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ORIGINAL RESEARCH

Temporal Associations and Outcomes of Breast Cancer and Heart Failure in Postmenopausal Women

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ABSTRACT

BACKGROUND Heart failure (HF) and breast cancer are 2 of the leading causes of death in postmenopausal women. The temporal association between HF and breast cancer in postmenopausal women has not been described.

OBJECTIVES This study sought to examine the temporal association between HF and breast cancer.

METHODS Postmenopausal women within the WHI (Women's Health Initiative) cohort were studied. All prevalent HF and prevalent breast cancer at enrollment were self-reported. Incident hospitalized HF and breast cancer diagnoses were adjudicated through 2017.

RESULTS Among a cohort of 44,174 women (mean age 63 ± 7 years), 2,188 developed incident invasive breast cancer and 2,416 developed incident hospitalized HF over a median follow-up of 14 and 15 years, respectively. When compared with a breast cancer- and HF-free cohort, there was no association between prevalent HF and incident invasive breast cancer and similarly, there was no association between prevalent breast cancer and incident hospitalized HF. Across the entire cohort, the median survival after incident hospitalized HF was worse compared with an incident invasive breast cancer diagnosis (5 and 19 years, respectively). In women with incident invasive breast cancer, prevalent HF was associated with an increased risk of mortality (hazard ratio: 2.28; 95% confidence interval: 1.31 to 3.95). In women with incident hospitalized HF, prevalent breast cancer was associated with an increased risk of mortality (hazard ratio: 1.66; 95% confidence interval: 1.03 to 2.68). Cause of death after incident HF was different only in women with prevalent and interim breast cancer compared with those without prevalent and interim breast cancer.

CONCLUSIONS In postmenopausal women, prevalent HF was not associated with a higher incidence of breast cancer and vice versa. However, the presence of incident invasive breast cancer or incident HF in those with prevalent HF or prevalent breast cancer, respectively, was associated with increased mortality. (J Am Coll Cardiol CardioOnc 2020;2:567–77) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CI = confidence interval

HF = heart failure

HR = hazard ratio

WHR = waist-hip ratio

WHI = Women's Health Initiative

Heart failure (HF) and cancer are 2 of the leading causes of death in the United States (1-3). HF and cancer share risk factors such as obesity, hypertension, diabetes mellitus, and the use of tobacco and alcohol, as well as pathophysiologic alterations such as heightened inflammation, oxidative stress, and immune dysregulation (4-8). Although cancer therapies, including certain chemotherapies and radiation, can cause myocardial dysfunction and may predispose patients to the development of incident HF (4-6,9), there have been conflicting results as to whether HF is associated with a higher risk of incident cancer (10-13).

Prior studies have evaluated the association of breast cancer with the development of cardiovascular disease in postmenopausal women (14-16). To our knowledge, no study to date has examined the association between HF and the subsequent development of invasive and noninvasive breast cancer in postmenopausal women. Aside from the above-mentioned risk factors, unique to women, hormonal factors such as early menarche, late menopause, and nulliparity, are also shared risk factors for both breast cancer and HF (17,18). In this study, we sought to further expand our understanding of the association between HF and breast cancer and subsequent outcomes in a cohort of postmenopausal women using the WHI (Women's Health Initiative) cohort. Specifically, we aimed to determine first, whether prevalent HF is a risk factor for incident breast cancer and whether prevalent breast cancer is a risk factor for incident hospitalized HF. Second, we aimed to determine whether prevalent HF increases the risk of mortality after incident breast cancer and whether prevalent breast cancer increases the risk of mortality after incident HF.

METHODS

DATA SOURCE AND STUDY POPULATION. The design of the WHI National Health Study has been previously described (19). Briefly, it is a large U.S.-based preventative study that enrolled 161,808 postmenopausal women (ages 50 to 79 years) between 1993 and 1998 at 40 U.S. clinical centers (19). Women were enrolled into either the clinical trial arm (2 hormone therapy trials: a trial of dietary modification and a trial of calcium and vitamin D supplementation; n = 68,132) or the observational study arm (n = 93,676). In 2010, a subcohort of 44,174 participants, including all women who had participated in the WHI Hormone Trials and additionally oversampled African Americans and Hispanic/Latina women, were evaluated both retrospectively and prospectively until February 28, 2017, for incident hospitalized HF events by trained physician adjudicators (20,21). Institutional review boards at all WHI clinical centers approved the WHI study, and all participants provided written informed consent.

BASELINE DEMOGRAPHIC AND CLINICAL INFORMATION. Each participant completed self-administered questionnaires, an interview, and a physical examination at the time of enrollment in WHI.

DEFINITION AND ADJUDICATION OF BREAST CANCER AND HF. Prevalent breast cancer and prevalent HF were defined as participants self-reporting the presence of these diseases at the time of enrollment. Incident breast cancer diagnosis and incident hospitalized HF were centrally adjudicated. For all cases of breast cancer, documentation was sent to the clinical coordinating center for centralized review and coding by trained cancer coders under the supervision of a cancer epidemiologist and physician. These include hospital discharge summaries, operative reports, history and physical examination, radiology reports, oncology consultation reports, and estrogen and progesterone hormone receptor results for breast cancers (22). The WHI adjudication criteria for incident HF have been previously described in detail elsewhere (20). Briefly, hospital records of suspected HF were abstracted to include evidence of new onset of symptoms, history of HF, general medical history, physical examination, diagnostic tests, biomarkers, and medications (21). Physician adjudicators reviewed this information for evidence of acute decompensated HF.

HF was further classified as definite acute decompensated HF, possible acute decompensated HF, chronic stable HF, unclassifiable, or HF unlikely (23). Only definite and possible decompensated HF cases were classified as incident hospitalized HF. Only the

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* author instructions page.

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TABLE 1 Baseline Characteristics of Participants by Prevalent Breast Cancer and Heart Failure

	Breast Cancer- and Heart Failure-Free Population (n = 42,817)	Prevalent Breast Cancer (n = 673)	Prevalent Heart Failure (n = 665)	Prevalent Breast Cancer and Heart Failure (n = 19)	p Value
Age, yrs	63 ± 7	63 ± 7	65 ± 7*†	64 ± 9	<0.001
Race					<0.001
White	21,810 (51)	28 (4)‡	191 (29)*†	1 (5)	
Black	13,736 (32)	491 (73)‡	375 (56)*†	16 (84)	
Other	7,271 (17)	154 (23)‡	99 (15)*†	2 (11)	
Coronary artery disease	3,846 (9)	74 (11)	413 (62)*†	12 (63)	<0.001
Myocardial infarction	900 (2)	15 (2)	232 (35)*†	8 (44)	<0.001
Angina	2,400 (6)	46 (7)	316 (49)*†	6 (33)	<0.001
CABG	324 (1)	4 (1)	71 (11)*†	1 (6)	<0.001
Atrial fibrillation	1,575 (4)	27 (4)	118 (19)*†	3 (17)	<0.001
Hyperlipidemia	5,561 (14)	122 (19)‡	192 (31)*†	3 (16)	<0.001
Hypertension	16,259 (38)	330 (50)‡	492 (76)*†	17 (90)	<0.001
Peripheral artery disease	927 (2)	28 (4)‡	87 (13)*†	2 (12)	<0.001
Diabetes	3,774 (9)	95 (14)‡	210 (32)*†	4 (21)	<0.001
Stroke	634 (2)	22 (3)‡	58 (9)*†	5 (26)	<0.001
Transient ischemic attack	885 (2)	20 (3)	64 (10)*†	3 (16)	<0.001
Hormone therapy	21,610 (52)	279 (42)‡	323 (49)†	6 (32)	<0.001
Pregnancy	16,049 (93)	228 (91)	268 (94)	6 (100)	0.483
Hysterectomy	18,721 (44)	368 (55)‡	381 (57)*	14 (74)	<0.001
Oophorectomy	11,536 (28)	240 (37)‡	238 (38)*	8 (50)	0.001
Nulliparity	4,640 (11)	114 (17)‡	59 (9)†	2 (11)	0.001
Age at menarche, yrs	13	13	13	12	0.467
Age at menopause, yrs	47 ± 7	46 ± 7‡	46 ± 8*	46 ± 9	0.001
Smoking status					0.064
Never	21,776 (52)	295 (46)	354 (53)	8 (50)	
Past	16,128 (38)	281 (43)	237 (36)	7 (44)	
Current	4,264 (10)	237 (36)	72 (11)	1 (6)	
Pack-year smoking	9 ± 18	7 ± 15‡	13 ± 23*†	9 ± 15	<0.001
Alcohol status					<0.001
Never	6,034 (14)	130 (19)	133 (20)	3 (16)	
Past	9,932 (23)	222 (33)	291 (44)	8 (42)	
Current	26,851 (63)	321 (48)	241 (36)	8 (42)	
Pulse, beats/min	70 ± 12	72 ± 13‡	71 ± 11	74 ± 16	0.005
Systolic blood pressure, mm Hg	129 ± 18	130 ± 17	135 ± 21*†	133 ± 20	<0.001
Diastolic blood pressure, mm Hg	76 ± 9	77 ± 9	76 ± 11	75 ± 10	0.475
Body mass index, kg/m^2	29.6 ± 6.2	30.2 ± 6.2‡	32.6 ± 7.7*†	34.3 ± 7.1	<0.001
Height, cm	161 ± 7	161 ± 7	161 ± 7	159 ± 8	0.359
Weight, kg	77 ± 17	79 ± 18	85 ± 21*†	87 ± 19	<0.001
Waist-hip ratio	0.82 ± 0.08	0.83 ± 0.07	0.85 ± 0.08*†	0.86 ± 0.07	<0.001
Total physical activity, MET-h/week	6.4 ± 10.5	6.5 ± 10.4	4.8±9.4*†	4.7 ± 7.2	<0.001
Hemoglobin, g/dl	13.4 ± 1.17	13.0 ± 1.11‡	13.1 ± 1.36*	12.5 ± 1.28	<0.001

Values are mean ± SD or n (%), unless otherwise indicated. *Significance ($p < 0.05$) when comparing prevalent heart failure to the breast cancer– and heart failure–free population. †Significance ($p < 0.05$) when comparing prevalent heart failure to prevalent breast cancer. ‡Significance ($p < 0.05$) when comparing prevalent breast cancer to the breast cancer– and heart failure–free population.

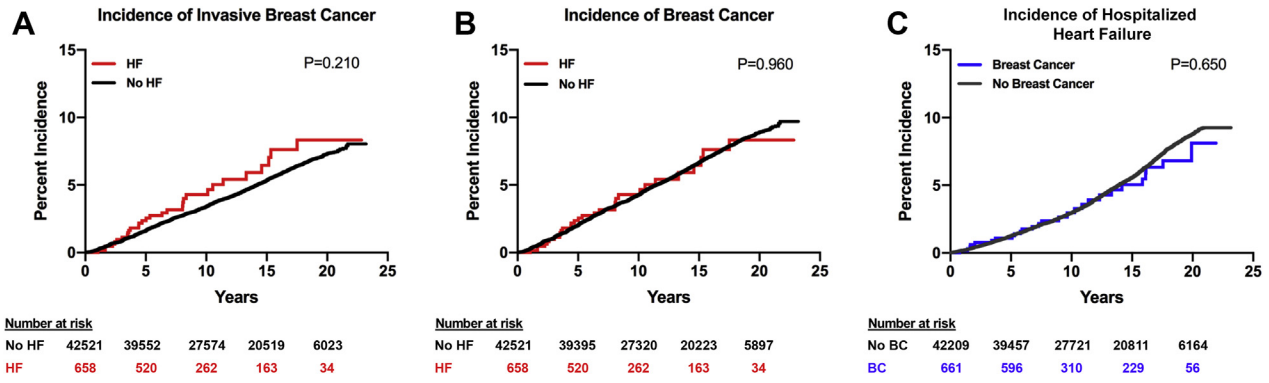
CABG = coronary artery bypass graft; MET = metabolic equivalent.

first acute decompensated HF event was considered incident. When computing incident HF, we excluded women who had chronic HF on their first adjudication. All follow-up forms and outcomes were updated through February 28, 2017 (18).

CAUSE OF DEATH. Cause of death in the study was centrally adjudicated and included death from cardiovascular disease, death from cancer, death from other causes, and death from unknown causes. Mortality information and cause of death was enhanced by serial National Death Index queries.

STATISTICAL ANALYSES. Baseline characteristics at enrollment are presented as mean ± SD or count with percentage. Differences in baseline characteristics

FIGURE 1 Cumulative Incidence of Invasive Breast Cancer, All Breast Cancer, and HF



Cumulative incidence of invasive breast cancer, all breast cancer (invasive and noninvasive), and heart failure (HF) among women with and without prevalent HF or prevalent breast cancer. **(A)** Cumulative incidence of invasive breast cancer among women with and without prevalent HF. **(B)** Cumulative incidence of all breast cancer among women with and without prevalent HF. **(C)** Cumulative incidence of HF among women with and without prevalent breast cancer.

across the 4 groups: 1) breast cancer- and HF-free cohort; 2) prevalent breast cancer; 3) prevalent HF; and 4) prevalent breast cancer and HF—were compared using analysis of variance for continuous variables and chi-square test for categorical variables. We performed 3 pairwise comparisons (with Bonferroni adjustment): 1) prevalent HF versus breast cancer- and HF-free cohort; 2) prevalent breast cancer versus breast cancer- and HF-free cohort; and 3) prevalent HF versus prevalent breast cancer. The cumulative incidence of HF, invasive breast cancer, and all incident breast cancer (invasive and noninvasive) was presented as events per 1,000 person-years with 95% confidence interval (CI). Multivariable Cox proportional hazards regression was used to examine the risk factors associated with incident HF, incident invasive breast cancer, and incident breast cancer. For Cox proportional hazards models of incident HF, incident invasive breast cancer, and all incident breast cancer, we adjusted for the following baseline covariates: age; race; body mass index (BMI); waist-hip ratio (WHR); diabetes mellitus; hypertension; myocardial infarction; coronary artery disease; atrial fibrillation; pulse; systolic blood pressure; smoking; alcohol use; total physical activity (metabolic equivalent-hours per week); hemoglobin; menopausal hormone therapy trial participation and menopausal hormone therapy trial arm; age at menarche; parity; oophorectomy; and hysterectomy. Only variables that were statistically significant ($p < 0.05$) in univariable analysis were subsequently included in the multivariable Cox proportional hazards regression.

The associations between prevalent HF with incident breast cancer and prevalent breast cancer with incident HF were determined using the Kaplan-Meier estimate with log-rank statistics and Cox proportional hazards model. To evaluate the association between incident breast cancer (invasive and all breast cancer) and all-cause mortality in participants with prevalent HF or prevalent and interim HF, we defined interim HF as a HF diagnosis at any time prior to the development of incident breast cancer in the HF-free population. Similarly, to evaluate the association between incident HF and all-cause mortality in participants with prevalent breast cancer or prevalent and interim breast cancer, we defined interim breast cancer as a diagnosis of breast cancer at any time prior to the development of incident hospitalized HF in the breast cancer-free population. Cox proportional hazards model adjusting for age was performed. However, additional covariates were not included in a multivariable model given the lack of updated comorbidities data at the time of development of incident breast cancer or incident heart failure. Formal hypothesis testing comparing survival after incident breast cancer to survival after incident HF was not performed. Numerical median and overall survival of the 2 conditions were reported. In a sensitivity analysis, we used the Fine and Gray Cox proportional subdistribution models to examine the association of incident breast cancer or HF by prevalent disease with all-cause mortality accounting for the competing risk of death. We also performed a sensitivity analysis modeling HF and breast cancer as time-varying covariates to determine its effect on

TABLE 2 Unadjusted Incidence Rates of Incident Disease in Women With and Without Breast Cancer and Heart Failure

Outcome	Group	Unadjusted Incidence Rate (per 1,000 Person-Years)	95% CI	p Value
Incident invasive breast cancer	Prevalent heart failure	4.5	3.2–6.5	0.210
	No heart failure	3.7	3.5–3.8	
Incident breast cancer	Prevalent heart failure	4.5	3.2–6.5	0.960
	No heart failure	4.6	4.4–4.7	
Incident heart failure	Prevalent breast cancer	3.5	2.4–5.1	0.650
	No breast cancer	4.1	3.9–4.2	

CI = confidence interval.

incident events and mortality. All analyses were 2-sided and a p value of 0.05 was considered statistically significant. Analyses were conducted with STATA (version 12, StataCorp. LP, College Station, Texas).

RESULTS

OVERALL PARTICIPANT CHARACTERISTICS AT ENROLLMENT. The mean age at enrollment of the study cohort of 44,174 women was 63 ± 7 years with 50% White and 33% Black participants. Participants were overweight and had abdominal obesity (average BMI was 29.6 ± 6.3 kg/m^2 and average WHR was 0.82 ± 0.08). Nearly one-half smoked tobacco and 39% had hypertension (23% had a systolic blood pressure >140 mm Hg at enrollment); other cardiovascular comorbidities were less common (**Table 1**). Prevalence of breast cancer at enrollment was 1.6% (n = 692 of 44,174) and prevalence of HF was 1.5% (n = 684 of 44,174). Nineteen women had both breast cancer and HF at enrollment. A total of 42,817 women constituted the breast cancer- and HF-free population.

BASELINE CLINICAL CHARACTERISTICS OF PARTICIPANTS BY PREVALENT BREAST CANCER AND HF. Baseline characteristics of the 4 groups are shown in **Table 1**. Women with prevalent breast cancer or prevalent HF were more likely to be Black and had a greater prevalence of cardiovascular risk factors compared with the breast cancer- and HF-free cohort. Compared with patients with prevalent breast cancer, patients with prevalent HF were older, heavier, had a higher burden of cardiovascular comorbidities, and were less active.

BREAST CANCER INCIDENCE. Over a median follow-up of 14 years (maximum of 23 years), 43,482 women were at risk for breast cancer. There was no difference in the incidence of invasive or all breast cancer between women with or without prevalent HF. Cumulative incidence and incidence rates by group are shown in **Figures 1A and 1B and Table 2**. The number of incident breast cancer events by prevalent HF are shown in Supplemental Table 1.

HF INCIDENCE. Over a median follow-up of 15 years (maximum of 23 years), 43,173 women were at risk for HF. There was no difference in the incidence of hospitalized HF between women with or without prevalent breast cancer. Cumulative incidence and incidence rates by group are shown in **Figure 1C** and **Table 2**. The number of incident HF events by prevalent breast cancer are shown in Supplemental Table 1.

ASSOCIATIONS WITH INCIDENT BREAST CANCER AND HF. Independent predictors of incident invasive breast cancer were age, BMI, WHR, alcohol use, age at menarche, parity, history of bilateral oophorectomy, physical inactivity, and low hemoglobin (**Table 3**). The results were similar when data included all incident breast cancer (**Table 4**). Independent predictors of incident HF were age, white race, BMI, WHR, smoking, alcohol use, diabetes, hypertension, coronary artery disease, atrial fibrillation, physical inactivity,

TABLE 3 Multivariable Associations With Incident Invasive Breast Cancer

Covariate	HR*	Lower 95% CI	Upper 95% CI	p Value
Age, yrs	1.01	1.01	1.02	<0.001
Body mass index, kg/m^2	1.02	1.02	1.03	<0.001
Waist-hip ratio	1.81	1.06	3.09	0.029
Alcohol use	1.04	1.01	1.08	0.004
Menarche	0.96	0.93	0.99	0.011
Parity	0.97	0.94	0.99	0.008
Bilateral oophorectomy	0.80	0.71	0.91	0.001
Total energy expenditure, MET-h/week	1.00	0.99	1.00	0.031
Hemoglobin, g/dl	1.04	1.01	1.08	0.025

*Prevalent heart failure and all other variables in Table 1 were not significant (p > 0.05) and not included in Table 3. for continuous variables, HRs represent each 1-U increase in parameter.

CI = confidence interval; HR = hazard ratio.

TABLE 4 Multivariable Associations With Incident Breast Cancer

Covariate	HR*	Lower 95% CI	Upper 95% CI	p Value
Age, yrs	1.01	1.00	1.01	0.008
Body mass index, kg/m^2	1.02	1.02	1.03	<0.001
Waist-hip ratio	2.09	1.31	3.34	0.002
Alcohol use	1.03	1.01	1.06	0.013
Menarche	0.97	0.95	1.00	0.03
Parity	0.97	0.95	0.99	0.011
Bilateral oophorectomy	0.84	0.75	0.94	0.003
Total energy expenditure, MET-h/week	1.00	0.99	1.00	0.018
Pulse, beats/min	1.00	1.00	1.01	0.022
Hemoglobin, g/dl	1.04	1.00	1.07	0.044

*Prevalent heart failure and all other variables in Table 1 were not significant ($p > 0.05$) and not included in Table 4. for continuous variables, HRs represent each 1-U increase in parameter.
Abbreviations as in Tables 1 to 3.

heart rate, systolic blood pressure, low hemoglobin, and trial participation (but not randomization to menopausal hormone therapy trial) (Table 5). Prevalent breast cancer was not a predictor of incident HF and similarly, prevalent HF was not a predictor of incident breast cancer in univariable- and multivariable-adjusted analyses. Shared predictors of both incident breast cancer and incident HF were age, BMI, WHR, alcohol use, physical inactivity, and heart rate (Tables 3 to 5).

MORTALITY IN THE BREAST CANCER AND HF-FREE POPULATION. A total of 37,654 participants were free of prevalent or incident breast cancer and HF, of whom 5,996 died over a median follow-up of 15 years after enrollment (incidence rate of 11 deaths per 1,000 person-years).

TABLE 5 Multivariable Associations With Incident Hospitalized Heart Failure

Covariate	HR*	Lower 95% CI	Upper 95% CI	p Value
Age, yrs	1.10	1.09	1.10	<0.001
White race	1.35	1.17	1.56	<0.001
Body mass index, kg/m^2	1.04	1.03	1.05	<0.001
Waist-hip ratio	3.03	1.88	4.88	<0.001
Smoking history	1.54	1.44	1.65	<0.001
Alcohol use	0.95	0.93	0.98	0.002
Diabetes mellitus	2.32	2.07	2.61	<0.001
Hypertension	1.41	1.28	1.56	<0.001
Myocardial infarction	1.92	1.58	2.33	<0.001
Coronary artery disease (excluding myocardial infarction)	1.47	1.27	1.69	<0.001
Atrial fibrillation	1.54	1.30	1.84	<0.001
Randomized to the hormone replacement therapy trial	1.40	1.20	1.64	<0.001
Total energy expenditure, MET-h/week	0.99	0.99	1.00	0.008
Systolic blood pressure, mm Hg	1.01	1.01	1.02	<0.001
Pulse, beats/min	1.00	1.00	1.01	0.003
Hemoglobin, g/dl	0.93	0.89	0.97	<0.001

*Prevalent breast cancer and all other variables in Table 1 were not significant ($p > 0.05$) and not included in Table 5. For continuous variables, HRs represent each 1-U increase in parameter.
Abbreviations as in Tables 1 to 3.

MORTALITY AFTER INCIDENT BREAST CANCER. A total of 2,188 participants developed incident invasive breast cancer, of whom 573 died over a median follow-up of 7 years. A total of 2,688 participants developed all incident breast cancer, of whom 639 died over a median follow-up of 7 years. Median survival after incident invasive breast cancer was 19 years (25th percentile was 9 years) and after all incident breast cancer was 19 years (25th percentile was 10 years) (Central Illustration). Women with prevalent HF or prevalent and interim HF had a higher risk of mortality after incident invasive breast cancer compared with women without HF (age-adjusted hazard ratio [HR]: 2.28; 95% CI: 1.31 to 3.95; and age-adjusted HR: 2.58; 95% CI: 1.88 to 3.55, respectively) (Table 6). The results were similar when the data included both invasive and noninvasive breast cancer (Table 6). The association of incident breast cancer by prevalent HF with all-cause mortality was unaffected by the competing risk of death ($p = 0.212$).

MORTALITY AFTER INCIDENT HF. A total of 2,416 participants developed incident hospitalized HF, of whom 1,362 died over a median follow-up of 3 years. Median survival after incident HF was 5 years (25th percentile was 1 year). Survival curves by log-rank statistics are shown in the Central Illustration. Women with prevalent breast cancer or prevalent and interim breast cancer had a higher risk of mortality after incident HF compared with women without breast cancer (age-adjusted HR: 1.66; 95% CI: 1.03 to 2.68; and age-adjusted HR: 1.27; 95% CI: 1.03 to 1.58, respectively) (Table 6). The association of incident HF by prevalent breast cancer with all-cause mortality was unaffected by the competing risk of death ($p = 0.335$).

SENSITIVITY ANALYSIS USING TIME-VARYING COVARIATES. When analyzing incident HF with breast cancer events modeled as a time-varying covariate, prevalent breast cancer was a significant predictor of incident HF only in univariable analysis. Breast cancer was no longer a significant predictor of HF after adjusting for age or the other significant predictors of incident HF included in Tables 3 to 5. Similarly, when analyzing incident breast cancer with HF events modeled as a time-varying covariate, prevalent HF was not a significant predictor of incident breast cancer in univariate analysis or when adjusting for other covariates. When HF and breast cancer events were modeled as time-varying covariates, there was no difference in

CENTRAL ILLUSTRATION **Associations Between Heart Failure and Breast Cancer in Postmenopausal Women Enrolled in the Women's Health Initiative**

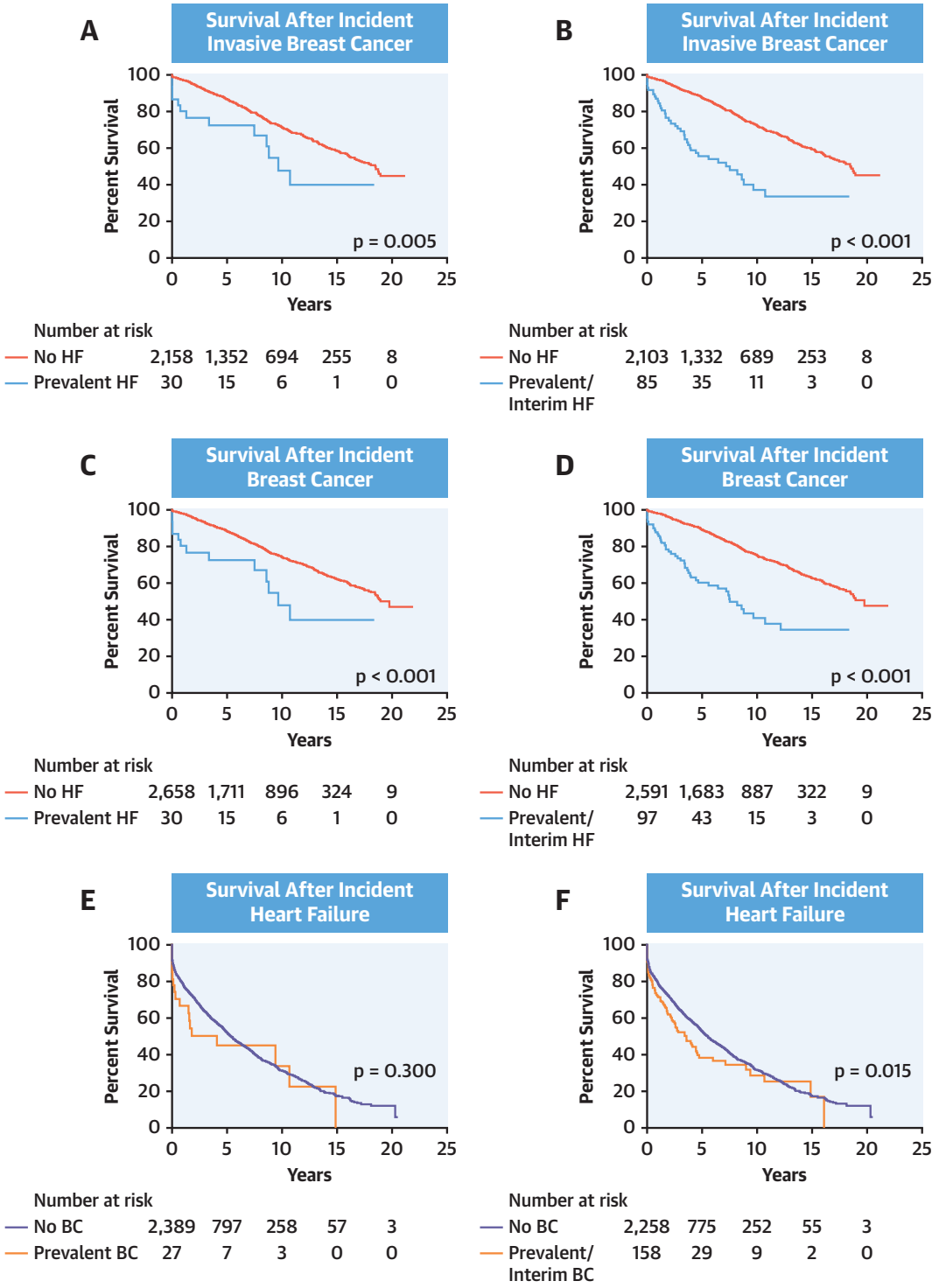


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TABLE 6 Associations With Prevalent and Interim Breast Cancer and Heart Failure With All-Cause Mortality After Development of Incident Disease

Outcome	Subgroup	HR (95% CI)*	p Value
Mortality after incident invasive breast cancer	Prevalent heart failure		
	Univariable	2.16 (1.25–3.75)	0.005
	Age-adjusted	2.28 (1.31–3.95)	<0.001
	Prevalent and interim heart failure		
	Univariable	3.20 (2.33–4.38)	<0.001
	Age-adjusted	2.58 (1.88–3.55)	<0.001
Mortality after incident breast cancer	Prevalent heart failure		
	Univariable	2.46 (1.42–4.26)	0.001
	Age-adjusted	2.57 (1.48–4.45)	0.001
	Prevalent and interim heart failure		
	Univariable	3.30 (2.44–4.46)	<0.001
	Age-adjusted	2.67 (1.20–3.60)	<0.001
Mortality after incident heart failure	Prevalent breast cancer		
	Univariable	1.29 (0.80–2.08)	0.300
	Age-adjusted	1.66 (1.03–2.68)	0.038
	Prevalent and interim breast cancer		
	Univariable	1.30 (1.05–1.61)	0.015
	Age-adjusted	1.27 (1.03–1.58)	<0.001

HR referent group is "no breast cancer" in mortality after incident heart failure analyses and "no heart failure" in mortality after incident breast cancer analyses.
Abbreviations as in Tables 1 to 3.

its effect on mortality. This was consistent with the analysis using prevalent and prevalent and interim events.

CAUSE OF DEATH. Cause of death after incident HF was different in women with prevalent and interim breast cancer compared with in those without prevalent breast cancer (Table 7). Otherwise, there was no significant difference in the cause of death between the different groups.

DISCUSSION

In this cohort of postmenopausal women enrolled in the WHI—despite shared risk predictors such as age, obesity, alcohol use, physical inactivity, and elevated resting heart rates—we found no significant association between the development of incident hospitalized HF and incident breast cancer diagnosis in participants with prevalent breast cancer and prevalent HF, respectively. Across the entire cohort, the median survival after incident hospitalized HF was worse compared with that after incident invasive breast cancer (5 and 19 years, respectively). Furthermore, having prevalent breast cancer or prevalent HF was associated with increased mortality in participants who subsequently developed incident breast cancer or incident hospitalized HF, respectively. We found no significant difference in the cause of death between the different groups, except among patients with incident HF in those with prevalent and interim breast cancer compared with in those without prevalent and interim breast cancer. To the best of our knowledge, this is the first study to examine the temporal association between breast cancer and HF in

CENTRAL ILLUSTRATION Continued

Although prevalent heart failure (HF) was not associated a higher incidence of breast cancer (BC) and vice versa, pre-existing BC or HF was associated with an increased mortality in those who develop an incident of the other. Kaplan-Meier survival curves with log-rank statistics in women with incident BC and HF grouped by prevalent or prevalent and interim HF and BC, respectively, are displayed. **(A)** Survival after an incident invasive BC diagnosis in women with and without prevalent HF. **(B)** Survival after an incident invasive BC diagnosis in women with and without prevalent and interim HF. **(C)** Survival after an incident invasive or noninvasive BC diagnosis in women with and without prevalent HF. **(D)** Survival after an incident invasive or noninvasive BC diagnosis in women with and without prevalent and interim HF. **(E)** Survival after incident hospitalized HF in women with and without prevalent BC. **(F)** Survival after incident hospitalized HF in women with and without prevalent and interim BC.

TABLE 7 Cause of Death by Incident Event

	Subgroup	Cancer Death	Cardiovascular Death	Other Cause of Death	Unknown Cause of Death	p Value
Incident heart failure						
	No prevalent breast cancer	166 (12)	703 (52)	332 (25)	144 (11)	0.496
	Prevalent breast cancer	4 (24)	9 (53)	3 (18)	1 (6)	
Incident heart failure						
	No prevalent and interim breast cancer	147 (12)	670 (53)	317 (25)	138 (11)	0.002
	Prevalent and interim breast cancer	23 (26)	42 (47)	18 (20)	7 (8)	
Incident breast cancer						
	No prevalent heart failure	312 (50)	143 (23)	94 (15)	77 (12)	0.967
	Prevalent heart failure	7 (54)	3 (23)	2 (15)	1 (8)	
Incident breast cancer						
	No prevalent and interim heart failure	301 (51)	131 (22)	91 (15)	70 (12)	0.18
	Prevalent and interim heart failure	18 (39)	15 (33)	5 (11)	8 (17)	

Values are n (%), representing the absolute number of cause-specific deaths and the percentage of all deaths, unless otherwise noted.

a large prospective cohort of postmenopausal women.

The relationship between risk factors for HF and cancer is complex and intersects at many levels. Prior studies have suggested systemic pathological processes such as inflammation, oxidative stress, and immune dysregulation that may be involved in the pathogenesis of both HF and malignancy (7,8,24). Age is an established risk factor for both HF and cancer, whereas lifestyle, obesity, and comorbidities (including diabetes mellitus and hypertension) are consistently linked to HF, but their relationship to cancer is site-specific (7,8,24). Furthermore, cancer therapies (radiation and chemotherapy) may constitute a risk for development of HF (7,8,24,25). In our analysis, age, obesity, alcohol use, physical inactivity, and heart rate were shared risk factors for both incident HF and incident breast cancer. Unique risk factors for breast cancer were reproductive attributes and for HF were cardiovascular comorbidities (including diabetes mellitus, hypertension, atrial fibrillation, and coronary artery disease). The lack of association between HF and breast cancer suggests that whereas there may be shared risk factors, neither disease increases the likelihood of developing the other and thus each may have its own distinct pathophysiology. Recent translational studies have shown that certain cytokines, such as serpinA3, that are upregulated in patients with HF can increase the proliferation of intestinal cancer cells in vitro (26). Whether these cytokines promote the development and/or proliferation of all cancers, including breast cancer, needs to be further examined. Because we did not have data for breast cancer therapies, the lack of association between prevalent breast cancer and the development of incident hospitalized HF in our study needs to be interpreted with caution. Moreover, only HF hospitalizations were considered, and it is possible that there were less severe cases of incident disease.

Our findings are in line with a recent analysis that demonstrated no increase in cancer risk among male physicians with HF (13). However, our findings are inconsistent with prior studies by Hasin et al. (10,11) and Banke et al. (12) that demonstrated a higher incidence of cancer in HF patients. The latter study provided a subgroup analysis for patients with breast cancer and showed an HR of 1.36 for incident breast cancer in HF patients (12). Although the results of our study are unlikely to be due to lack of power given the superimposed incidence curves through 20 years of follow-up, this is still a possibility due to the small number of prevalent HF and breast cancer cases at baseline and the small number of incident cases. When the analysis was restricted to invasive breast cancer, there was some separation of the breast cancer incidence curves in patients with HF versus no HF, but the difference did not reach statistical significance.

The incidence of breast cancer in our population was higher than the national average, likely due to enrichment of our population with older, postmenopausal women (27). However, the incidence of HF in our population was comparable to community studies (28,29), as well as studies that have described incident hospitalized HF (30,31). Several studies have evaluated the association between prevalent HF and cancer (10–13). Most of these studies were limited by their small sample size, single-center registry, and inclusion of all types of cancer, which limits

pathophysiologic understanding and generalizability. Our study is distinguished by its focus on the association between breast cancer and HF and outcomes in a large national cohort of postmenopausal women.

Despite the lack of association between HF and breast cancer incidence, incident invasive or all breast cancer in women with prevalent HF and similarly, incident hospitalized HF in women with prevalent breast cancer, were associated with an increased risk of all-cause mortality. Not surprisingly, women with incident HF had a poor prognosis with a median survival of 5 years and in comparison, women with incident invasive breast cancer fared better with a median survival of 19 years (32–34). These findings underscore the burden of HF in postmenopausal women and also highlight the significant impact of both disease processes on prognosis, which are consistent with prior published reports (10). Importantly, our results demonstrate that the additive prognostic implication of a prevalent comorbidity is affected by the mortality rate of the incident disease. For instance, prevalent and incident HF had a greater impact on mortality than prevalent and incident breast cancer, potentially secondary to a higher mortality from HF in and of itself irrespective of breast cancer. This knowledge may inform diagnostic and therapeutic decisions for women with HF and breast cancer and guide preventative and early detection strategies for women at risk. For example, postmenopausal women with either breast cancer or HF should undergo early counseling and aggressive screening and preventive measures for HF or breast cancer, respectively.

STUDY LIMITATIONS. Incident HF in this cohort of the WHI was defined as a HF hospitalization, which may underestimate the incidence of HF as a result of exclusion of outpatient HF (13). In our study, prevalent HF and breast cancer were self-reported, which may result in misclassification and over- or under-reporting (35). As mentioned earlier, we did not have data on cancer therapies, and the lack of association does not rule out interactions between therapies and risk of HF. Prevalent breast cancer cases in the WHI were diagnosed prior to the advent of trastuzumab, which is the current mainstay for HER2-positive disease and an important risk factor for cardiotoxicity (7,8,24,25). Similarly, it is plausible that the risk of cardiotoxicity was mitigated by use of neurohormonal antagonists. However, we are unable to ascertain this as information on HF therapies was not available. We did not have information regarding receptor status and staging of the prevalent breast cancer cases within the WHI, which may affect generalizability and interpretation. Similarly, data on comorbidities at the time of incident disease were not available, which may have had an impact on overall survival. It is well established that age is the strongest predictor of mortality in the general population. The HRs for mortality after incident breast cancer or HF were similar in unadjusted and age-adjusted analyses. This lends support to the strength of the associations observed. Lastly, this study was restricted to postmenopausal women, and hormonal factors in premenopausal women may play a role in the relationship between HF and breast cancer. Nonetheless, there was no association between the 2 conditions despite adjustment for hormone therapy.

CONCLUSIONS

Among a large cohort of postmenopausal women, prevalent HF was not associated with incident breast cancer and similarly, prevalent breast cancer was not associated with incident hospitalized HF. Importantly, the median survival time after incident hospitalized HF was worse than that of incident breast cancer. Despite the lack of association, the presence of prevalent HF or prevalent breast cancer in participants with incident breast cancer or incident HF, respectively, was associated with an increased risk of all-cause mortality.

AUTHOR DISCLOSURES

Dr. Nohria has received research support from Amgen, Inc.; and has consulted for Takeda Oncology. Dr. Fonarow has consulted for Abbott, Amgen, Bayer, Janssen, Novartis, and Medtronic. Dr. Chlebowski has consulted for Novartis, AstraZeneca, Genentech, Merck, and Immunomedics; and has received honorarium from Novartis and AstraZeneca. Dr. Mohammed serves on the Advisory Board for Pfizer; and has received research support from CardioCell, Abbott, Actelion, Corvia, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Prevalent HF was not associated with a higher incidence of breast cancer and vice versa. However, the presence of incident breast cancer or an incident hospitalized HF in those with prevalent HF or prevalent breast cancer, respectively, was associated with an increased risk of all-cause mortality. Importantly, the median survival time after an incident hospitalized HF was substantially worse than after an incident invasive breast cancer diagnosis.

TRANSLATIONAL OUTLOOK: These findings may inform diagnostic and therapeutic decisions for women with HF and breast cancer and guide preventative and early detection strategies for women at risk.

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 2017;135:e146–603.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

3. Weir HK, Anderson RN, Coleman King SM, et al. Heart disease and cancer deaths—trends and projections in the United States, 1969–2020. Prev Chronic Dis 2016;13:E157.

4. Bloom MW, Hamo CE, Cardinale D, et al. Cancer therapy-related cardiac dysfunction and heart failure: part 1: definitions, pathophysiology, risk factors, and imaging. Circ Heart Fail 2016;9:e002661.

5. Hamo CE, Bloom MW, Cardinale D, et al. Cancer therapy-related cardiac dysfunction and heart failure: part 2: prevention, treatment, guidelines, and future directions. Circ Heart Fail 2016;9:e002843.

6. Saiki H, Petersen IA, Scott CG, et al. Risk of heart failure with preserved ejection fraction in older women after contemporary radiotherapy for breast cancer. Circulation 2017;135:1388–96.

7. Blaes A, Prizment A, Koene RJ, Konety S. Cardio-oncology related to heart failure: common risk factors between cancer and cardiovascular disease. Heart Fail Clin 2017;13:367–80.

8. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation 2016;133:1104–14.

9. Versace VL, Berry NM, Chowdhury MH, et al. Characteristics of patients with haematological and breast cancer (1996-2009) who died of heart failure-related causes after cancer therapy. ESC Heart Fail 2016;3:253–60.

10. Hasin T, Gerber Y, McNallan SM, et al. Patients with heart failure have an increased risk of incident cancer. J Am Coll Cardiol 2013;62:881–6.

11. Hasin T, Gerber Y, Weston SA, et al. Heart failure after myocardial infarction is associated with increased risk of cancer. J Am Coll Cardiol 2016;68:265–71.

12. Banke A, Schou M, Videbaek L, et al. Incidence of cancer in patients with chronic heart failure: a long-term follow-up study. Eur J Heart Fail 2016;18:260–6.

13. Selvaraj S, Bhatt DL, Claggett B, et al. Lack of association between heart failure and incident cancer. J Am Coll Cardiol 2018;71:1501–10.

14. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. Epidemiology 2016;27:6–13.

15. Buttros DAB, Branco MT, Orsatti CL, Almeida-Filho BS, Nahas-Neto J, Nahas EAP. High risk for cardiovascular disease in postmenopausal breast cancer survivors. Menopause 2019;26:1024–30.

16. Abdel-Qadir H, Thavendiranathan P, Austin PC, et al. The risk of heart failure and other cardiovascular hospitalizations after early stage breast cancer: a matched cohort study. J Natl Cancer Inst 2019;111:854–62.

17. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012;13:1141–51.

18. Hall PS, Nah G, Howard BV, et al. Reproductive factors and incidence of heart failure hospitalization in the Women's Health Initiative. J Am Coll Cardiol 2017;69:2517–26.

19. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 1998;19:61–109.

20. Eaton CB, Pettinger M, Rossouw J, et al. Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. Circ Heart Fail 2016;9:e002883.

21. Eaton CB, Abdulbaki AM, Margolis KL, et al. Racial and ethnic differences in incident hospitalized heart failure in postmenopausal women: the Women's Health Initiative. Circulation 2012;126:688–96.

22. Curb JD, McTiernan A, Heckbert SR, et al., for the WHI Morbidity and Mortality Committee. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Ann Epidemiol 2003;13 Suppl 9:S122–8.

23. Rosamond WD, Chang PP, Baggett C, et al. Classification of heart failure in the Atherosclerosis Risk in Communities (ARIC) study: a comparison of diagnostic criteria. Circ Heart Fail 2012;5:152–9.

24. Bertero E, Canepa M, Maack C, Ameri P. Linking heart failure to cancer. Circulation 2018;138:735–42.

25. Mehta LS, Watson KE, Barac A, et al. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. Circulation 2018;137:e30–66.

26. Meijers WC, Maglione M, Bakker SJL, et al. Heart failure stimulates tumor growth by circulating factors. Circulation 2018;138:678–91.

27. Centers for Disease Control and Prevention. United States Cancer Statistics. 2015. Available at: https://gis.cdc.gov/Cancer/USCS/DataViz.html. Accessed May 13, 2019.

28. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397–402.

29. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175:996–1004.

30. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol 2008;101:1016–22.

31. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National burden of heart failure events in the United States, 2006 to 2014. Circ Heart Fail 2018;11:e004873.

32. Chlebowski RT, Aragaki AK, Anderson GL, et al. Association of low-fat dietary pattern with breast cancer overall survival: a secondary analysis of the Women's Health Initiative randomized clinical trial. JAMA Oncol 2018;4:e181212.

33. Goldberg RJ, Ciampa J, Lessard D, Meyer TE, Spencer FA. Long-term survival after heart failure: a contemporary population-based perspective. Arch Intern Med 2007;167:490–6.

34. Taylor CJ, Ordonez-Mena JM, Roalfe AK, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000–2017: population based cohort study. BMJ 2019;364:l223.

35. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 2016;133:e38–360.

KEY WORDS breast cancer, heart failure, incidence, mortality

APPENDIX For a supplemental table, please see the online version of this paper.