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Diabetes, Metformin Use, and Colorectal Cancer Survival in Postmenopausal Women

Furha Iram Cossor[a], **Lucile L. Adams-Campbell**[b], **Rowan T. Chlebowski**[c], **Marc J Gunter**[d], **Karen Johnson**[e], **Robert E. Martell**[a], **Anne McTiernan**[f], **Michael S. Simon**[g], **Thomas Rohan**[h], **Robert B. Wallace**[i], and **Jessica K. Paulus**[j]

Furha Iram Cossor: fcossor@tuftsmedicalcenter.org; Lucile L. Adams-Campbell: lla9@georgetown.edu; Rowan T. Chlebowski: rowanchlebowski@gmail.com; Marc J Gunter: mgunter@imperial.ac.uk; Karen Johnson: KJohnson@uthsc.edu; Anne McTiernan: amctiern@fhcrc.org; Michael S. Simon: simonm@karmanos.org; Thomas Rohan: thomas.rohan@einstein.yu.edu; Robert B. Wallace: robert-wallace@uiowa.edu; Jessica K. Paulus: jpaulus@tuftsmedicalcenter.org

[a]Tufts Medical Center, 800 Washington St., Box 245, Boston, MA, USA 02111

[b]Georgetown Lombardi Comprehensive Cancer Center, 3970 Reservoir Road, N.W., E501, Washington, D.C., USA 20057

[c]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 W Carson Street, Building J-3, Torrance CA, USA 90502

[d]Imperial College London, Norfolk Place, London, W2 1PG, United Kingdom

[e]University of Tennessee Health Science Center, 66 N. Pauline, Suite 633, Memphis, TN, USA 38163

[f]Fred Hutchinson Cancer Research Center, M4-B874, PO Box 19024, Seattle, WA, USA, 98109

[g]Dept of Oncology, Karmanos Cancer Institute at Wayne State University, 4100 John R, Detroit, MI, USA, 48201

[h]Albert Einstein College of Medicine, Jack and Pearl Resnick Campus, 1300 Morris Park Avenue, Belfer Building, Room 1301, Bronx, NY, USA 10461

[i]University of Iowa College of Public Health, S422 CPHB, 105 River St., Iowa City, IA, USA 52242

[j]Tufts Clinical and Translational Science Institute, Tufts Medical Center, 35 Kneeland St., 11th Floor, Boston, MA, USA 02111

Abstract

Background—Observational studies have associated metformin use with lower colorectal cancer (CRC) incidence but few studies have examined metformin's influence on CRC survival. We examined the relationships among metformin use, diabetes, and survival in postmenopausal women with CRC in the Women's Health Initiative (WHI) Clinical Trials and Observational Study.

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Corresponding Author: Furha I. Cossor, MD, MS, Department of Hematology/Oncology, Tufts Medical Center, 800 Washington St., Box 245, Boston, MA 02111, T: 1-617-636-2600, F: 1-617-636-4120, fcossor@tuftsmedicalcenter.org.

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Methods—2,066 postmenopausal women with CRC were followed for a median of 4.1 years, with 589 deaths after CRC diagnosis from all causes and 414 deaths directly attributed to CRC. CRC-specific survival was compared among women with diabetes with metformin use (n=84); women with diabetes with no metformin use (n=128); and women without diabetes (n=1854). Cox proportional hazard models were used to estimate associations among metformin use, diabetes and survival after CRC. Strategies to adjust for potential confounders included: multivariate adjustment with known predictors of colorectal cancer survival and construction of a propensity score for the likelihood of receiving metformin, with model stratification by propensity score quintile.

Results—After adjusting for age and stage, CRC specific survival in women with diabetes with metformin use was not significantly different compared to that in women with diabetes with no metformin use (HR 0.75; 95% CI 0.40 –1.38, p=0.67) and to women without diabetes (HR 1.00; 95% CI 0.61 – 1.66, p=0.99). Following propensity score adjustment, the HR for CRC-specific survival in women with diabetes with metformin use compared to non-users was 0.78 (95% CI 0.38 – 1.55, p=0.47) and for overall survival was 0.86 (95% CI 0.49 – 1.52; p=0.60).

Conclusions—In postmenopausal women with CRC and DM, no statistically significant difference was seen in CRC specific survival in those who used metformin compared to non-users. Analyses in larger populations of colorectal cancer patients are warranted.

Keywords

Metformin; Colorectal Neoplasm; Diabetes Mellitus; Survival Rate; Treatment Outcome; Female

INTRODUCTION

There is emerging evidence supporting the hypothesis that Type 2 Diabetes Mellitus (DM) is a risk factor for colorectal cancer (CRC). In several large population studies, DM or abnormal glucose metabolism was associated with an increased risk of CRC as well as several other neoplasms [1–5].

DM has also been associated with a relatively poor prognosis among CRC patients. In a recent retrospective study, patients with DM and colon cancer had significantly worse disease-free and overall survival as compared to colon cancer patients without DM in analyses adjusted for prognostic factors [6]. Another study reported that both men and women with DM had a 25% significantly increased risk of fatal colon cancer as compared to those without DM [1]. While the biological relationship between DM and CRC outcome is unclear, altered glucose metabolism, hyperinsulinemia and insulin-like growth factor (IGF-I) are potential mediators.

Metformin, an agent commonly used in diabetes therapy, increases insulin sensitivity and improves glycemic control [7], [8]. These properties, and the preclinical studies suggesting that metformin may have direct cancer growth inhibition potential via mammalian target of rapamycin (mTOR) pathway suppression [9], prompted interest in metformin as a potential anti-cancer agent. Subsequently, a number of observational studies have associated lower cancer incidence with metformin use as well as a lower risk of nonspecific cancer-related mortality[6], [8], [10], [11]. A recent meta-analysis also found a significantly lower risk of colorectal cancer in users vs non-users of Metformin[12]. Metformin use has even been associated with a decreased incidence of colorectal adenomas in patients with a prior history of colorectal cancer[13]. However, few epidemiologic studies have examined metformin use in relation to CRC-specific survival. In a Korean study, colorectal cancer patients with diabetes who took metformin had an improved overall and cancer-specific survival[14], and in a second study of patients in the United States, improvements in overall survival were

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noted[15]. In these studies, multivariate Cox proportional hazard regression models were used to adjust for confounding variables. We aim to evaluate the association between metformin use and colorectal-cancer specific survival advantage in a population of racially diverse postmenopausal women while applying propensity score methods to control for possible confounding.

In this study, we examined associations among metformin use, DM and CRC-specific and overall survival after CRC among postmenopausal women diagnosed with CRC in the Women's Health Initiative (WHI). We hypothesized that metformin use would be associated with improved survival as compared to non-use among women with CRC and DM.

Patients and Methods

Study population

The Women's Health Initiative (WHI) is a long-term national health study that includes four clinical trials (CT) and an observational study (OS) that focused on strategies to prevent or control heart disease, cancer, and osteoporotic fractures in postmenopausal women. The original WHI study included 161,808 postmenopausal women aged 50–79 years, enrolled at one of 40 WHI clinical centers across the United States between 1993 and 1998. Three randomized, controlled clinical trials (CT) enrolled 68,132 women into studies evaluating three prevention strategies: hormone therapy, dietary modification, and calcium with vitamin D supplementation. If eligible, women could choose to enroll in one, two, or all three of the trial components. The CT cohort was followed until March 2005, after which participants were invited to enroll in the WHI Extension Study for collection of health outcomes data without intervention through 2010. The Observational Study tracked the medical history and health habits of 93,676 women who were ineligible or not interested in joining the CT, and examined relationships between lifestyle, health, risk factors, and specific disease outcomes through 2010. All participants provided written informed consent and the study was approved by each of the clinical centers' institutional review boards. The Fred Hutchinson Cancer Research Center in Seattle, WA serves as the WHI Clinical Coordinating Center for data collection, management, and analysis. Further details on scientific rationale, eligibility requirements, and other design aspects of the WHI have been previously published[16].

Medical history updates were obtained by mail or telephone questionnaires biannually for CT participants and annually for OS participants. Reported cancer diagnoses were then verified by local, centrally trained physician adjudicators using medical records and pathology reports. CRC cases were confirmed by blinded adjudication at the Clinical Coordinating Center and coded using the Surveillance, Epidemiology, and End Results system. Eligibility criteria for the analysis described here included a diagnosis of CRC after WHI entry. Women who reported a history of CRC prior to WHI enrollment and CRC cases that were identified only at the time of death were excluded.

Eligible study subjects were divided into three comparison groups based on whether they had diabetes and used metformin. The definition of Type 2 diabetes (DM) was a positive answer to the question "did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?" or the reported use of medical therapy for diabetes at any time. Individuals diagnosed with diabetes before age 20 or who were ever hospitalized for diabetic coma were considered to have Type 1 Diabetes and excluded [17]. The study population was then divided into the following exposure cohorts: (1) women with CRC and DM and use of metformin at any time; (2) women with CRC and DM with no metformin use; and (3) women with CRC without DM.

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Data Collection

Prior to enrollment in the WHI, information on demographics, exposures, lifestyle, dietary habits, family history and medical history were obtained through the use of standardized questionnaires. Physical measurements including pulse, blood pressure, height, weight, and waist and hip circumference were taken by certified staff at the initial clinical visit. Details regarding medication information were obtained via interviewer-administrated questionnaires at baseline and at years 1, 3, 6, and 9 for CT participants and at year 3 for OS participants. For all medications, the data collected included product and generic name, dosage form, strength, and duration of use.

Outcome measures

In this analysis, survival outcomes in women with CRC and DM who used metformin, women with CRC and DM who did *not* use metformin, and women with CRC without DM were compared. CRC-specific survival was the primary outcome, measured from the date of CRC diagnosis to date of death due to CRC, or last known date alive. Patients who were not deceased or who died of causes other than CRC were censored at the last known date alive or date of death, respectively. Overall survival was analyzed as a secondary outcome, and defined as the period from the date of diagnosis of CRC to the date of death or last known date alive. For this secondary outcome, only those patients who were not deceased were censored at the last known date alive.

Statistical analyses

Patient demographic and treatment characteristics were compared between the three exposure cohorts as described above. For continuous variables that were normally distributed, the student's t-test was used; for non-normally distributed variables, the Wilcoxon rank sum test was used. For categorical variables the Chi-Square test was used; Fisher's exact test was used when the expected value in any cell was less than 5. Kaplan-Meier survival analyses stratified by exposure group were used to generate median survival curves for both CRC-specific and overall survival. Univariate Cox proportional hazard models were used to estimate hazard ratios and their 95% confidence intervals to compare CRC-specific and overall survival differences by known prognostic factors. These included age at diagnosis (ages 50–59 years, 60–69 years, or ≥70 years), race (black, white, or other), body-mass index (BMI) (by BMI category: <18.5–24.9, 25.0–29.9, 30.0 – 34.9, and ≥35), smoking status (never, past, or current), family history of colorectal cancer (yes/no), alcohol use (Nondrinker, Past drinker, <7 drinks/week,7+ drinks/week), dietary history (use of diabetic or high-fiber diet), physical activity level measured in total MET-hours per week (kcal/wk/kg as a continuous variable), stage at diagnosis (localized vs. regional and distant), insulin use (yes/no), total number of diabetic medications per patient (0, 1, 2, 3, or ≥4), aspirin use (yes/no), nonsteroidal anti-inflammatory drug (NSAID) use (yes/no), and metformin use (yes/no). Unadjusted, age-adjusted, and multivariate adjusted Cox proportional hazards models including age and stage at diagnosis were also conducted to estimate the effect of diabetes status on CRC-specific and overall survival.

Two separate analyses using different methodologies were conducted to address potential confounding of the association between metformin use, DM and survival outcomes. First, multivariate Cox proportional hazard models for CRC-specific and overall survival were built that included prognostic factors that had a significant impact on survival as determined by a univariate hazard ratio (HR) with a p-value <0.2. Patients with unknown stage at diagnosis were excluded from these multivariate models (n=26). As a second strategy, given the limited number of events, a propensity score model for the probability of metformin use was developed. A propensity score was generated from a logistic regression model for metformin use (ever/never) that included all prognostic factors listed above (age at

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diagnosis, race, BMI, smoking status, alcohol use, dietary history, physical activity level, stage at diagnosis, insulin use, total number of diabetic medications, aspirin use, and NSAID use). The likelihood of metformin use based on the identified predictors was computed for each patient and the area under the curve (AUC) was used to quantify the predictive strength of the model. The model generated had an AUC of 0.78. Propensity score quintiles were then used as a stratification variable in Cox proportional hazards models.

All analyses were performed using the SAS System for Windows, version 9.2 (SAS Institute, Cary, NC), and all reported p-values were 2-sided.

Results

Study population and demographic characteristics

Of the 161,808 women in the WHI cohort, 916 reported a history of CRC prior to WHI enrollment, and 2,167 had a CRC diagnosis while on study. After excluding those diagnosed at the time of death (N=101), there were 2,066 women who met eligibility criteria for this analysis, including 212 women with DM and 1,854 women without DM. Of women with DM, 84 women reported metformin use at any time while on study.

Detailed demographic, lifestyle, and staging information for the three exposure cohorts is presented in Table 1. The median age at diagnosis was slightly lower in women with diabetes on metformin (median 70 years; range 52–84 years) than women with DM who did not use metformin (70 years; range 56–88 years) or women without diabetes (70 years; range 51–92 years) (p=0.04). The cohort of women without DM had fewer African Americans and more whites than the cohorts of women with DM. Women without DM had a lower median BMI than either of the other cohorts. Women with diabetes were more likely to have been past alcohol drinkers or not drink at all, and a greater proportion of women without diabetes regularly consumed alcohol. The women without DM were also more active than women with DM (total median MET-hours per week 7.5 kcal/wk/kg in non-diabetics vs 7 for women with DM on metformin and 4.8 for women with DM not on metformin). There were no significant differences in family history of CRC, smoking status, use of a high-fiber diet, stage of disease at diagnosis, aspirin use, or NSAID use between groups. Among women with DM, metformin users reported a higher total number of diabetic medications than non-users, however there was no difference in insulin use by metformin status.

Metformin and clinical outcomes

Characteristics of invasive colorectal cancer cases by cohort are outlined in Table 2. Median follow up for all women with CRC was 4.1 years (range, 3 days – 14.4 years). In the entire study population, there were 589 deaths (28.5%) after CRC diagnosis, with 414 (20.0%) deaths directly attributable to CRC (Supplementary Table 1). Of 1854 women without DM, there were 516 deaths after CRC diagnosis (27.8%) overall and 365 deaths (19.7%) directly attributed to CRC (includes deaths due to colon, rectosigmoid and rectum cancer). In women with DM on metformin, there were 26 deaths after CRC diagnosis (31%) and 17 (20.2%) directly attributed to CRC. In women with DM not on metformin, there were 47 deaths overall (36.7%) and 32 (25%) due to CRC. Median time to death in women without DM, women with DM on metformin, and women with DM not on metformin was 1.7 years, 2.1 years, and 1.7 years, respectively, with no significant difference noted between groups (p= 0.64). Similarly, median time to CRC-related death in the same cohorts was 1.3, 1.9, and 1.1 years, respectively (p=0.60).

In the Kaplan-Meier survival analysis, there were no significant differences in overall survival or CRC-specific survival between groups (Figures 1 & 2). Univariate analysis with

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Cox proportional hazards models were used to determine if age, race, BMI, smoking habits, family history, alcohol use, stage of disease at diagnosis, use of a diabetic or high-fiber diet, activity level (measured in MET-hours per week), insulin use, number of diabetic medications used, aspirin use, NSAID use, metformin use, or history of prior removal of any part of the intestines, ulcerative colitis, or liver disease had an effect on overall survival or CRC-specific survival in the study population (Supplementary Table 2). Stage at diagnosis and activity level were significant predictors of both overall and CRC-specific survival, and diabetes status was a predictor of overall but not CRC-specific survival (Supplementary Table 3) for the entire study population. After adjustment for age and stage at diagnosis, there was no difference in CRC-specific or overall survival between women with DM on metformin compared to women with DM not on metformin (HR for CRC-specific survival 0.75, 95% CI 0.40 -1.38, p=0.67; HR for overall survival 0.84, 95% CI 0.51 – 1.37, p=0.48) (Table 3A). After propensity score adjustment, the hazard ratio for colorectal-cancer specific survival in women with DM on metformin compared to women with DM not using metformin was 0.78 (95% CI 0.38 – 1.55, p=0.47), and for overall survival was 0.86 (95% CI 0.49 –1.52, p=0.60) (Table 3A). In addition, no significant differences in CRC-specific or overall survival were found in women with DM on metformin as compared to women without DM (HR for CRC-specific survival 1.00, 95% CI 0.61 – 1.66, p=0.99; HR for overall survival 1.20, 95% CI 0.80 – 1.79) (Table 3B). Sensitivity analyses excluding those patients who had in-situ disease and those patients who had any other cancer also did not affect estimates of overall or colorectal cancer specific survival.

Discussion

In this cohort of postmenopausal women with CRC and DM, metformin use was not associated with statistically significant increases in CRC-specific survival as compared to non-use of metformin. However, the observed hazard ratio of less than one for the association between metformin use and CRC-specific survival was similar in direction and magnitude to those reported in recent studies[14], [15], [17].

In several recent observational studies, statistically significantly longer survival for patients with CRC who took metformin has been reported. In a retrospective analysis of 595 Korean patients with newly diagnosed CRC and Type 2 Diabetes, metformin use was associated with a lower risk of CRC-specific (HR, 0.66; 95% CI 0.45–0.975; p=0.037) and overall mortality (HR, 0.66; 95% CI 0.476–0.923; p= 0.015) [14]. Other studies have examined the association between metformin use and overall survival after CRC diagnosis. A retrospective analysis of 397 patients with CRC and Type II noninsulin-dependent diabetes mellitus (NIDDM) found that overall survival after CRC diagnosis in metformin users was 76.9 months (95% CI, 61.4–102.4) vs 56.9 months in non-users (95% CI, 44.8–68.8) (p = 0.048) [15]. In a cohort of 1,708 CRC patients from the United States Veteran's Administration (VA) Cancer Registry, a statistically significantly longer overall survival in metformin users was observed. However the comparison group in this study included both CRC patients with diabetes who did not use metformin as well as CRC patients without DM [18]. Several key differences exist between the above studies and our analysis. Observed survival differences using overall survival as an outcome could represent the beneficial effect of improved glycemic control on DM-related complications and overall death in users of metformin, and may not reflect cancer-specific effects. In our analysis, we evaluated both overall survival after CRC diagnosis as well as CRC-specific survival. In contrast to the report from the VA Cancer Registry [18], we categorized women with DM not on metformin as a distinct comparator cohort to attempt to address baseline differences in survival that may exist between women with and without DM. Finally, each of the above studies included men, while our cohort was restricted to women.

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Our study was limited by a small sample size and lack of statistical power despite the relatively large size of the overall WHI cohort. Fewer deaths in women with DM were seen in this WHI study in comparison to the aforementioned studies of CRC patients (13–15). Since only 73 deaths occurred in women with DM, there was only 70% power to detect a relatively large hazard ratio of 0.5 for the association between metformin use and CRC-specific survival. Selection bias also could have influenced the findings, since this survival analysis was restricted to women with incident CRC[19]. If metformin is indeed associated with a reduced risk of incident CRC, it is possible that we preferentially selected those women who may have "metformin-resistant" disease. We expect this bias would result in an attenuation of effect estimates. Third, though the method we used to establish a diagnosis of DM has been validated[17], misclassification of diabetes and metformin status was still possible. After the initial interview, follow up questionnaires obtained by the WHI did not ask about incident diabetes treated with lifestyle changes alone. Of note, however, is the WHI report on a random sample of 5884 women with measured fasting glucose levels who did not report a diagnosis of diabetes at baseline. In that analysis, only 3.4% of those women had diabetes using a criterion of a single fasting glucose level ≥126, making misclassification of the diabetes diagnosis less likely[17]. Nevertheless, our definition of diabetes may have excluded patients that developed mild or diet-controlled diabetes, and some of these patients may have been misclassified as patients without diabetes. Because diabetes itself is associated with an increased risk of colorectal cancer-related death, this bias could have biased our results toward the null. We were also unable to obtain data on either the duration of metformin use or the timing of metformin use in relation to CRC diagnosis. Thus, in our analysis, use of metformin was configured as a binary variable (metformin use: ever vs. never) and did not incorporate timing, duration or dosage of exposure. This possible mis-specification of exposure status is expected to be non-differential with respect to survival outcomes, and could be viewed as a type of non-differential exposure misclassification that would attenuate effect estimates[20]. In addition, information on cancer treatment was not available. Finally, we lacked indicators of diabetic disease severity (i.e. Hemoglobin A1c) and contraindications to metformin use (i.e. serum creatinine), both potential confounders of the association between metformin use and survival. We attempted to account for confounding in a robust way by creating a propensity score that included available possible proxies for diabetic severity (insulin use, number of diabetic medications, use of the diabetic diet) as well as other possible indications of metformin use also associated with CRC survival. The propensity score-adjusted hazard ratios were similar in magnitude as compared to those from the age and stage adjusted models. The consistency in results from different analytic approaches to adjust for confounding is reassuring, but the threat of residual confounding by unmeasured or imperfectly measured factors remains.

Our study has several strengths. First, the WHI is a large, prospective cohort study of postmenopausal women in which all cancer outcomes were verified by review of medical records and pathology reports. Secondly, women with DM were identified using a previously validated method that showed a high concordance rate between self-reported incidence rates of DM and fasting glucose levels in a subset of participants [17]. Also, because information on diabetes medication use was updated throughout the study, our method of capturing metformin users included not only those taking the medication at baseline but also women who initiated metformin at any point after enrollment. Finally, in concordance with the published literature, stage of disease at diagnosis and activity level were independent predictors of overall and colorectal cancer specific survival, and diabetes was a predictor of overall survival in this dataset (Supplementary Tables 2 and 3)[1], [6] [21], [22][23].

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In summary, we did not find evidence of a statistically significant association between metformin use and CRC-specific survival in this cohort of postmenopausal women with diabetes and CRC. Continued research on this topic should be pursued given the promising pre-clinical studies and results from similar analyses done on larger cohorts. In particular, analysis of large cohorts with detailed information on the timing and duration of metformin use is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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WHI INVESTIGATORS

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, Nancy Geller.

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, Charles Kooperberg, Barbara Cochrane, Julie Hunt, Marian Neuhouser, Lesley Tinker, Susan Heckbert, Alex Reiner.

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Regional Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson, Kathryn M. Rexrode, Brian Walsh, J. Michael Gaziano, Maria Bueche; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard, Lucile Adams-Campbell, Lawrence Lessin, Cheryl Iglesia, Brian Walitt, Amy Park; (The Ohio State University, Columbus, OH) Rebecca Jackson, Randall Harris, Electra Paskett, W. Jerry Mysiw, Michael Blumenfeld; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick, Mark A. Hlatky, Manisha Desai, Jean Tang, Stacy T. Sims; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson, Tamsen Bassford, Cheryl Ritenbaugh, Zhao Chen, Marcia Ko; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende, Maurizio Trevisan, Ellen Smit, Amy Millen, Michael LaMonte; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher, Michael Perri, Andrew Kaunitz, R. Stan Williams, Yvonne Brinson; (University of Iowa, Iowa City/ Davenport, IA) Robert Wallace, James Torner, Susan Johnson, Linda Snetselaar, Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller, Jane Cauley, N. Carole Milas; (University of Tennessee Health Science Center, Memphis, TN) Karen C. Johnson, Suzanne Satterfield, Rongling Li, Stephanie Connelly, Fran Tylavsky; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker, Stephen Rapp, Claudine Legault, Mark Espeland, Laura Coker, Michelle Naughton.

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker, Stephen Rapp, Claudine Legault, Mark Espeland, Laura Coker, Michelle Naughton.

Former Principal Investigators and Project Officers: (Albert Einstein College of Medicine, Bronx, NY) Sylvia Wassertheil-Smoller (Baylor College of Medicine, Houston, TX) Haleh Sangi-Haghpeykar, Aleksandar Rajkovic, Jennifer Hays, John Foreyt; (Brown University, Providence, RI) Charles B. Eaton, Annlouise R. Assaf; (Emory University, Atlanta, GA) Lawrence S. Phillips, Nelson Watts, Sally McNagny, Dallas Hall,; (Fred Hutchinson Cancer Research Center, Seattle, WA) Shirley A.A. Beresford, Maureen Henderson; (George Washington University, Washington, DC) Lisa Martin, Judith Hsia, Valery Miller; (Harbor-UCLA Research and Education Institute, Torrance, CA) Rowan Chlebowski (Kaiser Permanente Center for Health Research, Portland, OR) Erin LeBlanc, Yvonne Michael, Evelyn Whitlock, Cheryl Ritenbaugh, Barbara Valanis; (Kaiser Permanente Division of Research, Oakland, CA) Bette Caan, Robert Hiatt; (National Cancer Institute, Bethesda, MD) Carolyn Clifford[1]; (Medical College of Wisconsin, Milwaukee, WI) Jane Morley Kotchen (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Linda Pottern; (Northwestern University, Chicago/Evanston, IL) Linda Van Horn, Philip Greenland; (Rush University Medical Center, Chicago, IL) Lynda Powell, William Elliott, Henry Black; (State University of New York at Stony Brook, Stony Brook, NY) Dorothy Lane, Iris Granek; (University at Buffalo, Buffalo, NY) Maurizio Trevisan; (University of Alabama at Birmingham, Birmingham, AL) Cora E. Lewis, Albert Oberman; (University of Arizona, Tucson/Phoenix, AZ) Tamsen Bassford, Cheryl Ritenbaugh, Tom Moon; (University of California at Davis, Sacramento, CA) John Robbins; (University of California at Irvine, CA) F. Allan Hubbell, Frank Meyskens, Jr.; (University of California at Los Angeles, CA) Lauren Nathan, Howard Judd[1]; (University of California at San Diego, LaJolla/Chula Vista, CA) Robert D. Langer; (University of Cincinnati, Cincinnati, OH) Michael Thomas, Margery Gass, James Liu; (University of Hawaii, Honolulu, HI) J. David Curb[1]; (University of Massachusetts/Fallon Clinic, Worcester, MA) Judith Ockene; (University of Medicine and Dentistry of New Jersey, Newark, NJ) Norman Lasser; (University of Miami, Miami, FL) Mary Jo O'Sullivan, Marianna Baum; (University of

[1]deceased

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Minnesota, Minneapolis, MN) Karen L. Margolis, Richard Grimm; (University of Nevada, Reno, NV) Robert Brunner, Sandra Daugherty[1]; (University of North Carolina, Chapel Hill, NC) Gerardo Heiss, Barbara Hulka, David Sheps; (University of Tennessee Health Science Center, Memphis, TN) Karen Johnson, William Applegate; (University of Texas Health Science Center, San Antonio, TX) Robert Brzyski, Robert Schenken; (University of Wisconsin, Madison, WI) Gloria E. Sarto, Catherine Allen[1]; (Wake Forest University School of Medicine, Winston-Salem, NC) Mara Vitolins, Denise Bonds, Electra Paskett, Greg Burke; (Wayne State University School of Medicine/Karmanos Cancer Institute, Detroit, MI) Michael S. Simon, Susan Hendrix.

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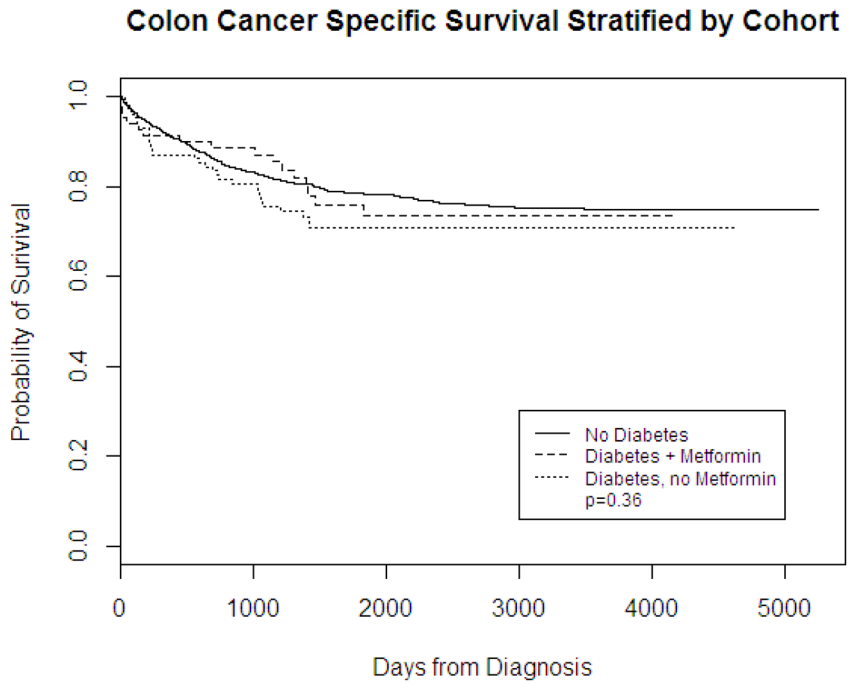

Figure 1.
Kaplan-Meier survival curve comparing colorectal cancer-specific survival between women without diabetes (No Diabetes), women with diabetes on metformin (Diabetes + Metformin), and women with diabetes not on metformin (Diabetes, no Metformin).

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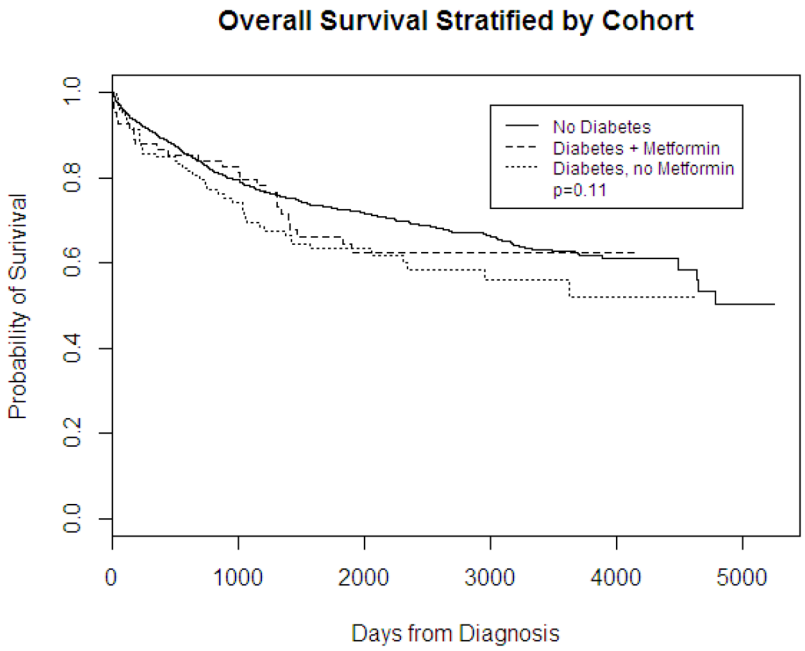

Figure 2.
Kaplan-Meier survival curve comparing overall survival between women without diabetes (No diabetes), women with diabetes on metformin (Diabetes + Metformin), and women with diabetes not on metformin (Diabetes, no Metformin).

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Table 1
Demographic and Treatment Characteristics of

Women's Health Initiative study participants with Colorectal Cancer, by Diabetes and Metformin Status

	No DM N=1854	DM + Metformin N=84	DM – Metformin N=128	p-values[a]
Age at diagnosis				
Median (range)	72 (51–92)	70 (52–84)	72 (56–88)	0.04
50–59, N, (%)	120 (6%)	5 (6%)	7 (5%)	
60–69, N, (%)	617 (33%)	38 (45%)	50 (39%)	
70–79+, N, (%)	1117 (60%)	41 (49%)	71 (55%)	
Ethnicity[d], N (%)				
American Indian/Alaskan Native	8 (0%)	0 (0%)	1 (1%)	
Asian/Pacific Islander	38 (2%)	3 (4%)	1 (1%)	
Black/African American	151 (8%)	18 (21%)	31 (24%)	<0.0001
Hispanic/Latino	42 (2%)	5 (6%)	3 (2%)	
White	1590 (85%)	56 (67%)	90 (70%)	
Other	21 (1%)	2 (2%)	2 (2%)	
BMI[d] (kg/m^2)				
Median	27.1	31.9	31.9	<0.0001
Range	15.5 – 66.6	20.1 – 49.8	19.0 – 65.3	
Category, N, (%)				
Underweight (<18.5)	7 (0%)	0 (0%)	0 (0%)	
Normal (18.5–24.9)	605 (33%)	4 (5%)	18 (14%)	
Overweight (25.0–29.9)	665 (36%)	26 (31%)	30 (23%)	
Obesity I (30.0 – 34.9)	365 (20%)	23 (27%)	33 (26%)	<0.0001
Obesity II (35.0 – 39.9)	131 (7%)	22 (26%)	30 (23%)	
Extreme Obesity (≥40)	66 (4%)	9 (11%)	16 (13%)	
Missing	15 (1%)	0 (0%)	1 (1%)	
Family history of colon cancer[d], N (%)				
Yes	353 (19%)	15 (17%)	25 (20%)	0.99
No	1346 (73%)	59 (70%)	95 (74%)	
Missing	155 (8%)	10 (12%)	8 (6%)	
Smoking status[d], N (%)				
Never smoked	884 (48%)	41 (49%)	72 (56%)	
Past smoker	805 (43%)	36 (42%)	44 (34%)	0.36
Current smoker	137 (7%)	6 (7%)	11 (9%)	
Missing	28 (2%)	1 (1%)	1 (1%)	
Alcohol use history, N (%)				
Nondrinker*	196 (11%)	18 (21%)	24 (19%)	<0.0001
Past drinker	325 (18%)	33 (39%)	40 (31%)	

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	No DM N=1854	DM + Metformin N=84	DM – Metformin N=128	p-values[a]
<7 drinks/week	1074 (58%)	29 (34%)	56 (44%)	
7+ drinks/week	245 (13%)	3 (4%)	6 (5%)	
Missing	14 (1%)	1(1%)	2 (2%)	
Diabetic diet[d], N (%)				
Yes	17 (1%)	59 (70%)	95(74%)	<0.0001
No	1837 (99%)	25 (30%)	33(26%)	
High-fiber diet[d], N (%)				
Yes	353 (19%)	12 (14%)	31(24%)	
No	1462 (79%)	68 (81%)	94(73%)	0.2
Missing	39 (2%)	4 (5%)	3(2%)	
Total MET-hours per week (kcal/wk/kg)[d]				
Mean	11.5	9.1	8.8	
Median (IQR)	7.5 (2 – 16.7)	7 (0.6 – 13.6)	4.8 (0.5 – 11.8)	0.02
Range	0 – 90.8	0 – 69.0	0 – 53.5	
Patients using Aspirin[d], N (%)				
Yes	390 (21%)	19 (23%)	28 (22%)	0.92
No	1464 (79%)	65 (77%)	100 (78%)	
Patients using NSAID[d], N (%)				
Yes	600 (32%)	32 (38%)	47 (37%)	0.35
No	1254 (68%)	52 (62%)	81 (63%)	
Clinical Trial or Observational Study[d], N, (%)				
CT	831 (45)	59 (70)	56 (44)	<0.0001
OS	1023 (55)	25 (30)	72 (56)	
Time from enrollment to CRC diagnosis (years)[e]				
Mean	5.7	5.9	5.1	
Median (IQR)	5.5 (2.8 – 8.3)	5.9 (3.7 – 8.1)	4.7 (2.3 – 7.4)	0.2
Range	0 – 13.8	0.8 – 11.7	0.2 – 14.5	
Stage[b,e], N (%)				
Localized	851 (46%)	38 (45%)	56(44%)	
Regional/Distant	978 (53%)	44 (52%)	72(56%)	0.37
Unknown	24 (1%)	2 (2%)	0(0%)	
Patients using insulin[f], N (%)				
Yes	N/A	18 (21%)	30 (23%)	0.73[c]
No		66 (79%)	98 (77%)	
Total number of diabetic medications[f] N (%)				

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	No DM N=1854	DM + Metformin N=84	DM – Metformin N=128	p-values[a]
0		0 (0%)	39 (30%)	
1		14 (17%)	66 (51%)	
2	N/A	54 (64%)	18 (14%)	<0.0001[c]
3		11 (13%)	3 (2%)	
4–5		5 (6%)	2 (2%)	

[a] P-value is for comparison between the three cohorts except where indicated

[b] Localized disease includes tumors staged as in situ or localized; regional/distant includes tumors staged as regional or distant.

[c] P-value is for comparison between diabetic Metformin users and non-users

[d] variable ascertained at WHI enrollment

[e] variable ascertained at the time of colorectal cancer diagnosis

[f] variable ascertained at any point after WHI enrollment

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Table 2

Characteristics of colorectal cancer cases by Diabetes/Metformin status

	No DM N (%)	DM + Metformin N (%)	DM − Metformin N (%)	p-values
Tumor size				
Mean (cm) (SD)	4.3 (22)	4.3 (21)	4.3 (21)	0.99
Microscopic focus<= 3·9 cm	56 (3)	1 (1)	8 (6)	
4·0–5·9 cm	603 (33)	25 (30)	42 (33)	0.33
>= 6·0 cm	477 (26)	20 (24)	34 (27)	
	718 (39)	38 (45)	44 (34)	
Number of positive lymph nodes				
Mean (SD)	1 (3)	2 (3)	1 (3)	0.89
None	1049 (57)	47 (56)	73 (57)	
1	155 (8)	10 (12)	16 (13)	
2–3	189 (10)	6 (7)	12 (9)	
>= 4	189 (10)	12 (14)	13 (10)	0.89
Positive, number not specified	16 (<1)	0	1 (<1)	
Unexamined	240 (13)	6 (7)	13 (10)	
Unknown	16 (<1)	3 (4)	0	
Stage of disease				
In situ	70 (4)	2 (2)	2 (2)	
Localized	781 (42)	36 (42)	54 (42)	
Regional	747 (40)	39 (46)	53 (41)	0.37
Distant	231 (12)	5 (6)	19 (15)	
Unknown	24 (1)	2 (2)	0	
Missing	1	0	0	
Morphologic grade				
Well differentiated	142 (8)	10 (12)	11 (9)	
Moderately differentiated	1109 (60)	51 (61)	70 (55)	
Poorly differentiated	365 (20)	14 (17)	35 (27)	0.29
Anaplastic	37 (2)	1 (1)	0 (0)	
Unknown/Not done	201 (11)	8(10)	12 (9)	
Location of cancer				
Proximal	1013 (55)	44 (52)	68 (53)	
Distal	570 (31)	27 (32)	43 (34)	
Rectum	247 (13)	12 (14)	16 (13)	0.96
Colon, NOS	11 (1)	1 (1)	0 (0)	
Overlapping lesion	13 (1)	0 (0)	1 (1)	

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Table 3

Metformin Treatment and Colorectal Cancer-Specific and Overall Survival

A. Metformin and Survival in Diabetics with CRC (N=212)

	Unadjusted HR (95% CI)	Age-adjusted HR (95% CI)	Multivariate-Adjusted* HR (95% CI)	Propensity Score-adjusted HR (95% CI)
Colorectal Cancer Specific Survival				
No Metformin	1.00	1.00	1.00	1.00
Metformin	0.77 (0.42 – 1.39)	0.76 (0.41 – 1.41)	0.75 (0.40 –1.38)	0.78 (0.38 – 1.55)
p-value	0.38	0.39	0.67	0.47
Overall Survival				
No Metformin	1.00	1.00	1.00	1.00
Metformin	0.82 (0.50 – 1.33)	0.85 (0.52 – 1.39)	0.84 (0.51 – 1.37)	0.86 (0.49 – 1.52)
p-value	0.41	0.52	0.48	0.60

B. Metformin and Survival in all CRC Patients (N=2066)

	Unadjusted HR (95% CI)	p-value	AHR† (95% CI)	p-value
Colorectal Cancer Specific Survival				
Non-Diabetic	1.00	Ref	1.00	Ref
Diabetics on Metformin	1.01 (0.61 – 1.66)	0.98	1.00 (0.61 – 1.66)	0.99
Diabetics not on Metformin	1.32 (0.92 – 1.89)	0.13	1.23 (0.86 – 1.77)	0.26
Overall Survival				
Non-Diabetic	1.00	Ref	1.00	Ref
Diabetics on Metformin	1.13 (0.76 – 1.67)	0.54	1.20 (0.80 – 1.79)	0.39
Diabetics not on Metformin	1.38 (1.03 – 1.87)	0.03	1.32 (0.98 – 1.78)	0.07

*Adjusted for age (by deciles) and stage at diagnosis (localized and regional/distant), excluding those with unknown stage at diagnosis (N=2 in those on Metformin, 0 in those not on Metformin)

†Adjusted for age and stage at diagnosis; subjects with unknown stage at diagnosis excluded from analysis (n=24 in non-diabetics, 2 in diabetics on Metformin)