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Mammography Interval and Breast Cancer Mortality in Women over the age of 75

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Abstract

Purpose—To evaluate the relationship between mammography interval and breast cancer mortality among older women with breast cancer.

Methods—The study population included 1,914 women diagnosed with invasive breast cancer at age 75 or later during their participation in the Women's Health Initiative, with an average follow-up of 4.4 years (3.1 SD). Cause of death was based on medical record review. Mammography interval was defined as the time between the last self-reported mammogram 7 or more months prior to diagnosis, and the date of diagnosis. Multivariable adjusted hazards ratios (HR) and 95% confidence intervals (CIs) for breast cancer mortality and all-cause mortality were computed from Cox proportional hazards analyses.

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Conflict of Interest

The authors indicate that they have no conflicts of interest

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For a list of all the investigators who have contributed to WHI science, please visit: http://www.whiscience.org/publications/WHI_investigators_longlist.pdf

Results—Prior mammograms were reported by 73.0 % of women from 7 months to ≤ 2 year of diagnosis (referent group), 19.4% (> 2 – < 5 years), and 7.5% (≥5 years or no prior mammogram). Women with the longest vs. shortest intervals, had more poorly differentiated (28.5% vs. 22.7%), advanced stage (25.7% vs. 22.9%) and estrogen receptor negative tumors (20.9% vs. 13.1%). Compared to the referent group, women with intervals of > 2 – < 5 years or ≥ 5 years had an increased risk of breast cancer mortality (hazard ratio (HR) 1.62, 95% confidence interval (CI) 1.03–2.54) and (HR 2.80, 95% CI, 1.57–5.00) respectively, p trend = 0.0002. There was no significant relationship between mammography interval and other causes of death.

Conclusions—These results suggest a continued role for screening mammography among women 75 years of age and older.

Background

Breast cancer is predominantly a disease of older women with 43 percent of incident cases, and 57.0 percent of deaths due to breast cancer occurring in women age 65 years and older [1] and a five and nine-fold greater incidence and mortality reported for older compared to younger women [2]. Despite the disproportionate impact of breast cancer on older women, randomized controlled trials of mammography screening are only inclusive of women through age 74 years [3,4], with few studies including women over the age of 65 years [5,6]. The lack of evidence supporting a direct benefit of mammography for women over age 74 led to the 2009 United States Preventive Services Task Force (USPSTF) statement questioning the utility of routine screening mammography for women age 75 years and older regardless of functional status [7]. The USPSTF statement resulted in significant controversy regarding the upper age limit for routine screening mammography.

A number of observational studies have shown a relationship between mammography screening and earlier stage and/or less aggressive disease at diagnosis [8–14] as well as reduction in overall or breast cancer related mortality among women undergoing regular screening [12–21], however others have shown none or low effectiveness of mammography [22–26]. In addition, only three studies have included women over the age of 75 [14,22,23]. We evaluated the relationship between mammography interval and breast cancer mortality among women 75 years of age and older with incident breast cancer who were participants in the Women's Health Initiative (WHI) study of 161,808 postmenopausal women. With an average of 12.2 (S.D. 2.6) years of follow-up and an age and race/ethnic diverse sample, the WHI affords a unique opportunity to assess the relationship between mammography and breast cancer outcomes in a large US cohort.

Materials and Methods

Study Population

The WHI includes an observational study (OS) (n=93,676) and three clinical trials (CT) (n=68,132) of hormone therapy (HT), dietary modification (DM), and calcium, vitamin D supplementation, and enrolled postmenopausal women of different race and ethnicity [27]. Recruitment occurred between October 1, 1993 and December 31, 1998 at 40 clinical centers in the United States. Eligibility included age 50–79 years, postmenopausal, no planned change in residence and an estimated survival of at least 3 years, and for those in

the hormone or dietary modification trials, no history of breast cancer. Study methods have been described previously [28,29]. Participants were initially followed through March, 2005, and were invited to enroll in an extension study from April 1, 2005 through September 30, 2010.

In the WHI, there were 2,824 women age 75 and older diagnosed with breast cancer through September 30, 2010. We excluded 472 women with a diagnosis of insitu breast cancer, 234 with a previous history of breast cancer, 25 with unknown stage, 19 whose breast cancer was ascertained only by death certificate and 11 with a histologic type suggestive of another primary site (adenoid cystic, carcinoid, neuroendocrine, spindle cell, Phyllodes tumor, and sarcoma). We also excluded 139 women who reported a mammogram less than 7 months from diagnosis suggesting the possibility of a diagnostic mammogram, and 10 who only reported a mammogram at study entry that occurred at an unknown date. The current analysis is based 1,914 women diagnosed with invasive breast cancer at age 75 years and older. All participants signed informed consent and all protocols and procedures were approved by institutional review boards of the participating institutions. Follow-up from the time of diagnosis was through the last documented follow-up contact, death, or September 30, 2010 (whichever came first) for a mean (SD) follow-up of 4.4 (3.1) years and a maximum of 15.3 years.

Breast Cancer Diagnosis, Screening and Mortality

Cancer diagnoses were updated annually in the OS or semiannually in the CT by mail and/or telephone questionnaires during the main study period, and were updated annually for all women (OS +CT) who participated in the extension study. Participant or next-of-kin reports of breast cancer were coded using criteria implemented in the Surveillance Epidemiology and End Results (SEER) Program [30] and verified by centrally trained physician adjudicators after review of medical records including pathology reports. Cause of death was based on medical record review by physician adjudicators at the local clinical centers, with final adjudication at the Coordinating Center. Screening mammography rates were protocol defined in the WHI CT and varied by trial at enrollment. In the HT, mammography screening was required annually, in the DM, mammography was required every other year, and in the OS, mammographic screening was left up to the discretion of the participant and her treating physician.

Mammography Interval

Mammography interval was defined as the time between the date of breast cancer diagnosis, and the date of the last self-reported mammogram completed prior to diagnosis. This variable was constructed using self-reported mammography completion information collected from the medical record update form which was mailed semiannually in the CT, and annually in the OS during the study intervention, and then annually for both the CT and OS participants through the first WHI extension phase (2005–2010). Participants were asked to indicate on each medical record update form, whether they had completed a mammogram since the date of their last medical record update form. The mammography completion date was estimated as the mid-time point between the date of the medical record update form on which the most recent mammogram was reported, and the date of the last prior medical

record update form. Information on whether the mammogram was for screening or diagnostic purposes was not collected. We only included in our analysis mammograms that occurred 7 or more months before the date of diagnosis in order to exclude the possibility of diagnostic mammograms.

Covariates

Self-administered questionnaires were used to collect base-line information on demographic and medical history variables [28,29]. Women identified their race or ethnicity by selecting from among six categories listed on the US Census at the time of the initiation of the study including: White, Black/African American, Hispanic, American Indian/Alaskan Native (Native American), Asian/Pacific Islander, or other. Other baseline variables included: year of diagnosis, education, marital status, history of prior breast biopsies, body-mass index (BMI) (weight in kilograms divided by height in meters squared), prior use of estrogen or estrogen and progesterone, and history of co-morbid medical conditions defined by the Charlson Comorbidity Index (CCI) [31]. The CCI is a prospectively verified method for classifying comorbid medical conditions that could affect the risk of mortality in longitudinal studies. Information on breast cancer summary stage, tumor grade, estrogen (ER) and Her2Neu status was derived from pathology reports using the SEER coding system [30].

Analysis

Baseline and prognostic characteristics of women with breast cancer were stratified by mammography interval (7 months to ≤ 2 years – reference group, > 2 to < 5 years, and ≥ 5 years or no reported prior mammograms) using Chi-square tests.

Hazards ratios (HR) and 95% confidence intervals (CIs) for breast cancer mortality were computed from Cox proportional hazards analyses. Mortality rates were defined as the time from the date of breast cancer diagnosis to date of death due to breast cancer. Event times were censored at the time of a non-breast cancer related death, or at the last documented follow-up time for those still alive. Tests for the proportional hazards assumptions were conducted by including interactions of the covariates with the logarithm of the time variable in the models. The assumption of proportionality was satisfied for all variables. Unadjusted analyses were used to examine the associations of breast cancer mortality with participant demographic and clinical characteristics. Multivariable models examining the relationship between mammography interval and breast cancer mortality were fit adjusting for age at breast cancer diagnosis, year of diagnosis (1994–2002 vs. 2003–2010), race/ethnicity (white/non-white), marital status (ever vs. never-married), education (high school or less, some college, college degree or higher), CCI at baseline, BMI at WHI baseline (25, 25–<30, > 30), study component (HT, DM- not in HT, OS), and HT assignment or use of hormones at baseline (placebo/non-user, estrogen alone, estrogen plus progesterone). Linear trends were tested by treating the integer-scored variables as continuous variables. Separate analyses were also conducted using all- cause mortality as the end point. In addition, we used Fine and Gray competing risk regression to calculate sub-distribution hazard ratios (sHR) and associated robust 95% CIs for breast cancer mortality in the presence of other causes of death. This method takes into account that the association of covariates with the cumulative

incidence function for breast cancer death depends on both the hazard for breast cancer death and the hazard for death from other causes [32].

Analyses were performed using SAS version 9.3 (SAS Institute IC., Cary, NC, USA) and Stata version 12 (StataCorp, College Station, TX). All P values were based on two-sided tests and considered significant at 0.05.

Results

Table 1 shows the socio-demographic and prognostic characteristics of 1,914 women diagnosed with invasive breast cancer at age 75 and older in the WHI CT and OS cohorts stratified by mammography interval. The mean age at diagnosis was 78.9 (SD=3.4), range 75–92 years, more than ½ of the women were diagnosed after 2003, the majority of women were self-identified as non-Hispanic white (91.8%), had some school after high school or were college graduates (79.5%) and reported 0 or 1 prior co-morbid conditions (87.3%). Regarding participation in the WHI, 16% were randomized to the HT, 23% were randomized to the DM (and not HT) and 60.8% were enrolled in the OS. Most of the women had a mammogram prior to diagnosis with 73% reporting a mammogram from 7 months to ≤ 2 years of diagnosis, 19.4% from > 2 to < 5 years of diagnosis and 7.5% ≥ 5 years (or reported no prior mammogram). The majority of women had local stage disease (77.2%), followed by regional stage (21.4%) and distant stage (1.5%). Most of the breast cancers were well or moderately differentiated (69.2%), ER positive (85.9%) and Her2neu negative (70.4%), however information on HER2neu was missing from 19.4% of the tumors. Compared to the referent group, women with the longest mammography interval were more likely to have poorly differentiated and ER negative tumors and regional or distant stage. Women with the longest mammography interval were also more likely to be obese, less educated, to report no breast biopsy at baseline and to be randomized to the HT trial. Women with longer mammography intervals were also more likely to be non-users of hormone therapy (Table 1).

Table 2 shows the multivariable adjusted relationship between mammography interval, breast cancer mortality, other and any cause of death. In a model adjusted for age at diagnosis, year of diagnosis, race/ethnicity, marital status, education, CCI, BMI, study component and hormone trial assignment or hormone use, longer mammography interval was associated with a significantly increased likelihood of death from breast cancer (p-trend 0.0002). Compared to the referent group, the cause-specific hazard ratio (HR) for death due to breast cancer for the interval of > 2 to < 5 years was 1.62, 95% confidence interval (CI, 1.03–2.54) and for the interval of > 5 years (including no prior reported mammogram), the HR was 2.80 (95% CI, 1.57–5.00). Similarly there was an increased likelihood of death due to any cause for an interval of 2–5 years (HR 1.23, 95% CI 0.94–1.61) and for 5 or more years (HR 1.73, 95% CI 1.20–2.50) (p=0.002). There was no significant association between mammography interval and other specific causes of death (p=0.25).

In order to account for the possibility of non-breast cancer related deaths as a competing risk, we evaluated the relationship between mammography interval and death due to breast cancer using the Fine and Gray methodology. Compared to the referent group, the cause-

specific hazard ratio sub-distribution hazard ratio (sHR) for death due to breast cancer for the interval of > 2 to < 5 years was 1.60, 95% confidence interval (CI, 1.02–2.52) and for the interval of > 5 years (including no prior reported mammogram), the sHR was 2.74 (95% CI, 1.53–5.03). Similarly there was no significant association between mammography interval and other specific causes of death (p=0.49) (Table 3).

Discussion

The purpose of this analysis was to assess the relationship between mammography interval and breast cancer mortality among women diagnosed with breast cancer in a large U.S. cohort. Our results suggest that longer time between diagnosis and the last self-reported mammogram was associated with higher rates of mortality due to either breast cancer as well as any cause of death. Importantly, the suggested relationship between mammography interval and breast cancer mortality is particularly relevant for women 75 years of age or older at diagnosis in light of the 2009 USPSTF recommendations which report lack of evidence as support for not performing screening mammography after the age of 74 (USPSTF) [7]. While provocative, these results need to be considered in light of limitations in the data collected and potential biases.

While pooled evidence from five Swedish randomized trials support the use of routine screening mammography for women over the age of 50 years [33,34], there are no clinical trials of mammography which have included women age 75 years and older to provide evidence supporting or refuting the use of routine screening in that age group [3]. A number of observational studies however have linked regular screening to earlier stage at diagnosis [8–14] and/or reduction in breast cancer related and overall mortality[12–14,14–21]. In support of our findings others have linked longer intervals between mammograms to advanced stage and/or aggressive tumor features [5,9,11,17] or to interval cancers not detected by screening [10,17]. Clinical benefits of screening have been demonstrated in other studies of older women with regular screening associated with earlier stage among women 75 years of age and older [11,14] as well as mortality reduction among women age 67 years and older [13], 75 years and older [14], and for women age 80 years and older, despite mild to moderate levels of co-morbidity [16]. Our data overall are consistent with results from the literature showing a trend toward later stage at diagnosis, ER/PR negativity and more poorly differentiated tumors among women with longer mammography intervals.

The U.S. Preventive Services Task Force (USPSTF) Recommendation Statement on Screening for Breast Cancer [7] recommends biennial screening mammography for women between the ages of 50 and 74 years and concludes that current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older [7]. These recommendations resulted in significant controversy regarding upper age limit and/or optimal screening intervals for older women. While there are no randomized trials evaluating the efficacy of mammographic screening for women age 75 years and older, the results from the WHI and other observational studies suggest a continued benefit of mammography screening for older women. Hendrick and Helvie used six Cancer Intervention and Surveillance Modeling Network models to compare mortality reduction for women who follow USPSTF 2009 recommendations to the American Cancer Society (ACS)

recommendations [34] and reported an almost 40 percent reduction in mortality attributed to annual screening starting at age 40 through 84 as recommended by the ACS.

Despite a potential for increased sensitivity and positive predictive value for mammograms in older women due to lower breast density related to aging [35], there tends to be decreased utilization of mammograms among older women [36–38]. This can be accounted for by a number of factors potentially related to aging including lack of knowledge of screening recommendations and/or lack of worry about breast cancer [37,39,40], lack of awareness of insurance coverage for screening [40] as well as impaired functional status [41,42], all of which may contribute to reduced screening among older women. Given higher rates of expected co-morbidity seen in older women, standard recommendations for screening for women age 75 and older should give strong consideration to potential benefits and risks of breast cancer diagnosis and/or treatment [43] and to a woman's predicted life expectancy [44] [45]. In the WHI cohort, women with a longer interval between their last mammogram and breast cancer diagnosis were more likely to be obese and less educated, both of which are potential barriers to screening and which could be potentially alleviated through better education and/or access to health care resources.

Strengths of our analysis include the large and diverse study population, long duration of follow-up, central adjudication of cancers and cause of death as well as yearly updates on mammography. Limitations include the fact that mammography use as measured in our study was self-reported resulting in the possibility of recall bias as well as the lack of information on the exact date that the mammogram was completed and the reason for the mammogram. We attempted to account for uncertainty in reporting mammography interval by using an interval of > 7 months to ≤ 2 years as our reference group in order to account for possible diagnostic mammograms that occurred at or near 6 months. It is also plausible that when women who are not in the habit of having regular screening mammograms, undergo mammography, that it is more likely for diagnostic purposes which could result in overly inflated HR's associated with breast cancer mortality. Our results however were similar after accounting for competing risks of death using the Fine and Gray methodology, which suggests the possibility of a true effect of mammography interval on breast cancer outcome. It is still possible however that other personal or behavioral characteristic that differ across the mammography interval groups may be responsible for observed mortality rate trends. Importantly we were interested in the impact of screening interval on breast cancer mortality among women diagnosed with breast cancer and therefore did not directly consider risks associated with mammography in those not diagnosed with breast cancer including non-diagnostic biopsies. Lastly, there is no information currently available in the WHI on cancer treatment, which could have an important impact on breast cancer mortality.

Conclusions

The results from the WHI analysis of mammography interval and breast cancer mortality suggest a continued role for mammography screening after the age of 75 years in light of the overall health of the individual woman.

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Table 1

Characteristics by mammogram interval – Breast Cancer cases age 75+ at diagnosis, excluding those with mammogram interval <= 7 mos

		All breast cancer at 75+ yrs		>7 mos to </= 2 yrs		>2 yrs to <5 yrs		>/= 5 yrs or no mammogram reported	
		N	%	N	%	N	%	N	%
Breast cancer-grade	*Well differentiated*	498	26.02	375	26.82	91	24.46	32	22.22
	Moderately differentiated	827	43.21	602	43.06	166	44.62	59	40.97
	Poorly differentiated/anaplastic	451	23.56	318	22.75	92	24.73	41	28.47
	Unknown/not done	138	7.21	103	7.37	23	6.18	12	8.33
Summary Stage (SEER)	*Localized*	1477	77.17	1078	77.11	292	78.49	107	74.31
	Regional	409	21.37	304	21.75	71	19.09	34	23.61
	Distant	28	1.46	16	1.14	9	2.42	3	2.08
Estrogen receptor positive	*Yes*	1557	85.93	1152	86.88	299	84.94	106	79.10
	No	255	14.07	174	13.12	53	15.06	28	20.90
Her2/Neu	*Positive*	195	10.19	145	10.37	36	9.68	14	9.72
	Negative or borderline	1347	70.38	994	71.10	254	68.28	99	68.75
	Unknown/Not done	372	19.44	259	18.53	82	22.04	31	21.53
Diagnosis year	*Before 2003*	715	37.36	528	37.77	138	37.10	49	34.03
	2003 and after	1199	62.64	870	62.23	234	62.90	95	65.97
Body-mass index (kg/m2), baseline	*<25*	640	33.65	487	35.04	109	29.46	44	30.99
	25 – <30	687	36.12	506	36.40	138	37.30	43	30.28
	>=30	575	30.23	397	28.56	123	33.24	55	38.73
Race/ethnicity	*White*	1756	91.75	1278	91.42	343	92.20	135	93.75
	All other	158	8.25	120	8.58	29	7.80	9	6.25
Education level	*High school diploma/GED or less*	391	20.51	284	20.40	77	20.75	30	20.98
	Some school after high school	758	39.77	544	39.08	149	40.16	65	45.45
	College graduate or above	757	39.72	564	40.52	145	39.08	48	33.57
Charlson Comorbidity Index at baseline	*0*	1196	64.47	874	64.45	230	63.71	92	66.67
	1	423	22.80	310	22.86	84	23.27	29	21.01
	2	165	8.89	123	9.07	29	8.03	13	9.42
	3+	71	3.83	49	3.61	18	4.99	4	2.90
Ever married	*No*	88	4.61	69	4.95	9	2.43	10	6.94

		All breast cancer at 75+ yrs		>7 mos to </= 2 yrs		>2 yrs to <5 yrs		>/= 5 yrs or no mammogram reported	
		N	%	N	%	N	%	N	%
	Yes	1820	95.39	1324	95.05	362	97.57	134	93.06
Breast biopsy at baseline	*No*	1278	70.45	919	69.41	257	71.99	102	76.69
	Yes	536	29.55	405	30.59	100	28.01	31	23.31
Study participation	*HT Randomized*	312	16.30	220	15.74	60	16.13	32	22.22
	DM Randomized and not in HT	438	22.88	304	21.75	103	27.69	31	21.53
	OS Enrolled	1164	60.82	874	62.52	209	56.18	81	56.25
Hormone trial assignment or use at baseline	*Placebo/Non-user*	1068	55.89	740	53.01	222	59.84	106	73.61
	Estrogen Alone	456	23.86	350	25.07	84	22.64	22	15.28
	Estrogen + Progesterone	387	20.25	306	21.92	65	17.52	16	11.11

HT - Hormone Trials

DM - Dietary Modification

OS – Observational Study

Table 2

Association between Mammogram Interval and Death from Breast Cancer, Other Cause, Any Cause Cause-specific Analysis

Diagnosed at age 75+			Cause of Death								
	At Risk		Breast Cancer			Other Cause			Any Cause		
Mammogram Interval	No.	%	Deaths	HR	95% CI	Deaths	HR	95% CI	Deaths	HR	95% CI
≤ 2 yrs	1336	73	64	1.0	Reference	162	1.0	Reference	226	1.0	Reference
> 2 yrs to < 5 yrs	357	20	28	1.62	1.03 to 2.54	47	1.08	0.77 to 1.50	75	1.23	0.94 to 1.61
≥ 5 yrs or No mammogram reported	136	7	15	2.80	1.57 to 5.00	20	1.33	0.83 to 2.15	35	1.73	1.20 to 2.50
p-trend					0.0002			0.25			0.002

For all analyses, follow-up is time from breast cancer diagnosis to death or end of follow-up. Risk estimates were adjusted for age at diagnosis, year of diagnosis (1994–2002, 2003–2010), race/ethnicity (white, non-white), marital status (ever/never married), education (high school or less, some college, college degree or higher), Charlson co-morbidity index (CCI) at WHI baseline, body mass index (BMI, kg/m2) at WHI baseline (<25, 25–<30, ≥30), study component (hormone trials (HT), dietary modification - not in HT, observational study), and hormone trial assignment/use at baseline (placebo/non-user, estrogen alone, estrogen + progestin).

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Table 3

Association between Mammogram Interval and Death from Breast Cancer, Other Cause, Cause-specific Analysis, using the Fine and Gray Competing Risk Aanalysis

	Cause of Death					
	Breast Cancer*			Other Cause**		
Mammogram Interval	**Deaths**	**SHR**	**Robust 95% CI**	**Deaths**	**SHR**	**Robust 95% CI**
≤ 2 yrs	64	1.0	Reference	162	1.0	Reference
> 2 yrs to < 5 yrs	28	1.60	1.02 to 2.52	47	1.01	0.71 to 1.44
≥ 5 yrs or No mammogram reported	15	2.74	1.50 to 5.03	20	1.22	0.78 to 1.92
p-trend			0.001			0.49

SHR - subdistribution hazard ratio

* Death from a cause other than breast cancer is the competing risk

** Breast cancer death is the competing risk

For all analyses, follow-up is time from breast cancer diagnosis to death or end of follow-up. Risk estimates were adjusted for age at diagnosis, year of diagnosis (1994–2002, 2003–2010), race/ethnicity (white, non-white), marital status (ever/never married), education (high school or less, some college, college degree or higher), Charlson co-morbidity index (CCI) at WHI baseline, body mass index (BMI, kg/m2) at WHI baseline (<25, 25–<30, ≥30), study component (hormone trials (HT), dietary modification - not in HT, observational study), and hormone trial assignment/use at baseline (placebo/non-user, estrogen alone, estrogen + progestin).