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Cardiometabolic Risk Factors and Survival After Cancer in the Women's Health Initiative

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST DISCLOSURES

Michael S. Simon reports personal fees from the Women's Health Initiative during the conduct of the study and that he is on a speakers' bureau for AstraZeneca for non–treatment-related genetic counseling and testing. Theresa A. Hastert reports personal fees from the Women's Health Initiative during the conduct of the study and grants from the American Cancer Society and the National Cancer Institute outside the submitted work. Ana Barac reports working on a data and safety monitoring board for CTI Biopharma and receiving honoraria from Bristol-Myers Squibb. Rowan T. Chlebowski reports personal fees from Novartis, Pfizer, AstraZeneca, Puma, Genentech, Immunomedics, and Merck during the conduct of the study. Aladdin H. Shadyab reports working as a consultant for Ranchio Biosciences, LLC. The other authors made no disclosures.

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Abstract

BACKGROUND: Cardiometabolic abnormalities are a leading cause of death among women, including women with cancer.

METHODS: This study examined the association between prediagnosis cardiovascular health and total and cause-specific mortality among 12,076 postmenopausal women who developed local- or regional-stage invasive cancer in the Women's Health Initiative (WHI). Cardiovascular risk factors included waist circumference, hypertension, high cholesterol, and type 2 diabetes. Obesity-related cancers included breast cancer, colorectal cancer, endometrial cancer, kidney cancer, pancreatic cancer, ovarian cancer, stomach cancer, liver cancer, and non-Hodgkin lymphoma. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for important predictors of survival.

RESULTS: After a median follow-up of 10.0 years from the date of the cancer diagnosis, there were 3607 total deaths, with 1546 (43%) due to cancer. Most participants (62.9%) had 1 or 2 cardiometabolic risk factors, and 8.1% had 3 or 4. In adjusted models, women with 3 to 4 risk factors (vs none) had a higher risk of all-cause mortality (HR, 1.99; 95% CI, 1.73–2.30), death due to cardiovascular disease (CVD) (HR, 4.01; 95% CI, 2.88–5.57), cancer-specific mortality (HR, 1.37; 95% CI, 1.1–1.72), and other-cause mortality (HR, 2.14; 95% CI, 1.70–2.69). A higher waist circumference was associated with greater all-cause mortality (HR, 1.17; 95% CI, 1.06–1.30) and cancer-specific mortality (HR, 1.22; 95% CI, 1.04–1.42).

CONCLUSIONS: Among postmenopausal women diagnosed with cancer in the WHI, cardiometabolic risk factors before the cancer diagnosis were associated with greater all-cause, CVD, cancer-specific, and other-cause mortality. These results raise hypotheses regarding potential clinical intervention strategies targeting cardiometabolic abnormalities that require future prospective studies for confirmation.

Keywords

cancer; cardiometabolic risk factors; survival; Women's Health Initiative

INTRODUCTION

Cardiometabolic abnormalities characterizing metabolic syndrome have long been linked to incident cardiovascular disease (CVD)[1–3] and diabetes[3] as well as deaths due to CVD and all causes.[4] Specific clinical characteristics of compromised cardiometabolic health include an increased waist circumference, elevated triglycerides, hypertension, elevated fasting glucose levels, and low high-density lipoprotein cholesterol levels.[5,6]

In cohort studies including women, metabolic syndrome has been statistically significantly associated with a risk of endometrial, pancreatic, gastric, colorectal, ovarian, and postmenopausal breast cancers and non-Hodgkin lymphoma.[7–10] To our knowledge, only 2 other large cohort studies have shown a significant relationship between indicators of cardiometabolic health and mortality across several cancer sites together[11,12]; however, no other group has comprehensively evaluated the relationship between cardiometabolic abnormalities determined before the cancer diagnosis and specific causes of death among postmenopausal women.

The continued improvement in outcomes after cancer due to advances in treatment and screening, which have resulted in an increase in the number of cancer survivors,[13] coupled with the high prevalence of obesity and related comorbidities,[14–16] highlights the need to better understand the relationship between cardiometabolic abnormalities and outcomes after cancer. We previously reported in the Women's Health Initiative (WHI) on the relationship between preexisting cardiometabolic abnormalities and a higher risk of death due to CVD and other causes after the diagnosis of breast cancer.[17] In this analysis, we evaluated associations between prediagnosis cardiometabolic abnormalities and mortality after cancer in an expanded cohort of WHI participants who were diagnosed with obesity-related cancers.

MATERIALS AND METHODS

Study Population

The WHI consists of an observational cohort (n = 93,676) and 3 overlapping clinical trials (n = 68,132), including trials of hormone therapy, dietary modification, and calcium plus vitamin D supplementation.[18,19] Women were eligible to participate in the WHI if they were between the ages of 50 and 79 years, were postmenopausal, and had a predicted survival of at least 3 years at study entry. Participants were recruited from 40 US clinical centers

between October 1, 1993, and December 31, 1998, and were initially followed through March 2005. WHI participants were subsequently followed through 2 extension studies, with follow-up now ongoing at least through 2020. The study design was approved by the institutional review boards at the participating centers.

Our study population included WHI participants who developed pathologically confirmed local- or regional-stage breast, colorectal, endometrial, kidney, pancreatic, ovarian, stomach, or liver cancer or non-Hodgkin lymphoma after enrollment in either the observational cohort or the clinical trial but before December 12, 2018 (n = 18,911). These cancers were chosen because of established associations between the risk of these cancers and either individual cardiometabolic features or metabolic syndrome. We excluded the following groups from the study cohort: those with cancer diagnosed at the time of death (n = 1114) or within 1 month of death (n = 339), those with a history of cancer at study entry or an unknown medical history (n = 1403), those with a distant (n = 1998) or unknown stage at diagnosis (n = 455), those with a second primary cancer (n = 1495), and those with missing information on waist circumference (n = 31). This resulted in an analytic cohort of 12,076 (Fig. 1). Women with distant-stage disease were excluded to include a more homogeneous study population of women with early-stage cancer.

Cardiometabolic Abnormalities

We used information on cardiometabolic abnormalities, including waist circumference and hypertension and self-reported histories of hypertension, diabetes, and high cholesterol. A high waist circumference was defined as ≥88 cm,[20] and hypertension was defined as a systolic blood pressure > 130 mg Hg and/or a diastolic blood pressure > 85 mm Hg based on measurements taken by trained study staff at WHI clinical sites or as self-reported use of medications to treat hypertension at the baseline. Participants were considered to have diabetes or elevated cholesterol on the basis of self-reported histories or the use of medication used to treat each disease at baseline entry into the WHI.[18,19] The use of information on self-reported diabetes has been previously validated in the WHI.[21]

Outcomes

Outcomes included all-cause mortality, mortality from cancer, mortality from CVD, and mortality from other causes. Participants were followed for outcomes from the date of their cancer diagnosis until the date of death or last contact before December 12, 2018. Deaths from CVD included deaths due to coronary heart disease, cerebrovascular accident, pulmonary embolism, possible coronary heart disease, other cardiovascular causes, and unknown CVD. The cause of death was determined by medical record or death certificate review and, in some cases, by a relative's report. Mortality findings and information on cause of death were enhanced by serial linkage to the National Death Index.[22]

Covariates

Standardized questionnaires were used at the baseline to collect information on the following: age at cancer diagnosis, race/ethnicity, education, affiliation with a current health care provider, smoking history, alcohol consumption, recreational physical activity, postmenopausal hormone therapy, and history of cancer before study enrollment.[18] Height,

weight, and waist circumference were measured at the baseline according to a standardized protocol by trained study staff at WHI clinical sites. The body mass index (BMI) was computed as the weight (in kilograms) divided by the height (in meters squared). The summary stage was based on a review at the clinical coordinating center of the pathology report using the Surveillance, Epidemiology, and End Results coding system.[22]

Statistical Analysis

The distributions of demographics, exposures, selected health behaviors, and cardiometabolic abnormalities at the baseline were summarized overall and by the number of cardiometabolic abnormalities (0, 1 or 2, or 3 or 4). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between each of the 4 cardiometabolic features identified at the baseline and death due to all causes as well as the competing risks of death due to cancer, CVD, and other causes. The survival time was calculated from the date of cancer diagnosis to death or last contact before December 12, 2018. The final models assessing individual abnormalities were mutually adjusted for the other 3 cardiovascular abnormalities as well as all variables listed in Table 1 (age group at cancer diagnosis, education, race/ethnicity, WHI study group, current health care provider, BMI, smoking status, alcohol intake, physical activity, and hormone therapy use). Sensitivity analyses were conducted that excluded BMI from the final model and were stratified by the time from WHI enrollment to cancer diagnosis (<5 and ≥5 years). In addition, we evaluated cancer site–specific mortality for the 3 most common cancers identified (stratified by the corresponding cancer site) and plotted the HRs and CIs associated with an increasing number of cardiometabolic abnormalities (ordinal variable: 0, 1 or 2, or 3 or 4). We also conducted a Kaplan-Meier analysis for overall survival by the number of abnormalities at the baseline.

All analyses were completed with SAS software (version 9.4; SAS, Carey, North Carolina). To test the proportionality assumption for the Cox proportional hazards regression analysis, an interaction term between the log of time and the ordinal exposure variable was added to each adjusted model, and we observed no statistically significant departures from proportionality. *P* values were 2-sided and were considered significant when they were <.005 (adjusted to take into consideration multiple comparisons).

RESULTS

Table 1 describes the demographic and clinical characteristics stratified by the number of cardiometabolic abnormalities. The median time between the baseline clinic visit and cancer diagnosis was 7.8 years (range, <1 to 22 years). Overall, the mean age at WHI study enrollment was 63.1 years (standard deviation [SD], 7.0 years), and the mean age at cancer diagnosis was 72.1 years (SD, 7.9 years); a majority of the participants were non-Hispanic White (87%) and were educated beyond high school (80%). The mean BMI at enrollment was 28.2 kg/m^2 (SD, 6.0 kg/m^2), and approximately one-third of the participants were in each of the established BMI categories (normal weight, overweight, and obese). The distribution of participants by the number of cardiometabolic abnormalities included 29% with no abnormalities, 63% with 1 or 2 abnormalities, and 8% with 3 or 4 abnormalities.

The most common cardiometabolic abnormality was hypertension (54%), which was followed by an increased waist circumference (43%), a history of high cholesterol (13%), and a history of diabetes (5%). Older women, African American women, and women with an increased BMI, less education, and less participation in moderate to strenuous activity were more likely to have a higher number of cardiometabolic abnormalities.

After a median follow-up of 10 years starting at the date of the cancer diagnosis, there were a total of 3607 deaths, including 1546 deaths due to cancer (42.9%), 733 due to CVD (20.3%), and 1328 due to other causes (36.8%). The most prevalent known “other” causes of death were dementia or Alzheimer disease (n = 236), chronic obstructive pulmonary disease (n = 89), and pneumonia (n = 72; Table 2).

Table 3 shows the unadjusted and adjusted HRs and 95% CIs for the association of cardiometabolic abnormalities and all-cause mortality and mortality due to cancer, CVD, and other causes. In the adjusted models, in comparison with women with no cardiometabolic abnormalities, the risk of death for women with 1 or 2 cardiometabolic abnormalities at WHI enrollment was 1.5 times greater (HR, 1.50; 95% CI, 1.36–1.65), and for women with 3 or 4 abnormalities, it was 2-fold greater (HR, 1.99; 95% CI, 1.73–2.30; *P* for trend <.001). For women with 3 or 4 abnormalities versus no abnormalities, the risk of death from CVD was 4 times greater (HR, 4.01; 95% CI, 2.88–5.57; *P* for trend <.001), the risk of death from other causes was 2.14-fold greater (HR, 2.14; 95% CI, 1.70–2.69; *P* for trend <.001), and the risk of death from cancer was 1.37 times greater (HR, 1.37; 95% CI, 1.1–1.72; *P* for trend = .001). An analysis for individual abnormalities showed that an elevated prediagnosis waist circumference at WHI enrollment was associated with a higher risk of death due to all causes (HR, 1.17; 95% CI, 1.06–1.30) and cancer (HR, 1.22; 95% CI, 1.04–1.42), whereas diabetes was associated with a higher risk of death due to all causes, CVD, and other causes, and hypertension was associated with higher mortality due to all causes, cancer, CVD, and other causes.

Excluding BMI from the adjusted models did not materially change the statistical significance of the results. Stratification by time from study entry to diagnosis had a significant impact on mortality due to cancer. Having 3 or 4 cardiometabolic abnormalities was associated with a 74% higher risk of death due to cancer for women diagnosed 5 or more years from study enrollment (HR, 1.74; 95% CI, 1.30–2.34) but not for women diagnosed less than 5 years from enrollment (HR, 0.91; 95% CI, 0.65–1.29).

Table 4 shows the adjusted HRs and 95% CIs for the association of cardiometabolic risk factors with mortality due to cancer for women diagnosed with 1 of the 3 most common cancer types evaluated in this analysis (breast, colorectal, and endometrial cancer). A higher number of cardiometabolic abnormalities was not associated with death due to breast, colorectal, or endometrial cancer individually.

Figure 2 shows the results of the Kaplan-Meier analysis for overall survival by the number of abnormalities at the baseline and demonstrates an increased risk of death for women with 1 or 2 cardiometabolic abnormalities or 3 or 4 cardiometabolic abnormalities versus none (log-rank *P* < .001).

DISCUSSION

The results from this analysis suggest that prediagnosis cardiometabolic abnormalities are associated with death after diagnosis in a group of postmenopausal women diagnosed with cancers previously associated with metabolic syndrome. Importantly, HRs for death increased with an increased number of cardiometabolic abnormalities. The results shown in this analysis are consistent with a prior WHI report demonstrating a significant relationship between cardiometabolic abnormalities and death due to CVD and other causes among women diagnosed with early-stage breast cancer.[17] The current study expands on our previous work with an expanded cohort of women diagnosed with 9 cancers previously associated with obesity.

The cardiometabolic abnormalities examined here have both unique mechanisms of action and shared mechanisms of action with cancer, and this may be in part explained through a common pathway of altered sensitivity to insulin, alterations in the hormonal profile, and chronic inflammation. The common soil hypothesis suggests that shared cellular and tissue mechanisms that are perturbed in the setting of obesity and physical inactivity may predispose individuals to cancer and CVD as well as diabetes.[23] There is a large body of mechanistic evidence supporting the role of the cardiometabolic abnormalities examined in this analysis as drivers of a higher risk of mortality after cancer. In a mouse model of obesity-induced lipogenesis, Liu et al[24] demonstrated the impact of dietary lipid loading on ovarian cancer cell adhesion and intraperitoneal tumor burden with histological analyses implicating changes in lipid regulatory factors, increased vascularity, and higher M1/M2 macrophage ratios in the increased tumor burden. Other studies have shown that the microenvironment provided by adipose tissue, particularly central or visceral adiposity, is rich in signaling molecules and acts as an endocrine organ promoting tumor progression and proliferation via various cellular mediators, adipokines, cytokines, and inflammatory markers.[25,26] Others have shown that inflamed breast adipose tissue may influence cancers by way of white adipose tissue cell death, which leads to macrophage infiltration forming crownlike structures that stimulate aromatase activity, which subsequently leads to peripheral estrogen production.[27] Hyperglycemia and insulin resistance could serve both as an energy reservoir and as drivers of a proinflammatory state as well as signals for various cell growth and proliferation pathways.[1,28,29]

Prior investigations have evaluated the relationship between metabolic syndrome or components of metabolic syndrome, a clinical condition characterized by the cardiometabolic exposures evaluated here, and cancer-specific outcomes. The literature suggests that a history of cardiometabolic abnormalities is associated with a poorer prognosis,[20,30] local or distant relapse,[1,31–34] cancer-specific mortality,[31,33,35–37] and overall survival.[31,33,35,36,38] Importantly, our analysis builds evidence for the relationship between cardiometabolic abnormalities and cancer outcomes among postmenopausal women, with 1 other study showing similar findings in men.[39]

To our knowledge, there have been only 2 other large published studies that have grouped together several relevant cancers and have also demonstrated a relationship between the exposures of interest and an increased risk of cancer mortality. In an analysis of the Third

National Health and Nutrition Examination Survey, Gathirua-Mwangi et al[11] evaluated the relationship between metabolic syndrome and overall cancer mortality (including lung cancer) in a population of 14,916 men and women followed longitudinally over a 12- to 18-year period of follow-up, of whom 687 died as a result of cancer. Their results demonstrated a significant relationship between having metabolic syndrome (vs not having metabolic syndrome) and higher total cancer mortality for men and women combined (HR, 1.33; 95% CI, 1.04–1.70) with an increasing risk associated with an increasing number of metabolic syndrome features (*P* for trend = .005). In contrast to our findings, elevated glucose was associated with an increased risk of dying from cancer, and as shown in our analysis, an elevated waist circumference was marginally associated with cancer death (HR, 1.32; 95% CI, 0.98–1.77). In another analysis of 25,038 participants in a community-based study of risk factors for stroke, REasons for Geographic and Racial Differences in Stroke (REGARDS) followed for 5 to 9 years, Akinyemiju et al[12] demonstrated a higher risk of all cancer mortality associated with metabolic syndrome (HR, 1.22; 95% CI, 1.03–1.45), and consistently with the results from the WHI, they demonstrated a trend toward worsening all cancer mortality with an increased number of metabolic syndrome features.

Although the relevance of coexisting comorbidities, including obesity, hypertension, diabetes, and high cholesterol, to cancer risk and cancer outcomes has been well established, the current analyses raise the hypothesis that, in patients with cancer, interventions targeting metabolic abnormalities, which include modifiable lifestyle factors, may affect cancer outcomes. In this regard, earlier findings from the WHI dietary modification trial, which included 48,835 postmenopausal women without a history of breast cancer who were randomized to a low-fat dietary pattern that statistically significantly increased vegetable, fruit, and grain intake, showed an association with a reduction in metabolic syndrome components as well as a reduction in cholesterol-lowering and antihypertensive medication use in comparison with randomization to a comparison group.[40] In addition, breast cancer incidence was a primary study endpoint, and with a long-term follow-up of 19.6 years, a statistically significant reduction in deaths from breast cancer (breast cancer followed by death directly attributed to the cancer) emerged (HR, 0.79; 95% CI 0.64–0.97; *P* = .02). This finding from a full-scale randomized trial represents a partial test of our study hypothesis, at least for the breast cancer outcome. Future studies should evaluate the potential impact of other interventions on outcomes in other cancers.

The strengths of our analysis include the large sample size, the long period of follow-up, physician-adjudicated cancer cases and outcomes, the inclusion of obesity-related cancers previously associated with metabolic syndrome, and a focus on women with early-stage disease who have the potential for long-term survival. This is especially important because of competing risks for morbidity and mortality among women with advanced-stage cancer. We acknowledge the limitations of residual confounding and the observational nature of our work. We could not comment on whether there was a differential impact of cardiometabolic risk factors by race or ethnicity because only 7% of the participants were Black and 6% belonged to other racial or ethnic groups in our study cohort. Other limitations include the lack of blood levels of glucose, triglycerides, and high-density lipoprotein and the reliance on participant questionnaires for information on the history of diabetes and high cholesterol, which could result in underestimations of those diagnoses, although prior

analyses in the WHI have demonstrated that 92% of self-reported diabetes cases were confirmed by medical record review.[41] Another limitation is the absence of information on cancer-directed therapy, which has been shown to have a direct impact on outcomes after cancer. Lastly, we evaluated the presence of cardiometabolic abnormalities that occurred at study entry, and we did not have data on these factors at the time of cancer diagnosis. The variability in the time between the assessment of cardiometabolic risk factors (median, 7.1 years; range, <1 to 20.6 years) could have potentially weakened the associations between cardiometabolic abnormalities and cancer-specific mortality in particular. In our sensitivity analysis, we showed that the time between study entry and diagnosis had no impact on the relationship between cardiovascular abnormalities and overall, CVD, or other-cause mortality; however, the relationship between cardiovascular abnormalities and death due to cancer was significant only for women who were diagnosed more than 5 years after study entry. These results might be explained by the possibility that the prevalence of the measured cardiometabolic risk factors could have changed over time, and this might have resulted in a stronger relationship with mortality for women diagnosed later; however, we were not able to assess this with our data set.

In conclusion, in a cohort of postmenopausal women with select early-stage cancers, a higher number of cardiometabolic abnormalities is associated with significantly higher overall mortality in addition to higher mortality due to cancer, CVD, and other causes. These findings suggest that interventions targeting these modifiable risk factors could potentially have a clinically meaningful impact on outcomes for cancer survivors. The results also point out a major gap in the survivorship care of patients with cancer and the need for improved efforts by public health systems to improve survival. This hypothesis requires future prospective studies for confirmation.

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LAY SUMMARY:

- This study uses information from the Women's Health Initiative (WHI) to find out whether cardiac risk factors are related to a greater risk of dying among older women with cancer. The WHI is the largest study of medical problems faced by older women in this country.
- The results show that women who have 3 or 4 risk factors are more likely to die of any cause, heart disease, or cancer in comparison with women with no risk factors.
- It is concluded that interventions to help to lower the burden of cardiac risk factors can have an important impact on survivorship among women with cancer.

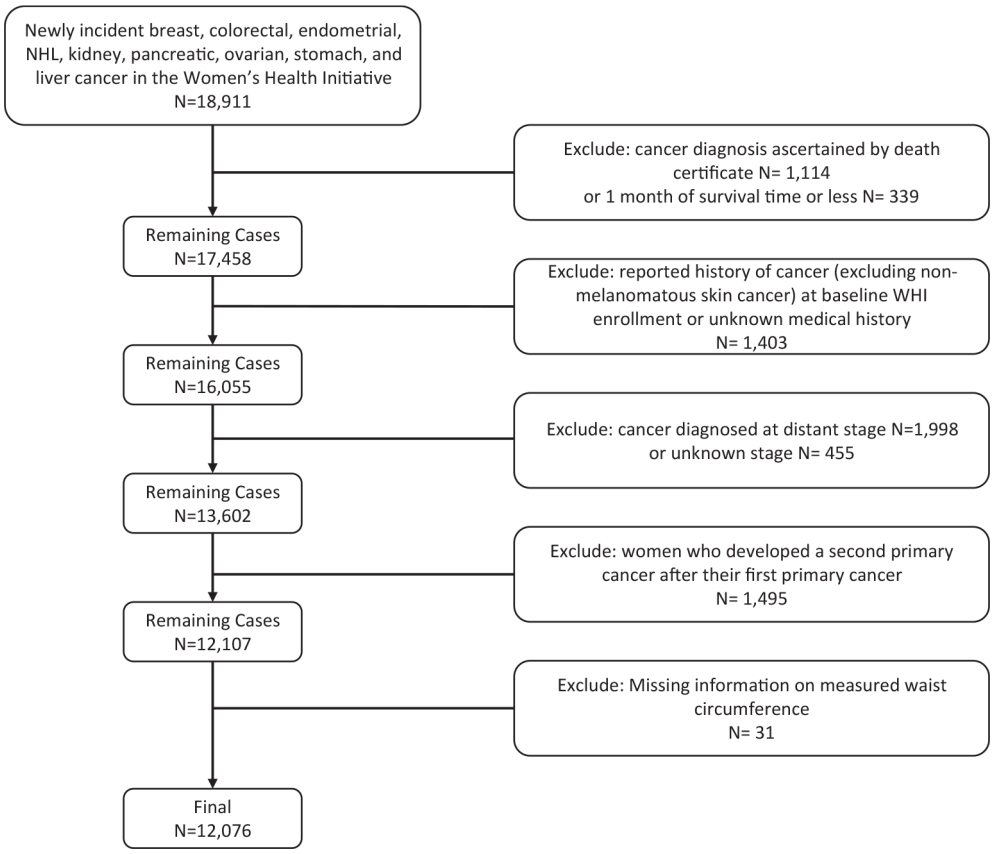

Figure 1.

Study inclusion and exclusion criteria. NHL indicates non-Hodgkin lymphoma; WHI, Women's Health Initiative.

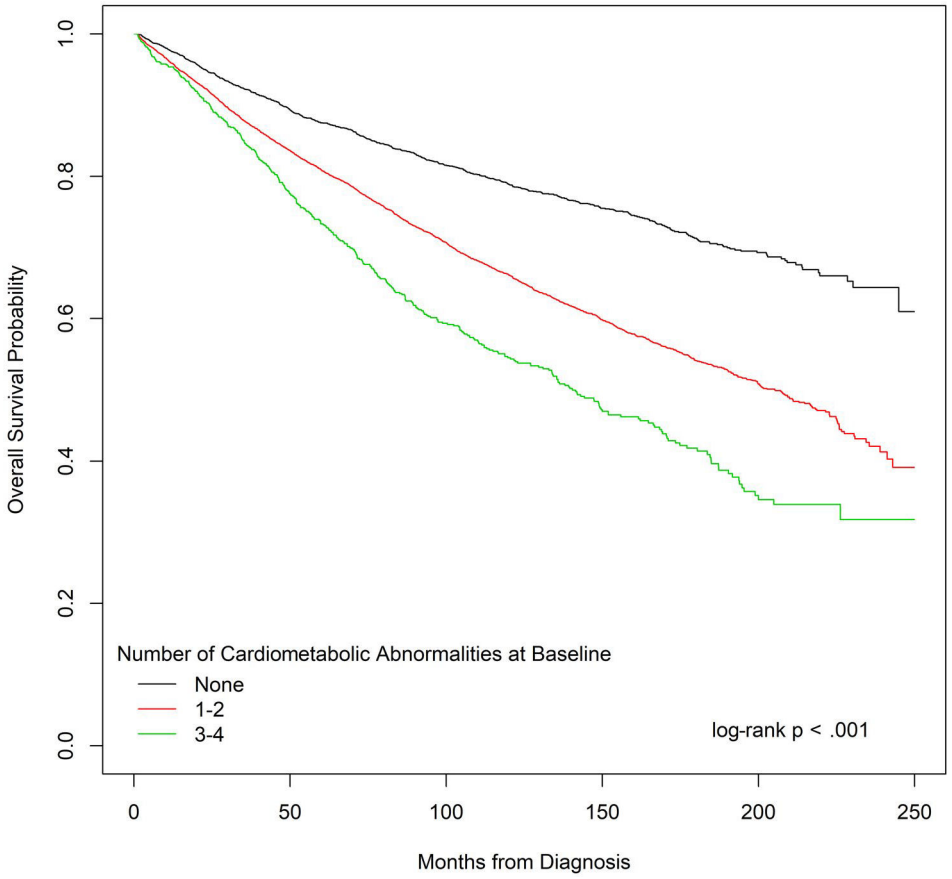

Figure 2.
Overall survival probability by the number of cardiometabolic abnormalities at the baseline.

TABLE 1.

Select Demographic and Clinical Characteristics Stratified by the Number of Cardiometabolic Abnormalities at Baseline Enrollment Into WHI

			No. of Cardiometabolic Abnormalities at Baseline					
	All Women		0		1 or 2		3 or 4	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Total	12,076		3508		7593		975	
Age group at diagnosis								
<60 y	747	6	316	9	395	5	36	4
60–64 y	1445	12	536	15	797	10	112	11
65–69 y	2277	19	708	20	1422	19	147	15
70–74 y	2882	24	791	23	1823	24	268	27
≥75 y	4725	39	1157	33	3156	42	412	42
Education								
High school or less	2343	20	484	14	1581	21	278	29
More than high school	9655	80	3000	86	5967	79	688	71
Race[a]								
White (not of Hispanic origin)	10,504	87	3184	91	6565	86	755	77
Black or African American	820	7	101	3	576	8	143	15
Other	752	6	223	6	452	6	77	8
WHI study								
Observational	6536	54	2105	60	3916	52	515	53
DM: intervention arm	1623	13	439	13	1072	14	112	11
DM: control arm	2548	21	639	18	1709	23	200	21
CT not randomized to DM	1369	11	325	9	896	12	148	15
Current health care provider								
No	630	5	221	6	394	5	15	2
Yes	11,353	95	3264	94	7137	95	952	98
BMI								
<25.0 kg/m^2	4004	33	2151	62	1823	24	30	3
25.0–29.9 kg/m^2	4037	34	1181	34	2588	34	268	28
30.0–34.9 kg/m^2	2357	20	134	4	1873	25	350	36

Characteristic	All Women		No. of Cardiometabolic Abnormalities at Baseline					
			0		1 or 2		3 or 4	
	No.	%	No.	%	No.	%	No.	%
>35.0 kg/m^2	1584	13	15	0	1246	17	323	33
Cardiometabolic abnormalities								
Waist circumference								
<88 cm	6927	57	3508	100	3390	45	29	3
≥88 cm	5149	43	0	–	4203	55	946	97
High cholesterol								
No	10,486	87	3508	100	6673	88	305	31
Yes	1590	13	0	–	920	12	670	69
Diabetes								
No	11,412	95	3508	100	7401	97	503	52
Yes	664	5	0	–	192	3	472	48
Hypertension								
No	5570	46	3508	100	2038	27	24	2
Yes	6506	54	0	–	5555	73	951	98
Lifestyle factors								
Smoking status								
Never smoked	5993	50	1754	51	3755	50	484	51
Past smoker	5247	44	1486	43	3333	44	428	45
Current smoker	684	6	221	6	418	6	45	5
Alcohol intake								
Nondrinker	1190	10	265	8	780	10	145	15
Past drinker	2002	17	410	12	1292	17	300	31
<1 drink/mo	1524	13	383	11	1008	13	133	14
<1 drink/wk	2508	21	704	20	1629	22	175	18
1 to <7 drinks/wk	3145	26	1153	33	1854	25	138	14
≥7 drinks/wk	1637	14	577	17	982	13	78	8
Episodes of moderate to strenuous activity								
No activity	1708	15	334	10	1180	16	194	21
Some activity of limited duration	4594	40	1178	36	2985	42	431	46

Characteristic	All Women		No. of Cardiometabolic Abnormalities at Baseline					
			0		1 or 2		3 or 4	
	No.	%	No.	%	No.	%	No.	%
2 or 3 episodes/wk	2147	19	692	21	1294	18	161	17
≥4 episodes/wk	2982	26	1113	34	1727	24	142	15
HT usage status								
Never used	5054	42	1193	34	3352	44	509	52
Past or current user	7010	58	2310	66	4235	56	465	48

Abbreviations: BMI, body mass index; CT, clinical trial; DM, dietary modification; HT, hormone therapy; WHI, Women's Health Initiative.

[a] *Other* includes Hispanic/Latino, Asian or Pacific Islander, American Indian or Alaskan Native, and other.

TABLE 2.

Numbers and Top 5 Causes of Death for Each Competing Risk Category

Cancer Deaths	No.	CVD Deaths	No.	Other Causes	No.
Total	1546	Total	733	Total	1328
Top 5 causes		Top 5 causes		Top 5 causes	
Breast cancer	597	Possible CHD	227	Unknown cause	398
Colon cancer	272	Other cardiovascular	221	Known other cause	268
Pancreas cancer	222	Cerebrovascular	177	Dementia/Alzheimer disease	236
Endometrial cancer	82	Definite CHD	94	COPD	89
Lymphoma	82	Pulmonary embolism	11	Pneumonia	72

Abbreviations: CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

TABLE 3.

HRs and 95% Cis for Cancer, CVD, and Other-Cause Mortality by the Presence of Cardiometabolic Abnormalities at Baseline Enrollment Into WHI

	All-Cause Mortality			Cancer Mortality			CVD Mortality			Other-Cause Mortality		
	Deaths	HR	95% CI	Deaths	HR	95% CI	Deaths	HR	95% CI	Deaths	HR	95% CI
Unadjusted	3607			1546			733			1328		
Waist circumference												
<88 cm	1876	Reference		817	Reference		368	Reference		691	Reference	
>88 cm	1731	1.33	1.24–1.42	729	1.25	1.14–1.39	365	1.44	1.25–1.67	637	1.35	1.21–1.51
History of high cholesterol												
No	3035	Reference		1333	Reference		597	Reference		1105	Reference	
Yes	572	1.29	1.18–1.41	213	1.08	0.93–1.24	136	1.57	1.30–1.89	223	1.40	1.21–1.62
History of diabetes												
No	3295	Reference		1444	Reference		660	Reference		1191	Reference	
Yes	312	1.83	1.63–2.05	102	1.32	1.08–1.61	73	2.18	1.72–2.78	137	2.29	1.92–2.73
Hypertension												
No	1235	Reference		630	Reference		161			444	Reference	
Yes	2372	1.74	1.62–1.86	916	1.28	1.16–1.42	572	3.25	2.73–3.87	884	1.84	1.64–2.06
Cardiometabolic abnormalities												
0	697	Reference		363	Reference		87	Reference		247	Reference	
1 or 2	2480	1.77	1.63–1.93	1037	1.39	1.23–1.56	534	3.10	2.48–3.89	909	1.88	1.63–2.16
3 or 4	430	2.56	2.27–2.88	146	1.58	1.30–1.91	112	5.49	4.15–7.26	172	3.02	2.49–3.67
P for trend			<.001			<.001			<.001			<.001
Adjusted[a]												
Waist circumference												
<88 cm	1876	Reference		817	Reference		368	Reference		691	Reference	
>88 cm	1731	1.17	1.06–1.30	729	1.22	1.04–1.42	365	1.13	0.90–1.43	637	1.15	0.97–1.36
History of high cholesterol											Reference	
No	3035	Reference		1333	Reference		597	Reference		1105		
Yes	572	1.06	0.96–1.16	213	0.99	0.85–1.16	136	1.14	0.93–1.39	223	1.09	0.93–1.27
History of diabetes												
No	3295	Reference		1444	Reference		660	Reference		1191	Reference	

	All-Cause Mortality			Cancer Mortality			CVD Mortality			Other-Cause Mortality		
	Deaths	**HR**	**95% CI**	**Deaths**	**HR**	**95% CI**	**Deaths**	**HR**	**95% CI**	**Deaths**	**HR**	**95% CI**
Yes	312	1.45	1.27–1.64	102	1.04	0.83–1.29	73	1.53	1.18–2.00	137	1.93	1.59–2.35
Hypertension												
No	1235	Reference		630	Reference		161	Reference		444	Reference	
Yes	2372	1.36	1.26–1.47	916	1.17	1.04–1.31	572	2.33	1.92–2.83	884	1.25	1.11–1.42
Cardiometabolic abnormalities												
0	697	Reference		363	Reference		87	Reference		247	Reference	
1 or 2	2480	1.50	1.36–1.65	1037	1.29	1.12–1.48	534	2.52	1.95–3.26	909	1.45	1.23–1.70
3 or 4	430	1.99	1.73–2.30	146	1.37	1.10–1.72	112	4.01	2.88–5.57	172	2.14	1.70–2.69
P for trend			<.001			.001			<.001			<.001

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; WHI, Women s Health Initiative.

[a]Adjustments were made for the following: age group at cancer diagnosis, education, race, WHI study group, current health care provider, body mass index, smoking status, alcohol intake, physical activity, and hormone therapy use.

TABLE 4.

Adjusted HRs and 95% CIs for Cancer Site-Specific Mortality by the Presence of Cardiometabolic Abnormalities at Baseline Enrollment Into WHI

		Site-Specific Cancer Mortality	
	No. of Deaths	**HR[a]**	**95% CI**
Breast cancer			
High waist circumference	266	1.21	0.93–1.58
History of high cholesterol	75	0.95	0.73–1.22
History of diabetes	29	0.83	0.55–1.26
Hypertension	330	1.10	0.92–1.32
Cardiometabolic abnormalities			
1 or 2	386	1.13	0.91–1.41
3 or 4	46	1.14	0.78–1.66
P for trend			.333
Colorectal cancer			
High waist circumference	139	1.27	0.88–1.85
History of high cholesterol	42	0.91	0.64–1.28
History of diabetes	25	1.10	0.70–1.73
Hypertension	193	1.43	1.09–1.86
Cardiometabolic abnormalities			
1 or 2	195	1.28	0.93–1.78
3 or 4	34	1.48	0.90–2.42
P for trend			.095
Endometrial cancer			.095
High waist circumference	49	0.85	0.39–1.86
History of high cholesterol	9	1.20	0.59–2.45
History of diabetes	5	1.14	0.44–2.96
Hypertension	39	0.64	0.39–1.04
Cardiometabolic abnormalities			
1 or 2	57	1.04	0.53–2.04
3 or 4	7	0.89	0.32–2.48
P for trend			.867

Abbreviations: CI, confidence interval; HR, hazard ratio; WHI, Women's Health Initiative

[a]Adjustments were made for the following: age group at cancer diagnosis, education, race, WHI study group, current health care provider, body mass index, smoking status, alcohol intake, physical activity, and hormone therapy use.