RESEARCH ARTICLE

High prevalence of diabetes mellitus and impaired glucose tolerance in liver cancer patients: A hospital based study of 4610 patients with benign tumors or specific cancers [version 1; referees: 2 approved]

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Abstract

Objective: The prevalence of diabetes mellitus (DM), impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) were hypothesised to be different among different tumor patients. This study aimed to study the association between the prevalence of DM, IGT and IFG and liver cancer, colorectal cancer, breast cancer, cervical cancer, nasopharyngeal cancer and benign tumor.

Methods: A hospital based retrospective study was conducted on 4610 patients admitted to the Internal Medical Department of the Affiliated Tumor Hospital of Guangxi Medical University, China. Logistic regression was used to examine the association between gender, age group, ethnicity , cancer types or benign tumors and prevalence of DM, IFG, IGT.

Results: Among 4610 patients, there were 1000 liver cancer patients, 373 breast cancer patients, 415 nasopharyngeal cancer patients, 230 cervical cancer patients, 405 colorectal cancer patients, and 2187 benign tumor patients. The prevalence of DM and IGT in liver cancer patients was 14.7% and 22.1%, respectively. The prevalence of DM and IGT was 13.8% and 20%, respectively, in colorectal cancer patients, significantly higher than that of benign cancers. After adjusting for gender, age group, and ethnicity, the prevalence of DM and IGT in liver cancers patients was 1.29 times (CI :1.12-1.66) and 1.49 times (CI :1.20-1.86) higher than that of benign tumors, respectively.

Conclusion: There was a high prevalence of DM and IGT in liver cancer patients.

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Referee Status: ✓ ✓

	Invited Referees 1	2
version 1 published 16 Jun 2016	✓ report	✓ report

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Background

High fat and carbohydrate diets, associated with dietary carcinogenesis, contribute to abnormal glucose tolerance and cancer[1,2]. Previous studies suggest that metabolic syndrome is associated with a modestly increased risk of second breast cancer events and breast cancer-specific mortality[3]. Blood glucose level in colorectal cancer patients has been shown to correlate significantly with local tumor malignancy[4]. Antidiabetic medication such as metformin treatment could significantly lower the risk of colorectal cancer in type 2 diabetes mellitus (T2DM) patients[5]. However, little is known on the correlation between prevalence of impaired glucose tolerance (IGT), diabetes mellitus (DM) and other types of cancers in comparison with benign tumors.

As an ethnic area, Guangxi Zhuang automonous region (abbreviated as Guangxi) located in southwest China, is well known for its high incidence of liver cancer and nasopharyngeal cancer[6,7]. Established risk factors including heavy alcohol consumption, chronic infection with the hepatitis B virus (HBV) or the hepatitis C virus (HCV), tobacco smoking, intake of aflatoxin-contaminated foods for the development of hepatocellular carcinoma (HCC) have been studied in Guangxi over the past several decades[8]. According to an American study, abnormal glucose tolerance was an independent predictor for cancer mortality[9]. Therefore, it is essential to investigate the prevalence of DM, IGT, and IFG (impaired fasting glucose) among patients with common types of cancer in such a high incidence area.

This study aimed to investigate the association between the prevalence of DM, IGT and IFG and liver cancer, colorectal cancer, breast cancer, cervical cancer, nasopharyngeal cancer and benign tumors.

Method

Data collection

This hospital based study was approved by the Medical Ethics Committee of the Affiliated Tumor Hospital of Guangxi Medical University, China. The data were retrieved from the Internal Medical Department of the hospital. All personal identification was encrypted.

Patients hospitalized in the Internal Medical Department between 2010 and 2012 with complete records of fasting plasma glucose (FPG) and 2-h postprandial glucose (2hPPG) upon hospitalization were included in this study. Clinical data were collected, including gender, age, ethnicity, DM history, diagnosis, pathological diagnosis, FPG, and 2hPPG. All diagnoses of cancers and benign tumors were based on CT scan results, endoscopic biopsy or surgical resection. Those who had serious cardiocelebral diseases, liver or kidney dysfunction and other conditions that may influence diabetic or prediabetic state were excluded from this study.

Measurement of glucose level

The glucose levels were included in the retrospective data. The 1999 World Health Organization (WHO) diagnostic criteria were used to diagnose DM, IFG and IGT[10]. Results of plasma glucose testing were categorized as follows. Normal glucose tolerance (NGT): FPG <6.1 mmol/L, and 2hPPG <7.8 mmol/L; Diabetes mellitus (DM): FPG ≥7 .0 mmol/L, 2hPPG ≥11.1 mmol/L, and with DM medical history. Impaired Fasting blood glucose (IFG): FPG ≥6.1 mmol/L and <7.0 mmol/L with the exclusion of cases with DM history or 2hPPG ≥11.1 mmol/L. Impaired glucose tolerance (IGT): FPG<7.0 mmol/L, and 2hPPG ≥7.8 mmol/L and <11.1 mmol/L with the exclusion of cases with DM history.

Statistical analysis

Descriptive data were presented as frequencies and percentages, followed by a chi-square test or Fisher's test as appropriate. Logistic regression was used to examine the association between gender, age group, ethnicity and cancer types or benign tumors and prevalence of DM, IFG, IGT. Data analyses were performed using the R language and environment (version 3.1.0)[11] and the Epicalc package (version 3.1.1.2)[12].

Results

Dataset 1. Patient data

http://dx.doi.org/10.5256/f1000research.8457.d122894

Dataset 2. Data analysis using R

http://dx.doi.org/10.5256/f1000research.8457.d122895

1. Demographic description and prevalence of DM, IGT, and IFG among different cancers and benign tumors:

A total of 4610 patients were included in this study. Figure 1 and Table 1 summarize the demographic characteristics of the patients, among whom 1000 were liver cancer patients, 373 breast cancer patients, 415 nasopharyngeal cancer patients, 230 cervical cancer patients, 405 colorectal cancer patients, and 2187 benign tumor patients. The patients in the 40–60 year age group comprised more than 50% of the total patients studied. Liver cancer, nasopharyngeal cancer, and colorectal cancer patients were predominantly male. Age and ethnic distribution among the studied groups were statistically different (P<0.001).

The prevalence of DM and IGT in liver cancer patients was 14.7% and 22.1%, respectively; 13.8% and 20% in colorectal cancer patients, which were significantly higher than that of benign cancers.

2. Association between prevalence of DM and cancer types and benign tumors

As shown in Table 2, adjusted for gender, ethnicity, and age group, the prevalence of DM in liver cancers patients was 1.29 times higher than that of benign tumors; male patients were 1.49 times of higher than that of female patients. Using the 0–30 year as reference, the prevalence of DM increased with age. The peak risk ratio was 10.3 times higher in the 61–70 year age group than that of 0–30 year age group. The Han ethnic group was 1.38 times more likely to have DM in comparison with the Zhuang ethnic group.

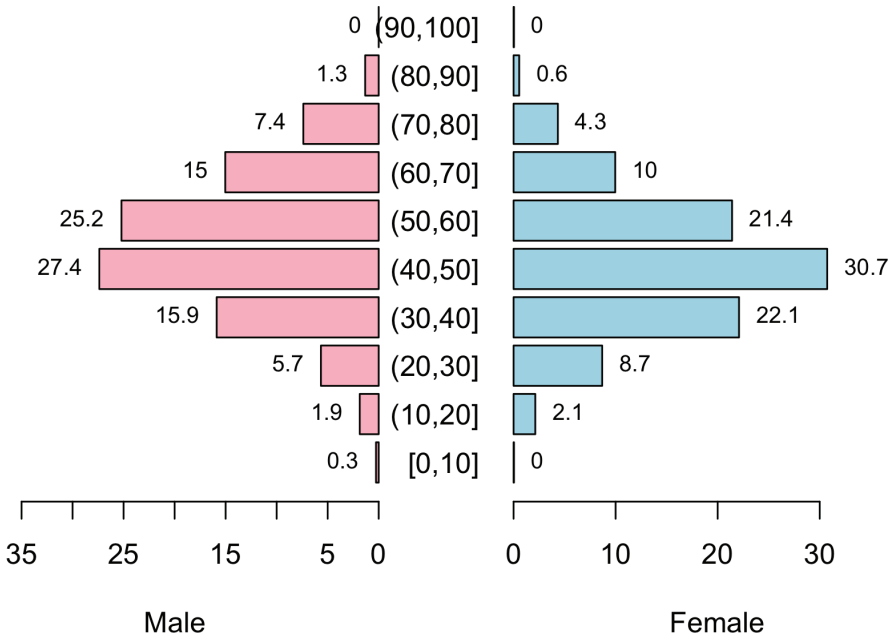

Figure 1. Population pyramid distribution by gender and age group.

Table 1. Demographic information and prevalence of DM, IFG, and IGT among patients with specific cancers or benign tumors.

	Liver cancer (N=1000)	Breast cancer (N=373)	Nasopharyngeal cancer (N=415)	Cervical cancer (N=230)	Colorectal cancer (N=405)	Benign tumors (N=2187)
Gender***						
Male	878 (87.8)	0(0.0)	294 (70.8)	0(0.0)	255 (63.0)	834 (38.1)
Female	122 (12.2)	373(100.0)	121 (29.2)	230(100.0)	150 (37.0)	1353 (61.9)
Age (median,IQR)***	49 (42,58)	48 (40,56)	46 (39,54)	48 (42,55)	59 (48,68)	46 (36,57)
Ethnic groups***						
Han	607 (60.7)	256 (68.6)	289 (69.6)	153 (66.5)	305 (75.3)	1438 (66.8)
other ethnicity	20 (2.0)	12 (3.2)	6 (1.4)	9 (3.9)	10 (2.5)	66 (3.1)
Zhuang	373 (37.3)	105 (28.2)	120 (28.9)	68 (29.6)	90 (22.2)	650 (30.2)
DM***	147 (14.7)	39 (10.5)	21 (5.1)	18 (7.8)	56 (13.8)	197 (9.1)
IFG**	28 (2.8)	27 (7.2)	25 (6.0)	6 (2.6)	22 (5.4)	98 (4.5)
IGT***	221 (22.1)	48 (12.9)	53 (12.8)	28 (12.2)	81 (20.0)	262 (12.0)

Data were given as n (%). * p-value<0.05; ** p-value<0.01; *** p-value < 0.001.

3. Association between prevalence of IGT and cancer types and benign tumors

As shown in Table 3, adjusted for gender, ethnicity, and age group, the prevalence of IGT in liver cancer patients was 1.49 times higher than that of benign tumors; male patients were 1.71 times higher than that of female patients. Using the 0–30 year as reference, there were an obvious age-dependent relationship between age groups and prevalence of IGT. There were no significant difference among the ethnic groups in terms of IGT prevalence (P=0.421).

4. Association between prevalence of IFG and cancer types and benign tumors

As shown in Table 4, adjusted for gender, ethnicity, and age group, the prevalence of IFG in liver cancers patients was 0.55 times lower

Table 2. Association between prevalence of DM and specific cancers or benign tumors.

	crude OR(95%CI)	adj. OR(95%CI)	P(LR-test)
Diagnosis: ref.=benign tumor			< 0.001
Breast cancer	1.17 (0.81,1.68)	1.28 (0.87,1.89)	
Cervical tumor	0.85 (0.51,1.4)	0.88 (0.52,1.48)	
Colorector cancer	1.6 (1.17,2.2)	0.95 (0.69,1.33)	
Liver cancer	1.72 (1.37,2.16)	1.29 (1.12,1.66)	
Nasopharyngeal cancer	0.53 (0.34,0.85)	0.46 (0.29,0.74)	
Gender: male vs female	1.74 (1.44,2.12)	1.49 (1.17,1.89)	0.001
Ethnicity: ref.=Zhuang			0.018
Han	1.47 (1.18,1.83)	1.38 (1.1,1.74)	
Other ethnicity	1.34 (0.73,2.45)	1.36 (0.73,2.53)	
Age group: ref.=(0,30)			< 0.001
(31,40)	1.88 (0.9,3.97)	1.87 (0.89,3.95)	
(41,50)	3.9 (1.96,7.79)	3.75 (1.87,7.52)	
(51,60)	8.94 (4.53,17.66)	8.14 (4.1,16.17)	
(61,70)	11.36 (5.69,22.69)	10.3 (5.13,20.68)	
>70	8.46 (4.09,17.54)	7.28 (3.49,15.18)	

Table 3. Association between prevalence of IGT and specific cancers or benign tumors.

	crude OR(95%CI)	adj. OR(95%CI)	P(LR-test)
Diagnosis: ref.=benign tumors			0.002
Breast cancer	1.07 (0.77,1.48)	1.28 (0.9,1.82)	
Cervical tumor	1 (0.66,1.52)	1.17 (0.76,1.8)	
Colorector cancer	1.81 (1.37,2.38)	1.25 (0.94,1.67)	
Liver cancer	2.05 (1.68,2.5)	1.49 (1.2,1.86)	
Nasopharyngeal cancer	1.06 (0.77,1.45)	0.88 (0.64,1.22)	
Gender: male vs female	2.01 (1.7,2.38)	1.71 (1.39,2.1)	< 0.001
Ethnicity: ref.=Zhuang			0.421
Han	1.07 (0.9,1.28)	1.04 (0.86,1.24)	
Other ethnicity	0.69 (0.38,1.25)	0.71 (0.39,1.3)	
Age group: ref.=(0,30)			< 0.001
(31,40)	1.66 (1.06,2.6)	1.55 (0.98,2.43)	
(41,50)	2.63 (1.73,3.99)	2.34 (1.53,3.58)	
(51,60)	3.18 (2.09,4.84)	2.67 (1.74,4.09)	
(61,70)	3.83 (2.47,5.94)	3.19 (2.04,4.98)	
>70	4.62 (2.89,7.38)	3.79 (2.35,6.12)	

Table 4. Association between prevalence of IFG and specific cancers or benign tumors.

	crude OR(95%CI)	adj. OR(95%CI)	P(LR-test)
Diagnosis: ref.=benign tumor			0.003
Breast cancer	1.64 (1.05,2.54)	1.57 (0.99,2.51)	
Cervical tumor	0.56 (0.24,1.3)	0.53 (0.23,1.24)	
Colorector cancer	1.21 (0.75,1.94)	0.92 (0.57,1.51)	
Liver cancer	0.6 (0.39,0.93)	0.55 (0.35,0.87)	
Nasopharyngeal cancer	1.34 (0.86,2.11)	1.26 (0.79,2.02)	
Gender: Male vs Female	0.96 (0.73,1.27)	1.08 (0.77,1.52)	0.641
Ethnicity: ref.=Zhuang			0.023
Han	1.73 (1.23,2.44)	1.59 (1.13,2.26)	
Other ethnicity	1.34 (0.52,3.46)	1.25 (0.48,3.24)	
Age group: ref.=(0,30)			< 0.001
(31,40)	1.99 (0.86,4.59)	2.06 (0.89,4.78)	
(41,50)	3.19 (1.45,7)	3.35 (1.52,7.41)	
(51,60)	2.97 (1.34,6.61)	3.13 (1.4,7.03)	
(61,70)	3.34 (1.45,7.67)	3.46 (1.49,8.01)	
>70	5.01 (2.13,11.78)	4.89 (2.06,11.65)	

than that of benign tumors. Using the 0–30 year as reference, the prevalence of IFG increased with age. The Han ethnic group was 1.59 times higher in prevalence of IFG in comparison with the Zhuang ethnic group.

Discussion

This study showed that the prevalence of DM and IGT in liver cancer patients was 14.7% and 22.1%, respectively. After adjustment for gender, age group, and ethnicity, the prevalence of DM and IGT in liver cancer patients was 1.29 times (CI :1.12–1.66) and 1.49 times (CI :1.20–1.86) higher, respectively, than that of benign tumors. In comparison, the prevalence of DM and IGT in patients with breast cancer, cervical cancer, colorectal cancer, and nasopharyngeal cancer was not significantly different from that of benign tumors after adjusted for gender, age group, and ethnicity.

A previous study suggested high blood glucose levels in colorectal cancer patients with larger tumor diameters and lower tumor differentiation[4]. Our study also found that the prevalence of DM and IGT was high in colorectal cancer patients in the preliminary analysis, although no statistical difference was found after adjustments for other factors. So far, there have been very few studies on the relationship between prevalence of DM and IGT and liver cancer. However, the relationship between obesity, overweight and higher rates of death due to cancer of esophagus, colon, rectum, liver, gallbladder, pancreas and kidney, non-Hodgkin's lymphoma, and multiple myeloma has been well established by a large sample prospective study[13]. The reason why a high prevalence of DM and IGT is correlated with liver cancer may be explained as follows: As a regulator of energy storage and metabolism, insulin was produced and secreted by pancreatic β cells, which stimulated glucose uptake by adipose tissue and muscle, suppressing the release of glucose from the liver. Desensitization of tissues to insulin and insulin resistance led to a compensating increase in pancreatic insulin production called hyperinsulinemia, which may have possible direct oncogenic effects on proliferative and anti-apoptosis signaling in cancer cells.

High prevalence of DM and IGT correlated with liver cancer had important implications both in prevention and treatment of liver cancer. Metformin, a commonly used drug for type 2 diabetes, led to a lower incidence and mortality of breast cancer[14–18]. In a similar way, the control of high blood glucose levels would possibly improve clinical outcomes of liver cancer patients.

Strengths and limitations

As a hospital based study recently conducted in Guangxi with a high incidence of liver cancers, this study provided evidence for government and public health planners which may be useful in the prevention of liver cancer. Further prospective cohort studies

should be conducted to learn the strength of association between DM, IGT and liver cancer; moreover, to learn how much the control of diabetic or pre-diabetic conditions contributes to the prevention and treatment of liver cancer.

Conclusion

This study showed a high prevalence of DM and IGT in liver cancer patients. The control of diabetic or pre-diabetic conditions may contribute to the prevention and treatment of liver cancer.

Data and software availability

F1000Research: Dataset 1. Patient data, 10.5256/f1000research.8457.d122894[19]

F1000Research: Dataset 2. Data analysis using R, 10.5256/f1000research.8457.d122895[20]

Author contributions

RC was principal investigator of the study, conceptualized the research, collected the data, performed data analysis, and drafted the manuscript. YY and BL conceived the study, assisted in development of data analysis, manuscript writing, and provided supervision and suggestions.

Competing interests

No competing interests were disclosed.

Grant information

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Data Source

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Version 1

Referee Report 23 August 2016

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✔ **Nirun Intarut**
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This is a retrospective study that was carried out in a hospital in China, involving 4610 participants. In summary, this study investigated the association between the DM, IGT and IFG and liver cancer, colorectal cancer, breast cancer, cervical cancer, nasopharyngeal cancer and benign tumors. The study shows the high prevalence of DM and IGT in liver cancer.

My suggestion if possible, is to include tobacco consumption or exposure to secondhand smoke into this study. Because there is a high prevalence of smoking and also high exposure to secondhand smoke in China [1-3], there could be evidence to show its association between DM and liver cancer [4-7].

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 24 June 2016

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The article entitled “High prevalence of diabetes mellitus and impaired glucose tolerance in liver cancer patients: A hospital based study of 4610 patients with benign tumors or specific cancers” is very meaningful on providing evidence for government to prevent liver cancer in China. They found that the prevalence of DM and IGT in liver cancers patients was significantly higher than in benign tumors. Overall, I appreciate the study. The following is some comments and suggestions on the study topic.

Some studies[1-3] showed that DM is an independent risk factor of hepatocellular carcinoma, but some other studies[4,5] provided an inconsistent conclusion: only among people who were infected with both HBV and HCV or alcoholic hepatitis can this increase the risk of hepatocellular carcinoma. Furthermore, a systematic review[6] pointed out that among 23 case control or follow up studies, only less than 40% of studies indicated that DM is an independent risk factor of hepatocellular carcinoma, and also few studies can exclude the influence of food habits and obesity etc. The reason for this inconsistency is not clear, and needs further study. DM possibly is not an independent risk factor on hepatocellular carcinoma, but among people who were hepatitis virus infected or alcoholic with DM will increase the probability getting hepatocellular carcinoma.

According to the above, I suggest that, if available, please add the information about some habits such as alcoholic beverage drinking history, some indices including BMI for example to exclude the influence of such factors which are both related to DM and hepatocellular carcinoma, and the status of virus hepatitis in the analysis. Moreover, a retrospective study cannot provide the causal relationship between DM and hepatocellular carcinoma, if we want to know the relationship clearly, a population based case control and prospective cohort study are needed.

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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