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ORIGINAL PAPER

Glucose metabolism disorders in cancer patients in a Chinese population

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Abstract *Background* Characteristics of glucose metabolism disorders (GMDs) in different cancers and the contributory role of GMDs in developing cancers are still not so clear. *Methods* Two thousand four hundred and five patients with malignancy who had been hospitalized in the First Affiliated Hospital of Jinan University were pooled as case group. Two thousand and sixteen non-cancer people who finished health examinations in the Affiliated Yangcheng Hospital of Guangzhou Medical College were enrolled as control group. We compared glucose metabolism among patients with different kinds of malignancy. Based on logistic regression models, we analyzed factors that affect the development of carcinoma. *Results* (1) Among 2,408 malignancy patients, the total prevalence of diabetes mellitus (DM) and impaired fasting glucose (IFG) reached 28.0%. Pancreatic cancer, lymphoma, liver cancer, leukemia, and colorectal cancer showed most striking hyperglycemia. (2) Leukemia and esophageal cancer accounting for 12.5% and 12.1%, respectively, were the most likely to suffer from hypoglycemia. (3) Older cancer patients seem to be more vulnerable to hyperglycemia, while the younger tend to be more likely to develop hypoglycemia. (4) High level of fasting plasma glucose (FPG) was associated with lung cancer, breast cancer, leukemia, lymphoma, thyroid cancer, bladder cancer, and pancreatic cancer. Patients with DM increased risks for developing colorectal cancer, liver cancer, esophageal cancer, thyroid cancer, cervical cancer, and pancreatic cancer. *Conclusions* GMDs are frequent events in malignancy patients. Hyperglycemia and hypoglycemia are found in the same kinds or different kinds of cancers, and the incidence of hyperglycemia is higher than that of hypoglycemia. Characteristics of GMDs were dissimilar in different cancers and different ages. Hyperglycemia was a risk factor for many cancers.

Keywords Cancer · Glucose metabolism · Diabetes mellitus · Impaired fasting glucose · Hyperglycemia · Hypoglycemia

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Introduction

Data indicate gradually increasing incidence in cancer alongside with economic development, aging, unhealthy lifestyle, and environmental changes [1–3]. According to

the WHO, around 10 million individuals develop cancer each year, and this figure is expected to increase to 15 million in 2020. Glucose metabolism disorders (GMDs), which include diabetes mellitus (DM), impaired fasting glucose regulation (IFG), impaired glucose tolerance (IGT), and hypoglycemia, are common diseases with their attack rates rising rapidly [4]. As in many other countries, DM is also a serious public health problem in China. According to the statistics, the total number of people with diabetes is estimated to rise from 171 million in 2000 to 366 million in 2030, and China is ranked second in the world in the incidence of diabetes [5]. As a result of high morbidity, GMDs and cancer have become hotspots in the medical field.

Many epidemiological studies support the hypothesis that diabetes is associated with an increased likelihood of cancer [6–12], hyperinsulinemia [13–15], insulin-like growth factors (IGFs) [13, 14, 16, 17], hyperglycemia [18–20], and medicines for controlling blood glucose [21, 22] being suggested as possible biological risk factors. Meanwhile, there are several plausible explanations for the mechanisms by which GMDs develop in cancer patients, including drugs for chemotherapy [23–26], ectopic hormone [27, 28], and destruction of cancer cells or cytokine [28]. However, the prevalent characteristics of GMDs in cancer patients are still unclear, and the disparities of GMDs among different types of cancers are also unknown.

It has already been shown that if cancer was accompanied with GMDs, they tended to interact with each other and worsen prognosis [9, 29–32]. Whereas, it seems that most attention has been focused on the increased risks of malignancy among patients with GMDs [7, 8, 12] hitherto, but the reverse also applies and cancer patients may also face with the threat of GMDs [23, 26, 33, 34]. Moreover, the focus in many reports was merely on the relationship between a single malignant neoplasm and hyperglycemia [6, 9, 10, 35–40], rather than a range of cancer. Therefore, we conducted a case–control study on the prevalence of GMDs among cancer patients and compared the glucose metabolism characteristics between different cancers. Meanwhile, we analyzed the relationship between GMDs and cancer in a Chinese population.

Materials and methods

Case ascertainment

From January 2002 to June 2008, cases and controls were recruited in the southern part of China. Two thousand four hundred and five malignancy patients who had been hospitalized in the first affiliated hospital of Jinan University were treated as case group. It was required that the case group never had a serious wound, operation, or infection in 2 weeks previous hospitalization. If they were suffering from fever or agony, the biochemical data would be examined after the stress state.

Control ascertainment

Two thousand and sixteen non-cancer people who finished the health examinations in the affiliated Yangcheng Hospital of Guangzhou Medical College were used as control group. All of them checked biochemical items, tumor markers, B Ultrasound, and X-ray in order to exclude cancer.

Data collection

We retrospectively reviewed cancer patients in our hospital between January 2002 and June 2007, and those with incomplete information were excluded. We extracted the eligible cases and marked down their gender, age, body height, body weight, smoking history, drinking history, diabetes history, family history, the time when diagnosed with cancer, treatment modalities, and the pathological types of cancer. At the same time, we also recorded their fasting plasma glucose (FPG), uric acid (UA), triglyceride (TG), and cholesterol (CHOL) levels. If there were several checks on the biochemical levels while the patient was in hospital, we chose the median. The body mass index (BMI) was also calculated. Symptoms such as sweating, nervousness, feeling faint, heart palpitations, hunger, and headache were marked down and with FPG together to identify hypoglycemia. Namely, we diagnosed the case with FPG $\leq$ 3.9 mmol/l [24] and any symptoms above as hypoglycemia.

Statistical analysis

All statistical analyses were performed using SPSS 13.0 for Windows. Data were analyzed using the chi-square and independent samples *t*-test (where appropriate). Multivariate logistic regression with stepwise method was used to assess the association between potential factors and the development of cancer. Odds ratios (OR) and 95% confidence intervals (95% CI) were applied to estimate this relationship. Statistical significance was defined as a ***P*** value less than 0.05.

Results

The baseline data which were generated with 2,405 patients and 2,016 controls are outlined in Table 1. Gender and age were similarly distributed among cases and controls

Table 1 Clinical characteristics in cases and control

Characteristic	Cases	Controls	*P*
Gender			
Male	1347	1077	0.352
Female	1058	939	
Age	55.77 ± 16.91	54.92 ± 12.80	0.059
DM			
Number	327	135	0.000
Percentage	13.6	6.7	
IFG			
Number	347	235	0.017
Percentage	14.4	11.7	
LFPG			
Number	127	11	0.000
Percentage	5.3	0.5	

FPG fasting plasma glucose; DM: FPG ≥ 7.0 mmol/l; IFG: FPG < 7.0 mmol/l, ≥6.1 mmol/l; LFPG: FPG ≤ 3.9 mmol/l

($P > 0.05$). Among 2,408 malignancy patients, the total prevalence of DM and IFG reached 28.0% of which DM and IFG accounted for 13.6% and 14.4%, respectively, with the higher incidence rate as compared with controls ($P < 0.05$) (Table 1). In addition, we found that 5.3% of cases in cancer patients had LFPG, which was also significantly higher than that in controls (0.5%, $P = 0.000$) (Table 1).

In 2,405 cases of cancer patients, the malignant tumors from the same kinds and the different kinds of organs presented with different characteristics of GMDs (Table 2): for example, some cancers such as cancers of breast and pancreas, only tended to show hyperglycemia; some cancers such as cancers of nasopharynx, esophagus, thyroid, and bladder, only tended to show hypoglycemia; and still some cancers tended to show not only hyperglycemia but also hypoglycemia, such as cancers of lung, colorectum, liver, etc. The presented data indicated that hyperglycemia was found in 57.1% of pancreatic cancers, 35.6% of liver cancers, 34.4% of leukemias, 31.9% of colorectal cancers, 30.0% of intracalvarium cancers, 27.2% of lung cancer, and 26.0% of breast cancer, with the higher incidence rate as compared with controls ($P < 0.05$) (Table 2). However, leukemia had the highest incidence rates of hypoglycemia (12.5%), which was followed by esophageal cancer (12.1%), Lymphoma (9.0%), liver cancer (7.4%), intracalvarium cancer (5.7%), colorectal cancer (5.6%), nasopharyngeal cancer (5.2%), bladder carcinoma (5.1%), lung cancer (4.7%), and thyroid cancer (4.3%) in turn, higher than that of controls (0.5%) ($P < 0.05$) (Table 2). However, in the cases studied, there were no significant differences in the incidence rates of hyperglycemia and hypoglycemia between the cancers of stomach and cardia, cervix, prostate, and skin and controls (0.5%) ($P > 0.05$) (Table 2).

Table 2 Characteristics of FPG in different kinds of cancer

Cancer kinds	Total *n* (%)	HFPG		LFPG	
		n (%)	*P*	*n* (%)	*P*
Lung	364(15.1)	99(27.2)	0.002	17(4.7)	0.000
Intestine	301(12.5)	96(31.9)	0.000	17(5.6)	0.000
Liver	242(10.1)	86(35.5)	0.000	18(7.4)	0.000
Breast	169(7.0)	44(26.0)	0.049	0(0.0)	0.694
Leukemia	160(6.7)	55(34.4)	0.000	20(12.5)	0.000
Stomach and cardia	157(6.5)	35(22.3)	0.319	2(1.3)	0.553
Nasopharynx	134(5.6)	29(21.6)	0.437	7(5.2)	0.000
Esophagus	91(3.8)	20(22.0)	0.476	11(12.1)	0.000
Intracalvarium	87(3.6)	26(30.0)	0.000	5(5.7)	0.000
Lymphoma	78(3.2)	28(35.9)	0.003	7(9.0)	0.000
Thyroid	73(3.0)	13(17.8)	0.922	3(4.3)	0.000
Cervix	70(2.9)	19(27.1)	0.137	1(1.4)	0.365
Bladder	59(2.6)	16(27.2)	0.172	3(5.1)	0.000
Prostate	42(1.7)	12(28.6)	0.179	1(2.4)	0.611
Skin	41(1.7)	10(24.3)	0.424	0(0.0)	1.000
Pancreas	35(1.5)	20(57.1)	0.000	1(2.9)	0.521
Controls	2016(100)	370(18.4)		11(0.5)	

HFPG: FPG ≥ 6.1 mmol/l; LFPG: FPG ≤ 3.9 mmol/l

Table 3 Characteristics of FPG in different ages (years) of cancer patients

Total *n* (%)	Age				
	≤25	26–40	41–55	56–70	≥71
Cases	129(5.3)	318(13.2)	653(27.1)	815(33.9)	490(20.4)
Controls	32(1.6)	54(2.7)	1399(72.1)	320(15.9)	220(10.91)
DM *n* (%)					
Cases	13(10.1)	24(7.5)	61(9.3)	137(16.8)	92(18.8)
Controls	0(0.0)	0(0.0)	89(6.3)	28(8.7)	18(8.1)
P	0.185	0.089	0.008	0.001	0.001
IFG *n* (%)					
Cases	15(11.6)	32(10.1)	97(14.9)	124(15.2)	79(16.1)
Controls	1(3.1)	1(1.9)	157(11.2)	46(3.3)	25(11.4)
P	0.278	0.095	0.012	0.543	0.109
LFPG *n* (%)					
Cases	21(16.3)	26(8.2)	31(4.7)	29(3.6)	20(4.1)
Controls	0(0.0)	0(0.0)	8(0.6)	2(0.6)	1(0.5)
P	0.045	0.06	0.000	0.005	0.008

FPG: fasting plasma glucose; DM: FPG ≥ 7.0 mmol/l; IFG: FPG < 7.0 mmol/l, ≥6.1 mmol/l; LFPG: FPG ≤ 3.9 mmol/l

All of the cases were then divided into groups according to age. As shown in Table 3, the constituent ratio of cancer increased with age before 55 and peaked between 56 and 70 years old, but decreased slightly after 71. Characteristics of FPG were almost similarly distributed among cases and controls before 40. However, after 41, cancer patients tended

to be more frequent to develop DM or hypoglycemia. Patients older than 71 were most likely to undergo DM (18.8%), and patients younger than 25 were least likely to undergo hypoglycemia (16.3%).

Finally, logistic regression analysis was used to identify factors predictive for or protective against developing cancer in these patients (Table 4). A significant positive statistical interaction was found between FPG and lung cancer, breast cancer, leukemia, lymphoma, thyroid carcinoma, bladder carcinoma, and pancreatic cancer. Among these, pancreatic cancer was detected with overwhelming greater OR value, which reached 3.28 (95% CI: 1.82, 5.91). DM was related to the significantly increased morbidity rates, ranging, however, from 3- to 20-fold for different types of cancers as follows: colorectal cancer, hepatoma, esophageal cancer, thyroid carcinoma, cervix cancer, and pancreatic cancer. Among these, risks for developing pancreatic cancer or cervix cancer were 20.91 times (95% CI: 1.77, 246.45) and 15.75 times (95% CI: 2.07, 120.04) enhanced by DM, respectively. Increasing age increased the incidence of lung cancer, colorectal cancer, stomach cardic cancer, esophageal cancer, bladder carcinoma, prostatic carcinoma, and skin cancer. On the contrary, females were less likely to undergo cancer of liver, stomach and cardic, esophagus, bladder, and pancreas compared with males. As far as smoking is concerned, it was associated with a twofold elevation of morbidity in lung cancer (OR = 2.35, 95% CI: 1.28, 4.32) and nasopharyngeal carcinoma (OR = 2.00, 95% CI: 1.02, 3.91). In addition, a notably increased risk of liver cancer and esophageal cancer in drinking people was observed, with OR values as 2.11 (95% CI: 0.91, 4.89) and 4.07 (95% CI: 1.49, 11.13), respectively. Unexpectedly, BMI, TG, and CHOL tended to be associated with decreased risks in many kinds of cancer.

Discussion

This is the first study to investigate the characteristics of glucose metabolism in different kinds of cancer in China, and the characteristics of glucose metabolism in different ages of cancer patients are also analyzed, which has seldom been done before. Moreover, we observed the associations between many potential risk factors and different cancers at the same time.

In our study, we found that among 2,045 malignancy patients, the total prevalence of DM and impaired IFG reached 28.0%, and 5.3% patients had hypoglycemia. Pancreatic cancer, lymphoma, and liver cancer seemed to be more vulnerable to hyperglycemia, with the ratio of 57.1, 35.9, and 35.6, respectively. In addition, leukemia, colorectal cancer, breast cancer, intracranial cancer, land ung cancer also faced the elevated risks for hyperglycemia. Presently, plenty of studies investigating the relationships between malignancy and DM have been reported, but most of them were focused on pancreatic cancer [33, 41, 42], breast cancer [10, 39, 43–45], prostatic carcinoma [38, 46–50], or colorectal cancer [36, 37, 51, 52], whereas the evidence of changed glucose metabolism in lung cancer, intracranial cancer, lymphoma, or leukemia was sparse. In our study, risks to develop hyperglycemia in these four kinds of cancers were increased unexpectedly. Characteristics of FPG were almost distributed similarly among cases and controls in patients before 40 years old. We deduced that body status might be strong enough to compensate before 40 years old, so patients could still maintain a balance of glucose metabolism. In addition, patients older than 71 were most likely to encounter DM. It was also found that hyperglycemia tend to accompany with cancer in aging patients.

Leukemia (12.5%), esophageal cancer (12.1%), lymphoma (9.0%), liver cancer (7.4%), and colorectal cancer (5.6%) were ranked the first five risks to be exposed to hypoglycemia. However, some hypoglycemia cases in leukemia might be considered to be pseudohypoglycemia [53]. Cancer patients younger than 25 were extremely likely to be suffered from hypoglycemia.

It was estimated that roughly 40% of cancer patients actually died of malnutrition rather than their disease itself. Glucose as an important energy provider for the body influences the metabolism of protein, fat, or other nutrient substances. Cancer patients showed a significantly delayed clearance of glucose [54]. They were resistant to the effect of insulin on glucose metabolism when further along in the disease process, as evident by more significant weight loss and malnutrition [55, 56]. As proved by probands, insulin resistance can cause hyperglycemia [57]. Meanwhile, cancer patients also display increased glucose production [58] and recycling, and a lack of response to infused glucagon, probably reflecting decreased glycogen stores in the face of an increased glucose requirement [54]. In this condition, patients may develop hypoglycemia [59]. In other words, cancer patients demand more glucose but do not make good use of it, reflecting hypoglycemia [60, 61] or hyperglycemia [23, 25, 33, 34], and inducing malnutrition which can lead to death. Moreover, after chemotherapy, glycemia levels may increase [23, 25] with a corresponding reduction in insulin [26]. Furthermore, ectopic hormone [27, 28], such as adrenal corticosteroid also can elevate plasma glucose. Thus, as have been seen in our study, cancer patients present GMDs frequently.

Logistic regression analysis showed that aging, smoking, and FPG were associated with lung cancer; corresponding parts for colorectal cancer were age and DM. Drinking and DM might play a role in liver cancer

Table 4 Multiple logistic regression analysis examining association between cancers and potential influencing factors

Cancer sites	OR value (95% CI)									
	Gender	Age	Smoke	Drink	BMI	DM history	FPG	CHOL	CHOL	UA
Lung		1.06(1.04–1.09)	2.35(1.28–4.32)				1.32(1.05–1.67)	0.73(0.57–0.92)	0.70(0.51–0.97)	1.00(0.99–1.00)
Colorectal		1.05(1.03–1.07)				3.98(1.10–14.43)		0.69(0.55–0.87)	0.44(0.27–0.70)	1.00(0.99–1.00)
Liver	0.24(0.12–0.48)			2.11(0.91–4.89)	0.81(0.73–0.90)	10.05(2.35–51.11)			0.43(0.27–0.69)	
Breast[a]							1.37(0.98–1.94)			
Leukemia		0.93(0.89–0.96)			0.87(0.75–1.01)		1.41(0.99–2.02)	0.26(0.16–0.41)		
Stomach and cardic	0.51(0.25–1.02)	1.03(1.01–1.06)			0.71(0.62–0.82)			0.63(0.45–0.89)	0.67(0.45–1.00)	
Nasopharynx		0.96(0.93–1.00)	2.00(1.02–3.91)		0.85(0.76–0.95)					
Esophagus	0.30(0.11–0.80)	1.09(1.05–1.14)		4.07(1.49–11.13)	0.68(0.59–0.79)	8.62(1.39–53.55)				
Intracalvarium		0.97(0.94–1.00)			0.81(0.72–0.92)					
Lymphoma					0.79(0.69–0.89)		1.23(0.99–1.53)	0.59(0.41–0.84)		
Thyroid		0.92(0.88–0.96)			0.84(0.73–0.98)	14.32(1.56–131.49)	1.49(1.09–2.02)			
Cervix[a]		0.94(0.89–0.99)			0.85(0.73–0.99)	15.75(2.07–120.04)				
Bladder	0.25(1.10–0.61)	1.09(1.05–1.13)			0.88(0.75–1.02)		1.42(0.95–2.10)	1.55(1.00–2.40)	0.40(0.18–0.87)	
Prostate[b]		1.25(1.14–1.37)							0.37(0.14–1.00)	
Skin		1.12(1.06–1.18)						1.57(0.94–2.60)		
Pancreas	0.17(0.03–0.94)				0.56(0.41–0.77)	20.91(1.77–246.45)	3.28(1.82–5.91)			0.98(0.97–0.99)

[a] Compared with females in control group

[b] Compared with males in control group

etiology. High level of FPG may lead to the development of breast cancer and leukemia. Increasing age, drinking, and DM were associated with an increased risk of esophageal cancer. More similar information could be found in Table 4. In other words, high level of FPG and a disease history of DM are associated with many different cancers which is consistent with numerous previous studies [6–12]. In contrast, we have not observed any associations between DM and prostate cancer, which is consistent with most previous epidemiologic studies which showed no [62–65] or a negative relationship [38, 49, 50].

Several pathways have been proposed by which DM might lead to the development of cancer. In order to begin with, the most obvious change in diabetic patients is reduced insulin sensitivity with compensatory hyperinsulinemia and elevated levels of IGF-1, which may in turn stimulate cell proliferation, and play an important role in cancer development and metastasis [14, 66–68]. A number of subsequent studies, supported the hypothesis of reciprocal associations for IGF-I and IGF-I receptor (IGF-IR), with other cancer sites including breast, colorectal, endometrium, and lung. Several cellular actions of IGF-I favor tumor growth, as it is mitogenic, anti-apoptotic, pro-angiogenic [67], and increases cell migration in vitro [17]. IGF-IR is frequently expressed in human cancers and play a role in preventing apoptosis, enhancing cell proliferation, and inducing expression of vascular endothelial growth factor (VEGF) [67, 69]. Besides, hyperglycemia causes dysfunction of the vital cellular signal system regulated by the protein kinase C (PKC) family, which induces the processes of tumor growth and metastasizing in carcinogenesis. Further, medicines for controlling plasma glucose, such as sulfonylureas [70], insulin [22, 70], and thiazolidinediones [21], are related to cancer development and death.

Despite the biological plausibility of the association, some issues should be considered when discussing the role of cancer as a cause of GMDs or DM. First, certain common health conditions, are likely to cause cancer and DM [7]. Second, it is not easy to differentiate whether cancer causes DM or whether risk factors for cancer, such as obesity and physical inactivity, are associated with DM. Third, it is likely that a diagnosis of cancer and subsequent therapy increase vigilance and, thus, the possibility of a diagnosis of GDMs. These issues should likely be considered as alternative factors affecting the association between cancer and GMDs, directly or otherwise.

Unexpectedly, BMI, TG, and CHOL seem to be associated with decreased risks in many kinds of cancer, which is inconsistent with former studies [71–75]. However, numbers of cases in our study were chosen when cancers were in the advanced stage. Many cases were undergoing hypermetabolism and negative nitrogen balance or even cachexia. This may affect our results to some degrees. If we want to understand the causal association among BMI, TG, CHOL, and cancer, more prospective multiple center cohort studies are demanded.

One limitation of our study is that it is only a hospital case–control study, which is not based on geographically defined population. Moreover, only the characteristics of FPG metabolism are observed, but nothing is known about postprandial plasma glucose. Furthermore, we do not prospectively observe the association between GMDs, therapeutic measures of GMDs (by pills or insulin), and cancer prognosis. Nonetheless, to our knowledge, this is the first study to analyze characteristics of glucose metabolism in different kinds and ages of cancer patients in China.

In conclusion, the results of our study suggest that the morbidity of GMDs is elevated among malignancy patients. Pancreatic cancer mainly presents with hyperglycemia, whereas, lung cancer, colorectal cancer, liver cancer, and leukemia present with either hyperglycemia or hypoglycemia. Older people seem to be more vulnerable to hyperglycemia, while the younger tend to be more likely to develop hypoglycemia. Hyperglycemia plays a contributory role for lung cancer, breast cancer, leukemia, lymphoma, thyroid cancer, bladder cancer, and pancreatic cancer. A disease history of DM raises risks of developing colorectal cancer, liver cancer, esophageal cancer, thyroid cancer, cervical cancer, and pancreatic cancer. Since this is a case–control study, the results may require larger epidemiology analysis for authentication.

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