RESEARCH COMMUNICATION

Incidences of Cancers in Diabetic and Non-diabetic Hospitalized Adult Patients in Taiwan

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Abstract

Background: The study was to investigate the relationship between diabetes mellitus (DM), specific cancers, age, and gender. Methods: This was a retrospective study that examined the frequency of different forms of cancer among male and female patients with or without DM admitted to a single hospital in Taiwan between January 2009 and June 2010. Results: Of 101,002 study patients admitted to the hospital, 15,901 (15.74%) were diagnosed with DM and 16,748 (16.58%) with a malignancy. The frequency of DM differed between males and females (17.5% vs 14.2%; P < 0.001), and males had a higher cancer incidence than females (20.2% vs 13.5%; P < 0.001). Patients with DM had a greater frequency of cancer diagnosis than non-DM patients (18.1% vs 16.3%, respectively), with pancreatic, liver, uterine, urinary tract, lung, and secondary cancers being more frequent in DM compared with non-DM patients. In contrast, the proportion of patients with thyroid, esophagus, breast, NPC, and other cancers was lower in DM versus non-DM patients. Conclusions: This study found that DM was associated with the incidence of specific cancers and that males had a higher frequency of cancer than females. The association of DM and cancer depended upon cancer type, gender, and age.

Keywords: Age interval - pancreatic cancer – hepatoma - secondary cancer – hyperinsulinemia - obesity

Asian Pacific J Cancer Prev, **12**, 1577-1581

Introduction

Both cancer and long term diabetes mellitus (DM) and associated cardiovascular complications are major health problem in both developed and developing countries. Of adult patients diagnosed with DM over 90% had type 2 DM. The relationship between DM and cancer risk has been investigated for more than a decade. Increased risk of cancer has been reported by some studies but others have showed decreased risk (Johnson et al., 2010; Atchison et al., 2011). Obesity increases the risks of multiple diseased including type 2 DM and cancer (Bianchini et al., 2002; Calle et al., 2004) and numerous epidemiological studies have demonstrated that high body mass index (BMI) is positively associated with increased risk of many common cancers, such as liver, endometrium, breast, pancreatic, and colorectal cancers (Kuriyama et al., 2005; Johnson et al., 2010).

The reasons for an association of cancer and DM are unclear. In vitro studies have shown that endogenous or exogenous insulin can act as a growth-promoting mitogen by binding to the insulin receptor resulting in activation of insulin signaling cascades, and subsequently growth in the pancreas (Conover et al., 1992). High levels of insulin can enhance insulin-like growth factor-1 (IGF-1) known to be associated with cell proliferation and the risk of cancer. Increased insulin levels promote synthesis of IGF-1 and down-regulate IGF-1 binding proteins in the liver, leading to an increase in the bioavailability of active IGF-1. In addition, anabolic signals produced by insulin and IGF-1 can promote tumor development by inhibiting apoptosis, stimulating cell proliferation, and enhancing angiogenesis (Khandwala et al., 2000; Campbell et al., 2010). Obesity may influence cancer development by causing hyperinsulinemia resulting in increased IGF-1 activity.

There are other factors that may also influence a relationship between DM and cancer. For example, age is a potential risk factor common to both, and the incidence of DM increases with age. Most cancers have increased mortality with greater age however some cancers are more prevalent in younger age groups. The relationship of age, DM, and cancer has not been well studied.

This was a retrospective study that investigated the association of DM with cancer diagnosed in Chinese patients admitted to a hospital in Taiwan. It utilized the International Classification of Disease-9 (ICD-9) diagnostic codes to identify the disease states of different patients and assessed the presence of different cancer types in patients with and without DM. It also investigated the

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age and gender distribution of cancer in DM and non-DM adult patients.

Subjects and Methods

Study population

Patients were identified through admission data from Chang Gung Memorial Hospital (CGMH) in Linkou, Taiwan during the period of 2009 January to June 2010. Patients were included if their hospital admission was due to main diagnosis according to the ICD-9 codes. Patients had to be > 20 years of age. Patients with malignant neoplasm had to have their diagnosis validated by at least 2 specialists based on examinations of medical records, laboratory and imaging results, and histological or cytological analyses. Patients diagnosed with malignant neoplasm were categorized into different groups according to anatomic organ system (Table 1). Among the cancer groups, body of uterus, cervix uteri, ovary (and other uterine adnexa), and breast cancers were female specific and prostate cancer was male specific. All of the subjects were Chinese residents of Taiwan. The study was approved by the Institutional Review Board of CGMH.

DM was defined as a fasting glucose level exceeding 126 mg/dL or a postprandial glucose level exceeding 200 mg/dL (American Diabetes Association. 2010). The diagnostic code of malignancy was defined as codes from 140 to 208.91 in the ICD-9 clinical modification format.

Statistical analysis

All data analyses were performed using SPSS (v16.0, SPSS Inc. Chicago, IL. USA) (Levesque, 2007). Incidence proportions were computed for various cancers and DM by gender and age. Multivariate conditional logistic regression, adjusted for age and gender, was used to estimate odds ratio (OR) and 95% confidence interval (CI) for associations between DM and the incidence of specific cancers. Chi-square tests were used to determine if the difference in frequency of a specific cancer between DM and non-DM patients was significant.

Results

A total of 180,125 admission file were extracted and 101,002 patients were identified that met the entry criteria. The mean age was 53.3 ± 18.2 years and 54,151 were female (mean age, 51.0 ± 18.3 years) and 46,851 were male (mean age, 55.9 ± 17.6 years). Among the 101,002 study patients, 15,901 (mean age: 65.3 years; range: 20-99 years) (15.7%) were diagnosed with DM (Table 1). Of the DM patients, 8,205 (17.5%) were male (mean age: 63.8 years; range: 20-99 years) and 7,696 (14.2%) were female (mean age: 66.82 years; range: 20-99 years). Overall, incidence of DM was higher in males than females (17.5% vs 14.2%, respectively). The incidence of DM increased with age for both males and females. For ages 20-29 years the incidence of DM was 1.5% and 1.31% for males and females, respectively. For ages 60-69 years in males the frequency of DM was 26.61% and for ages 70-79 years in females the incidence of DM was 33.7%.

There were 16,748 (16.6%) patients diagnosed with cancer and the frequency of cancer was higher in males than females (9,464 [20.2%] male and 7,284 [13.45%] female [$P < 0.0001$]) . About a third (29.9% [n = 5,010] of the patients were diagnosed with 2 different cancers, 7.44% (n = 1,247) with three separate cancers, and 0.30% (n = 51) (0.30%) with four cancers. The highest incidence of cancer was in ages 70-79 years for males and 50-59 years for females.

DM was higher in females > 60 years of age than in males of the same age group (Figure 1). For females, cancer was most incident in ages 50-59 years and DM was most common in ages 70-79 years. Females, ages 50 to 59 years, were most likely to have both cancer and DM. Although overall females had a lower risk of cancer than males, they had a higher risk of specific cancers as compared to males.

For patients with both cancer and DM, pancreatic and liver cancers had an increased OR of 3.46 and 1.81, respectively, compared to non-DM patients, and the incidence of uterine, urinary tract, lung, and secondary

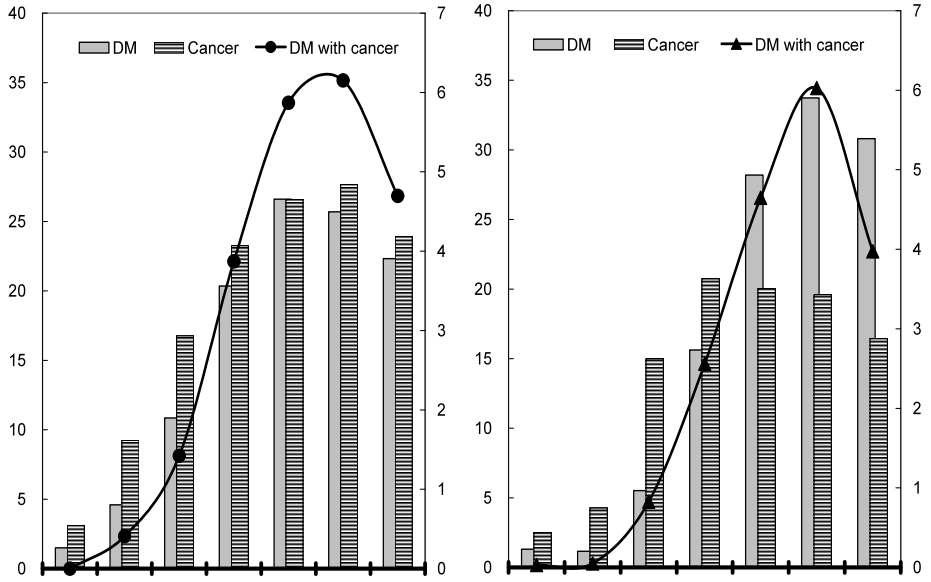

Figure 1. Age, Gender Distribution of Percentages of DM, Cancer, and Coexistence of DM with Cancer in101,002 Patients

Table 1. Case Numbers of Patients with Malignant Neoplasms in DM and non-DM Subjects

Cancers	Number	(M/F)	DM		Non-DM		Chi-square
Study patients	101,002	(46,851/54,151)	15,901		85,101		
Pancreas	281	(176/105)	110	(0.69%)	171	(0.20%)	116.35***
Liver	2,959	(2,102/857)	736	(4.63%)	2,223	(2.61%)	191.56***
Uterus (F)	376	(0/376)	70	(0.91%)	306	(0.66%)	6.03*
Urinary tract	878	(580/298)	168	(1.06%)	710	(0.83%)	7.68**
Lung	1,800	(1,119/681)	320	(2.01%)	1,480	(1.74%)	5.72*
Secondary	5,179	(2,839/2,340)	890	(5.60%)	4,289	(5.04%)	8.55**
Gastric	611	(387/224)	111	(0.70%)	500	(0.59%)	2.72
Prostate (M)	590	(590/0)	115	(1.40%)	475	(1.23%)	1.62
Hematologic	810	(435/375)	141	(0.89%)	669	(0.79%)	1.71
Colon	1,869	(1,054/815)	314	(1.97%)	1,555	(1.83%)	1.60
Skin	204	(116/88)	34	(0.21%)	170	(0.20%)	0.13
Cervical (F)	443	(0/443)	65	(0.84%)	378	(0.81%)	0.08
Oropharynx	1,334	(1,218/116)	190	(1.19%)	1,144	(1.34%)	2.29
Overy (F)	373	(0/373)	45	(0.58%)	328	(0.71%)	1.42
Others	4,159	(2,262/1,897)	589	(3.70%)	3,570	(4.20%)	8.18**
NPC	372	(268/104)	37	(0.23%)	335	(0.39%)	9.46**
Breast (F)	1,513	(0/1,513)	127	(1.65%)	1,386	(2.98%)	43.22***
Esophagus	386	(358/28)	33	(0.21%)	353	(0.41%)	15.12***
Thyroid	299	(85/214)	19	(0.12%)	280	(0.33%)	19.93***
Total cancer	16,748	(9,464/7,284)	2,878	(18.1%)	13,870	(16.30%)	31.42***

*: p<0.05; **: p<0.01; ***: p<0.001

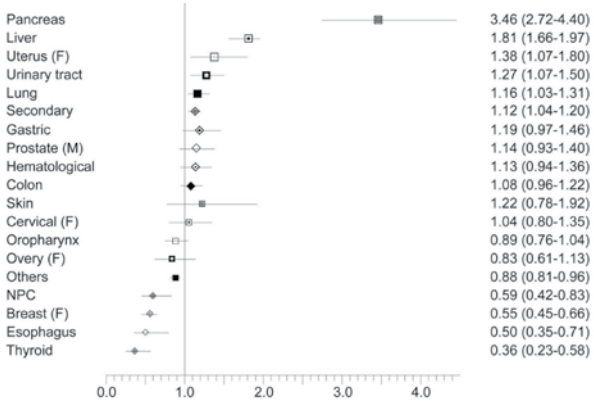

Figure 2. Odds ratio (95% Confidence Interval) of Different Cancers between DM and non-DM Patients

cancer were also significantly (P < 0.05) increased in DM patients (Figure 2). In contrast, thyroid, esophagus, female breast cancer, nasopharyngeal carcinoma (NPC), and other cancer types were significantly (P < 0.05) decreased in DM patients (Table 4). Males and females with DM had a lower frequency of having cancer compared to non-DM patients for all age groups, excluding females, ages 30-39 years.

Sub-analysis of specific cancers indicated that patients with DM, regardless of gender and age, had a decreased risk of getting most types of cancers, excluding pancreatic and liver cancer, compared with those without DM. In females, ages 40 to 49 years, DM was associated with an increased risk of uterine, urinary tract, lung, secondary, gastric, skin, cervical, and ovary cancer, and in males, ages 30-49 years DM was associated with a greater risk of skin cancer.

Discussion

Prior studies have found that patients with DM are at increased risk for certain cancers (Calle et al., 2004; Lee et al., 2011; Ben et al., 2011; Inoue et al., 2006). Different studies have resulted in various estimates of the cancer risk for DM patients; however, the risk of specific cancer types has not been not fully evaluated. A diagnosis of DM has been associated with a 27% and a 21% increase in the risk of cancer in men and women, respectively (Inoue et al., 2006). In contrast, this study found that although patients with DM versus those without had a higher risk for cancer (20.22% vs 15.84%, respectively) there was no difference in the frequency of cancer between males of the 2 groups. In this study only in females 60-79 year of age was DM associated with an increased risk of cancer. This difference between ours and previous findings may be due to differences in the patient populations. Similar to prior study (Jee et al., 2008), males had a higher incidence of overall cancer as compared to females. More studies need to be conducted to confirm these results.

This study found that DM may have influenced the risk of developing specific cancers. DM patients, regardless of gender, had a higher frequency of pancreatic (except for males 40-49 years of age) and liver cancer than non-DM patients which is consistent with previous findings (Chari et al., 2005). However, another a prior study found that a history of DM resulted in a higher risk of liver cancer for both males and females but a higher risk of pancreatic cancer only for males (Inoue et al., 2006). The present analysis found that DM was associated with higher risk in females independent of age for getting uterine, urinary tract, gastric, and secondary cancers. There was no evidence in this study that DM resulted in an increased incidence of colon or rectal cancer as has been shown previously (Larsson et al., 2005; Limburg et al., 2005; Campbell et al., 2010).

The association of DM and pancreatic cancer may reflect the dysfunction of the pancreas due to the cancer. Destruction of the Islet cells by the cancer may result in

abnormal secretion of insulin and the development of DM suggesting that pancreatic cancer may be a diabetogenic state. Hence, DM may be both an early manifestation as well as an etiologic factor of pancreatic cancer (Ben et al., 2011). DM associated with pancreatic cancer is often new-onset that resolves following cancer resection, and appears to be associated with conventional risk factors for DM (Pannala et al., 2008). Also, patients with DM have a threefold increased risk for developing pancreatic cancer (Jamal et al., 2009; Chu et al., 2010), and patients with new-onset DM have a poorer prognosis following an operation for pancreatic cancer than patients with long-term DM. Additional studies are required to help further clarify the relationship between DM and pancreatic cancer.

DM is known to increase the risk of primary liver cancer in the presence of other risk factors such as hepatitis C or B or alcoholic cirrhosis (El-Serag et al, 2001). Hepatitis C infection and alcoholic cirrhosis account for most of liver cancer among veterans (Khan et al., 2006; Polesel et al., 2009; Hung et al., 2010). In this study, DM increased the OR for liver cancer to 1.81. In contrast, community-based cross-sectional and case-controlled studies found that DM was not a risk factor for liver cancer in a dual hepatitis C and B endemic area (Tung et al., 2010).

Women with type 2 DM and gestational DM reported a modest increase in risk of breast cancer (Xue et al., 2007). The prospective Nordic study and US study based on the Nurses' Health Study II illustrated a decreased risk of breast cancer was observed among overweight and obese women and DM patients (Michels et al., 2006; Vigneri et al., 2009). Our study showed decreased relative risk of breast cancer in all female age groups. This inverse association between DM and breast cancer is consistent with previous epidemiologic study (Inoue et al., 2006). Insulin resistance and long term hyperinsulinemia induce menstrual cycle irregularity and chronic anovulation may reduce the risk of breast cancer.

In the cohort of patient studied here, DM was associated with a reduction in the incidence of thyroid cancer in females. This is in contrast to recent reports that found that insulin resistance and obesity increased the incidence of thyroid cancer (Paes et al., 2010). In contrast, a higher BMI has been shown to correlate with lower incidence of thyroid cancer for all patients except women > 45 years of age (Mijović et al., 2010). One possible interpretation of these findings is that perhaps hyperinsulinemia in the initial stage of type 2 DM increases cancer growth, and anovulatory status in type 2 DM may decrease the development of thyroid cancer.

The main limitation of this study was the data was from only an 18 month period which may have biased the findings. Also, the time sequence of DM and cancer (ie, which disease state developed first) was not addressed.

In conclusions, the findings of this study showed that the presence of DM may influence the development of certain cancer types and that in some cases gender and age may affect this risk. DM was associated with an increase in pancreatic and liver cancer for both males and females. The presence of DM appeared to decrease breast and thyroid cancer in females. These findings suggest that patients with DM should be carefully screened for early signs of cancer.

Acknowledgements

There is no conflict of interest existing with this paper.

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