Tohoku J. Exp. Med., 2012, **226**, 259-265

Age- and Sex-Specific Risks of Colorectal Cancers in Diabetic Patients

Hua-Fen Chen,[1,2] Peter Chen,[3] Ying-Hwa Su,[4] Hui-Fang Su[5] and Chung-Yi Li[6,7]

[1]Department of Endocrinology, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[2]School of Medicine, Fujen Catholic University, New Taipei City, Taiwan
[3]Department of Gastroenterology, Central Medicine Hospital Group, New Taipei City, Taiwan
[4]Department of Nursing, College of Medicine, National Cheng Kung University, Tainan City, Taiwan
[5]Department of Health Care Management, National Taipei University of Nursing and Health Sciences, Taipei City, Taiwan
[6]Department and Graduate Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan City, Taiwan
[7]Department of Public Health, College of Public Health, China Medical University, Taichung, Taiwan

Diabetes has been reported to increase the risk of colorectal neoplasm in most but not all studies. However, the 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 sex- and age-specific risks of colorectal cancer in association with diabetes. Diabetic patients (*n* = 615,532) and age- and sex-matched control individuals (*n* = 614,871), selected from the claim datasets, were followed up from 2000 to 2006. The rates of admission due to colon and rectum cancers were estimated using the person-years approach, and the age- and sex-specific hazard ratio (HR) for both the malignancies were determined using the Cox regression model. The overall incidence rate of colon cancer was 9.94 per 10,000 patient-years for the diabetic patients, as opposed to 7.84 per 10,000 patient-years for the control-group patients. The corresponding observation for rectal cancer was 7.16 and 6.28 per 10,000 patient-years. Diabetic patients aged ≥ 45 years had significantly high HRs for developing colon cancer (1.20-1.45-fold). We also noted a significantly high HR of rectal cancer in diabetic men (1.18-fold) aged ≥ 45 years, but not in diabetic women. In conclusion, diabetes may significantly increase the risk of colorectal cancer, especially in patients aged 45-64 years. Diabetologists should keep this relationship in mind while treating middle-aged diabetic men and should also advise these patients to undergo regular screening tests for colorectal cancer.

Keywords: cohort studies; colonic neoplasm; diabetes mellitus; hazard ratio; rectal neoplasm
Tohoku J. Exp. Med., 2012, **226** (4), 259-265.

Nearly one million newly diagnosed colorectal cancer cases are reported to occur in 2002 globally, which accounted for approximately 10% of all incident cancer (Parkin et al. 2005). Many studies have reported that diabetes, which is associated with obesity and physical inactivity, increases the risk of colorectal cancer (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), but some studies have not reported any association (O'Mara et al. 1985; Kune et al. 1988; La Vecchia et al. 1994; Steenland et al. 1995). Indeed, there is a discrepancy in the results reported for sex- and age-specific incidence and relative hazard ratio of colorectal cancer. Some of the previous studies have reported that both male and female diabetic patients are at high risk of developing colorectal cancer (Le Marchand et al. 1997; Weiderpass et al. 1997; Yang et al. 2004), whereas some other studies have shown that the risk of developing colorectal cancer is high in either diabetic men alone (Adami et al. 1991; Wideroff, L. et al. 1997; Khaw et al. 2004; Limburg et al. 2006; Inoue et al. 2006) or diabetic women alone (Nilsen and Vatten 2001). The inconsistency in age- and sex-specific results of previous studies may be attributable to dissimilarities in patient characteristics, care received by the study patients, and possibly, differential accuracy of diagnosis. To the best of our knowledge, very few studies have investigated the incidence rate and relative risk of colorectal cancer in diabetic patients, especially patients under 45 years of age, by stratifying the population

Received March 12, 2012; revision accepted for publication March 21, 2012. doi: 10.1620/tjem.226.259
Correspondence: Chung-Yi Li, Ph.D., Department and Graduate Institute of Public Health, College of Medicine, National Cheng Kung University, #1, University Rd., Tainan 701, Taiwan.
e-mail: cyli99@mail.ncku.edu.tw

by age and sex (Larson et al. 2005a, Larson et al. 2005b).

In Taiwan, colorectal cancer is the second most common form of cancer in both men and women, and its incidence is increasing in both the sexes (Bureau of Health Promotion, 2008). Moreover, it is the fourth most common malignancy among Taiwanese aged 25-44 years (Bureau of Health Promotion, 2008). The mortality rate in patients with diabetes mellitus has been increasing in Taiwan since the early 90s, and diabetes is now the fourth leading cause of death in Taiwan. Thus, the association of diabetes with colorectal cancer is of great significance from both the clinical and public health points of view. The association, if any, is of particular importance in the case of young patients with diabetes because younger diabetic patients are expected to have greater lifetime likelihood of developing colorectal cancer. In this study, we used the National Health Insurance (NHI) database to estimate the incidence density and relative risks of malignant neoplasms of the colon and rectum among the diabetic population in Taiwan by stratifying the population by age and sex.

Methods

Source of data

A universal NHI program, which is implemented by the Bureau of NHI (BNHI) under the jurisdiction of the Department of Health, was established in Taiwan in March 1995. Approximately 96% of the total Taiwanese population enrolled in the NHI program (Chiang, 1997), and 95% of the hospitals and 90% of the clinics all over the island were brought under the purview of the state-run BNHI (Lu and Hsiao 2003) by the end of 1996. The BNHI gathers all the 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 quarterly expert reviews on a random sample of every 50-100 ambulatory and inpatient claims from each hospital and clinic (Chiang et al. 1997). The NHRI safeguards the privacy and confidentiality of all the beneficiaries and transfers the health insurance data to health researchers after ethical approval has been obtained. For our analysis, access to the National Health Insurance Research Database was approved by the NHRI Review Committee.

Diabetes cohort

Details of the claims data and methods of selection of diabetic patients and control-group patients have been described in our previous report (Chen et al. 2011). Briefly, we considered a patient to be diabetic if she or he had diagnosed as having diabetes (ICD-9 250 or A-code 181) in 2000, and again within the subsequent 12 months. To avoid accidental inclusion of miscoded patients, we further selected only those whose first and last outpatient visits were at least 30 days apart (Chen et al. 2011). Additionally, we excluded those patients who were admitted to the hospitals for any malignant neoplasm (ICD-9: 140-208) between 1997 and the date of initial ambulatory care visit for diabetes treatment in 2000. In Taiwan, major illness/injury certificates are issued to all patients with malignant neoplasms. In order to avoid incorrect exclusion of cancer patients, we excluded those patients with a major illness/injury certificates for an admission. Thus, the final cohort of diabetic patients consisted of 615,532 patients. The date of the first outpatient visit in 2000 was the index date for each patient.

Control group

The control-group subjects were identified from the registry of beneficiaries. We excluded people with claims for ambulatory care for diabetes or hospitalized for any type of malignancy (ICD-9: 140-208) and were issued major illness/injury certificates between 1997 and 1999, and then we selected age- and sex-matched control subjects by using the frequency matching procedure. Because of missing information on the age or sex of 661 diabetic patients, we could select only 614,871 control subjects. The index date for subjects in the control group was their date of enrollment to NHI. If their date of enrollment was before January 1, 2000, the index date was set as January 1, 2000, which was the starting point for the follow-up analysis.

Data linkage

We used the unique personal identification number (PIN) of the individuals in both the groups and linked them to the inpatient claims data obtained between the years 2000 and 2006 in order to identify the first primary or secondary diagnoses of primary malignant neoplasm of colon (ICD-9: 153) and malignant neoplasm of rectum (ICD-9: 154)—the end points of this study. To avoid incorrect assessment of malignant neoplasms, we included only those patients who possessed major illness/injury certificates for those admissions. The day of hospitalization of the patients was considered as the date on which the clinical endpoint of interest occurred. The study period was from January 1, 2000, to December 31, 2006.

Statistical analysis

The geographic location of each individual's NHI unit—either near the location of employment or residential area—was classified under north, central, south, or east and under either of the following urbanization statuses—urban or rural—as per 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 was the sum of the person-time values (person-years in the current study) of the at-risk population. We assumed that a 2-year follow-up for 1 person or a 1-year follow-up for 2 persons both equal 2 person-years. Using person-years may be helpful in cases where the observation time (i.e., follow-up period) differs between the study participants. To assess the independent effects of diabetic status on the risk of colon and rectal cancers, we used Cox proportional hazard regression models, adjusting for age, sex, geographic area, and urbanization statuses simultaneously in this model. The latter 2 geographic variables were adjusted for possible geographic variations in cancer incidence and mortality (Chen et al. 2002). The study participants who died in the hospital because of unfavorable clinical outcomes were censored from the survival analysis, and the date of censoring was the date of their deaths. If there was no in-hospital mortality in the case of an individual, the date of censoring was either the date of their withdrawal from NHI or the date of termination of the study, i.e., December 31, 2006. All the statistical analyses were performed using the Statistical Analysis Software (version 9.2; SAS Institute, Cary, NC). A P value of < 0.05 was considered statistically significant.

Results

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

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

We observed that 2,776 and 2,536 patients from the diabetic and control groups, respectively, had been hospitalized for the above diagnoses between 2000 and 2006 (Table 3). The overall incidence density calculated for the diabetic men and women was 8.11 and 6.31 per 10,000 person-years, respectively, and the corresponding values for the men and women from the control group were 6.73 and 5.86 per 10,000 person-years, respectively. Once again, we observed that the incidence of rectal cancer increased with age in patients of both the sexes regardless of their diabetic status, and a high incidence density was again observed in those aged > 64 years. As compared to the control group, the diabetic group had a slightly but significantly higher risk of rectal cancer for men (HR = 1.18; 95% CI = 1.09-1.27); no such difference was observed in the case of women from both the groups (HR = 1.06; 95% CI = 0.98-

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 (± S.D.)	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	40,537	35	1.30 (0.87-1.73)	40,537	47	1.83 (1.30-2.35)	1.37 (0.88-2.12) [d]
45-65	141,899	519	5.53 (5.05-6.00)	141,899	735	8.15 (7.56-8.74)	1.45 (1.29-1.63) [d]
> 65	113,127	963	13.31 (12.47-14.15)	113,129	1,131	16.43 (15.47-17.39)	1.21 (1.10-1.31) [d]
Total	295,563	1,517	7.85 (7.46-8.25)	295,566	1,913	10.36 (9.89-10.82)	1.30 (1.21-1.39) [e]
Women							
< 45	29,080	17	0.88 (0.46-1.30)	29,079	28	1.51 (0.95-2.07)	1.78 (0.96-3.30) [d]
45-65	154,911	522	5.08 (4.64-5.51)	154,911	615	6.20 (5.71-6.69)	1.20 (1.06-1.35) [d]
> 65	135,317	1,110	12.56 (11.82-13.30)	135,318	1,293	15.28 (14.45-16.12)	1.20 (1.11-1.30) [d]
Total	319,308	1,649	7.83 (7.45-8.21)	319,310	1,936	9.57 (9.15-10.00)	1.21 (1.13-1.29) [e]
Overall	614,871	3,166	7.84 (7.57-8.11)	615,532	3,849	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	40,537	23	0.85 (0.50-1.20)	40,537	31	1.21 (0.78-1.63)	1.34 (0.78-2.31) [d]
45-65	141,899	504	5.36 (4.90-5.83)	141,899	619	6.87 (6.33-7.41)	1.24 (1.10-1.40) [d]
> 65	113,127	774	10.69 (9.93-11.44)	113,129	848	12.32 (11.49-13.15)	1.13 (1.02-1.24) [d]
Total	295,563	1,301	6.73 (6.36-7.09)	295,566	1,498	8.11 (7.70-8.52)	1.18 (1.09-1.27) [e]
Women							
< 45	29,080	14	0.72 (0.35-1.10)	29,079	20	1.08 (0.61-1.55)	1.43 (0.71-2.85) [d]
45-65	154,911	450	4.38 (3.97-4.78)	154,911	483	4.87 (4.44-5.30)	1.11 (0.97-1.26) [d]
> 65	135,317	771	8.72 (8.10-9.33)	135,318	774	9.13 (8.49-9.78)	1.02 (0.92-1.13) [d]
Total	319,308	1,235	5.86 (5.34-6.19)	319,310	1,277	6.31 (5.96-6.65)	1.06 (0.98-1.14) [e]
Overall	614,871	2,536	6.28 (6.03-6.52)	615,532	2,776	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.

1.14). In a further analysis of age- and sex-specific HRs, the highest HR was observed in diabetic men aged 45-64 years (HR = 1.24; 95% CI = 1.10-1.40). The relative risk estimates were not statistically significant in diabetic women of any age group.

Discussion

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

We observed that diabetes was associated with higher risk of developing both colon and rectal cancers in men, but in women, diabetes was associated with a high risk of developing colon cancer alone, which is consistent with the findings from previous studies (Weiderpass et al. 1997). Some of the previous studies reported that diabetes was associated with increased risk of colon cancer but not rectal cancer in both men and women (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 diabetes is positively associated with the development of colon cancer in men but not diabetic women, and that diabetes in both the sexes is not associated with the development of rectal cancer. The discrepancy across the results of these studies is probably due to different methodologies that were adopted, including dissimilarity in the baseline characteristics and ethnicities of the patients, in methods of outcome assessment, and duration of follow-up. Because our study investigated colon and rectal cancers in the same population by using the same methodology, findings from our study may effectively remedy the limitations encountered by previous studies that were unable to simultaneously investigate the risk of development of the 2 cancers with detailed sex and age specifications, without compromising the statistical power.

In our study, diabetes-related cancer risk was more evident for malignant neoplasm of the colon than for rectal cancer. Similar findings had been reported by Weiderpass et al. (1997) and Yang et al. (2004). Similar to the observations of Weiderpass et al. (1997), our observations showed that diabetic men were more likely to have a higher relative risk of developing both colon and rectal cancers than diabetic women were. Further, age- and sex-stratification analysis revealed that diabetic men aged ≥ 45 years had a significantly high relative risk of developing colorectal cancer. Similarly, La Vecchia et al. (1994) from Italy reported that there is no association between diabetes and colorectal cancer risk in diabetic patients aged < 40 years, but there is a strong association between the 2 said conditions among diabetic patients aged > 60 years. The above findings may imply a positive relationship between the duration of diabetes and the risk of colorectal cancer, which however needs further investigations.

The biologic mechanism by which diabetes may predispose to colorectal cancer is still not clearly identified. Type 2 diabetes, which is characterized by insulin resistance and compensatory hyperinsulinemia, may predispose to colon neoplasms since insulin is an important growth factor for colonic epithelial cells (Giovannucci et al. 1995), regulating growth through direct activation of insulin receptor or insulin-like growth factor (IGF)-I receptor and inhibition of IGF-binding protein (Larsson et al. 2005b). An elevated level of C-peptide, a marker of insulin secretion, was observed to be associated with an increased risk of colorectal cancer in many studies (Kaaks et al. 2000; Ma et al. 2004). Furthermore, long-term insulin therapy was reported to be associated with an increased risk of developing colorectal adenoma (Chung et al. 2008) and carcinoma (Yang et al. 2004) along with increased cancer-related mortality (Bowker et al. 2006). The results of some studies suggest that colorectal cancer progression occurs through the adenoma-carcinoma sequence, which may have accelerated activity in the diabetic population (Berster and Göke 2008). In addition, slower bowel transit, which contributes to increased exposure of the colonic mucosa to toxic substances and leads to increased production of carcinogenic bile acids in patients with diabetes mellitus, may promote the development of colonic tumor in these patients (Will et al. 1998).

There are several methodological strengths in our study. First, using an insurance dataset in clinical research is advantageous because longitudinal records for a large sample of geographically dispersed patients are easily accessible. 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 study population also made it possible for us to perform age- and gender-stratified analyses without compromising statistical power, particularly in the case of very young patients. Fourth, since the diagnosis of colorectal cancers can depend on the medical resources and the physicians from different locations, an adjustment for the geographic area and urbanization status was able to reduce such geographic confounding. Last, we excluded those patients with any malignancies detected 3 years before the index date so that we could estimate relatively accurate incidence and relative risks of colorectal cancer in our study participants.

This study also has limitations. First, there can be a potential classification bias because of exclusive reliance on the claims data. The accuracy of a single diabetes diagnosis in the NHI claims data from the year 2000 was reported to be 74.6% (Lin et al. 2005). We used at least 2 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 cases of new-onset or undiagnosed diabetes in the control group. Second, to ensure the accuracy of diagnosis, we considered only the hospitalized cancer patients with major illness/injury certificates as true cancer patients, which might have led to the exclusion of some patients who were waiting for the pathological diagnosis and had not received major illness/injury certificates. Such bias introduced by disease misclassification, however, was likely to be a non-differential bias, which tends to lead to underestimation rather than overestimation of the true relative risks. Third, a number of risk factors for colorectal cancer and medications used were not taken into account in our analysis, which might have also confounded the results.

In this study, we observed that diabetic men, especially those aged 45 years or more, had a significantly high risk of developing both colon and rectal cancers, while diabetic women had a significantly high risk of developing colon cancer alone.

Acknowledgments

This study was partially supported by a grant from the National Scientific Council (NSC100-2314-B-006-052). The interpretation and conclusions contained herein do not represent those of BNHI, Department of Health or NHRI.

Conflict of Interest

We declare no conflict of interest.

References

Adami, H.O., McLaughlin, J., Ekbom, A., Berne, C., Silverman, D., Hacker, D. & Persson, I. (1991) Cancer risk in patients with diabetes mellitus. *Cancer Causes Control*, **2**, 307-314.

Berster, J.M. & Göke, B. (2008) Type 2 diabetes mellitus as risk factor for colorectal cancer. *Arch. Physiol. Biochem.*, **114**, 84-98.

Bowker, S.L., Majumdar, S.R., Veugelers, P. & Johnson, J.A. (2006) Increased cancer-related mortality for patients with type 2 diabetes who use sulphonylureas or insulin. *Diabetes Care*, **29**, 254-258.

Bureau of Health Promotion (2008) http://www.bhp.doh.gov.tw/BHPnet/Portal/Them_Show.aspx?Subject=200712250031&Class=2&No=200805020001. [Accessed April 21, 2011]

Chen, C.J., You, S.L., Lin, L.H., Hsu, W.L. & Yang, Y.W. (2002) Cancer epidemiology and control in Taiwan: a brief review. *Jpn. J. Clin. Oncol.*, **32**, S66-81.

Chen, H.F., Chen, P. & Li, C.Y. (2010) Risk of malignant neoplasms of liver and biliary tract in diabetic patients with different age and sex stratifications. *Hepatology*, **52**, 155-163.

Chen, H.F., Chen, P. & Li, C.Y. (2011) Risk of malignant neoplasm of pancreas in relation to diabetes: a population-based study in Taiwan. *Diabetes Care*, **34**, 1177-1179.

Chiang, T.L. (1997) Taiwan's 1995 healthcare reform. *Health Policy*, **39**, 225-239.

Chung, Y.W., Han, D.S., Park, K.H., Eun, C.S., Yoo, K.S. & Park, C.K. (2008) Insulin therapy and colorectal adenoma risk among patients with type 2 diabetes mellitus: a case-control study in Korea. *Dis. Colon Rectum*, **51**, 593-597.

Giovannucci, E. (1995) Insulin and colon cancer. *Cancer Causes Control*, **6**, 164-179.

Inoue, M., Iwasaki, M., Otani, T., Sasazuki, S., Noda, M. & Tsugane, S. (2006) Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch. Intern. Med.*, **166**, 1871-1877.

Kaaks, R., Toniolo, P., Akhmedkhanov, A., Lukanova, A., Biessy, C., Dechaud, H., Rinaldi, S., Zeleniuch-Jacquotte, A., Shore, R.E. & Riboli, E. (2000) Serum c-peptide, insulin-like growth factor (IGF)-I, IGF binding proteins, and colorectal risk in women. *J. Natl. Cancer Inst.*, **92**, 1592-1600.

Khaw, K.T., Wareham, N., Bingham, S., Luben, R., Welch, A. & Day, N. (2004) Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer-Norfolk study. *Cancer Epidemiol. Biomarkers Prev.*, **13**, 915-919.

Kune, G.A., Kune, S. & Watson, L.F. (1988) Colorectal risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. *Cancer Res.*, **48**, 4399-4404.

La Vecchia, C., Negri, E., Franceschi, S., D'Avanzo, B. & Boyle, P. (1994) A case-control study of diabetes mellitus and cancer risk. *Br. J. Cancer*, **70**, 950-953.

Larsson, S.C., Giovvannucci, E. & Wolk, A. (2005a) Diabetes and colorectal cancer incidence in the cohort of Swedish men. *Diabetes Care*, **28**, 1805-1807.

Larsson, S.C., Orsini, N. & Wolk, A. (2005b) Diabetes and risk of colorectal cancer: a meta-analysis. *J. Natl. Cancer Inst.*, **97**, 1679-1687.

Le Marchand, L., Wilkens, L.R., Kolonel, L.N., Hankin, J.H. & Lyu, L.C. (1997) Associations of sedentary life style, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Res.*, **57**, 4787-4794.

Limburg, P.J., Anderson, K.E., Johnson, T.W., Jacobs, D.R. Jr., Lazovich, D., Hong, C.P., Nicodemus, K.K. & Folsom, A.R. (2005) Diabetes mellitus and subsite-specific colorectal cancer risks in the Iowa Women's Health Study. *Cancer Epidemiol. Biomarkers Prev.*, **14**, 133-137.

Limburg, P.J., Vierkant, R.A., Fredericksen, Z.S., Leibson, C.L., Rizza, R.A., Gupta, A.K., Ahlquist, D.A., Melton, L.J. 3rd., Sellers, T.A. & Cerhan, J.R. (2006) Clinically confirmed type 2 diabetes mellitus and colorectal cancer risk: a population-based, retrospective cohort study. *Am. J. Gastroenterol.*, **101**, 1872-1879.

Lin, C.C., Lai, M.S., Syu, C.Y., Chang, S.C. & Tseng, F.Y. (2005) Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. *J. Formos. Med. Assoc.*, **104**, 157-163.

Lu, J.F.R. & Hsiao, W.C. (2003) Does Universal health insurance make health care unaffordable? Lessons from Taiwan. *Health Aff.*, **22**, 77-88.

Ma, J., Giovannucci, E., Pollak, M., Leavitt, A., Tao, Y., Gaziano, J.M. & Stampfer, M.J. (2004) A prospective study of plasma c-peptide and colorectal cancer risk in men. *J. Natl. Cancer Inst.*, **96**, 546-553.

Nilsen, T.I.L. & Vatten, L.J. (2001) Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinemia hypothesis. *Br. J. Cancer*, **84**, 417-422.

O'Mara, B.A., Byers, T. & Schoenfeld, E. (1985) Diabetes mellitus and cancer risk: a multisite case-control study. *J. Chronic Dis.*, **38**, 435-441.

Parkin, D.M., Bray, F., Ferlay, J. & Pisani, P. (2005) Global cancer statistics, 2002. *CA Cancer J. Clin.*, **55**, 74-108.

Steenland, K., Nowlin, S. & Palu, S. (1995) Cancer incidence in the National Health and Nutritional Survey I Follow-up data: diabetes, cholesterol, pulse, and physical activity. *Cancer Epidemiol. Biomarkers Prev.*, **4**, 807-811.

Weiderpass, E., Gridley, G., Nyrén, O., Ekbom, A., Persson, I. & Adami, H.O. (1997) Diabetes mellitus and risk of large bowel cancer. *J. Natl. Cancer Inst.*, **89**, 660-661.

Wideroff, L., Gridley, G., Mellemkjaer, L., Chow, W.H., Linet, M., Keehn, S., Borch-Johnsen, K. & Olsen, J.H. (1997) Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J. Natl. Cancer Inst*., **89**, 1360-1365.

Will, J.C., Galuska, D.A., Vinicor, F. & Calle, E.E. (1998) Colorectal cancer: another complications of diabetes mellitus? *Am. J. Epidemiol.*, **147**, 816-825.

Yang, Y.X., Hennessym, S. & Lewis, J.D. (2004) Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology*, **127**, 1044-1050.