disease, cerebrovascular disease, pulmonary embolism, possible coronary heart disease, other CVD, and unknown CVD (18). Cancer deaths were obtained from the same sources, and anatomic site was determined based on codes from the International Classification of Diseases, Ninth Revision. Appendix Table 1 shows the distribution of CVD and cancer deaths by diabetes status and racial/ethnic group.

Race/ethnicity

At baseline, WHI participants self-reported their race/ ethnicity, choosing from the listed categories, which included white, black, Hispanic, American Indian/Alaska Native, Asian, and American Indian. Because of sample size limitations, data on American Indians (n = 713) were not included in analyses reported here. We also excluded 1,849 women who reported their race/ethnicity as "other" and 413 women who did not supply information on race/ethnicity.

Covariates

All covariates were measured at baseline. Body mass index (weight (kg)/height (m)²) was computed based on measured weight and standing height. Waist circumference also was measured. Demographic and health-history data were self-reported and included date of birth (age), cigarette smoking status, family history of diabetes, personal history of hypertension or high cholesterol requiring medication, family history of CVD, and hormone therapy use. Recreational physical activity level was assessed using questions about frequency and duration of several types of activity. All WHI participants completed a standardized food frequency questionnaire to estimate average daily nutrient intake over the 3-month period before enrollment (19). Dietary quality, assessed using the Alternate Healthy Eating Index (20, 21), was computed based on food items and nutrients derived from the food frequency questionnaire. Higher scores on the Alternate Healthy Eating Index are indicative of a better-quality diet.

Because many WHI participants are retired, individual income may not necessarily reflect socioeconomic status; therefore, neighborhood-level socioeconomic status was used in the analyses. Detailed methodology for determing neighborhood-level socioeconomic status has been described elsewhere (22, 23). Briefly, the WHI neighborhood-level socioeconomic status was created using an index of 6 variables: 1) percentage of adults older than 25 years of age with less than a high school education; 2) percentage of male unemployment; 3) percentage of households with an income below the poverty line; 4) percentage of households receiving public assistance; 5) percentage of households with children that were headed only by a woman; and 6) median household income.

Statistical analyses

Baseline characteristics by race/ethnicity for postmenopausal women with diabetes at baseline or during follow-up versus women without diabetes at either time were summarized using means and standard deviations for continuous variables and percentages for categorical variables. Hazard ratios and 95% confidence intervals for death (all-cause, CVD, and cancer mortality) comparing women with either prevalent or incident diabetes to women without diabetes were estimated using Cox proportional hazards models. For each participant, diabetes status was modeled as a time-varying binary covariate. For example, a woman with no diabetes at study entry who reported diabetes in her 27th month would contribute person-time to the "without diabetes" group from 0 to 26 months, and would contribute person-time to the "with diabetes" group after 26 months. The time to event of interest was defined as the interval between study enrollment and the earliest of the following: 1) date of last annual medical update during which the participant was alive or in August, 2009 (censorship) or 2) date of death (event).

For each mortality outcome (i.e., all-cause, CVD, cancer) among each race/ethnicity subgroup, model 1 included timevarying diabetes status and age; model 2 included further adjustment of study arm, body mass index, smoking status, medical history of hypertension, high cholesterol requiring medication, family history of CVD, hormone therapy use, region of residence in the United States, neighborhood-level socioeconomic status score, physical activity level, and dietary quality score. To calculate the population attributable risk percentage (PARP) and 95% confidence intervals among race/ ethnicity subgroups, we used mortality risk estimates from multivariate Cox proportional hazards models and the proportion of persons who had prevalent or incident diabetes from study enrollment to August 2009. We used methods described by Spiegelman et al. (24) to determine partial PARPs to estimate the proportion of deaths that hypothetically would not have occurred in this study population if no women were exposed (i.e., did not have diabetes).

RESULTS

Among the 158,833 women included in the analyses, the average age was 63 years; 84.1% were white (n = 133,541), 9.2% were black (n = 14,618), 4.1% were Hispanic (n = 14,618)6,484), and 2.6% were Asian (n = 4,190). At baseline, 4.4% of the participants had a history of diabetes diagnosis (n =7,169). The annual incidence of reported diabetes diagnosis or medication initiation was 0.80%, and the cumulative incidence was 5.45% (n = 10.307 incident diabetes cases) over 1,288,375 person-years of follow-up. Baseline characteristics of women who reported diabetes at baseline or during followup versus women who did not report diabetes during the study are summarized in Tables 1 and 2. In general, women who reported diabetes had higher baseline body mass indexes and worse dietary quality scores, were less active, and had more medical conditions, including hypertension and high cholesterol, than did women who did not report having diabetes.

In multivariable-adjusted analyses, within each race/ethnicity subgroup, women with diabetes were had a 2–3 times higher

Table 1. Means and Standard Deviations for Selected Baseline Characteristics of Continuous Variables by Race/Ethnicity for Women With (n = 21,584) and Without (n = 137,249) Diabetes, Women's Health Initiative, United States, 1993–2009

	Asian (<i>r</i>	ı = 4,190)	Black (n	= 14,618)	Hispanic	(<i>n</i> = 6,484)	White (n = 133,541)		
Characteristic	With Diabetes (<i>n</i> = 665)	Without Diabetes (<i>n</i> = 3,525)	With Diabetes (<i>n</i> = 3,964)	Without Diabetes (<i>n</i> = 10,654)	With Diabetes (<i>n</i> = 1,349)	Without Diabetes (<i>n</i> = 5,135)	With Diabetes (<i>n</i> = 15,606)	Without Diabetes (<i>n</i> = 117,935)	
Age, years	63.5 (7.4)	63.0 (7.6)	61.8 (6.8)	61.5 (7.2)	60.5 (6.6)	60.2 (6.8)	64.0 (7.0)	63.5 (7.2)	
Body mass index ^a	27.2 (5.0)	24.3 (4.4)	33.3 (6.8)	30.5 (6.5)	31.5 (6.0)	28.4 (5.6)	31.5 (6.5)	27.1 (5.4)	
Waist circumference, cm	86.1 (11.2)	77.3 (10.1)	98.0 (13.9)	89.7 (13.5)	94.2 (13.0)	85.2 (12.2)	96.7 (14.9)	84.6 (12.9)	
Physical activity, MET-hours/ week ^b	11.5 (14.0)	13.3 (14.2)	8.3 (11.4)	10.1 (13.2)	8.6 (12.1)	10.9 (14.1)	9.8 (12.0)	13.2 (13.9)	
Dietary quality score	37.9 (9.8)	39.2 (10.6)	32.0 (10.2)	33.6 (11.0)	31.2 (9.2)	33.4 (10.2)	34.6 (10.5)	37.2 (10.9)	
NSES score	76.0 (7.8)	77.2 (7.1)	62.4 (11.8)	64.4 (11.9)	66.0 (10.5)	69.0 (10.4)	76.0 (7.1)	77.3 (6.9)	

Abbreviations: MET, metabolic equivalents; NSES, neighborhood-level socioeconomic status.

^a Weight (kg)/height (m)².

^b Total energy expended from recreational physical activity.

		Asian (n = 4,190)	Black (<i>n</i> = 14,618)				Hispanic (<i>n</i> = 6,484)				White (n = 133,541)			
Characteristic	With Diabetes (<i>n</i> = 665)		Without Diabetes (n = 3,525)		With Diabetes (<i>n</i> = 3,964)		Without Diabetes (n=10,654)		With Diabetes (<i>n</i> = 1,349)		Without Diabetes (<i>n</i> = 5,135)		With Diabetes (<i>n</i> = 15,606)		Without Diabetes (n=117,935)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Region																
Northeast	30	4.5	174	4.9	696	17.6	1,799	16.9	170	12.6	600	11.7	3,867	24.8	29,024	24.6
South	33	5.0	224	6.3	1,954	49.3	4,968	46.6	553	41.0	2,176	42.4	3,796	24.3	27,603	23.4
Midwest	26	3.9	138	3.9	940	23.7	2,613	24.5	45	3.3	203	3.9	3,630	23.3	27,582	23.4
West	576	86.6	2,989	84.8	374	9.4	1,274	12.0	581	43.1	2,156	42.0	4,313	27.6	33,726	28.6
Smoking status																
Never	482	72.8	2,518	71.9	1,855	47.9	5,227	50.1	801	60.5	3,205	63.7	7,766	50.3	58,010	49.8
Former	155	23.4	844	24.1	1,591	41.1	4,003	38.3	407	30.8	1,479	29.4	6,615	42.9	50,896	43.7
Current	25	3.8	141	4.0	427	11.0	1,210	11.6	115	8.7	345	6.9	1,044	6.8	7,605	6.0
Hormone therapy use																
Never used	209	31.7	967	27.8	1,985	50.9	4,847	46.3	604	45.8	1,960	39.3	5,554	36.7	35,449	30.0
Past user	146	22.1	719	20.6	991	25.4	2,559	24.8	317	24.0	1,080	21.6	3,990	26.4	25,940	22.7
Current user	305	46.2	1,796	51.6	925	23.7	3,030	28.9	399	30.2	1,951	39.1	5,586	36.9	52,933	46.3
Medical history																
Hypertension	373	56.3	1,126	32.1	2,681	69.1	5,262	50.1	596	44.6	1,356	26.7	8,014	51.8	33,750	28.8
High cholesterol requiring medication	212	32.4	630	18.3	774	20.7	1,421	14.1	244	20.1	662	14.0	3,281	22.4	13,866	12.5
Family history of diabetes	382	57.9	1,161	33.0	2,407	61.4	4,331	41.0	819	61.2	1,957	38.7	7,515	48.4	32,364	27.6
Family history of cardiovascular disease	260	42.5	1,121	33.9	1,722	48.1	4,115	42.8	625	50.0	2,011	42.5	8,896	60.1	59,993	53.4

Table 2. Selected Baseline Characteristics of Categorical Variables by Race/Ethnicity for Women (n = 21,584) and Without (n = 137,249) Diabetes, Women's Health Initiative, United States, 1993–2009

risk of all-cause, CVD, and cancer mortality than did those without diabetes (Table 3). Adjustment for a range of potential confounders, including CVD risk factors, family history of CVD, and neighborhood socioeconomic status, caused a similar modest attenuation of hazard ratios for all race/ethnicity categories, except for a smaller attenuation among Asian women. However, all confidence intervals within each race/ ethnicity category overlapped all of the others. The percentages of women with prevalent or incident diabetes from study enrollment to August 2009 were, in decreasing frequency, 27.1% for blacks, 20.8% for Hispanics, 15.9% for Asians, and 11.7% for whites. PARP takes into account both the prevalence of diabetes and the risk associated with the disease. For all-cause mortality, whites had the lowest PARP (11.1, 95% confidence interval (CI): 10.1, 12.1), followed by Asians (12.9, 95% CI: 4.7, 20.9), blacks (19.4, 95% CI: 15.0, 23.7), and Hispanics (23.2, 95% CI: 14.8, 31.2). For CVD mortality, a similar pattern was observed; the PARP for diabetes appeared to be highest in Hispanics (30.6, 95% CI: 8.7, 49.7) and then in blacks (25.9, 95% CI: 17.8, 33.7) compared with whites, who had statistically lower PARPs with smaller confidence intervals than did blacks (14.9, 95% CI: 12.7, 17.1), but not Hispanics, who had very wide 95% confidence interval. For cancer mortality, the PARPs for

diabetes appeared higher for Hispanic and Asian women than for either black or white women; however, in relation to group mean differences, confidence intervals were relatively wide and overlapping.

DISCUSSION

Consistent with findings from other studies, results from the WHI show that postmenopausal women with diabetes experience a higher risk of all-cause, CVD, and cancer mortality than did women without diabetes (1). However, the hazard ratios for mortality outcomes were not significantly different between racial/ethnic subgroups according to diabetes status. Both black and Hispanic women, who are at higher-than-average risk of developing diabetes, had higher proportions of all-cause and CVD mortality attributable to diabetes than did whites.

These findings, which reflect the probability of dying conditioned upon having diabetes, are in stark contrast to the overall mortality data for the country as a whole. National data show that, relative to whites, blacks with diabetes are 2.1 times more likely to die and Hispanics are 1.5 times more likely to die (Asians are at much lower risk) (25). Differences evident in the country as a whole probably reflect survivor bias to some extent (the WHI sample is probably disproportionately weighted toward

		Asian	(<i>n</i> = 4,190))		Black (/	ı= 14,618)		Hispani	c (<i>n</i> = 6,48	34)	White (<i>n</i> = 133,541)			
	No.	%	HR ^a	95% CI	No.	%	HR	95% CI	No.	%	HR	95% CI	No.	%	HR	95% CI
Follow-up among subjects with DM, person-years	4,099				26,686				7,914				94,438			
Total follow-up, person-years	38,726				130,540				55,297				1,378,798			
Prevalence of exposure ^b		15.9				27.1				20.8				11.7		
All-cause mortality																
Deaths among subjects with DM ^c	58	14.15			534	20.01			113	14.28			2,175	23.03		
Deaths among subjects without DM ^c	199	5.75			932	8.97			261	5.51			11,239	8.75		
Model 1 ^d			2.44	1.71, 3.47			2.46	2.17, 2.78			2.99	2.30, 3.89			2.72	2.56, 2.88
Model 2 ^e			2.12	1.43, 3.15			2.11	1.83, 2.44			2.3	1.72, 3.23			2.2	2.00, 2.36
PARP ^f			12.9	4.7, 20.9			19.4	15.0, 23.7			23.2	14.8, 31.2			11.1	10.1, 12.1
CVD-related mortality																
Deaths among subjects with DM ^c	17	4.15			207	7.76			31	3.92			713	7.55		
Deaths among subjects without DM ^c	57	1.65			281	2.71			51	1.08			2,798	2.18		
Model 1 ^d			2.6	1.42, 4.87			3.31	2.71, 4.04			4.08	2.42, 6.87			3.86	3.50, 4.20
Model 2 ^e			2.26	1.14, 4.46			2.65	2.10, 3.35			3.05	1.66, 5.61			2.87	2.57, 3.20
PARP ^f			13.6	-1.4, 28.0			25.9	17.8, 33.7			30.6	8.7, 49.7			14.9	12.7, 17.1
Cancer mortality																
Deaths among subjects with DM ^c	26	5.37			126	4.72			42	5.31			588	6.23		
Deaths among subjects without DM ^c	88	2.54			342	3.29			111	2.34			4,642	3.61		
Model 1 ^d			2.1	1.20, 3.60			1.4	1.16, 1.80			2.21	1.44, 3.39			1.67	1.49, 1.86
Model 2 ^e			2.06	1.09, 3.88			1.38	1.05, 1.81			2.13	1.30, 3.47			1.44	1.27, 1.62
PARP ^f			14.5	1.6, 26.9			6.7	0.6, 12.8			17.5	5.4, 29.1			4.3	3.2, 5.5

Table 3. Comparison of the Rates of Death From All-Causes, Cardiovascular Disease, and Cancer by Race/Ethnicity in Women With and Without Diabetes (*n* = 158,833), Women's Health Initiative, United States, 1993–2009

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; PARP, population attributable risk percent.

^a Hazard ratios and 95% confidence intervals were estimated from a Cox proportional hazards model for each race/ethnicity subgroup.

^b Includes both prevalent and incident diabetes from study enrollment to August 2009.

^c Mortality per 1,000 person-years.

^d Model 1 was adjusted for age.

^e Model 2 was adjusted for age, study arm, body mass index, smoking status, medical history of hypertension, high cholesterol requiring medication, family history of cardiovascular disease, hormone therapy use, region of residence within the United States, neighborhood socioeconomic status score, physical activity level and dietary quality score.

^f PARP was calculated based on method by Spiegelman et al. (24).

healthier older women). Nevertheless, to our knowledge, our study is the first to show that the hazard ratios for mortality outcomes were not significantly different between racial/ethnic subgroups according to diabetes status in postmenopausal women. These results withstood adjustment for a very comprehensive set of physiological and behavioral risk factors.

Although the probability of dying conditioned upon diabetes did not differ significantly by racial/ethnic group, the percentages of women with prevalent or incident diabetes from study enrollment to August 2009 were significantly different by race (i.e., 27.1% for blacks, 20.8% for Hispanics, 15.9% for Asians, and 11.7% for whites) (26). We also observed that both black and Hispanic women, who are at higher-than-average risk of developing diabetes (26), appeared to have higher proportions of all-cause and CVD mortality attributable to diabetes than did whites. Therefore, because of the "amplifying" effect of diabetes prevalence, efforts to eliminate racial and ethnic disparities in deaths from diabetes should focus on prevention of type 2 diabetes mellitus.

According to the National Diabetes Facts, the prevalence rates of diagnosed diabetes by race/ethnicity are 12.6% for blacks, 11.8% for Hispanics, 8.4% for Asians, and 12.6% for whites (27). This race/ethnicity pattern was similar to what was observed in our study population except that the WHI had higher observed rates for all subgroups, a finding consistent with the fact that our population was more advanced in age.

Several limitations are worth noting. First, although type 2 diabetes mellitus represents the vast majority of newly incident diabetes cases in postmenopausal women, the WHI cannot absolutely eliminate the possibility of late-onset type 1 diabetes. We therefore indicate diabetes in general, in keeping with other WHI publications (26, 28–31). Second, in order to be able to assess risks within groups, the WHI included a disproportionately larger sample size for blacks, Hispanics, and Asians compared with the general US population. Because the WHI is not a representative national sample, we cannot generalize the results to a larger population without making additional inferential assumptions. Although participants in the WHI overall have higher educational levels and socioeconomic statuses than the general US population, we did adjust for neighborhood SES. We noted that multivariable-adjusted hazard ratios were similarly attenuated for each group but less so for Asians. Third, only self-reported prevalence of diabetes and treated incident diabetes were ascertained; thus, prevalence and incidence of diabetes may be underestimated. However, our previous validation study showed that self-reports of treated diabetes were sufficiently accurate to allow use in epidemiologic studies (16). Forth, diabetes is a chronic disease that requires prolonged and regular treatment (32). Measures of quality of care for diabetes, types of antidiabetic medication used, and medication adherence could affect diabetes-related mortality rates. However, we could not control for these factors in the present study. Several previous studies assessed racial/ethnic variation in the management of diabetes and utilization of preventive health services and noted disparities (33–35). However, results have been inconsistent. For example, Nwasuruba et al. (34) found that among 1,720 adults with diabetes in the 2002-2004 Texas Behavioral Risk Factor Surveillance Survey, Hispanics had poorer access to care than did whites or blacks. Using data obtained from 19,483 diabetic managed care organization enrollees, Oster et al. (33) found that blacks and Hispanics had more healthcare visits (means, 7.0 and 6.5, respectively) in the past year than did whites (mean, 5.7; P < 0.0001). None of these studies have focused on postmenopausal women, and this could be an area of future research. We also lacked laboratory measures of glycosylated hemoglobin, lipids and other metabolic markers to validate or explain results. Other limitations include missing data; however, the rates of retention in the WHI were over 95% during the average follow-up period of 7 years (36).

The present study has several strengths. First, it included a large, racially diverse sample of well-characterized postmenopausal women. Second, the prospective design enabled an examination of factors that contributed to mortality. Third, this study was to our knowledge the first to show that the hazard ratios for mortality outcomes were not significantly different between race/ethnicity subgroups according to diabetes status in postmenopausal women. These results withstood adjustment for a very comprehensive set of physiological and behavioral risk factors. The present study sheds new light on an ever-present problem of all-cause, cardiovascular, and cancer mortality in postmenopausal white, black, Hispanic, and Asian women with and without diabetes.

In conclusion, postmenopausal women with diabetes had a 2–3 fold higher risk of all-cause, CVD, and cancer mortality than did women without diabetes; however, the hazard ratios did not differ significantly between race/ethnicity subgroups according to diabetes status. It should be noted, however, that risk given diabetes is a multiplier against overall diabetes rates, which tend to be much higher in blacks and Hispanics than in whites and Asians. Because of significant racial/ethnic disparities in diabetes prevalence and incidence, black and Hispanic women have higher proportions of all-cause and CVD mortality attributable to diabetes than do white women. Our study suggested that efforts to eliminate racial and ethnic disparities in the rate of death from diabetes should focus on prevention of type 2 diabetes mellitus.

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REFERENCES

- 1. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: Diagnosed and Undiagnosed Diabetes in the United States, All Ages, 2010. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
- Ma Y, Hebert J, Ebbeling C, et al. International aspects of coronary heart disease epidemiology. In: Becker RC, Alpert JS, eds. *Cardiovascular Medicine-Practice and Management*. London, UK: Arnold; 2001:1–15.

- Vaccarino V, Parsons L, Every NR, et al. Impact of history of diabetes mellitus on hospital mortality in men and women with first acute myocardial infarction. The National Registry of Myocardial Infarction 2 participants. *Am J Cardiol.* 2000; 85(12):1486–1489.
- 4. Kamalesh M, Subramanian U, Ariana A, et al. Diabetes status and racial differences in post-myocardial infarction mortality. *Am Heart J.* 2005;150(5):912–919.
- Luo J, Chlebowski R, Wactawski-Wende J, et al. Diabetes and lung cancer among postmenopausal women. *Diabetes Care*. 2012;35(7):1485–1491.
- Matthews CE, Sui X, LaMonte MJ, et al. Metabolic syndrome and risk of death from cancers of the digestive system. *Metabolism*. 2010;59(8):1231–1239.
- Ren X, Zhang X, Zhang X, et al. Type 2 diabetes mellitus associated with increased risk for colorectal cancer: evidence from an international ecological study and population-based risk analysis in China. *Public Health*. 2009;123(8):540–544.
- Sellers TA, Jensen LE, Vierkant RA, et al. Association of diabetes with mammographic breast density and breast cancer in the Minnesota Breast Cancer Family Study. *Cancer Causes Control.* 2007;18(5):505–515.
- 9. Guastamacchia E, Resta F, Triggiani V, et al. Evidence for a putative relationship between type 2 diabetes and neoplasia with particular reference to breast cancer: role of hormones, growth factors and specific receptors. *Curr Drug Targets Immune Endocr Metabol Disord*. 2004;4(1):59–66.
- He J, Stram DO, Kolonel LN, et al. The association of diabetes with colorectal cancer risk: the Multiethnic Cohort. *Br J Cancer*. 2010;103(1):120–126.
- Vinikoor LC, Long MD, Keku TO, et al. The association between diabetes, insulin use, and colorectal cancer among Whites and African Americans. *Cancer Epidemiol Biomarkers Prev.* 2009;18(4):1239–1242.
- 12. Cavicchia PP, Adams SA, Steck SE, et al. Racial disparities in colorectal cancer incidence by type 2 diabetes mellitus status. *Cancer Causes Control*. 2013;24(2):277–285.
- 13. Ritenbaugh C, Patterson RE, Chlebowski RT, et al. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. *Ann Epidemiol.* 2003;13(9 suppl):S87–S97.
- Stefanick ML, Cochrane BB, Hsia J, et al. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol.* 2003;13(9 suppl):S78–S86.
- Langer RD, White E, Lewis CE, et al. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol.* 2003;13(9 suppl):S107–S121.
- Margolis K, Qi L, Brzyski R, et al. Validity of diabetes selfreports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. *Clin Trials*. 2008;5(3):240–247.
- Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol.* 2003;13(9 suppl):S122–S128.
- Schnall E, Wassertheil-Smoller S, Swencionis C, et al. The relationship between religion and cardiovascular outcomes and all-cause mortality in the Women's Health Initiative Observational Study. *Psychol Health*. 2010;25(2):249–263.
- Patterson RE, Kristal AR, Tinker LF, et al. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol.* 1999;9(3): 178–187.

- McCullough ML, Willett WC. Evaluating adherence to recommended diets in adults: the Alternate Healthy Eating Index. *Public Health Nutr.* 2006;9(1A):152–157.
- McCullough ML, Feskanich D, Stampfer MJ, et al. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. *Am J Clin Nutr.* 2002;76(6):1261–1271.
- 22. Shih R, Ghosh-Dastidar B, Margolis K, et al. Neighborhood socioeconomic status and cognitive function in women. *Am J Public Health*. 2011;101(9):1721–1728.
- 23. Shih R, Griffin B, Salkowski N, et al. Ambient particulate matter air pollution and venous thromboembolism in the Women's Health Initiative Hormone Therapy trials. *Environ Health Perspect*. 2011;119(3):326–331.
- Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. *Cancer Causes Control.* 2007;18(5):571–579.
- Morbidity and Mortality Weekly Report (MMWR), Health Disparities and Inequalities Report—United States. 2011; 60(suppl):1–116.
- Ma Y, Hebert JR, Manson JE, et al. Determinants of racial/ ethnic disparities in incidence of diabetes in postmenopausal women in the U.S.: The Women's Health Initiative 1993– 2009. *Diabetes Care*. 2012;35(11):2226–2234.
- 27. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011. (http://www.cdc.gov/ diabetes/pubs/pdf/ndfs_2011.pdf). (Accessed June 21, 2013).
- 28. de Boer IH, Tinker LF, Connelly S, et al. Calcium plus vitamin D supplementation and the risk of incident diabetes in the

Women's Health Initiative. *Diabetes Care*. 2008;31(4): 701–707.

- Tinker LF, Bonds DE, Margolis KL, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. *Arch Intern Med.* 2008;168(14): 1500–1511.
- 30. Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med.* 2012;172(21): 144–152.
- Ma Y, Balasubramanian R, Pagoto SL, et al. Elevated depressive symptoms, antidepressant use, and diabetes in a large multiethnic national sample of postmenopausal women. *Diabetes Care*. 2011;34(11):2390–2392.
- 32. Standards of medical care in diabetes—2011. *Diabetes Care*. 2011;34(suppl 1):S11–S61.
- Oster NV, Welch V, Schild L, et al. Differences in selfmanagement behaviors and use of preventive services among diabetes management enrollees by race and ethnicity. *Dis Manag.* 2006;9(3):167–175.
- Nwasuruba C, Osuagwu C, Bae S, et al. Racial differences in diabetes self-management and quality of care in Texas. *J Diabetes Complications*. 2009;23(2):112–118.
- Tseng CW, Tierney EF, Gerzoff RB, et al. Race/ethnicity and economic differences in cost-related medication underuse among insured adults with diabetes: the Translating Research Into Action for Diabetes Study. *Diabetes Care*. 2008; 31(2):261–266.
- Howard BV, Manson JE, Stefanick ML, et al. Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. *JAMA*. 2006;295(1): 39–49.

(Appendix follows)

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	Asian	(<i>n</i> = 4,190)	Black (n = 14,618)	Hispanio	c (<i>n</i> = 6,484)	White (r	1=133,541)	Total (<i>n</i> = 158,833)		
Cause of Death	No. With Diabetes	No. Without Diabetes	No. With Diabetes	No. Without Diabetes							
CVD subclassification											
Definite CHD	7	8	47	50	8	10	573	240	635	308	
Cerebrovascular CHD	25	2	57	43	19	8	782	141	883	194	
Pulmonary embolism	0	0	13	6	1	0	83	8	97	14	
Possible CHD	10	5	88	77	10	7	688	182	796	271	
Other CVD	11	2	64	24	13	5	585	128	673	159	
Unknown CVD	4	0	12	7	0	1	87	14	103	22	
Total	57	17	281	207	51	31	2,798	713	3,187	968	
Cancer site											
Breast	7	1	48	21	21	3	536	48	612	73	
Ovarian	3	0	17	1	11	3	339	29	370	33	
Endometrial	2	0	2	0	1	0	87	9	92	9	
Colon	7	0	39	10	10	3	329	50	385	63	
Rectosigmoid	0	0	1	0	0	0	10	2	11	2	
Rectum	2	1	3	2	1	0	38	3	44	6	
Uterine	0	0	2	4	2	1	20	2	24	7	
Other	63	20	200	82	64	29	3,064	409	3,391	540	
Unknown	4	4	30	6	1	3	219	36	254	49	
Total	88	26	342	126	111	42	4,642	588	5,183	782	

Appendix Table 1. Number of Deaths From Cardiovascular Disease and Cancer by Cause, Women's Health Initiative, United States, 1993–2009

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.