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ORIGINAL REPORT

Diabetes, Metformin, and Breast Cancer in Postmenopausal Women

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A B S T R A C T

Purpose

Emerging evidence suggests that metformin may reduce breast cancer incidence, but reports are mixed and few provide information on tumor characteristics. Therefore, we assessed associations among diabetes, metformin use, and breast cancer in postmenopausal women participating in Women's Health Initiative clinical trials.

Patients and Methods

In all, 68,019 postmenopausal women, including 3,401 with diabetes at study entry, were observed over a mean of 11.8 years with 3,273 invasive breast cancers diagnosed. Diabetes incidence status was collected throughout follow-up, with medication information collected at baseline and years 1, 3, 6, and 9. Breast cancers were confirmed by review of central medical records and pathology reports. Cox proportional hazards regression, adjusted for breast cancer risk factors, compared breast cancer incidence in women with diabetes who were metformin users or nonusers with breast cancer incidence in women without diabetes.

Results

Compared with that in women without diabetes, breast cancer incidence in women with diabetes differed by diabetes medication type ($P = .04$). Women with diabetes receiving medications other than metformin had a slightly higher incidence of breast cancer (hazard ratio [HR], 1.16; 95% CI, 0.93 to 1.45), and women with diabetes who were given metformin had lower breast cancer incidence (HR, 0.75; 95% CI, 0.57 to 0.99). The association was observed for cancers positive for both estrogen receptor and progesterone receptor and those that were negative for human epidermal growth factor receptor 2.

Conclusion

Metformin use in postmenopausal women with diabetes was associated with lower incidence of invasive breast cancer. These results can inform future studies evaluating metformin use in breast cancer management and prevention.

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INTRODUCTION

Diabetes mellitus is a common condition that has been associated with increased incidence of breast cancer,[1-3] a finding recently challenged by reports from large population-based studies.[4,5] Nonetheless, diabetes is linked to adverse breast cancer outcome.[6] A meta-analysis[7] and two recent studies[6,8] found that patients with breast cancer and diabetes had significantly higher all-cause mortality than those without diabetes. In addition, all patients with breast cancer with higher fasting levels of insulin,[9] higher levels of C-peptide (a marker of insulin production),[10] or increased insulin resistance by homeostasis model assessment (HOMA) score[11] are at increased risk of death from breast cancer.

Metformin is a biguanide, commonly used for treating type 2 diabetes, that increases insulin sensitivity and improves glycemic control.[12,13] On the basis of these properties and preclinical evidence of its inhibition of breast cancer growth,[14,15] metformin has been studied for anticancer effects.

Following early reports,[16] a meta-analysis of observational studies in individuals with type 2 diabetes associated metformin use with a 30% lower overall incidence of cancer compared with patients with diabetes receiving other therapies[17] and, in a cohort study,[18] with 44% lower cancer mortality compared with an age-matched general population.

Although some observational studies[19-21] describe lower incidence of breast cancer with metformin use, results are mixed,[22,23] and information on breast cancer subtypes is sparse.[24] Consequently, we examined relationships among diabetes, metformin use, and breast cancer in the Women's Health Initiative (WHI) clinical trials.

PATIENTS AND METHODS

Study Population

The WHI program includes four clinical trials and an observational study.[25] General eligibility required age between 50 and 79 years, being accessible for follow-up, and estimated survival of ≥ 3 years. The clinical trials excluded women with prior breast cancer and had additional eligibility requirements largely related to medical history. The study population included all clinical trials participants (N = 68,132), excluding only those reporting bilateral mastectomy, diabetic coma, or diabetes diagnosed at younger than age 21 (to exclude likely type 1 diabetes), or those with missing baseline diabetes information, leaving 68,019 women for these analyses.

Study implementation details have been published.[25,26] Protocols had institutional review board approval from the clinical centers, and all participants provided written informed consent. At baseline, participants completed questionnaires that collected information on demographics, medical history, and breast cancer risk. All reported medications were matched to the Master Drug Data Base (MDDB; Medi-Span, Indianapolis, IN), a procedure repeated in years 1, 3, 6, and 9. The initial study period ended on March 31, 2005, with reconsenting participants observed for subsequent clinical outcomes.

Identification of Women With Diabetes

At baseline, participants were asked "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?" Medical history was updated semiannually during the initial study period and annually thereafter when participants were asked "Since the date given on this form, has a doctor prescribed any of the following pills or treatments?" Choices included "pills for diabetes" and "insulin shots for diabetes." Women with diabetes were defined as those reporting targeted diabetes at baseline or at subsequent medical history update or reporting use of antidiabetic medications at any time.

This approach to identifying women with diabetes has been evaluated.[27] Fasting glucose levels were determined in a random sample of 5,884 baseline specimens from the entire WHI population. Glucose levels ≥ 140 mg/dL (the pre-1997 diabetes diagnostic threshold prevalent during most of the WHI recruitment) were seen in 4.7% of women without reported diabetes and in 95.3% of women with reported diabetes.[27]

Breast Cancer Screening and Diagnosis

Baseline mammogram and clinical breast examinations not suggestive of cancer were eligibility requirements. Mammograms and breast examinations were mandated annually in the hormone therapy trials and biennially in the dietary trial. Breast cancers were initially verified by pathology report review at the local clinical center by trained physician adjudicators.[28] Final adjudication and coding for stage and hormone receptor and human epidermal growth factor receptor 2 (HER2) status (both by local laboratory criteria) were performed at the Clinical Coordinating Center by using Surveillance, Epidemiology, and End Results (SEER) criteria.[29]

Statistical Methods

Baseline characteristics of women with diabetes were compared with those of women without diabetes by χ^2 test of association. In addition, baseline characteristics of women with treated diabetes using metformin either as monotherapy or with other diabetes medications were compared with women with treated diabetes not using metformin and with women without diabetes. The 3,407 women with diabetes identified at entry were included in these comparisons.

Cox regression models with a time-dependent categorical exposure variable that incorporated all collected information on diabetes diagnoses and medication use were used to compute hazard ratios (HRs) and 95% CIs for breast cancer incidence. The two exposures of interest were (1) a two-level categorical variable that classified women as either having or not having diabetes and (2) a four-level categorical variable that further classified women with diabetes as metformin users, users of other antidiabetic medication without metformin, or having unknown diabetes treatment, with women without diabetes as comparators. If treated diabetes was reported but medication data were not available at that time, the exposure was coded as "unknown treatment" and was later updated to metformin users or users of other diabetes medication when medication data became available. For example, a woman with no diabetes on entry who reported treated diabetes after 26 months and metformin use beginning at year 3 would be analyzed in the "no diabetes" group for time 0 to 26 months, the "diabetes therapy unknown" group for 26 to 36 months, and the "metformin use" group after 36 months. A 2 *df* test of significance was used to compare women who used metformin with women without diabetes and to compare users of other diabetes medication with women without diabetes.

The Cox proportional hazard analyses were adjusted for the baseline covariates of age (linear), first-degree relatives with breast cancer, prior breast biopsy, age at menarche, age at menopause, age at parity, age at first live birth, number of months of breastfeeding, education, smoking, alcohol use, body mass index (BMI; linear), physical activity, duration of prior use of estrogen alone and duration of use of estrogen plus progestin (considered separately), and bilateral oophorectomy. The baseline hazard functions were allowed to vary by age (10-year group), the four hormone therapy trial randomization arms, the dietary trial randomization arms, race/ethnicity, and enrollment in the WHI extension study. The strategy of using both covariate adjustment and allowing the hazard functions to vary by group provides a more refined adjustment for age and has been used by others.[30] A variant of Kaplan-Meier incidence curves that allows for time-dependent exposures[31] was used to display cumulative hazard functions.

Separate analyses were conducted by breast cancer subtypes. Tumor characteristics and stage and hormone receptor and HER2 status were compared in groups defined by diabetes and associated medication use.

Subgroup comparisons involved age, BMI (as a linear continuous variable), physical activity, alcohol use, use of estrogen alone, use of estrogen plus progestin, and recency of diabetes diagnosis (prevalent *v* incident cases). The 14 tests (both exposures times seven subgroups) were planned with statistical significance based on the nominal *P* value for interaction from a multivariable Cox regression model. With regard to multiplicity,[32] less than one would be expected to be significant ($P < .05$) by chance alone.

Subgroups were time-dependent variables with BMI updated annually; physical activity updated at years 1, 3, 6, and 9; and age continuously adjusted by summing age at baseline with length of follow-up.

Post hoc analyses were conducted to assess whether metformin association was mediated through weight loss. Change in weight (year 1 minus baseline) was examined since medication data were available at both visits and was assessed among only recent users (those beginning use < 6 months before baseline) by use of linear regression adjusted for age, height, race/ethnicity, physical activity, and self-reported health. The least squares regression model incorporated change in weight as the response variable and metformin use as the exposure variable of interest.

All analyses were conducted by using SAS software, version 9.1 (SAS Institute, Cary, NC) and R software version 2.11 (R Foundation for Statistical Computing; http://www.r-project.org/). All statistical tests were two-sided.

RESULTS

Women with diabetes were older and more likely to be black, to engage in less recreational physical activity, and to be obese (Table 1). Use of medication for diabetes at baseline is outlined in Table 1. Reflecting general practice trends, the percentage of women with diabetes who used metformin increased year by year from 20.3% at baseline to 30.6%, 41.0%, 51.6%, and 55.0% in years 1, 3, 6, and 9, respectively. Women with diabetes who used metformin were similar to those who used other medications except they were somewhat less

Table 1. Baseline Characteristics by Diabetes of Women in the Women's Health Initiative Clinical Trials*

Characteristic	Diabetes: Yes (n = 3,401) No.	%	Diabetes: No (n = 64,618) No.	%	P
Age group at screening, years					< .001
Mean	64.0		62.6		
SD	6.7		7.0		
50-59	918	27.0	22,893	35.4	< .001
60-69	1,711	50.3	29,635	45.9	
70-79	772	22.7	12,090	18.7	
Race/ethnicity					< .001
White	2,115	62.2	53,322	82.5	
Black	862	25.3	6,104	9.4	
Hispanic	216	6.4	2,655	4.1	
American Indian	30	0.9	261	0.4	
Asian/Pacific Islander	116	3.4	1,402	2.2	
Unknown	62	1.8	874	1.4	
Education					< .001
0-8 years	127	3.8	974	1.5	
Some high school	258	7.6	2,423	3.8	
High school diploma/GED	736	21.8	11,742	18.3	
School after high school	1,410	41.8	25,520	39.8	
College degree or higher	844	25.0	23,536	36.7	
Smoking status					.009
Never	1,738	51.9	32,627	51.1	
Past	1,392	41.6	26,154	40.9	
Current	219	6.5	5,117	8.0	
Alcohol consumption, drinks per week					< .001
Nondrinker/past drinker	2,045	60.8	17,678	27.6	
< 1	974	28.9	22,424	35.0	
1-14	325	9.7	21,862	34.1	
> 14	22	0.7	2,150	3.4	
Physical activity, METs					< .001
Inactive 0	774	24.3	11,033	18.9	
< 5	918	28.8	13,785	23.6	
5-12	771	24.2	14,120	24.2	
≥ 12	724	22.7	19,478	33.3	
Percent energy from fat ≥ 30					.010
No	389	11.7	8,430	13.3	
Yes	2,930	88.3	55,046	86.7	
Body mass index, kg/m^2 (baseline categories)					< .001
< 25	286	8.4	18,221	28.3	
25-< 30	870	25.7	23,315	36.3	
≥ 30	2,230	65.9	22,775	35.4	
Age at menarche, years					< .001
< 12	979	28.9	13,835	21.5	
12-13	1,712	50.6	35,453	55.1	
≥ 14	694	20.5	15,109	23.5	
Age at menopause, years					< .001
< 45	951	31.1	13,670	23.0	
45-54	1,648	53.9	37,845	63.7	
> 54	461	15.1	7,900	13.3	
Self-reported health					< .001
Excellent	65	1.9	10,739	16.7	
Very good	634	18.8	27,283	42.5	
Good	1,663	49.4	21,663	33.7	
Fair/poor	1,006	29.9	4,574	7.1	

(continued in next column)

Table 1. Baseline Characteristics by Diabetes of Women in the Women's Health Initiative Clinical Trials* (continued)

Characteristic	Diabetes: Yes (n = 3,401) No.	%	Diabetes: No (n = 64,618) No.	%	P
Use of aspirin					< .001
No	2,554	75.1	52,056	80.6	
Yes	847	24.9	12,562	19.4	
Enrollment onto CEE trial					< .001
Active CEE	425	24.2	4,871	18.2	
Placebo	429	24.4	4,982	18.6	
Not enrolled without uterus	902	51.4	16,899	63.2	
Enrollment onto CEE + MPA trial					.009
Placebo	380	23.1	8,103	21.4	
Active CEE + MPA	369	22.4	7,707	20.4	
Not enrolled without uterus	896	54.5	22,053	58.2	
Enrollment onto dietary modification trial					< .001
Intervention	907	26.7	18,618	28.8	
Control	1,408	41.4	27,866	43.1	
Not enrolled	1,086	31.9	18,134	28.1	
Age at first birth, years					< .001
Never pregnant/no term pregnancy	341	11.6	6,910	11.7	
< 20	709	24.0	9,337	15.9	
20-29	1,677	56.8	38,100	64.7	
30+	223	7.6	4,499	7.6	
Duration of breastfeeding, years					.18
No breastfeeding	1,622	48.5	30,660	48.0	
≤ 1	1,267	37.9	23,795	37.3	
> 1	452	13.5	9,374	14.7	
Hysterectomy at random assignment					< .001
No	1,645	48.4	37,863	58.6	
Yes	1,756	51.6	26,752	41.4	
Bilateral oophorectomy					< .001
No	2,476	76.4	51,177	81.1	
Yes	765	23.6	11,890	18.9	
Use of estrogen only at baseline					< .001
Never	2,357	69.4	42,898	66.4	
Prior	535	15.7	8,887	13.8	
Current	505	14.9	12,791	19.8	
Use of estrogen plus progestin at baseline					< .001
Never	2,975	87.5	49,380	76.4	
Prior	178	5.2	5,560	8.6	
Current	247	7.3	9,662	15.0	
Duration of menopausal hormone therapy at baseline, years					< .001
None	2,001	58.8	30,786	47.6	
< 5	717	21.1	14,397	22.3	
5-< 10	259	7.6	7,474	11.6	
10-< 15	164	4.8	5,322	8.2	
15+	260	7.6	6,636	10.3	

(continued in next column)

Table 1. Baseline Characteristics by Diabetes of Women in the Women's Health Initiative Clinical Trials* (continued)

Characteristic	Diabetes: Yes (n = 3,401) No.	%	Diabetes: No (n = 64,618) No.	%	*P*
Benign breast disease					< .001
No	2,594	82.4	46,249	79.9	
Yes, one biopsy	415	13.2	8,424	14.5	
Yes, ≥ two biopsies	138	4.4	3,230	5.6	
No. of first-degree relatives with breast cancer					.61
0	2,694	85.9	52,048	86.2	
1+	444	14.1	8,354	13.8	
Gail risk					< .001
< 1.25	1,460	42.9	22,043	34.1	
1.25-1.75	959	28.2	20,998	32.5	
≥ 1.75	982	28.9	21,577	33.4	
Diabetes medication (baseline)					
Metformin					
Total	556	20.3	0		
Monotherapy	159	5.8	0		
Plus other	397	14.5	0		
Oral medication, no metformin	1,506	55.1	0		
Insulin, no metformin	671	24.6	0		

Abbreviations: CEE, conjugated equine estrogen; GED, General Educational Development; MET, metabolic equivalent of task; MPA, medroxyprogesterone acetate; SD, standard deviation.

*The Women's Health Initiative included clinical trials and an observational study. The clinical trials included two hormone therapy trials evaluating (1) estrogen plus progestin for women with no prior hysterectomy, and (2) estrogen alone for women with no prior hysterectomy; a dietary modification trial; and a calcium plus vitamin D supplementation trial.

likely to be black, to never have smoked, and to be older; they were less likely to use sulfonylureas and were not using insulin (Table 2).

During the study, the annual frequency of mammography was similar in women with and without diabetes (annualized rates of 62.0% and 61.2%, respectively) and, in women with diabetes, the frequency was somewhat greater in metformin users (65.0%) compared with nonusers (59.0%).

During 801,066 person-years over a mean of 11.8 years (standard deviation [SD], 3.1 years), a cumulative total of 11,290 women were diagnosed with diabetes, 3,273 with invasive breast cancer, and 754 with ductal carcinoma in situ (DCIS; Table 3). There was no difference in the incidence of invasive breast cancer (HR, 0.99; 95% CI, 0.85 to 1.14) or DCIS (HR, 0.99; 95% CI, 0.73 to 1.36) between all women with diabetes and women without diabetes. However, when women with diabetes were compared with women without diabetes, incidence of invasive breast cancer was associated with diabetes medication type ($P = .04$). The incidence of invasive breast cancer was lower in women with diabetes who used metformin (HR, 0.75; 95% CI, 0.57 to 0.99). In contrast, the incidence was slightly higher in women with diabetes who used other medications (HR, 1.16; 95% CI, 0.93 to 1.45; Table 4 and Fig 1). Incidence of DCIS was not associated with metformin use (Table 4).

In women with diabetes, metformin use was associated with a lower incidence of breast cancers positive for both estrogen receptor (ER) and progesterone receptor (PR; HR, 0.64; 95% CI, 0.45 to 0.92) and negative for HER2 overexpression (Table 4). Although the analysis was limited by few patients, metformin use was also associated with more HER2-positive cancers.

In exploratory analyses, the other diabetes medication group was further divided into insulin users and nonusers. In comparison with women without diabetes, HRs were 1.09 (95% CI, 0.83 to 1.42) for nonusers of insulin and 1.34 (95% CI, 0.92 to 1.95) for users of insulin. The number of women using metformin alone was insufficient to provide a reliable association estimate.

Breast cancers in metformin users were somewhat more likely to be ductal and less likely to be poorly differentiated, but none of the differences were statistically significant. In metformin users, the incidence of localized cancers was substantially lower than that in nonusers (65 [0.25%] *v* 90 [0.31%] cases [annualized %], respectively) and the incidence of regional or metastatic cancers was closely comparable (37 [0.14%] *v* 36 [0.13%] cases [annualized %], respectively; Table 5).

Subgroup analysis results were null. The metformin association with breast cancer was not modified by age, with a *P* value for the interaction term (*P*-int) of 0.47, physical activity (*P*-int = 0.65), use of estrogen alone (*P*-int = 0.73), use of estrogen plus progestin (*P*-int = 0.36), alcohol use (*P*-int = 0.59), or recency of diabetes diagnosis (*P*-int = 0.68). There was no significant interaction with BMI (*P*-int = 0.74) despite an HR for metformin of 1.01 (95% CI, 0.64 to 1.58) for BMI less than 30; HR, 0.43 (95% CI, 0.24 to 0.78) for BMI 30 to less than 35; and HR, 0.86 (95% CI, 0.57 to 1.30) for BMI ≥ 35.

Use of metformin was associated with weight loss (mean, −1.4 kg for baseline to year 1 [95% CI, −2.6 to −0.1) compared with use of other medications for diabetes or in women without diabetes ($P = .02$). However, adjusting for weight loss did not appreciably change the metformin association with breast cancer (HR, 0.75; 95% CI, 0.57 to 0.99).

DISCUSSION

In this prospective cohort of postmenopausal women, the incidence of invasive breast cancer was lower in women with diabetes treated with metformin compared with women without diabetes. Fewer cancers that were positive for both ER and PR and fewer cancers that were HER2 negative were diagnosed in metformin users.

The predominance of prior observational studies[2,3,33] have associated diabetes with higher incidence of breast cancer. However, this association has recently been challenged in two large population-based cohort analyses.[4,5] In the first, the British Columbia Linked Health Database covering 99% of the British Columbia population of about 4.8 million residents was used to generate a retrospective cohort. With 2,381 patients, incidence of breast cancer was not associated with diabetes status (HR, 1.01; 95% CI, 0.92 to 1.10; $P = .88$).[5,34] In the second, the Danish National Diabetes Register and Cancer Registry were linked to perform a cohort analyses of the entire Danish population. In that setting, although incidence of several cancers, including those of the liver, pancreas, and lung, were significantly associated with diabetes, incidence of breast cancer was not ($P = .37$).[4] In addition, time-varying analyses found evidence of potential detection bias, suggestive of increased cancer surveillance soon after diabetes detection.[4,5,34] Similar to women in these recent contemporary cohort

Table 2. Baseline Characteristics by Diabetes and Metformin Use at Baseline (n = 2,733)

Characteristic	Women With Diabetes: Other Medication (n = 2,177) No.	%	Women With Diabetes: Metformin* (n = 556) No.	%	*P*
Age group at screening, years					.03
Mean	63.9		64.6		
SD	6.8		6.5		
50-59	602	27.7	117	21.0	.006
60-69	1,088	50.0	300	54.0	
70-79	487	22.4	139	25.0	
Race/ethnicity					< .001
White	1,344	61.7	378	68.0	
Black	577	26.5	100	18.0	
Hispanic	123	5.6	39	7.0	
American Indian	21	1.0	2	0.4	
Asian/Pacific Islander	71	3.3	27	4.9	
Unknown	41	1.9	10	1.8	
Education					.16
0-8 years	74	3.4	16	2.9	
Some high school	171	7.9	33	6.0	
High school diploma/GED	483	22.3	117	21.3	
School after high school	910	42.1	225	40.9	
College degree or higher	525	24.3	159	28.9	
Smoking status					.01
Never	1,140	53.3	269	49.2	
Past	860	40.2	254	46.4	
Current	139	6.5	24	4.4	
Alcohol consumption, drinks per week					.31
Nondrinker/past drinker	1,333	61.9	337	61.4	
< 1	599	27.8	168	30.6	
1-14	209	9.7	41	7.5	
> 14	11	0.5	3	0.5	
Physical activity, METs					.53
Inactive 0	514	25.7	133	24.1	
< 5	592	29.6	160	28.9	
5-12	469	23.4	126	22.8	
≥ 12	428	21.4	134	24.2	
Percentage of energy from fat ≥ 30	1,886	89.2	478	87.5	.27
Baseline body mass index, kg/m^2					.61
< 25	164	7.6	43	7.8	
25-< 30	542	25.0	149	26.9	
≥ 30	1,462	67.4	361	65.3	
Age at menarche, years					.89
< 12	630	29.0	165	30.1	
12-13	1,100	50.7	273	49.7	
≥ 14	440	20.3	111	20.2	
Age at menopause, years					.28
< 45	615	31.8	151	28.9	
45-54	1,024	53.0	297	56.9	
> 54	293	15.2	74	14.2	
Self-reported health					.73
Excellent	40	1.9	9	1.6	
Very good	386	17.9	95	17.3	
Good	1,076	49.9	289	52.5	
Fair/poor	655	30.4	157	28.5	
Use of aspirin	556	25.5	160	28.8	.12
Enrollment onto estrogen alone trial					.13
Active	267	23.5	77	28.6	
Placebo	301	26.5	59	21.9	
Not enrolled	566	49.9	133	49.4	

(continued in next column)

Table 2. Baseline Characteristics by Diabetes and Metformin Use at Baseline (n = 2,733) (continued)

Characteristic	Women With Diabetes: Other Medication (n = 2,177) No.	%	Women With Diabetes: Metformin* (n = 556) No.	%	*P*
Enrollment onto estrogen plus progestin trial					.32
Active	236	22.6	71	24.7	
Placebo	221	21.2	69	24.0	
Not enrolled	586	56.2	147	51.2	
Enrollment onto dietary modification trial					.52
Intervention	582	26.7	143	25.7	
Control	914	42.0	225	40.5	
Not enrolled	681	31.3	188	33.8	
Age at first birth, years					.53
Never pregnant/no term pregnancy	213	11.1	55	11.7	
< 20	463	24.2	99	21.1	
20-29	1,093	57.2	277	58.9	
30+	143	7.5	39	8.3	
Duration of breastfeeding, years					.58
None	1,012	47.3	273	49.7	
≤ 1	837	39.1	203	37.0	
> 1	290	13.6	73	13.3	
Hysterectomy at random assignment	1,134	52.1	269	48.4	.12
Bilateral oophorectomy	497	23.9	119	22.4	.46
Use of estrogen only					.92
Never	1,504	69.1	389	70.0	
Prior	365	16.8	90	16.2	
Current	307	14.1	77	13.8	
Use of estrogen plus progestin					.97
Never	1,910	87.7	489	88.1	
Prior	112	5.1	28	5.0	
Current	155	7.1	38	6.8	
Duration of menopausal hormone therapy, years					.12
None	1,282	58.9	335	60.3	
< 5	477	21.9	100	18.0	
5-< 10	158	7.3	54	9.7	
10-< 15	106	4.9	24	4.3	
15+	154	7.1	43	7.7	
Benign breast disease					.49
No	1,626	82.4	444	80.4	
Yes, one biopsy	258	13.1	83	15.0	
Yes, ≥ two biopsies	89	4.5	25	4.5	
No. of first-degree relatives with breast cancer					.60
0	1,709	85.3	439	86.2	
≥ 1	294	14.7	70	13.8	
Gail risk					.10
< 1.25	929	42.7	212	38.1	
1.25-1.75	629	28.9	164	29.5	
≥ 1.75	619	28.4	180	32.4	
Diabetes medication					
Metformin (biguanide)	0	0	556	100.0	
Insulin	671	30.8	0	0.0	
Sulfonylureas	1,580	72.6	352	63.3	
Thiazolidinediones	36	1.7	10	1.8	
Alpha-glucosidase inhibitors	26	1.2	11	2.0	

Abbreviations: GED, General Educational Development; MET, metabolic equivalent of task; SD, standard deviation.
*Monotherapy or combination therapy.

Table 3. Incidence of Breast Cancer by Diabetes Status in Women's Health Initiative Clinical Trial Participants

Incidence of Breast Cancer	Women Without Diabetes		Women With Diabetes				
	No.	Annual %	No.	Annual %	HR*	95% CI	P†
Invasive breast cancer	2,926	0.42	347	0.44	0.99	0.85 to 1.14	.85
Ductal carcinoma in situ	677	0.10	77	0.10	0.99	0.73 to 1.36	.96

Abbreviation: HR, hazard ratio.

*HRs and *P* values from a proportional hazards model adjusting for age, first-degree relative with breast cancer, benign breast disease, age at menarche, age at menopause, parity, age at first birth, education, number of months of breastfeeding, smoking, alcohol consumption, body mass index, physical activity, duration of use of estrogen alone, duration of use of estrogen plus progesterone, bilateral oophorectomy, and mammogram within 2 years of baseline; stratified according to age (10-year groups), hormone therapy trial randomization, dietary trial randomization or overall survival enrollment, enrollment onto Women's Health Initiative extension, and race/ethnicity.

†*P* value from a 1-*df* test comparing diabetics with nondiabetics.

reports, women with diabetes in our WHI cohort did not have a higher incidence of breast cancer compared with women without diabetes, a finding potentially influenced by the relatively high frequency of metformin use in these women.

Until recently, observational studies[19,20] examining metformin use and incidence of breast cancer were limited and were mixed with two of four studies[22,23] reporting significantly lower incidence of breast cancer for women with diabetes who used metformin. Ruitter et al[21] have just reported findings from analyses that used the Dutch National Medical Register (a drug-dispensing database) to generate a cohort of 85,289 women. In this setting, a statistically significantly lower incidence of breast cancer was seen in women who used metformin compared with those who used sulfonylurea derivatives (HR, 0.95; 95% CI, 0.91 to 0.98).[21] The metformin results in this study add to such analyses by comprehensively adjusting for breast cancer risk factors, including BMI, physical activity, smoking, and frequency of mammography.

Although some preclinical work suggested predominant metformin influence on triple-negative cancers,[35] our review found only one prior study that examined metformin influence on breast cancer subtypes. In 90 women with diabetes and breast cancer, the incidence of PR-positive tumors was higher in metformin users.[24] Further studies are clearly needed in this area.

Women with diabetes present with a more advanced stage of breast cancer.[36-38] However, many[39-41] but not all[42] studies find lower mammographic screening rates in women with diabetes. In the WHI clinical trials, mammograms were mandated by protocol. Consequently, mammogram frequency was comparable in women with and without diabetes, and no significant difference in cancer stage was seen comparing women with diabetes who were not users of metformin with women without diabetes. Women with diabetes who were metformin users had a somewhat higher frequency of mammography compared with nonusers. Metformin nonusers were more commonly receiving insulin and therefore more likely to be under subspecialty care. Because providers of subspecialty care are described as less likely to order screening procedures,[43] a difference in screening could result. In any event, analyses were adjusted for mammography frequency.

Clinical studies also support a metformin influence on cancer. In a preoperative study,[44] women without diabetes with invasive breast cancer randomly assigned to metformin for 2 weeks had reduced Ki-67, a measure of tumor proliferation,[45] compared with nonusers. In a retrospective neoadjuvant therapy analysis, patients with breast cancer who had diabetes and used metformin had a higher frequency of complete response (24%) than patients who had diabetes and did not use metformin (8%) and patients without diabetes (16%; $P = .02$).[46] Finally, in retrospective analyses, patients with diabetes and HER2-positive breast cancer who used metformin had better clinical outcome that nonusers.[47] In post hoc analyses in an adjuvant setting, use of metformin was not associated with improved survival in patients with triple-negative breast cancer, but there was a trend for decreased distant recurrence compared with women without diabetes.[48]

Table 4. Incidence of Breast Cancer by Diabetes Treatment in Women's Health Initiative Clinical Trial Participants

Incidence of Breast Cancer	Women Without Diabetes		Women With Diabetes and Associated Therapy								
			Other Diabetic Medication				Metformin				
	No.	Annual %	No.	Annual %	HR	95% CI	No.	Annual %	HR	95% CI	P*
Invasive breast cancer	2,926	0.42	129	0.47	1.16	0.93 to 1.45	104	0.40	0.75	0.57 to 0.99	.04
Hormone receptor status											
ER positive/PR positive	1,839	0.26	78	0.29	1.08	0.81 to 1.44	59	0.23	0.64	0.45 to 0.92	.04
ER positive/PR negative	387	0.055	17	0.062	1.27	0.68 to 2.37	14	0.054	1.14	0.58 to 2.23	.72
ER negative/PR negative	371	0.053	18	0.066	1.78	1.05 to 3.03	14	0.054	0.68	0.29 to 1.59	.06
HER2 overexpression											
Yes	346	0.049	12	0.044	0.76	0.34 to 1.72	20	0.078	1.30	0.75 to 2.57	.43
No	1,720	0.24	82	0.30	1.18	0.89 to 1.56	59	0.23	0.58	0.40 to 0.84	.007
Ductal carcinoma in situ	677	0.10	25	0.09	0.89	0.52 to 1.53	29	0.11	1.16	0.72 to 1.89	.74

NOTE. HRs and *P* values from a proportional hazards model adjusting for age, first-degree relative with breast cancer, benign breast disease, age at menarche, age at menopause, parity, age at first birth, education, No. of months of breastfeeding, smoking, alcohol consumption, body mass index, physical activity, duration of use of estrogen alone, duration of use of estrogen plus progesterone, bilateral oophorectomy, mammogram within 2 years of baseline, and stratified according to age (10-year age groups), hormone therapy trial randomization, dietary trial randomization or OS enrollment, enrollment onto Women's Health Initiative extension, and race/ethnicity.

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PR, progesterone receptor.

**P* value from a 1-*df* test comparing diabetics with nondiabetics.

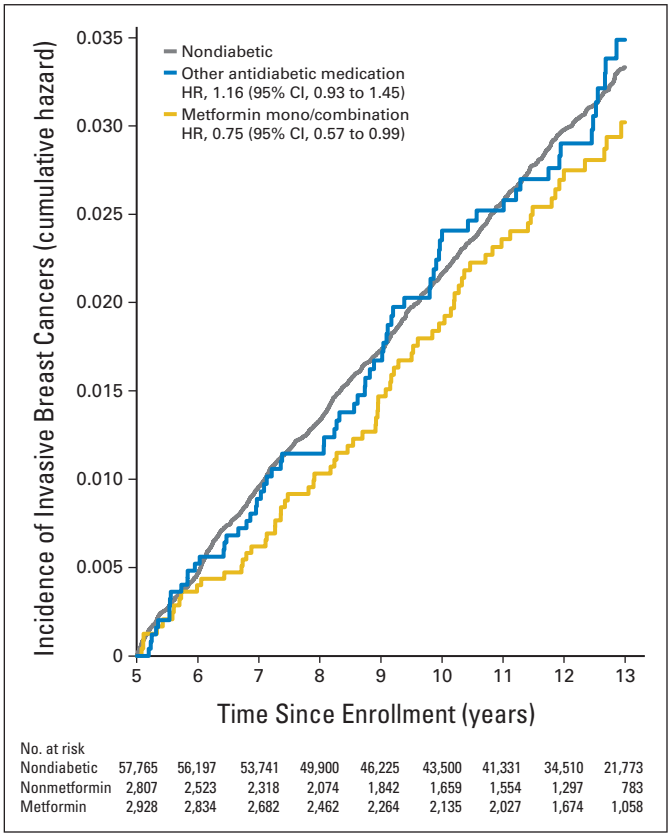

Fig 1. Incidence of invasive breast cancers in the Women's Health Initiative. Cumulative hazard functions of invasive breast cancer that allow for the time-dependent exposure variables of diabetes status and metformin use.[31] Cumulative hazard functions began 5 years after enrollment to ensure that adequate numbers of ultimate metformin users were receiving the drug. Hazard ratios (HRs) and 95% CIs from a multivariate-adjusted Cox proportional hazards analysis.

An inhibitory influence of metformin on breast cancer is biologically plausible but the potential mediating mechanism is not understood. Proposed mechanisms include indirect insulin-mediated effects and direct effects on cancer cells via influence on the AMPK pathway with resultant inhibition of the mammalian target of rapamycin (mTOR) pathway.[15,49]

We have previously presented metformin findings with similar trends but with less strong associations that were based on the entire WHI population, including participants in both clinical trials and observational studies.[50] Our analyses included only participants in the clinical trials because medication information in the observational study was available only through year 3 compared with through year 9 in the clinical trials.

Diagnoses of diabetes were not based on medical record review; rather, they were determined by ongoing direct query and review of the use of antidiabetic medication. As described in Patients and Methods, this approach has been evaluated,[27] and the associations seen compare favorably with the commonly used International Classification of Disease, Ninth Revision (ICD-9) clinical modification codes[51]; confirmation studies suggest 72% sensitivity and 96% specificity for identification of diabetes.[52]

The strengths of our study include the prospective cohort design; the large, diverse population well characterized for risk of breast cancer; serial assessment of mammography; breast cancer verification via review of pathology reports; and information on diabetes and the use of diabetes

Table 5. Invasive Breast Cancer Characteristics by Diabetes and Use of Metformin

Characteristic	Women With Diabetes: Metformin Use No.	%	Women With Diabetes: No Metformin Use No.	%	Women Without Diabetes No.	%	*P*
Tumor size, cm							.14
No tumor found/no primary mass	0	0.0	1	0.8	14	.5	
Microscopic focus or foci	1	1.0	0	0.0	76	2.8	
Mammographic diagnosis only, tumor not clinically palpable	0	0.0	0	0.0	3	.1	
≤ 0.5	7	7.3	6	5.1	265	9.6	
> 0.5-1	23	24.0	25	21.2	768	27.8	
> 1-2	42	43.8	54	45.8	1,066	38.6	
> 2	23	24.0	32	27.1	567	2.6	
Mean	1.8		1.8		1.6		.11
SD	1.4		1.4		1.3		
Positive lymph nodes							.07
No	59	65.6	84	75.7	1,996	76.2	
Yes	31	34.4	27	24.3	623	23.8	
SEER stage							.07
Localized	65	62.5	90	70.3	2,190	75.3	
Regional	34	32.7	33	25.8	652	22.4	
Distant	3	2.9	3	2.3	35	1.2	
Grade							.15
Well differentiated	24	23.1	23	18.0	752	25.9	
Moderately differentiated	48	46.2	52	40.6	1,111	38.2	
Poorly differentiated	21	20.2	37	28.9	759	26.1	
Histology							.08
Ductal	76	73.1	85	66.4	1,880	64.6	
Lobular	5	4.8	15	11.7	273	9.4	
Ductal and lobular	9	8.7	10	7.8	387	13.3	
Tubular	0	0.0	3	2.3	88	3.0	
Other	14	13.5	15	11.7	280	9.6	
Estrogen receptor status							.73
Positive	74	71.2	99	76.7	2,273	77.7	
Negative	17	16.3	19	14.7	421	14.4	
Borderline	1	1.0	1	0.8	4	.1	
Unknown/not done/missing	12	11.5	10	7.8	228	7.8	
Progesterone receptor status							.75
Positive	62	59.6	79	61.2	1,881	64.3	
Negative	29	27.9	35	27.1	761	26.0	
Borderline	1	1.0	3	2.3	18	.6	
Unknown/not done/missing	12	11.5	12	9.3	266	9.1	
HER2 (ERBB2)							.08
Positive	20	19.2	12	9.3	346	11.8	
Negative	59	56.7	82	63.6	1,720	58.8	
Borderline	1	1.0	0	0.0	21	.7	
Unknown/not done/missing	24	23.1	35	27.1	839	28.7	
Triple-negative status (ER negative, PR negative, HER2 negative)							.47
Triple negative	9	8.7	11	8.5	186	6.4	
Other (includes borderline)	71	68.3	82	63.6	1,872	64.0	
Unknown/missing ER/PR/HER2/all/some	24	23.1	36	27.9	868	29.7	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results.

medication updated throughout. This database allowed for time-dependent, exposure-related analyses of use of diabetes medication and risk of breast cancer. Limitations of our study include lack of information on the severity of diabetes and reliance on local laboratory assessment of hormone receptor and HER2 status, precluding information on quality control. Especially noteworthy are the substantial differences in baseline characteristics of women with and without diabetes for factors including obesity and physical activity that could result in residual confounding despite adjustment in analyses for many breast cancer risk factors.

Our findings are of most direct relevance to women with diabetes, most of whom were overweight or obese. However, consideration of the totality of available evidence does provide support for the ongoing clinical studies of metformin,[53] including a prospective, full-scale, multicenter adjuvant trial[54] and proof of principal studies in prevention settings.[55]

In a large population of postmenopausal women, use of oral metformin was associated with lower incidence of invasive breast cancer. The influence of metformin on breast cancer subtypes requires further study. Our results inform future studies evaluating use of metformin in the management and prevention of breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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