Diabetes and prognosis in older persons with colorectal cancer

J Luo*,1, H-C Lin2, K He1 and M Hendryx2

1Department of Epidemiology and Biostatistics, School of Public Health – Bloomington, Indiana University, Bloomington, IN, USA and 2Department of Applied Health Science, School of Public Health – Bloomington, Indiana University, Bloomington, IN, USA

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Background: Epidemiological studies have reported that diabetes significantly increases overall mortality in patients with colorectal cancer. However, it is unclear whether diabetes increases colorectal cancer-specific mortality. We used the US Surveillance Epidemiology and End Results (SEER) database linked with Medicare claims data to assess the influence of pre-existing diabetes on prognosis of patients with colorectal cancer.

Methods: Data from 61,213 patients aged 67 or older with colorectal cancer diagnosed between 2003 and 2009 were extracted and prospectively followed through the date of death or the end of 2012 if the patient was still alive. Diabetes cases with and without complications were identified based on an algorithm developed for the Chronic Condition Data Warehouse (CCW). Cox models were used to estimate hazard ratios (HRs) for total mortality. The proportional subdistribution hazards model proposed by Fine and Gray was used to estimate HRs for colorectal cancer-specific mortality.

Results: Compared with patients without diabetes, colorectal cancer patients with pre-existing diabetes had significantly higher risk of overall mortality (HR = 1.20, 95% confidence interval (95% CI): 1.17–1.23). The HR for overall mortality was more pronounced for patients who had diabetes with complications (HR = 1.50, 95% CI: 1.42–1.58). However, diabetes was not associated with increased colorectal cancer-specific mortality after accounting for non-colorectal cancer outcomes as competing risk.

Conclusions: Pre-existing diabetes increased risk of total mortality among patients with colorectal cancer, especially among cancer patients who had diabetes with complications. The increased risk of total mortality associated with diabetes was primarily explained by increased cardiovascular-specific mortality, not by increased colorectal cancer-specific mortality.

Colorectal cancer is the fourth most common cancer in the United States, and more than two-thirds of patients diagnosed with colorectal cancer are aged ≥65 years (SEER, 2012a, b). Co-morbidity exerts a strong effect on the probability of survival after a cancer diagnosis (Gross et al, 2006; Barone et al, 2008), and there is a critical need for improved understanding of how co-morbid chronic conditions affect outcomes in patients with cancer (Extermann, 2003). Type 2 diabetes is one of the most common chronic diseases (Cowie et al, 2009) and appears to be an independent risk factor for colorectal cancer incidence (Larsson et al, 2005); pre-existing diabetes is present in ~18% of colorectal cancer cases (Gross et al, 2006). Accumulating epidemiological studies have reported that diabetes significantly increases total mortality in patients with colorectal cancer (Barone et al, 2008; Stein et al, 2010). However, it is unclear whether the higher total mortality in colorectal cancer patients with diabetes is driven by a worse colorectal cancer prognosis or by competing risks such as diabetes-related cardiovascular disease or different clinical practices for cancer patients with pre-existing diabetes.

In the majority of epidemiological applications, competing risk has been ignored (i.e., patients experiencing competing events were censored at the time of these events), which may substantially overestimate the absolute risk of the event of interest and lead to biased findings (Putter et al, 2007; Wolbers et al, 2009). We overcame this limitation through applying an improved analytic approach – proportional subdistribution hazard model proposed...
by Fine and Gray (Fine and Gray, 1999) to estimate colorectal cancer-specific mortality by accounting for non-colorectal cancer outcomes as competing risk.

We used the US Surveillance Epidemiology and End Results (SEER, 2012a,b) database linked with Medicare claims data, a unique population-based source of information, to assess the influence of pre-existing diabetes on prognosis of patients with colorectal cancer. Our study hypothesis was that diabetes would adversely influence colorectal cancer prognosis, including total and cancer-specific mortality. This study aims to address the following questions: (1) Is there a mortality difference between diabetic and non-diabetic patients with colorectal cancer? (2) Is mortality outcome among colorectal cancer patients the result of colorectal cancer prognosis or of risk from non-cancer mortality? (3) Is diabetes associated with unfavourable tumour characteristics? (4) Does the impact of pre-existing diabetes on cancer prognosis differ by patients with and without diabetes complications? Addressing these questions will have great potential to advance the understanding of how pre-existing diabetes influences colorectal cancer prognosis. In particular, we can begin to understand whether diabetes per se may worsen colorectal cancer prognosis, or whether any competing risks may be more important in determining mortality outcomes.

### Data resource: SEER–Medicare data

The Surveillance, Epidemiology and End Results (SEER, 2012a, b)–Medicare-linked database is used in this project. The SEER programme is an epidemiologic surveillance system sponsored by the US National Cancer Institute (NCI), consisting of population-based tumour registries that routinely collect information on all newly diagnosed cancer cases that occur in persons residing in SEER areas (SEER, 2012a,b). Since 2000, the SEER areas capture ~25% of the US population (SEER, 2012a, b). Cancer registries participating in the SEER programme are required to meet strict standards with respect to case ascertainment and data quality. The information collected about each incident cancer diagnosis includes the patient’s demographic characteristics (such as age, sex and race), date of diagnosis, cancer characteristics (e.g., histology, stage and grade), type of surgical treatment and/or radiation therapy recommended or provided within 4 months of diagnosis, follow-up of vital status and cause of death if applicable (Warren et al, 2002c).

The Medicare programme, federally funded and administered by the Center for Medicare and Medicaid Services (CMS, 2012), provides health insurance for people aged ≥ 65 years, people under age 65 with certain disabilities and people of all ages with end-stage renal disease (permanent kidney failure requiring dialysis or a kidney transplant) (CMS, 2012). Separate file claims can be obtained for inpatient, outpatient, physician and supplier, skilled nursing facility, and hospice services provided to beneficiaries enrolled in fee-for-service plans. Claim files contain diagnosis and procedure codes, dates of services, charges and amount paid. The SEER–Medicare data reflect the linkage of two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer. The linkage was first completed in 1991 and has been updated biennially. For each of the linkages, 94 per cent of persons aged ≥ 65 in the SEER files were matched to the Medicare enrolment file; the deficit reflects the 3% of elderly people who do not enrol in Medicare and another 3% who do not have sufficient or accurate enough information for the linkage (Engels et al, 2011).

### Study population

As of December 2012, the data include all Medicare-eligible persons documented in the SEER data who were diagnosed with cancer through 2009, and their Medicare claims through 2010. Our cohort included patients aged ≥ 67 years in the SEER database who had a first primary diagnosis of invasive colorectal cancers between 2003 and 2009. Sixty-seven years was selected as the age cutoff to ensure that each patient would have at least 2 years of Medicare eligibility before their cancer diagnosis. To ensure a complete assessment of pre-existing diabetes (exposure) and cancer treatment received, we only included patients who were continually enrolled in both Medicare Parts A and B and excluded patients who were enrolled in health maintenance organisation plans over the inclusive 2-year period before colorectal cancer diagnosis and 3 months after cancer diagnosis. Patients in health maintenance organisation plans were excluded because these patients do not have complete claim records. In addition, we excluded patients who had end-stage renal disease or disability alone or who were diagnosed exclusively by death certificates or at autopsy. After considering these inclusion and exclusion criteria, our final study cohort consisted of 61,213 patients with colorectal cancer. Of them, 46,483 (75.9%) patients were diagnosed with colon cancer, and 14,730 (24.1%) were diagnosed with rectal cancer.

### Measurements

**Outcomes.** Our primary outcome is colorectal cancer-specific mortality. However, we also examined total mortality as an outcome for comparison with previous findings.

**Pre-existing diabetes status.** We adapted an algorithm developed for the Chronic Condition Data Warehouse (CCW Chronic Condition Data Warehouse, 2013) by the Centers for Medicare & Medicaid Services (CMS, 2012) (CCW Chronic Condition Data Warehouse, 2013) to identify pre-existing diabetes. Diabetes status was determined on the basis of either a single inpatient claim or at least two outpatient claim diagnoses with the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code of 250.xx during the interval beginning 2 years before and 3 months after colorectal cancer diagnosis. Extending the time interval to 3 months after diagnosis allowed us to capture previously undiagnosed diabetes as other studies have done (Yang et al, 2013). To avoid ‘rule out’ diagnoses on outpatient claims, a patient’s diagnosis must have appeared on at least two different claims that were made > 30 days apart. We did not include diabetes medications in the definition since Medicare did not begin covering oral medications without an intravenous equivalent until January 2006. We defined diabetes with complication with ICD-9-CM codes 250.4–250.6 or 250.8–250.9 based on the definition of comorbidities described in the National Cancer Institute SEER–Medicare website.

**Co-morbidity.** Medicare claims were used to calculate the NCI combined co-morbidity index score proposed by Klabunde et al (2007) and as identified by Charlson et al (1987). The NCI index (Klabunde et al, 2000) is composed of two weighted co-morbidity scores derived separately from inpatient and outpatient claims. The NCI combined index uses weights derived from comorbidity conditions identified in either Medicare inpatient or outpatient claims into a single co-morbidity index. Study has shown that the new NCI combined index is a more refined, easier to implement co-morbidity measurement algorithm appropriate for investigators using administrative claims databases to study commonly occurring cancers (Klabunde et al, 2007). Two conditions (diabetes without and with complications) pertaining to diabetes were removed from the NCI Co-morbidity Index to reduce correlation with diabetes. ICD-9-CM diagnostic codes recorded in Medicare claims over 2 years before colorectal cancer diagnosis were searched to create this co-morbidity index. Conditions reported...
Table 1. Characteristics of 61,213 colorectal cancer patients by diabetes status*

| Diabetes                        | No diabetes | Total no. (%) | Without complication | With complicationb |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| All patients                    | 46,400      | 14,613 (24.2) | 12,298 (20.1)        | 2,515 (4.1)         |

| Age (year)                      |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| 65–74                           | 16,708 (50) | 5,965 (40)    | 4,912 (34)           | 1,053 (42)          |
| 75–84                           | 20,744 (44) | 6,682 (45)    | 5,556 (45)           | 1,126 (45)          |
| 85+                             | 8,948 (19)  | 2,166 (15)    | 1,830 (15)           | 336 (13)            |
| Sex (female, %)                 |             |               |                      |                     |
| Without complication            | 25,762 (54) | 7,785 (53)    | 6,501 (53)           | 1,284 (51)          |

| Race                            |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| White                           | 40,650 (68) | 12,167 (82)   | 10,206 (83)          | 1,961 (78)          |
| Black                           | 3,411 (7)   | 1,779 (12)    | 1,383 (11)           | 396 (16)            |
| American Indian/Alaska Native   | 115 (0)     | 61 (0)        | 47 (0)               | > 11 (~)            |
| Asian or Pacific Islander       | 2,025 (4)   | 754 (5)       | 616 (5)              | 138 (6)             |
| Unknown                         | 199 (0)     | 52 (0)        | 46 (0)               | < 11 (~)            |

| Marital status                  |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| Single (never married)          | 3,623 (8)   | 1,169 (8)     | 954 (8)              | 215 (9)             |
| Married                         | 22,715 (49)| 7,151 (48)    | 6,010 (49)           | 1,141 (45)          |
| Separated                       | 270 (1)     | 121 (1)       | 101 (1)              | 20 (1)              |
| Divorced                        | 2,881 (6)   | 1,003 (7)     | 807 (7)              | 196 (8)             |
| Widowed                         | 14,881 (32)| 4,711 (32)    | 3,871 (32)           | 840 (33)            |
| Unknown                         | 2,030 (4)   | 658 (4)       | 555 (4)              | 103 (4)             |

| Median Income                   |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| Lowest quartile                 | 11,092 (24)| 4,210 (28)    | 3,436 (28)           | 774 (31)            |
| Second quartile                 | 11,483 (25)| 3,823 (26)    | 3,193 (27)           | 630 (25)            |
| Third quartile                  | 11,666 (25)| 3,644 (25)    | 3,056 (25)           | 588 (23)            |
| Highest quartile                | 12,159 (26)| 3,136 (25)    | 2,613 (21)           | 523 (21)            |

| No. of comorbidities            |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| 0                               | 37,348 (81)| 9,624 (65)    | 8,502 (69)           | 11,222 (45)         |
| 1                               | 5,323 (12)  | 2,313 (14)    | 1,855 (15)           | 458 (18)            |
| >2                              | 3,729 (8)   | 2,876 (19)    | 1,941 (16)           | 935 (37)            |

| Cancer site at diagnosis        |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| Colon                           | 34,851 (75)| 11,632 (79)   | 9,598 (78)           | 2,034 (81)          |
| Rectum                          | 11,549 (25)| 3,181 (21)    | 2,700 (22)           | 481 (19)            |

| Cancer stage                    |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| Localised                       | 20,088 (43)| 6,478 (44)    | 3,336 (43)           | 1,142 (45)          |
| Regional                        | 17,520 (38)| 5,758 (39)    | 2,822 (39)           | 936 (37)            |
| Distal                          | 6,679 (14) | 1,921 (13)    | 1,617 (13)           | 304 (12)            |
| Unknown                         | 2,113 (5)  | 656 (4)       | 523 (4)              | 133 (5)             |

| Grade                           |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| Grade I: well differentiated    | 4,132 (9)   | 1,335 (9)     | 1,097 (9)            | 238 (10)            |
| Grade II: moderately differentiated | 28,262 (61)| 9,258 (63)    | 7,723 (63)           | 1535 (61)           |
| Grade III: poorly differentiated | 7,762 (17) | 2,403 (16)    | 1,981 (16)           | 422 (17)            |
| Grade IV: undifferentated       | 659 (1)     | 205 (1)       | 171 (1)              | 34 (1)              |
| Unknown                         | 5,585 (12) | 1,612 (11)    | 1,326 (11)           | 286 (11)            |

| Cancer-direct surgery           |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| No                              | 5,099 (11) | 1,533 (10)    | 1,237 (10)           | 296 (12)            |
| Yes                             | 40,915 (88)| 13,158 (89)   | 10,967 (89)          | 2191 (87)           |
| Unknown                         | 386 (1)    | 122 (1)       | 94 (1)               | 28 (1)              |

| Radiation therapy               |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| No                              | 41,187 (89)| 13,395 (9)    | 11,089 (90)          | 2,306 (92)          |
| Yes                             | 4,626 (10) | 1,214 (8)     | 1,043 (9)            | 171 (7)             |
| Unknown                         | 585 (1)    | 204 (1)       | 164 (1)              | 38 (2)              |

| Chemotherapy                    |             |               |                      |                     |
|---------------------------------|-------------|---------------|----------------------|---------------------|
| Yes                             | 4,055 (9)  | 1,338 (9)     | 1,161 (9)            | 177 (7)             |

*a All tests are significant at \( P < 0.05 \) between two groups (non-diabetes vs diabetes) or among three groups (non-diabetes, diabetes without complication and diabetes with complication). 

b There are \( n = 6 \) cases of Unknown race with diabetes and complications. To comply with the SEER-Medicare rules the cell sizes were suppressed for confidentiality reasons as per the SEER-Medicare data usage agreement.
within 1 month of cancer diagnosis were excluded to avoid misclassifying complications or conditions directly resulting from cancer diagnosis or treatment as co-morbidities (Klabunde et al., 2007).

Cancer stage and tumour characteristics. The colorectal cancer information was extracted from SEER data. The cancer stage was categorised as localised (confined to primary site), regional (spread to regional lymph nodes), distant (cancer has metastasised) or unknown (unstaged). Other tumour characteristics included tumour grade (grade I – well differentiated; grade II – moderately differentiated; grade III – poorly differentiated and grade IV – undifferentiated), and different histological subtypes of colorectal cancer (colon or rectum).

Cancer treatment. The SEER programme routinely collects information regarding certain anti-cancer therapies (i.e. surgery, radiation therapy) occurring within 4 months of diagnosis (first course of therapy). For surgery, we divided patients into two categories: cancer-directed surgery performed or not. For the method of radiation therapy performed as part of the first course of treatment, we collapsed patients who received any radiation (such as beam radiation, radioactive implants, radioisotopes or combination) as yes for radiation. As SEER does not report information pertaining to chemotherapy administration, we searched claims records to identify chemotherapy. Patients who had at least one claims record for chemotherapeutic administration, treatment or agents in any of inpatient and outpatient claims files within 6 months after primary diagnosis were considered chemotherapy recipients. We used codes including ICD-9-CM diagnosis codes (V58.1, V66.2 and V67.2), ICD-9-CM procedure code (99.25) and HCPCS codes (964xx, 965xx, Q0083-Q0085, J93XX, J8510, J852x, J8530, J856x, J8600, J8610, J870x and J8999) (Warren et al., 2002a; Yang et al., 2013).

Covariates. In the multivariate model, we adjusted for demographic variables including patient’s demographic characteristics (age at diagnosis, sex, race and marital status), and socioeconomic status (median household income). The median income in each patient’s census tract was used as a proxy measure for socioeconomic status. It was estimated at census tract level using the 2000 census and stratified into quartiles. Race was categorised as white, black, American Indian/Alaska Native, Asian or Pacific Islander and others.

Supplementary Table 1 shows all of the ICD-9 codes listed in the paper.

Statistical analysis. Distribution of baseline patients’ characteristics, tumour characteristics and stage at diagnosis were compared between patients with and without diabetes. χ²-tests were used to evaluate differences for categorical covariates, and t-tests were used for continuous variables. Age-adjusted and multivariate-adjusted Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (95% CI) for overall survival. The proportional subdistribution hazard model proposed by Fine and Gray (1999) was used to estimate HRs for colorectal cancer-specific mortality associated with diabetes status by accounting for non-colorectal cancer outcomes as competing risk. In the multivariate models, we adjusted for covariates including age at diagnosis (67–69, 70–74, 75–79, 80–84 and 85 +), sex, race (white, black, American Indian/Alaska Native, Asian or Pacific Islander, other), marital status (never married, married, separated, divorced and widowed), grade (grade I – well differentiated; grade II – moderately differentiated; grade III – poorly differentiated and grade IV – undifferentiated), census tract median income (quartiles) and co-morbidity (0, 1, 2 +).

The underlying time metric in the Cox model was follow-up time since diagnosis of cancer to the date of death or the end of 2012 if the patient was still alive. The date of death from any cause was used for total mortality; the date of death from colorectal cancer was used for cancer-specific mortality for colorectal, colon and rectal cancer patients. The proportionality assumption was confirmed for all exposure variables of interest and for all potential confounding variables, based on graphs of scaled Schoenfeld residuals (Hess, 1995).

RESULTS

Of a total of 61 213 colorectal cancer patients, 14 813 (24.2%) had diabetes including 12 298 without complications and 2515 with complications. Over an average of 38 months of follow-up (median = 33 months, range 0–96 months), 28 682 (46.9%) patients died from all causes, and 15 879 (25.9%) patients died from colorectal cancer.

Baseline patients’ characteristics by diabetes status are shown in Table 1. Compared with patients without diabetes, patients with diabetes were significantly younger, males, members of non-White race groups, unmarried and from low-median income areas.

Figure 1. Survival curves among colorectal cancer patients by diabetes status (A) for total survival rates (log-rank test P-value <0.0001); (B) colorectal-cancer-specific survival rates (log-rank test P-value = 0.001).
Patients with diabetes were also more likely to have one or more co-morbidities, and were less likely to have radiation therapy performed as part of the first course of cancer treatment. There was no substantial difference between the diabetes group and the non-diabetes group in terms of the stage of diagnosis, tumour grade and whether the patient underwent cancer-directed surgery or chemotherapy, although P-values for statistical tests were significant due to the large sample size. The patterns were similar when comparing patients with complication to patients without complication among patients with diabetes (Table 1).

Figure 1 shows the crude total and colorectal cancer-specific survival curves by diabetes status. Diabetes with complications had the lowest total survival rates and the lowest colorectal cancer-specific survival rates among patients with diabetes and patients with diabetes but no complications.

Compared with patients without diabetes, we observed that colorectal cancer patients with pre-existing diabetes had significantly higher risk of total mortality (HR = 1.20, 95% CI: 1.17–1.23 for patients in all stages, HR = 1.29, 95% CI: 1.21–1.29 for patients in localised or regional stage and HR = 1.21, 95% CI: 1.06–1.18 for patients in distant stage) after adjusting for potential confounders. The risks of total mortality were more pronounced for patients who had diabetes with complications (HR = 1.50, 95% CI: 1.42–1.58 for patients in all stages, HR = 1.53–1.73 for patients in localised or regional stage and HR = 1.21, 95% CI: 1.07–1.37 for patients in distant). Similar findings were observed when we separated colon and rectal cancer patients with an exception that the results for distant-stage rectal cancer patients became non-significant (Table 2). We observed that diabetes was significantly associated with cardiovascular-specific mortality regardless of the site of cancer, especially for diabetes with complications (HR = 2.27, 95% CI: 2.06–2.50) (Table 2).

In contrast, we did not observe a significantly increased risk for colorectal-specific mortality among patients with colon, rectal or colorectal cancer regardless of stage and diabetes severity (Table 3). There was one exception, as diabetes with complications and advanced-stage colon cancer was significantly associated with colorectal cancer mortality.

Finally, we performed analyses stratified by sex for colorectal-specific mortality associated with diabetes. No significant difference was found between females and males (data not shown).

### DISCUSSION

The present study found that colorectal cancer patients with pre-existing diabetes had significantly higher risk of total mortality than those cancer patients without diabetes. The risk was more pronounced among those who had diabetes with complications. Further performing specific mortality analyses using the competing risk method, diabetes was significantly associated with cardiovascular-specific mortality, but not with colorectal cancer-specific mortality.

Our findings were in agreement with the majority of the literature in term of total mortality as an outcome (Barone et al., 2008; Stein et al., 2010; Huang et al, 2011; Dehal et al, 2012; van de Poll-Franse et al, 2012; Bella et al, 2013; Jeon et al, 2013; Poll-Franse et al, 2008; Stein et al, 2010; Huang et al, 2011; Dehal et al, 2012).
Walker et al., 2013; Yang et al., 2013), although not all studies have found this relationship (Jullumstro et al., 2009; Call et al., 2010; Chen et al., 2010; Noh et al., 2010; Huang et al., 2012). Subgroup analyses of two meta-analyses studies (Barone et al., 2008; Stein et al., 2010) based on six studies showed that colorectal cancer patients with diabetes had 32% increased risk of total mortality compared with those without diabetes (95% CI: 1.24–1.41). Among studies (Will et al., 1998; Polednak, 2006; Siddiqui et al., 2008; Jullumstro et al., 2009; Huang et al., 2011, 2012; van de Poll-Franse et al., 2012; Bella et al., 2013; Cossor et al., 2013; Walker et al., 2013) that examined cancer-specific mortality associated with pre-existing diabetes, the findings are inconsistent. Of them, one study (Huang et al., 2011) found a significant increased risk for colon cancer-specific mortality. Two (van de Poll-Franse et al., 2012; Bella et al., 2013) found a significantly increased risk for only rectal cancer patients but not for colon cancer, and one (Siddiqui et al., 2008) found an association between poorly controlled pre-existing diabetes and the risk of death attributed to colorectal cancer. Other studies found no significant association between diabetes and subsequent death from colorectal cancer. In addition, an earlier study on this topic (Meyerhardt et al., 2003) showed diabetes had worse disease-free survival associated with diabetes.

However, among all previous studies examining cancer-specific mortality, none of them considered competing risk correctly; rather, they censored patients experiencing competing events at the time of these events, which may substantially overestimate the absolute risk of the event of interest (Putter et al., 2007; Wolbers et al., 2009). For the purpose of comparison with previous studies, we used conventional epidemiology methods to analyse colorectal-cancer-specific mortality; the resulting HRs were 1.05 (95% CI: 1.01–1.09) and 1.17 (95% CI: 1.08–1.27) for colorectal-cancer-specific mortality associated with pre-existing diabetes without and with complications, respectively. Comparing the two analytic approaches, our analyses suggest that findings for cancer-specific mortality using conventional epidemiological methods were overestimated.

The potential influence of diabetes on cancer prognosis is complex. Diabetes may directly influence cancer progression and outcome via physiologic effects of hyperinsulinemia and/or hyperglycaemia (Richardson and Pollack, 2005; Morss and Edelman, 2007). Although our data did not directly assess the association between insulin and colorectal cancer prognosis, experimental and epidemiological evidence suggests that hyperinsulinemia may be an underlying mechanism to explain the association between diabetes and cancer incidence and outcome (Larsson et al., 2005; Berster and Goke, 2008; Giovannucci et al., 2010). Second, pre-existing diabetes may also have indirect adverse effects on cancer outcome by influencing patients or providers to make different clinical decisions regarding cancer screening and cancer treatment. Research has documented underuse of colorectal cancer screening among elderly diabetic women compared with those without diabetes (McBean and Yu, 2007), which may lead to

### Table 3. Effect of pre-existing diabetes on cancer-specific mortality in patients with colorectal cancer, by stage

|                     | Overall | Localised or regional stage | Distant stage |
|---------------------|---------|-----------------------------|--------------|
|                     | No. of cases/No. of observations | Age-adjusted HR (95% CI) | Multivariate-adjusted HR (95% CI)* | No. of cases/No. of observations | Multivariate-adjusted HR (95% CI)* | No. of cases/No. of observations | Multivariate-adjusted HR (95% CI)* |
| **Colorectal cancer** |         |                             |               |                                |                             |                                |                             |
| No diabetes         | 12 214/46 400 | Referent                   | Referent      | 6291/37 608 | Referent                       | 4855/6679 | Referent                       |
| Diabetes            | 3665/14 813   | 0.97 (0.94–1.01)           | 0.99 (0.95–1.03) | 1978/12 236 | 0.98 (0.93–1.03)               | 1386/1921 | 1.02 (0.96–1.08)               |
| Diabetes without complications | 3025/12 298   | 0.96 (0.92–1.001)          | 0.98 (0.94–1.02) | 1611/10 158 | 0.97 (0.91–1.02)               | 1158/1617 | 1.00 (0.94–1.07)               |
| Diabetes with complications | 640/2515     | 1.01 (0.93–1.09)           | 1.04 (0.95–1.12) | 367/2078  | 1.07 (0.96–1.19)               | 228/304   | 1.13 (0.99–1.29)               |
| **Colon cancer**    |         |                             |               |                                |                             |                                |                             |
| No diabetes         | 8806/34 851  | Referent                   | Referent      | 4454/28 483 | Referent                       | 3638/4981 | Referent                       |
| Diabetes            | 2768/11 632  | 0.97 (0.93–1.01)           | 0.99 (0.94–1.03) | 1455/96 444 | 0.98 (0.93–1.05)               | 1097/1508 | 1.02 (0.95–1.09)               |
| Diabetes without complications | 2253/9598    | 0.95 (0.91–1.00)           | 0.97 (0.92–1.01) | 1166/79 56 | 0.96 (0.90–1.02)               | 906/1265  | 0.98 (0.91–1.06)               |
| Diabetes with complications | 515/2034     | 1.05 (0.96–1.15)           | 1.09 (0.996–1.20) | 289/1688  | 1.12 (0.99–1.26)               | 191/243   | 1.22 (1.06–1.42)               |
| **Rectal cancer**   |         |                             |               |                                |                             |                                |                             |
| No diabetes         | 3408/11 549  | Referent                   | Referent      | 1837/91 25 | Referent                       | 1217/1698 | Referent                       |
| Diabetes            | 897/3181     | 1.00 (0.93–1.07)           | 1.02 (0.95–1.11) | 523/2592  | 1.02 (0.92–1.12)               | 289/413   | 1.02 (0.89–1.16)               |
| Diabetes without complications | 772/2700    | 1.01 (0.94–1.10)           | 1.05 (0.97–1.14) | 445/2202  | 1.02 (0.92–1.13)               | 252/352   | 1.05 (0.92–1.21)               |
| Diabetes with complications | 125/481      | 0.91 (0.76–1.09)           | 0.90 (0.75–1.08) | 78/390     | 0.99 (0.79–1.25)               | 37/61     | 0.83 (0.59–1.15)               |

*In the multivariate models, we adjusted for covariates including age at diagnosis (65–69, 70–74, 75–79, 80–84 and 85 +), sex (males, females), race/ethnicity (white, black, American Indian/Alaska Native, Asian or Pacific Islander, others), marital status (never married, married, separated, divorced and widowed), grade (grade I – well differentiated; grade II – moderately differentiated; grade III – poorly differentiated and grade IV – undifferentiated), census tract median income (quartiles) and co-morbidity (0, 1, 2 +).
In conclusion, our large population-based study provides additional evidence that pre-existing diabetes increased risk of total mortality among colorectal cancer patients. The increased total mortality associated with diabetes was mainly driven by increased risk of dying from cardiovascular diseases. Preventing diabetes and reducing diabetes complications may improve the survival rate of colorectal cancer patients.

ADDENDUM

To comply with SEER-Medicare data rules on confidentiality, data in the ‘Diabetes/With complication (Race)’ cell in Table 1 has been updated since Advance Online Publication and a footnote added to the table.

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