Title: Risks of Colorectal Cancers Associated with Diabetes Were Particularly Increased in Middle-aged Men

Running title: Colorectal Cancer in Diabetic Patients

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Diabetes is reported to increase risk of colorectal neoplasm in most but not in all studies, and data on age- and sex-specific incidence rates and relative risks associated with diabetes are limited. We carried out this population-based cohort study to investigate the overall and age-specific risks of colorectal cancer in association with diabetes. Diabetic patients (n=615,532) and age-sex-matched controls (n=614,871), selected from the claim datasets, were followed from 2000 to 2006. Incidence rates of admissions due to colon and rectum cancer were estimated using person-years approach; and age-sex-specific hazard ratio (HR) of both malignancies were evaluated with Cox regression model. The overall incidence rate of colon cancer was 9.94 per 10,000 patient-years for diabetic patients, as opposed to 7.84 per 10,000 patient-years for controls. The corresponding figures for rectal cancer were 7.16 and 6.28 per 10,000 patient-years. Diabetic patients aged ≥45 years had significantly increased HRs of colon cancer (1.20-1.45 fold). We also noted significantly increased HR of rectal cancer in male diabetes (1.18-fold) aged ≥45 years, but not in females. In conclusion, diabetes may significantly increase the risk of colorectal cancers especially in those aged 45-64. Diabetolgists must pay more attentions in caring middle-aged male diabetic patient, who should also be suggested to receive regular screening for colorectal cancer.

Keywords: cohort studies; colonic neoplasm; diabetes mellitus; hazard ratio; rectal neoplasm.

Nearly one million newly diagnosed colorectal cancer cases are reported to occur globally, which accounted for approximately 10% of all incident cancer (Parkin et al. 2005). Diabetes, which is also associated with obesity and physical inactivity, has been reported to increase the risk of colorectal cancer in many, (Adami et al. 1991; Le Marchand et al. 1997; Weiderpass et al. 1997; Wideroff et al. 1997; Will et al. 1998; Khaw et al. 2004; Limburg et al. 2005; Larsson et al. 2005a, 2005b; Limburg et al. 2006; Inoue et al. 2006; Eddi et al. 2011) but not all (O'Mara et al. 1985; Kune et al. 1988; La Vecchia et al. 1994; Steenland et al. 1995) studies. Nonetheless, there is discrepancy in results regarding sex- and age-specific incidence and size of relative hazard of colorectal cancers. Some of the previous studies reported that male and female diabetes were both associated with higher risks of colorectal cancers, (Le Marchand et al. 1997; Weiderpass et al. 1997; Yang et al. 2004) but other studies showed that the increased risks of colorectal malignancies were merely limited to men (Adami et al. 1991; Wideroff L et al. 1997; Khaw et al. 2004; Limburg et al. 2006; Inoue et al. 2006) or to women only (Nilsen and Vatten 2001). Inconsistency in age- and sex-specific results noted in previous studies could be due to dissimilarities in characteristics of patient population, cares received by study patients, and possibly differential accuracy of diagnosis. To our best knowledge, the study investigating the incidence rate and relative risk of colorectal cancer in diabetes with different age and sex stratifications in the same diabetes population is very scarce in the literature especially for those younger patients under aged 45.

In Taiwan, colorectal malignancies are the second commonest cancer in both men and women, and it has the increasing trend in incidence for both genders (Bureau of Health Promotion, 2008). Moreover, it is the fourth commonest malignancies in those Taiwanese aged 25-44 (Bureau of Health Promotion, 2008). On the other hand, the

mortality rate of diabetes mellitus has been increasing in Taiwan since early 90's, and diabetes is now the fourth leading cause of death in Taiwan. Thus, the association of diabetes with colorectal cancer is of great importance from both clinical and public health points of view. The association, if any, for younger diabetic patients is of particular importance since younger diabetic patients are expected to have greater lifetime likelihood of developing colorectal cancer. This study aimed to use the National Health Insurance (NHI) database to estimate the incidence density and relative risks of malignant neoplasm of colon and rectum according to various age and sex stratifications among the diabetic population in Taiwan.

Methods

Source of data

A universal NHI program, which is administered by the Bureau of NHI (BNHI) under the jurisdiction of the Department of Health, has been implemented in Taiwan since March 1995. Approximately 96% of the total Taiwanese population has enrolled in the NHI program, (Chiang, 1997) and the state-run BNHI had contracted with 97% of hospitals as well as 90% of clinics all over the island (Lu and Hsiao 2003) by the end of 1996. The BNHI accumulates all administrative and claims data, and the National Health Research Institute (NHRI) cooperates with the BNHI to establish an NHI research database. The NHRI transfers the health insurance data to health researchers after ethical approval has been obtained. To ensure the accuracy of the claim files, the BNHI performs expert reviews on a random sample of every 50-100 ambulatory and inpatient claims in each hospital and clinic quarterly (Chiang et al. 1997). The NHRI safeguards the privacy and confidentiality of all beneficiaries and transfers the health insurance data to health researchers after ethical approval has been obtained. In this analysis, access of the NHIRD has been approved by the NHRI Review Committee.

Diabetes cohort

Details of claim data and methods of selection of diabetic and control groups were described in our previous report (Chen et al. 2011). Briefly, we identified a diabetic patient if she or he had an initial diabetes diagnosis (ICD-9 250 or A-code 181) at any time in 2000, and then experienced another one or more diabetes diagnosis within the subsequent 12 months. To avoid accidental inclusion of miscoded patients, we further

selected only those with the first and last outpatient visits at least 30 days apart (Chen et al. 2011). Additionally, we excluded those patients admitted to the hospitals for any kinds of malignant neoplasm (ICD-9: 140-208) between 1997 and the date of initial diabetic ambulatory care visit in 2000 from our diabetic group. In Taiwan, major illness/ injury certificates are issued to all patients suffer from malignant neoplasm. To avoid mis-ascertainment of cancer patients, we excluded only those patients using major illness/ injury certificates for the particular admissions. The final diabetic cohort thus consisted of 615,532 patients. The date of first outpatient visit in 2000 was the index date for each diabetic patient.

Control group

The control group was identified from the registry of beneficiaries. After excluding those people included in diabetic ambulatory care claims and hospitalized for any kinds of malignancy (ICD-9: 140-208) with major illness/ injury certificates between 1997 and 1999, we selected control subjects by using age- and sex- frequency matched technique. Because of missing information on age or sex for 661 diabetic patients, we could only choose 614,871 control subjects in this analysis. The index date for subjects in the control group was the first date of enrollment to NHI. If their first date of enrollment was before January 1, 2000, the index date was set as January 1, 2000, which was the starting point for follow-up in this study.

Data linkage

With the unique personal identification number (PIN), we linked the study subjects in both diabetic and control groups to the inpatient claim data from 2000-2006 to identify the first episode of primary or secondary diagnoses of primary malignant

neoplasm of colon (ICD-9: 153), malignant neoplasm of rectum (ICD-9: 154) as the end points of this study. To avoid mis-ascertainment of malignant neoplasm, we again retrieved only those patients using major illness/ injury certificates for those certain admissions. The date of encountering each clinical endpoint in interest was the first day of hospitalization. The study period was from January 1, 2000 to December 31, 2006.

Statistical analysis

The geographic area of each member's NHI unit, either the location of employment or residential area, was grouped into four geographic areas (North, Central, South, East) or two urbanization statuses (urban and rural) according to the National Statistics of Regional Standard Classification (Chen et al. 2010).

In the statistical analyses, the age- and gender-specific incidence density was first calculated with person-years as the denominator under the Poisson assumption. The incidence density was used when the denominator is the sum of the person-time (person-years in the current study) of the at risk population. The amount that one person is followed-up for two years or two persons are followed-up for one year is both equal to two person-years. Using person-time may handle situations where the amount of observation time (i.e., follow-up period) differs between study subjects. To assess the independent effects of diabetic status on the risks of colon and rectal cancers, we conducted Cox proportional hazard regression models with age, sex, geographic area, and urbanization statuses adjusted simultaneously in the model. The latter two geographic variables were adjusted for possible geographic variations of cancer incidence and mortality in Taiwan (Chen et al. 2002). Moreover, we also assessed the relative hazards of malignant neoplasm of colon and rectum in relation to

diabetes accompanied by each inflammatory bowel disease with Cox proportional hazard regression models with age, gender, geographic area, urbanization statuses adjusted in the model. The study subjects who died in the hospital for clinical outcomes not of interest were censored in the survival analysis, and the date of censoring was the date of their deaths. If the study subject did not encounter in-hospital mortality, the date of censoring was either the date of their last withdrawal from NHI or the date of termination of the study i.e. December 31, 2006. All statistical analyses were performed with SAS (version 9.2; SAS Institute, Cary, NC). A P value <0.05 was considered statistically significant.

Results

The mean ± standard deviation (SD) age of the diabetic group was 60.00 ± 12.84 years while that of the control subjects was 60.09 ± 12.73 years. The proportion of people aged <45, 45-64, >64 years were 11.32, 48.27, 40.41% in both control group and diabetic population, respectively. The proportion of men to women was 51.93: 48.07 in both groups. The characteristics of the study subjects are shown in Table 1. The median time of follow-up was 6.9 years for both groups.

Table 2 displays the overall and age- and sex-specific incidence densities and relative hazards of malignant neoplasm of colon. A total of 3,849 diabetic patients were hospitalized with a diagnosis of malignant neoplasm of colon during a 7-year period, while 3,166 people from the control group were admitted to the hospital for the same diagnosis. The overall incidence densities for diabetic men and women were 10.36 and 9.57 per 10,000 person-years, respectively while those for control men and women were 7.85 and 7.83 per 10,000 person-years, respectively. For both groups, the incidence of colon cancer increased with age irrespective of diabetic status and sex, and the highest incidence was observed in those aged >64 years. Moreover, the diabetic group had a significantly elevated risk of suffering from malignant neoplasm of colon with an overall hazard ratio (HR) of 1.30 (95% CI=1.21-1.39) in men and HR=1.21 (95% CI=1.13-1.29) in women. There was a significant interaction of diabetic status with age (P <0.0001) in both sexes so that we further conducted the age-specific stratified analysis. Diabetes was associated with a significantly increased hazard of colon cancers in those aged≥45 years in both sexes, and the highest age- and sex-specific HR was observed for the diabetic men aged 45-65 years (HR=1.45; 95% CI=1.29-1.63).

Regarding malignant neoplasm of rectum, we found 2,776 and 2,536 people who were hospitalized for the above diagnoses in the diabetic and control group, respectively between 2000 and 2006 (Table 3). The overall incidence density calculated for diabetic men and women was 8.11 and 6.31 per 10,000 person-years, respectively, and the corresponding data for control men and women were 6.73 and 5.86 per 10,000 person-years. Again, we observed that the incidence of rectal cancer increased with age in both sexes regardless of diabetic status, and the higher incidence density was again found in those aged >64 years. As compared to the control group, the diabetes was slightly but significantly associated with an increased risk of rectal cancer for men (HR=1.18 (95% CI=1.09-1.27)), but not for women (HR=1.06; 95% CI=0.98-1.14). Further analysis of age- and sex-specific HRs showed the highest HR observed in diabetic men aged 45-64 years (HR=1.24; 95% CI=1.10-1.40). And the relative risk estimates were not statistically significant in diabetic women of all age stratifications.

Discussion

The overall incidence densities of colon and rectal cancers were higher in patients with diabetes than in controls. The incidence densities of colon and rectal cancers increased with age, and those aged >64 had the highest incidence of above malignancies in both groups. Furthermore, men tended to have higher incidence rate than women regardless of diabetic status. Our data also demonstrated that age and sex may significantly modify the relationship between diabetes and risk of colorectal cancer, in which male diabetes patients aged 45-64 had the most increased relative risk.

We observed that diabetic men were associated with higher risks of both colon and rectal cancers, but diabetic women only suffered from increased risk of colon cancer, which were consistent with the previous findings (Weiderpass et al. 1997). Some of the previous studies reported that diabetic men and women were associated with increased risk of colon cancers but not rectal cancers (Le Marchand et al. 1997; Yang et al. 2004). Other studies (Wideroff et al. 1997; Inoue et al. 2006; Limburg et al. 2006) indicated that diabetic men but not diabetic women were positively associated with colon cancer, and diabetic patients with both sexes were not associated with rectal cancer. Discrepancy of these study results was probably due to different methodology including dissimilarity in baseline characteristics and ethnicities, difference in methods of outcome ascertainment, and variation of length of follow-up. Because our study investigated colon and rectal cancers in the same population and with the same methodology, findings from our study may effectively remedy the limitations encountered by previous studies that were unable to simultaneously investigate the two cancers with detailed sex and age specifications without

compromising the statistical power.

Our study found that the diabetes related cancer risk was more evident for malignant neoplasm of colon than for rectal cancer. Similar finding was also noted in the studies by Weiderpass et al. (1997) and Yang et al. (2004). Like the observation from Weiderpass et al. (1997), our study also revealed that diabetic men were more likely than diabetic women to suffer from higher relative risks of both colon and rectal cancer. Further age- and sex-stratification analysis revealed that diabetic male patients aged ≥45 years had significantly increased relative risks of colorectal cancers. Similarly, La Vecchia et al. (1994) from Italy reported no association of diabetes with colorectal cancer risk in diabetic subjects aged <40 years, but the association became stronger among diabetic subjects > 60 years. The above findings may have implied the positive relationship between duration of diabetes and risk of colorectal cancers, which needs further investigations.

The biologic mechanism with which diabetes may cause colorectal cancers is still not clearly identified. Type 2 diabetes, characterized by insulin resistance and compensatory hyperinsulinemia may be an important growth factor of colonic epithelial cells (Giovannucci et al. 1995) via direct activation of insulin receptor or insulin-like growth factor (IGF)-I receptor and inhibition of IGF binding protein (Larsson et al. 2005b). Elevated level of c-peptide, a marker of insulin secretion, was observed to be related to an increased risk of colorectal cancers in many studies (Kaaks et al. 2000; Ma et al. 2004). Furthermore, chronic insulin therapy was reported to be associated with an increased risk of colorectal adenoma (Chung et al. 2008) and carcinoma (Yang et al. 2004) as well as associated with increased cancer-related mortality (Bower et al. 2006). Some laboratory research results suggested that

colorectal cancer progression occurs via the adenoma-carcinoma sequence, which may be accelerated in diabetic population (Berster and Göke 2008). In addition, slower bowel transit, which contributes to increased exposure to toxic substances to colonic mucosa, and increased production of carcinogenic bile acids among persons with diabetes mellitus, may promote colonic tumor development and growth (Will et al. 1998).

There are several methodological strengths in our study. First, the advantage of using insurance dataset in clinical research is easy access to the longitudinal records for a large sample of geographically disperse patients. Second, as the NHI database covers nearly the entire population of Taiwan, there is less probability of selection and recall bias as well as non-response and loss to follow-up of cohort members. Third, such a large number of study subjects also made it possible for us to make age- and gender-stratified analyses without compromising the required sample size to achieve adequate statistical power particularly in those of very young age group. Fourth, since the diagnosis of colorectal cancers can be dependent on medical resources and physicians' behavior, adjustment for geographic area and urbanization status was able to reduce such geographic-related confounding. Last, we could exclude those patients with any malignancies three years before the index date so that we could estimate relatively accurate incidence and relative risks of colorectal cancer in our study subjects.

This study also has limitations. First, there would be potential misclassification bias with exclusive reliance on the claim data. The accuracy of a single diabetes diagnosis in the NHI claim data in 2000 was reported to be 74.6% (Lin et al. 2005). We used at least two diabetes-related diagnoses with the first and the last visits >30

days apart, which greatly reduced the possibility of disease misclassification. Nonetheless, there might still be a mixture of new onset or undiagnosed diabetes in the control group. Second, to ensure the accuracy of diagnosis, only the hospitalized cancer patients with major illness/ injury certificates were deemed as true cancer patients in our study, which might have missed some patients who had been waiting for the pathological diagnosis and had not received major illness/ injury certificates. Such disease misclassification bias, however, was likely to be non-differential, which tends to underestimate rather overestimate the true relative risks. Third, a number of risk factors for colorectal cancer and medications use were not taken into account in our analysis, which might have also confounded the study results.

This study concluded that diabetic men, especially those aged 45 and over had a significantly increased risk of colon and rectal cancers while diabetic women were only associated with significantly increased risk of colon cancers.

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Conflict of Interest

We declare no conflict of interest.

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Table 1. Characteristics of the study subjects.

Variables [a]	Control group		Diabetic group	
	n	%	n	%
Socio-demographic Characteristics				
Age				
<45	69,617	11.32	69,825	11.34
45-64	296,810	48.27	297,142	48.27
>64	248,444	40.41	248,562	40.39
Mean age (±SD)	60.00	12.84	60.09	12.73
Sex				
Female	319,308	51.93	319,310	51.93
Male	295,563	48.07	295,566	48.07
Geographic area				
Northern	269,239	44.29	269,920	44.41
Central	151,693	24.96	141,321	23.25
Southern	168,995	27.80	178,627	29.39
Eastern	17,938	2.95	17,944	2.95
Urbanization status				
Urban area	407,323	66.81	415,154	68.16
Rural area	202,343	33.19	193,949	31.84
Total	614,871	100.00	615,532	100.00

[a]Inconsistency between total population and population summed for individual variable was due to missing information.

Table 2. Overall and age- and sex-specific incidence densities and relative hazards of malignant neoplasm of colon (ICD-9: 153) in the diabetic and control groups.

Variables [a]	Control group			Diabetic group			Adjusted HR (95% CI) [c] in association with diabetic group
	No of patients	No of events	ID (per 10,000 patient-years) (95% CI) [b]	No of patients	No of events	ID (per 10,000 patient-years) (95% CI) [b]	
Men							
<45	40537	35	1.30 (0.87-1.73)	40537	47	1.83 (1.30-2.35)	1.37 (0.88-2.12) [d]
45-65	141899	519	5.53 (5.05-6.00)	141899	735	8.15 (7.56-8.74)	1.45 (1.29-1.63) [d]
>65	113127	963	13.31 (12.47-14.15)	113129	1131	16.43 (15.47-17.39)	1.21 (1.10-1.31) [d]
Total	295563	1517	7.85 (7.46-8.25)	295566	1913	10.36 (9.89-10.82)	1.30 (1.21-1.39) [e]
Women							
<45	29080	17	0.88 (0.46-1.30)	29079	28	1.51 (0.95-2.07)	1.78 (0.96-3.30) [d]
45-65	154911	522	5.08 (4.64-5.51)	154911	615	6.20 (5.71-6.69)	1.20 (1.06-1.35) [d]
>65	135317	1110	12.56 (11.82-13.30)	135318	1293	15.28 (14.45-16.12)	1.20 (1.11-1.30) [d]
Total	319308	1649	7.83 (7.45-8.21)	319310	1936	9.57 (9.15-10.00)	1.21 (1.13-1.29) [e]
Overall	614871	3166	7.84 (7.57-8.11)	615532	3849	9.94 (9.62-10.25)	1.25 (1.19-1.31) [f]

[a]Inconsistency between total population and population summed for individual variable was due to missing information.
[b]Based on Poisson assumption, ID= incidence density.
[c]HR= hazard ratio.
[d]Based on Cox proportional hazard regression with adjustment for geographic area and urbanization status,
[e]Based on Cox proportional hazard regression with adjustment for age, geographic area and urbanization status,

[f]Based on Cox proportional hazard regression with adjustment for age, sex, geographic area and urbanization status,

Table 3. Overall and age- and sex-specific incidence densities and relative hazards of malignant neoplasm of rectum (ICD-9: 154) in the diabetic and control groups.

Variables [a]	Control group			Diabetic group			Adjusted HR (95% CI) [c] in association with diabetic group
	No of patients	No of events	ID (per 10,000 patient-years) (95% CI) [b]	No of patients	No of events	ID (per 10,000 patient-years) (95% CI) [b]	
Men							
<45	40537	23	0.85 (0.50-1.20)	40537	31	1.21 (0.78-1.63)	1.34 (0.78-2.31) [d]
45-65	141899	504	5.36 (4.90-5.83)	141899	619	6.87 (6.33-7.41)	1.24 (1.10-1.40) [d]
>65	113127	774	10.69 (9.93-11.44)	113129	848	12.32 (11.49-13.15)	1.13 (1.02-1.24) [d]
Total	295563	1301	6.73 (6.36-7.09)	295566	1498	8.11 (7.70-8.52)	1.18 (1.09-1.27) [e]
Women							
<45	29080	14	0.72 (0.35-1.10)	29079	20	1.08 (0.61-1.55)	1.43 (0.71-2.85) [d]
45-65	154911	450	4.38 (3.97-4.78)	154911	483	4.87 (4.44-5.30)	1.11 (0.97-1.26) [d]
>65	135317	771	8.72 (8.10-9.33)	135318	774	9.13 (8.49-9.78)	1.02 (0.92-1.13) [d]
Total	319308	1235	5.86 (5.34-6.19)	319310	1277	6.31 (5.96-6.65)	1.06 (0.98-1.14) [e]
Overall	614871	2536	6.28 (6.03-6.52)	615532	2776	7.16 (6.90-7.43)	1.12 (1.06-1.18) [f]

[a]Inconsistency between total population and population summed for individual variable was due to missing information.
[b]Based on Poisson assumption, ID= incidence density.
[c]HR= hazard ratio.
[d]Based on Cox proportional hazard regression with adjustment for geographic area and urbanization status

[e]Based on Cox proportional hazard regression with adjustment for age, geographic area and urbanization status
[f]Based on Cox proportional hazard regression with adjustment for age, sex, geographic area and urbanization status