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Dietary Energy Density Is Positively Associated with Risk of Pancreatic Cancer in Urban Shanghai Chinese[1,2]

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Abstract

Regular consumption of energy-dense foods predisposes to obesity and type 2 diabetes, both of which are suggested risk factors for pancreatic cancer. The aim of this study was to investigate whether energy density of foods is an independent risk factor for pancreatic cancer. In this population-based case-control study in urban Shanghai, 908 patients with pancreatic cancer and 1067 normal controls, aged 35–79 y, were recruited. The energy density for overall diet was calculated from food-frequency questionnaire data. Energy density (adjusted for age, sex, and total energy intake) was significantly higher in cases (6.08 ± 0.04 kJ/g) than in controls (5.91 ± 0.04 kJ/g) ($P = 0.003$). Energy density was positively associated with pancreatic cancer risk (OR: 1.16 per unit increase; 95% CI: 1.07, 1.27; $P < 0.001$). In adjusted analysis, the risk of pancreatic cancer was 72% greater (OR: 1.72; 95% CI: 1.25, 2.35; $P = 0.001$) in the highest quintile of energy density compared with the lowest quintile. In this case-control study, dietary energy density is positively associated with risk of pancreatic cancer. This association should be further investigated in prospective studies. J. Nutr. 143: 1626–1629, 2013.

Introduction

Pancreatic cancer is one of the most aggressive cancers, with a median survival time <6 mo (1). The incidence rate of pancreatic cancer in urban Shanghai increased >2-fold from 1973 to 2000 (2). However, little is known about its etiology and risk factors.

Dietary energy density (DED) is defined as the amount of energy theoretically able to be metabolized per unit weight of food (3). High energy density, as demonstrated by both short- and long-term intervention trials, can lead to increased energy intake and weight gain (3–5). Wang et al. (6) showed in the large prospective European Prospective Investigation into Cancer and Nutrition (EPIC) study that low dietary energy density was associated with a decreased risk of incident type 2 diabetes, which may be a potential risk factor for pancreatic cancer (7–10). Low energy density was also associated with intake patterns characterized by relatively more fresh fruits and vegetables and less meat and soft drinks (6).

The purpose of this study was to investigate the relation between DED and the risk of pancreatic cancer in a large-scale, population-based case-control study in urban Shanghai.

Participants and Methods

Study population. A population-based case-control study of pancreatic cancer was carried out in urban Shanghai during December 2006-January 2011. All participants were long-term residents of Shanghai and between 35 and 79 y of age. Details of the study design and participant recruitment have been described elsewhere (11). Briefly, 908 incident cases were recruited via an "instant case reporting system" in 37 urban Shanghai hospitals. Related hospital records, pathology reports, pathology slides, and/or imaging materials (computed tomography and/or positron emission tomography–computed tomography and/or MRI) were collected for case ascertainment by a group of local pathological and clinical experts. Patients with endocrine and other nonadenocarcinoma tumors ($n = 16$) were excluded, leaving 892 patients in risk analyses. At the same time, a total of 1067 controls were randomly selected from a list provided by the Shanghai Residents Registry, with frequency matching by 5-y age group (i.e., 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and 75–79 y) and sex. The study was approved by the institutional review boards of the Shanghai Cancer Institute and Yale University, and written informed consent was given by all participants.

Assessment of diet. Diet intake information on the most recent 5 y before the interview was ascertained by using a 107-item validated FFQ (12,13). The FFQ was developed from a similar dietary questionnaire used in the Shanghai Women's Health Study and the Shanghai Men's Health Study. The validity of the questionnaire was assessed by the FFQ and the multiple 24-h dietary recalls. In women, the correlation coefficients were 0.59–0.66 for macronutrients, 0.41–0.59 for micronutrients, and 0.41–0.66 for major food groups (12). In men, the correlation coefficients were 0.38–0.64 for macronutrients, 0.33–0.58

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for micronutrients, and 0.35–0.72 for food groups (13). Participants were asked how often they had regularly consumed each food, on average, in last 5 y, choosing from 5 possible frequency responses ranging from "never" or "once per year" to "every day," and how much they consumed each time (in "liang," 1 liang = 50 g). The average intake (g/d) of each food item was then calculated. For seasonal foods (i.e., fresh vegetables and fruits), the duration of intake (mo/y) was also asked, and the average intake of these foods was further multiplied by the number of months and then divided by 12. Average nutrient intakes (per day) were computed by multiplying the average intake (g/d) by the nutrient density content from the China Food Composition Tables (14). The energy and weight of each food item were summed for all caloric beverages and solid foods (e.g., not including tea or pure water consumption, for which energy content is almost zero) to derive the total energy intake (kJ/d) and the total weight of foods (g/d). DED was calculated as the available dietary energy per unit weight of foods (kJ/g) as follows:

$$\mathrm{DED} = \frac{\sum_{i=1}^{n} \mathrm{Energy}_i}{\sum_{i=1}^{n} \mathrm{Quantity}_i}$$

Assessment of other factors. A detailed structured questionnaire was completed in face-to-face interviews carried out by trained study staff. It included questions on age, sex, educational level, disease history, family history of cancer, cigarette smoking, tea and alcohol drinking, and medication use. Smoking was coded as 0, 0.025 to <13.7, 13.7 to <27.4, 27.4 to <41.1, ≥41.1 pack-years. The following anthropometric information was also requested: height at age 21 y, adult usual body weight, and adult usual BMI calculated as body weight in kilograms divided by the square of height in meters.

Calculations and statistical analyses. Results were expressed as means ± SDs for continuous variables and frequencies (percentages) for categorical variables. Differences between cases and controls were tested by t tests for continuous variables and by χ^2 tests for categorical variables. DED was defined both as a continuous variable and a categorical variable (5 groups by distributions in control participants). Associations between DED and risk of pancreatic cancer were examined by using unconditional logistic regressions. The first model was adjusted for age (continuous), sex, and adult BMI (continuous). The second model was further adjusted for the following potential confounding factors: education (primary school or lower, middle or high school, college or higher), family history of cancer (none, nonpancreatic cancer, pancreatic cancer), smoking (0, 0.025 to <13.7, 13.7 to <27.4, 27.4 to <41.1, ≥41.1 pack-years), self-reported history of type 2 diabetes (yes, no), and self-reported history of pancreatitis. The third model further included the following dietary factors: regular alcohol consumption (g/d, continuous), total energy intake (kJ/d, continuous), and green tea drinking (g/d, continuous). We repeated the analyses using energy-adjusted DED computed as residuals from the regression model developed by Willett et al. (15).

Values in the text are means ± SEMs. All statistical analyses were performed by using STATA statistical software (version 9.2; StataCorp).

Results

Characteristics of the cases and controls are shown in **Table 1**. Pancreatic cancer patients consumed a more-energy-dense diet than control participants. Energy density (adjusted for age, sex, and total energy intake) was significantly higher in cases (6.08 ± 0.04 kJ/g) than in controls (5.91 ± 0.04 kJ/g) ($P = 0.003$).

Increased risk of pancreatic cancer was associated with DED as shown in **Table 2**. This was true both for the continuous association per unit increase in energy density and according to quintiles of energy density. A 1-unit increase in DED was associated with a 16% increase in risk (OR: 1.16; 95% CI: 1.07, 1.27; $P < 0.001$). Compared with the lowest quintile of DED, the highest quintile showed a 72% increased risk (OR: 1.72; 95% CI: 1.25, 2.35; $P = 0.001$). Adjusting for percentage of energy from fat instead of total energy intake did not materially change the results (highest vs. lowest quintile OR: 1.84; 95% CI: 1.32, 2.56; $P < 0.001$). We repeated the analyses in men and women separately and found similar trends in both sexes, although with reduced statistical power because of smaller sample sizes: with DED as continuous variable (OR: 1.20; 95% CI: 1.07, 1.33 in men; OR: 1.14; 95% CI: 0.99, 1.30 in women; model 3). We also repeated the analyses in different SEER (Surveillance, Epidemiology, End-Stages) separately and found similar trends in all stages (data not shown).

In analyses using energy-adjusted residuals (see Participants and Methods), the results were unchanged. The correlation coefficient was 0.168 ($P < 0.001$) between raw energy density and total energy intake and 0.0002 ($P = 0.99$) between energy-adjusted residuals and total energy intake. A 1-unit increase in energy-adjusted residuals was associated with an 18% increase in risk (OR: 1.18; 95% CI: 1.08, 1.28; $P < 0.001$; model 3). Compared with the lowest quintile of energy-adjusted residuals, the highest quintile showed an 80% increased risk (OR: 1.80; 95% CI: 1.31, 2.47; $P < 0.001$).

To show the composition of an energy-diluted diet, we summarized the mean intake of major food groups by categories of DED (**Table 3**). After adjusting for age, sex, and total energy intake, compared with the most energy-dense group, participants in the most energy-diluted group consumed significantly more fresh fruits, vegetables, white meat, soy products, and dairy products; a moderate amount of alcohol; fewer staple foods (rice, noodles, breads, etc.) and had less total energy intake.

TABLE 1 Characteristics of case patients with pancreatic cancer and normal controls in urban Shanghai, 2006–2011[1]

Characteristic	Cases	Controls	*P*
n	892	1067	
Sex, *n (%)*			0.51
Men	519 (58.2)	605 (56.7)	
Women	373 (41.8)	462 (43.3)	
Age, *y*	64.9 ± 9.6	65.1 ± 9.9	0.57
Adult BMI, kg/m^2			
Men	23.9 ± 6.9	23.5 ± 3.1	<0.001
Women	23.7 ± 9.9	22.7 ± 3.7	<0.001
Education, *n (%)*			0.46
Primary school or lower	172 (19.3)	208 (19.5)	
Middle school	526 (59.0)	651 (61.0)	
College or higher	194 (21.7)	208 (19.5)	
Family history of cancer, *n (%)*			<0.001
None	556 (62.3)	753 (70.6)	
Nonpancreatic cancer	303 (34.0)	296 (27.7)	
Pancreatic cancer	33 (3.7)	18 (1.7)	
Regular alcohol use	398 (44.6)	512 (48.0)	0.14
Tobacco use, *n (%)*			0.06
0 pack-years	494 (55.4)	626 (58.7)	
0.025–<13.7 pack-years	84 (9.4)	110 (10.3)	
13.7–<27.4 pack-years	106 (11.9)	132 (12.4)	
27.4–<41.1 pack-years	112 (12.6)	123 (11.5)	
≥41.1 pack-years	96 (10.8)	76 (7.1)	

[1] Values are means ± SDs or *n* (%).

TABLE 2 RR of pancreatic cancer by quintiles of DED in urban Shanghai, 2006–2011[1]

	Total	*P*	Q1	Q2	Q3	Q4	Q5	*P*
Cases, *n*	892		148	172	154	198	220	
Controls, *n*	1067		214	213	214	213	213	
Median DED, *kJ/g*	5.72		4.60	5.25	5.72	6.39	7.55	
Model 1	1.12 (1.04, 1.21)[2]	0.003	1.0	1.17 (0.87, 1.56)	1.05 (0.78, 1.41)	1.36 (1.02, 1.82)	1.50 (1.12, 2.00)	0.003
Model 2	1.15 (1.06, 1.24)[2]	<0.001	1.0	1.26 (0.93, 1.69)	1.11 (0.82, 1.50)	1.47 (1.09, 1.97)	1.65 (1.23, 2.23)	0.001
Model 3	1.16 (1.07, 1.27)[2]	<0.001	1.0	1.28 (0.95, 1.73)	1.14 (0.84, 1.56)	1.51 (1.11, 2.05)	1.72 (1.25, 2.35)	0.001

[1] Values are ORs (95% CIs) unless otherwise indicated. Model 1 was adjusted for age, sex, and adult BMI. Model 2 was further adjusted for education (primary school or lower, middle or high school, college or higher), family history of cancer (none, nonpancreatic cancer, pancreatic cancer), smoking (0, 0.025–<13.7, 13.7–<27.4, 27.4–<41.1, ≥41.1 pack-years), self-reported history of type 2 diabetes (yes, no), and self-reported history of pancreatitis. Model 3 was further adjusted for green tea drinking (continuous), alcohol consumption (continuous), and total nonalcohol energy intake (continuous). DED, dietary energy density; Q, quartile.
[2] ORs for 1-unit increase in DED.

Discussion

We found, separate from age, sex, BMI, cigarette smoking, family history of cancer, and total energy intake, a positive association between DED and risk of pancreatic cancer. The risk was elevated by 72% in the highest energy density quintile compared with the lowest one. This finding, if confirmed, could be helpful in understanding the etiology of pancreatic cancer and may provide scientific evidence for its prevention.

Our study adds new information on the association of dietary intake and pancreatic cancer. In the EPIC study, Wang et al. (6) found a low-energy-dense diet to be associated with a lower risk of type 2 diabetes. DED assesses the quality of the whole diet instead of its elements. There are 3 major determinants of DED. One is fat, because fat is the most energy-dense nutrient and fat content varies substantially between various foods (16). The other is water, because its energy content is zero and its amount varies greatly among foods. In addition, fiber also has the potential to influence DED, because it has a low energy content and is able to bind water, but its range of concentrations in commonly eaten foods is much smaller. Therefore, an advantage of our study was our evaluation of the quality of diet using DED rather than the proportions of a single food or a group of foods.

The energy density of the whole diet accounts for the complicated interactions between various foods in the context of a free-living population. DED is a weighed energy density of individual elements in a diet, and thus is less informative in biological relations between a single food or nutrient and cancer risk. Large proportions of foods with high energy density, such as fatty foods, contribute to a more energy-dense diet, whereas foods with a high water content contribute to an energy-diluted diet. In our study, energy-diluted diets included fewer staple foods, more fresh fruits and vegetables, more white meat, more soy and dairy products, and more (i.e., modest amounts of) alcohol.

Our study is the first, to our knowledge, to examine the association between DED and pancreatic cancer risk in a large, population-based case-control setting of >900 cases. The participants in our study were more representative of the urban Shanghai population. Cases in our study were recruited from 37 major hospitals in urban Shanghai, and controls were randomly selected from the whole population in the same area. Furthermore, the ascertainment of our cases was thorough. Patients were included as potential cases once reported by a physician, and then confirmed by a group of pathological and clinical experts on the basis of hospital records, pathology reports and slides, and/or imaging material.

The limitations of our study merit consideration. Dietary intake in our study was assessed by a semiquantitative FFQ with its associated limitations. Disease bias (i.e., people with cancer try to explain their disease as a consequence of their dietary choices) also influences participants' recall of food intake. For example, patients might overestimate their intake of "unhealthy" foods and underestimate their intake of "healthy"

TABLE 3 Intake pattern of food groups by quintiles of DED in urban Shanghai, 2006–2011[1]

	Q1	Q2	Q3	Q4	Q5	*P*
n[2]	362	385	368	411	433	
Median DED, *kJ/g*	4.60	5.25	5.72	6.39	7.55	
Staple foods, *g/d*	288 ± 2	311 ± 2	334 ± 1	357 ± 2	381 ± 2	<0.001
Fruits, *g/d*	270 ± 5	223 ± 3	176 ± 3	129 ± 3	83 ± 5	<0.001
Vegetables, *g/d*	485 ± 6	433 ± 4	381 ± 4	329 ± 4	278 ± 6	<0.001
Red meat, *g/d*	49.0 ± 1.2	48.8 ± 0.8	48.5 ± 0.7	48.3 ± 0.8	48.1 ± 1.2	0.63
White meat, *g/d*	86.4 ± 2.2	78.2 ± 1.5	70.0 ± 1.2	61.8 ± 1.5	53.7 ± 2.2	<0.001
Soy products, *g/d*	186 ± 4	159 ± 3	132 ± 2	105 ± 3	78 ± 4	<0.001
Dairy products, *g/d*	165 ± 4	137 ± 3	108 ± 2	80 ± 3	51 ± 4	<0.001
Alcohol, *g/d*	163 ± 8	122 ± 6	82 ± 5	41 ± 6	0.8 ± 8	<0.001
Green tea, *g/d*	96.6 ± 5.2	96.7 ± 3.6	96.8 ± 2.9	96.9 ± 3.6	97.0 ± 5.2	0.97
Total energy[3], *MJ/d*	7.6 ± 0.08	7.7 ± 0.06	7.9 ± 0.05	8.0 ± 0.06	8.1 ± 0.08	<0.001

[1] Values are means ± SEs unless otherwise indicated and were adjusted for age, sex, and total energy intake. DED, dietary energy density; Q, quintile.
[2] Cases and controls combined.
[3] Total energy intake was adjusted for age and sex.

foods. However, to record usual dietary habits, the questionnaire asked participants about food intakes in the previous 5 y. Given that patients might change their diet during this period because of their as yet undiagnosed disease, the questionnaire also asked about changes in diet during the last year. In Shanghai, most food is home-produced (i.e., typically, housewives purchase raw materials from markets and cook at home, and fast food is less available or popular than in developed countries). Thus, if undiagnosed cases reduced their intake of high-protein, high-fat foods, they would tend to turn to grains, vegetables, and fruits because of their increasing inability to tolerate foods requiring pancreatic enzymes for digestion. The diet change questionnaire gave us some clues about how patients changed their diets 1 y before diagnosis. We found that 57% of cases did not change their diets (i.e., did not change any food group intake), 39% of cases reduced their red meat consumption (beef, lamb, and pork), 27% of cases reduced poultry consumption (chicken and duck), 14% of cases increased their intake of vegetables, and 10% increased their intake of fruits. There was no significant difference in total energy intake between cases and controls (P = 0.67). Therefore, whole-diet energy density of cases tended to decrease, which weakened the association of DED with pancreatic cancer risk in our study. We also repeated all risk analyses using energy-adjusted residuals of energy density, which removed the effect of total energy intake, and the results remained the same. Another limitation is the use of self-reported history of type 2 diabetes, which was reported to be a potential risk factor for pancreatic cancer. However, the questionnaire included several other related questions to help participants recall their medical history. In all, 339 participants reported they had been "told by a doctor that they have type 2 diabetes"; among these, 326 (96.2%) reported that they had been "diagnosed based upon blood tests," 309 (91.2%) reported that they had "used oral anti-diabetic drugs," and 104 (30.7%) reported that they had "used insulin." In addition, self-reported adult height and body weight were used in statistical analyses, which would reflect their normal status before cancer development better but which is also less accurate.

The mechanism for an association between DED and risk of pancreatic cancer is not yet understood. It has been reported that a high-energy-dense diet increased the risk of type 2 diabetes, which would result in insulin resistance and induced compensatory hyperinsulinemia (6). High concentrations of insulin would enhance insulin-like growth factor (IGF)-1 synthesis and downregulate IGF-1 binding proteins, leading to an increase in the bioavailability of free IGF-1, which transduces its downstream signaling pathways to promote tumor development by inhibiting apoptosis, stimulating cell proliferation, and enhancing angiogenesis (7). Foods that are high in DED tend to be more palatable than foods that are low in DED, and high palatability is associated with increased food intake in single-meal studies and with increased energy intake at subsequent meals, so-called passive overeating. In our study, DED was positively associated with increased total energy intake, but with adjustment, the association between DED and risk of pancreatic cancer was independent of total energy intake, BMI, and self-reported history of type 2 diabetes (Table 2). Future studies are needed to elucidate the possible mechanisms of the association between high DED and the development of pancreatic cancer.

In summary, we have shown in a large-scale, population-based case-control study that higher-energy-dense diets are associated with increased risk of pancreatic cancer risk, independent of age, BMI, cigarette smoking, family history of cancer, history of type 2 diabetes, and total energy intake. This finding has potential implications for preventing pancreatic cancer through modification of diet and merits further research.

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