HIGHLIGHT ARTICLE

Diabetes and Pancreatic Cancer

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ABSTRACT

Research suggests a possible link between type 2 diabetes and several malignancies. Animal models have shown that hyperinsulinemic state underlying diabetes promotes tumor formation through stimulation of insulin-IGF-1 pathway; a possible role of inflammation is also proposed. One such link which has been under considerable study for years is that between diabetes and pancreatic cancer. Although epidemiological evidence points towards a reciprocal link between the two, the cause-effect relationship still remains unclear. This link was the subject of a large German epidemiological study presented at the American Society of Clinical Oncology Annual Meeting 2014 (Abstract 1604), which underscored the link between diabetes and some cancers. Schmidt et al. performed a retrospective database analysis over a 12 year period and reported an increased risk of certain types of cancer in diabetic patients. The most significant association (HR 2.17) was found for pancreatic cancer. Given the high mortality of pancreatic cancer, prevention through timely screening could play an important role in improving prognosis. Older subjects with recent-onset diabetes represent a high-risk group and hence are potential targets for pancreatic cancer screening thereby enabling its early diagnosis at a curable stage.

Introduction

Pancreatic cancer is an ominous disease, and although it is the 10th most prevalent cancer, it is the 4th leading cause of cancer mortality, with a 5-year overall survival of only 6%. Up to 45% of the pancreatic cancer cases can present as new-onset diabetes. There is a mounting body of evidence showing that diabetes mellitus is a risk factor for pancreatic cancer [1, 2]. Most of the studies have been finding a relative risk close to 2 of pancreatic cancer in diabetic patients [3, 4]. However, some early studies found that new-onset diabetes has the strongest association with pancreatic cancer and is largely the responsible for the link between diabetes and pancreatic adenocarcinoma. As diabetes could be a manifestation of pancreatic cancer, it has been controversial if diabetes is a real risk factor for pancreatic cancer. Recent cohorts have been favoring diabetes mellitus and even metabolic syndrome as a real risk factor for pancreatic cancer [5-7].

What We Knew Before ASCO 2014?

The lifetime risk for developing pancreatic cancer is 1 in 78 and increases linearly with age. Worldwide, more than 200,000 people succumb to this deadly form of cancer each year while in the US it is the 4th leading cause of cancer-related death [1, 2]. The tumor follows a silently relentless course in a majority of cases manifesting only once it has reached an advanced stage, either producing local invasion or distant metastases, when it is beyond cure. Unlike breast and colonic cancers, no screening tests are as yet available that could allow for early detection thereby enabling early intervention. The last 30 years may have seen extensive advancement in the understanding of etiology, genetics, diagnostic tools and treatment but have not favorably impacted the prognosis, which remains unchanged with less than 5% patients surviving 5years [2]. Surgical resection remains the only hope for cure for tumors caught early but such tumors account for less than 15% of all cases. Factors that are known to predispose to pancreatic cancer include smoking, strong family history, certain genetic syndromes and chronic pancreatitis [5].

The reciprocal relationship between diabetes and pancreatic cancer has been studied extensively. Diabetes may be considered both a cause and effect of pancreatic cancer [8, 9] but the temporal association remains yet to be determined as is the pathophysiological mechanism behind it. Most of the epidemiological data supporting the link between diabetes and pancreatic cancer comes from cohort and case-control studies and meta-analyses. Long-standing adult-onset diabetes is a risk factor for pancreatic cancer with a relative risk estimate of about 2 compared with non-diabetic population in most observational studies and meta-analyses (Table 1) [3, 10-12].

The underlying mechanisms proposed in epidemiological

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Table 1: Association of diabetes and pancreatic cancer risk.

Study	Population Studied	Relative Risk of Pancreatic Cancer	95% Confidence Interval
Gullo et al (1994)	Case control	3.04	2.21-4.17
Everhart et al (1995)	Meta-analysis (20studies)	2.10	1.1-2.7
Huxley et al (2005)	Meta-analysis (36studies)	1.82	1.66-1.89
Ben et al (2011)	Meta-analysis (35 cohort studies)	1.94	1.66-2.27

Table 2: Solid cancers for which there is an increased risk in diabetic patients.

Type of Cancer	Hazard Ratio	Confidence Interval
Pancreatic	2.17	1.86-2.52
Esophageal	1.32	1.03-1.69
Kidney	1.30	1.11-1.52
Lung	1.15	1.05-1.28
Colorectal	1.13	1.04-1.22
Endometrial	1.43	1.08-1.90

and animal studies include weight gain, hyperinsulinemia as well as accelerated IGF-1 and 2 signaling, known to promote tumor formation [13]. There is also the emerging role of certain anti-diabetic medication in either increasing the risk of cancer as in the case of insulin or ameliorating it as in metformin [14].Conversely, 50-80% of patients with pancreatic cancer have concomitant diabetes, which often predates the diagnosis of cancer by one to two years [15]. Evidence shows that patients with new-onset diabetes are at a higher risk of subsequently developing pancreatic cancer. This new-onset diabetes improves or even resolves after tumor resection [16]. This suggests that diabetes in such cases may even be the result of tumors that have not come to light as yet. Tumor-mediated destruction of beta cells and insulin resistance resulting from tumor-secreted humoral factors are the implicated mechanisms [17].

What We Learnt at ASCO 2014?

Schmidt et al. (Association of diabetes and cancer-diagnoses in primary care practices in Germany Abstract No 1604) presented a retrospective cohort study based upon data from a health service database of primary care practices in Germany [18]. The objective was to compare the incidence of different types of cancers in diabetic versus non-diabetic population. The patients were followed up for a maximum of 12 years. The cohort identified for the study was stratified on the basis of their diabetes status and included 78,599 patients with diabetes and 392,995 patients without diabetes. The analysis showed that the overall incidence of cancer was higher in the diabetic population. The risk for certain cancers (lung, esophageal, pancreatic, kidney, colorectal and endometrial cancer) was found to be higher than the non-diabetic cohort while other cancers including breast, prostate, liver, stomach, thyroid, urinary bladder, gall bladder and non-Hodgkin's lymphoma did not show a significant increase in risk in the diabetic cohort. Table 2 shows the hazard ratio for the incidence of different cancers using stratified Cox regression analysis. The greatest risk in the diabetic population was seen for the development of pancreatic cancer (HR 2.17).

Discussion

Epidemiological evidence of a significantly high risk of cancer with diabetes continues to accumulate in the face of an ever-expanding global epidemic of diabetes. Research has largely focused on studying the association between diabetes and cancer but so far has not been able to establish either a temporal or a causal relationship between the two pathologies.

The retrospective study reviewed here was a large population-based study with a long follow-up of more than 12 years, which presented new data underscoring the previously known association between diabetes and cancer in general and pancreatic cancer in particular. The latter association was particularly strong, with a hazard ration of 2.17. Given the retrospective nature of the study, the temporal patterns of association between diabetes and pancreatic cancer could not be made clear, nor could the causative link between the two diseases be ascertained. The question arises whether this increased risk was a direct result of diabetes or whether the prescribed treatment for diabetes could have influenced the risk of these patients developing cancer. In the diabetic cohort, no differentiation was made between type 1 and type2 diabetes while in the cohort designated non-diabetic the possibility of undiagnosed diabetes could not be excluded. A sub-group analysis to investigate the risk of developing cancer in diabetic patients stratified by whether or not they were receiving treatment for diabetes and the nature of treatment would also add valuable information. Despite the limitations, the analysis reinforces the increased risk of cancer in diabetic patients. As evidence keeps coming in, highlighting the possibility of a connection between diabetes and pancreatic cancer, there is now need for further studies to elucidate the mechanism of interaction between the two and investigate the possible pathways that link them together.

Conflict of Interest

The authors have no conflicts of interest.

References

1. Jemal A, Siegal R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006. CA Cancer J Clin. 2006; 56: 106-30. [PMID:16514137]

2. Niederhiber JE, Brennan MF, Menck HR. The National Cancer DataBase report on pancreatic cancer. Cancer. 1995; 76: 1671-7. [PMID:8635074]

3. Ben Q, Cai Q, Li Z, Yuan Y, Ning X, Deng S, Wang K. The relationship between new-onset diabetes mellitus and pancreatic cancer risk: a case-control study. Eur J Cancer. 2011; 47(2): 248-54. [PMID:20709528]

4. Chu CK, Mazo AE, Goodman M, Egnatashvili V, Sarmiento JM, Staley CA, Galloway JR, et al. Preoperative diabetes mellitus and long-term survival after resection of pancreatic adenocarcinoma. Ann SurgOncol. 2010; 17(2): 502-13. [PMID:19885697]

5. Silverman DT, Schiffman M, Everhart J, Goldstein A, Lillemoe K D, Swanson G M, Schwartz A G, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br J Cancer. 1999; 80(11): 1830-1837. [PMC:2363127]

6. Pezzilli R, Pagano N. Is Diabetes Mellitus a risk factor for Pancreatic cancer? World J Gastroenterol. 2013; 14; 19(30): 4861-6. [PMID:7745774]

7. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care. 2012; 35(11): 2402-11. [PMID:23093685]

8. Li J, Cao G, Ma Q, Liu H, Li W, Han L. The bidirectional interaction between pancreatic cancer and diabetes. World J Surg Oncol. 2012; 24: 10: 171. [PMID:22920886]

9. Chari ST, Leibson CL, RabeKG,Timmons LJ, Ransom J, de Andrade M, Petersen GM. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. Gastroenterology. 2008; 134(1): 95-101. [PMID:18061176]

10. Gullo L, Pezzilli R, Morselli-Labate AM. Diabetes and the risk of pancreatic cancer. Italian Pancreatic Cancer Study Group. N Engl J Med.1994; 331: 81-4.

11. Everhart J, Wright D (1995) Diabetes mellitus as a risk factor for pancreatic cancer: a meta-analysis. JAMA. 1995; 273: 1605-1609. [PMID:7745774]

12. Huxley R, Ansary-Moghaddam, Berrington de Gonzalez A, Barzi F, Woodward M. Type II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005; 92: 2076-2083. [PMID:15886696]

13. Handelsman Y, Leroith D, Bloomgarden ZT, Dagogo-Jack S, Einhorn D, Garber AJ, Grunberger G, et al. Diabetes and cancer-An AACE/ACE consensus statement. Endocr Pract. 2013; 19(4): 675-693. [PMID:23978590]

14. Cui YF, Andersen DK. Diabetes and pancreatic cancer. Endocr-Relat Cancer. 2012; 19: F9-F26.

15. Pannala R, Leirness JB, Bamlet WR, Basu A, Peterson GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology. 2008; 134: 981-987. [PMC:2323514]

16. Fogar P, Pasquali C, Basso D, Sperti C, Panozzo MP, Tessari G, D'Angeli F, et al. Diabetes mellitus in pancreatic cancer follow-up. Anticancer Res. 1994; 14(6B): 2827-2830. [PMID:7532931]

17. Li D. Diabetes and pancreatic cancer. Mol Carcinog. 2012; 51(1): 64-74. [PMID:22162232]

18. Schmidt N, Kostev K, Ziller V, Kowall B, Rathmann W. Association of diabetes and cancer-diagnoses in primary care practices in Germany. J Clin Oncol.2014; 32 (5 suppl): 1604.