Group 3
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Type 2 Diabetes and Risk of Incident Cancer in China
Reference: ***Research Paper***

T2DM and Risk of Incident Cancer in China: A Prospective Study Among 0.5 Million Chinese Adults

Background

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs. Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths[Data from CDC website]. The cancer burden continues to grow globally, exerting tremendous physical, emotional and financial strain on individuals, families, communities and health systems.

Diabetes is a chronic(long-lasting) health condition that affects how the human body turns food into energy. Diabetes occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Type 2 diabetes results from the body's ineffective use of insulin. The majority of people with diabetes have type 2 diabetes. This type of diabetes is largely the result of excess body weight and physical inactivity. Overtime, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves. Adults with diabetes have a two-to-three-fold increased risk of heart attacks and strokes[1]. It is the cause of 2.6% of global blindness[2], and is among the leading causes of kidney failure[3].

Diabetes has very high prevalence and is a leading cause of mortality worldwide. The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014.The global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014 [1].In 2016, an estimated 1.6 million deaths were directly caused by diabetes. Another 2.2 million deaths were attributable to high blood glucose in 2012.

In China, diabetes and cancer are major public health threats. In 2013, 10.9% of Chinese adults had diabetes and 35.7% had prediabetes [4]. As for cancer, in 2015 alone, approximately 4.3 million new cancer cases and 2.8 million cancer deaths occurred in China[5]. On April 6, 2018, China National Cancer Center released the latest national report on the incidence and mortality rate of cancer . It is estimated that there were 3.8 million (equivalent to the population of L.A.) new cases of malignant tumors and 2.3 million deaths in 2016. That is, on average, 7 people were diagnosed with cancer while 4 people died of cancer every minute in China.With the continuous demographic

and social transition, such as urbanization, increasingly sedentary lifestyles, overnutrition and aging, the burden of diabetes and cancer may keep rising.

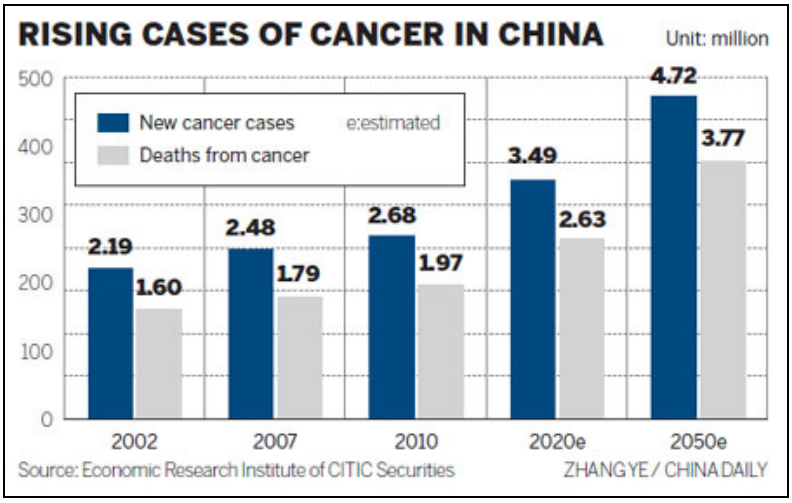


Figure 1. Rising cases of cancer in China, via Economic Research Institute of CITIC Securities

In recent years, multiple studies have focused on the link between diabetes and different cancers. However, the explicit association between baseline T2DM and risk of incident cancer in the Chinese population remains unknown. Although there was evidence for association between T2DM and certain cancer, a review which assesses different evidence on the link between type 2 diabetes mellitus(T2DM) and different types of cancers raised controversy over the association between diabetes and site-specific cancers in different studies[6]. Meanwhile, no consensus has been reached regarding the association between diabetes and cancer risk in the Chinese population.

The primary research question investigated in this paper was the association of type 2 diabetes mellitus, T2DM for short, and the new-onset cancer risk in 508,892 Chinese adults aged between 30 and 79. Secondary research questions that stemmed from the research included the association between T2DM and point-specific and rare cancers. All participants must not have been diagnosed with cancer prior to baseline (2004 to 2008), and they could not have a history of type 1 diabetes.

For the purposes of the study, the primary exposure was T2DM diagnosis by a physician and T2DM diagnosis by screen-detection. The term exposure characterizes factors associated with our outcome of interest. Since the primary data was collected through observation from the China Kadoorie Biobank Study and other national centers for disease information collection, there were a host of secondary exposures documented. Secondary exposures that relate to T2DM documented in the study were family history of diabetes and cancer, alcohol consumption, cigarette smoking, diet, non sedentary recreation measured in task hours per day, blood pressure, blood glucose levels, etc.

The primary outcome of this research study were total incident cancers and site-specific cancers in the population sample as defined by ICD-10 codes (*International Statistical Classification of Disease and Related Health Problems, Tenth Revision*). The outcomes were documented by collecting mortality information from disease registries like the Chinese Center for Disease Control and Prevention's National Disease Surveillance Points system. Among the incident cancers of interest included various cancer types such as colon, rectum, liver, female breast and lung cancers.

The authors believe that Type II Diabetes Mellitus and cancer are growing concerns in China because of "demographic and social transitions occurring in China, such as urbanization, increasingly sedentary lifestyles, overnutrition, and aging." (Am J Epidemiol, Pan et al., p 1380). The authors also felt that their study was necessary because of the flaws in recent studies of Type II Diabetes Mellitus and cancer in China.

A sufficient cause is a "'complete causal mechanism' that inevitably produces disease," according to Rothman's sufficient-component cause model, while a necessary cause is a "causal component that is a member of every sufficient cause." (Essentials of Epi, Ch 15, p 405) That is, in order for the exposure to be a sufficient cause it must always cause the disease and for it to be a necessary cause the exposure must always be present in the disease pathway. In this study, the authors did not hypothesize that the exposure of Type II Diabetes Mellitus was either a necessary or sufficient cause of cancer, because they did not argue that those with Type II Diabetes Mellitus would always get cancer nor that all who get cancer have Type II Diabetes Mellitus.

Significance

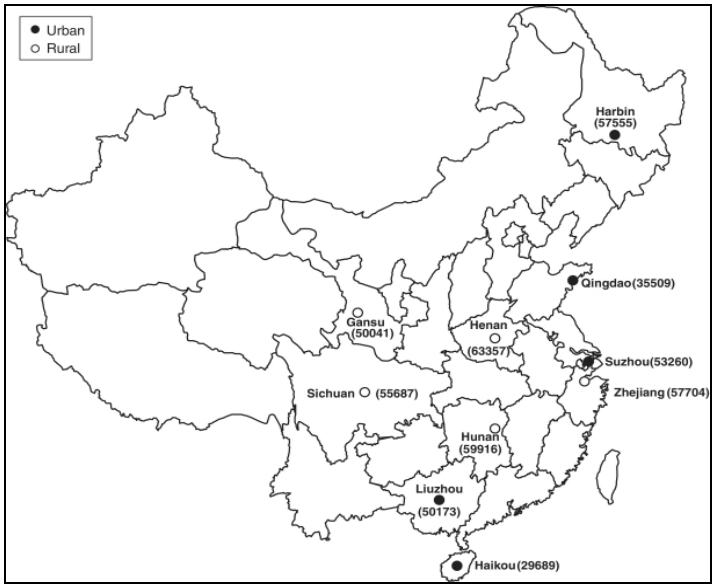
Having established a link between the two diseases in previous studies, consensus was lacking regarding the association between them in China. Also, prior findings did not examine the association between T2DM and incident cancer. The study by Pan et al. aims to expand upon the prior findings of association between type 2 diabetes mellitus(T2DM) and cancer, and investigate whether there is any association between incident cancer and T2DM.

Previous studies such as the pooled analysis and the China Kadoorie Biobank Study only showed significant results in linking the two diseases. The research question addressed in the present study, which the previous studies lacked, is whether T2DM is associated with an increased risk of new-onset cancer in China, for all cancer and certain site-specific cancers. Supervision of T2DM patients for early detection or prevention of onset-cancer as a plausible preventative strategy is also suggested, requiring further evidence from clinical-based trials as a future course for a related research.

Interventional studies are designed to assess the direct impact of prevention or treatment on a disease, evaluating measures of outcome(s) based on data-type and the quality of the data [6]. Being a prospective observational study, with large, geographically diverse sample size drawn from the China Kadoorie Biobank Study, the aim was to show association and not causation between the two diseases. An experimental or interventional study would be required to show beyond the association established by researchers and by the other global findings in research.

Study Population

The population for this study was based on the China Kadoorie Biobank (CKB) data, which consisted of permanent residents of China spanning from 100 to 150 rural villages or urban residential communities. Initially, individuals between 35 to 74 years of age were invited to participate from 10 geographic regions formed by 5 rural and 5 urban settings (**Figure 2**). The regions chosen were defined by disease patterns present locally, stability of the population, capacity and commitment of the communities, availability of death and disease registries, and exposures to risk factors of interest [8]. CKB was able to recruit 512,891 participants between the time period of



June 2004 to July 2008, with an age range of 30 to 79 years. Those outside of the initially established target age range by a small margin were included in the study to promote participation [8].

Figure 2. Location of 10 survey sites and numbers recruited at baseline (shown in brackets). Open circles indicate rural areas and solid circles indicate urban areas [7].

Aim of the Study

The main aim of the study by Pan et al. being the investigation of any association between T2DM and incident cancer in Chinese adults, the data collected by the CKB seemed to be the ideal fit for this study. This large established biobank seemed to be the ideal source, with rich resources for studies about the Chinese population. The target population for this study being individuals with both prior physician-diagnosed T2DM and screen-detected T2DM, not all cases of CKB source population were included in the study. Various procedures were followed to collect the data at baseline, including questionnaires, blood samples and physical attributes.

Because this study was primarily intended as an analysis of a subset of residents in China, the eligibility requirements included age range, residence in particular areas and from there the researchers further enforced inclusion and exclusion criteria based on health characteristics related to the exposures and outcomes of interest.

Selection Criteria

For the baseline information collection, a Regional Coordinating Centre (RCC) and a survey team analyzed responses from eligible patients, consisting of about 15 full-time staff with medical qualifications and fieldwork experience, were established in each of the 10 study areas [8].To determine inclusion based on prior physician-diagnosed T2DM, participants were asked, in a questionnaire, “Has a physician ever told you that you had diabetes?”. To determine inclusion based on screen-detected T2DM, those who responded no to the above question were given a blood spot test of blood glucose level on-site using a SureStep Plus Meter. Those participants who had a blood glucose level of 7.8-11.0 mmol/L were invited to undergo another fasting glucose test the next day in order to have reduced noise associated with a diet that may have spiked blood glucose levels. The final inclusion criteria based on screen-detection involved three cases in which participants scored greater than 7.0 mmol/L blood glucose level after 8 hours of fasting, less than 8 hours of fasting and greater than 11.0 mmol/L blood glucose level. Individuals excluded after eligibility requirements were satisfied included those who were thought to have Type 1 Diabetes, based on a combination of their age below 30, blood glucose levels and self-reported Type 1 Diabetes. Furthermore, those that had a baseline history of the outcome of interest, cancer, or parental history of cancer were excluded as well. Additionally, those without data on BMI or menopausal status were excluded to avoid confounding exposures.

In general, the study was pretty rigorous in its selection criteria for subjects with Type 2 Diabetes. There were multiple assurance checks to determine that screen-detection of blood glucose levels passed enough criteria to be certain that they were close to true: screens before and

after fasting, self-reporting, regularly calibrated equipment, third-party testing services in the United States (known to have higher regulatory standards for quality assurance). Although, researchers admitted that there were slight discrepancies between the sample prevalence of newly diagnosed T2DM against other similar studies (2.7%).

The study excluded 2578 participants with a baseline history of physician-diagnosed cancer and 1340 participants without information on parental history of cancer. In addition, they also excluded 2 participants without data on body mass index and 44 women without data on menopausal status. Besides, 35 participants were excluded because they were judged highly likely to be type I diabetes cases. It is appropriate that the sample consists of people without pre-diagnosed cancer and have clear information on general health and family history disease.

The prevalence of exposure (T2DM) is shown in Table 1. Among the 508,892 participants without a prior cancer diagnosis, the mean age at baseline was 51.5 (standard deviation, 10.7) years. A total of 29,835 participants (5.9%) had T2DM at baseline, of whom 15,881 (3.1% of all participants) reported physician-diagnosed T2DM and 13,954 (2.7% of all participants) had screen-detected T2DM . Compared with participants without diabetes, those who had T2DM were older, more likely to be female and urban residents, had higher body mass indices, and were more likely to be postmenopausal (if female), former regular smokers or alcohol drinkers, and less physically active. Educational level and parental history of cancer also differed significantly among participants with and without T2DM.

Table 1:Baseline Characteristics of Participants According to Diabetes Mellitus Status

Characteristics	**Total**	**No T2DM**	**With T2DM**
Total	508892(100%)	479057(94.1	298359(5.9%)
Sex *Male* *Female*	 208832(41.0%) 300060(59.0%)	 197302(41.2%) 281755(58.5%)	 11530(38.6%) 18302(61.4%)
Age group(years) *30-59* *60-69* *70-79*	 385861(75.8%) 90597(17.8%) 32434(6.4%)	 369070(77.0%) 81237(17.0%) 28759(6.0%)	 16791(56.3%) 9360(31.4% 3684(12.3)
Education level *Primary or illiterate* *Above primary*	 258151(50.7%) 250741(49.3%)	 242182(50.5%) 236875(49.5%)	 15969(53.5%) 13866(46.5%)
Household Reg *Rural* *Urban*	 285033(56.0%) 223859(44.0%)	 273291(57.1%) 205766(42.9%)	 11742(39.4%) 18093(60.6%)

Menopausal Status *Premenopausal* *Perimenopausal* *Postmenopausal*	 128443(42.8%) 14733(4.9%) 156884(52.3%)	 125441(44.5%) 14002(5.0%) 142312(50.5%)	 3002(16.4%) 731(4.0%) 14572(79.6%)

Study design

The study design was primarily a prospective cohort study. Researchers used the data from the China Kadoorie Biobank (CKB) study. They had trained staff interview participants at baseline using a standardized electronic questionnaire to group them into exposed and unexposed categories as well as documenting confounding variables. The exposure of T2DM was measured either by pre-physician diagnosed or screen-detected. To improve the accuracy of the measurement, 10 milliliter non fasting venous blood samples were collected from participants using ethylenediaminetetraacetic acid Vacutainers. Blood spot tests for measurement of blood glucose level were conducted on-site using a SureStep Plus meter that was regularly calibrated with the manufacturer's quality control solution.

The baseline time of the study was June 2004 - July 2008 and the follow up time period began at the end of baseline and ran through December 31, 2013. This means the actual study time was just over five and a half years. Participants were followed up for morbidity and mortality information on yearly basis. The time intervals between exposure and outcome varied from person to person, but there was a regular collection of outcomes data. The other information the researchers collected include demographic and socioeconomic characteristics, lifestyle and behaviours, general health, family history of disease, mental disorders, reproductive history, physical activity and basic physical measurements such as weight, height, blood measurements.

The benefits of this kind of study are that risk can be measured directly. While the initial screening was used to characterize the study participants, with a few follow-ups for higher accuracy, there were no periodic or consistent follow-ups until end-point.

The end-points were retroactively determined by looking up hospitalization and death information of the study participants. Measures of association were calculated by merging the initial screening information and the endpoint information.

Results

The overall findings of the study indicate that the exposure of type 2 diabetes is associated with the increased risk of the outcome of new-onset cancer; for total and several site-specific cancers. The findings are consistent regardless of the source of diagnosis of T2DM, screen-detected or physician diagnosed, except in the case of colorectal cancer which shows stronger association when T2DM is screen detected in the participating Chinese population.

Table 2: Association Between Type 2 Diabetes Mellitus and Risk of Incident Cancer in the China Kadoorie Biobank Study, 2004–2013

Type of Cancer	T2DM Status				Risk of Cancer in Persons With Diabetes (Relative to No Diabetes)[a]			
	T2DM		No T2DM					
	No. of Cases	Rate per 100,000 P-Y[b]	No. of Cases	Rate per 100,000 P-Y[b]	Model 1[c]		Model 2[d]	
					HR	95% CI	HR	95% CI
All cancers	1,457	576.3	16,006	491.7	1.12	1.06, 1.18	**1.13**	1.07, 1.19
Esophagus	87	40.8	1,572	48.2	0.79	0.64, 0.99	0.86	0.69, 1.08
Stomach	148	56.5	2,061	63.4	0.88	0.74, 1.04	0.91	0.77, 1.08
Colon and rectum	190	63.1	1,721	53.1	1.16	0.99, 1.35	1.13	0.97, 1.32
Liver	194	86.1	1,746	52.8	1.50	1.29, 1.74	**1.51**	1.29, 1.76
Pancreas	71	23.5	427	13.1	1.83	1.42, 2.37	**1.86**	1.43, 2.41
Lung	310	107.2	3,217	99.7	1.05	0.93, 1.18	1.11	0.98, 1.25
Female breast[e]	128	79.1	1,344	67.2	1.24	1.03, 1.50	**1.21**	1.01, 1.47

Abbreviations: CI, confidence interval; HR, hazard ratio; P-Y, person-years; T2DM, type 2 diabetes mellitus.
a T2DM was treated as a fixed baseline variable for analyses.
b Standardized to the sex, age (5-year intervals), and study area of the study population.
c Model 1 stratified by sex, age (5-year intervals), and study area of the study population.
d Model 2 stratified by sex, age (5-year intervals), and study area of the study population. Results were adjusted for education, parental history of cancer, body mass index, cigarette smoking, alcohol drinking, and physical activity.
e For women only (*n* = 300,060). Rates were standardized to the age and study area of the study population. Model 2 additionally adjusted for education, parental history of cancer, body mass index, cigarette smoking, alcohol drinking, physical activity, and menopausal status.

Table 2: Data summary from the China Kadoorie Biobank Study, 2004–2013. Incident Cancer risks in presence versus absence of type 2 Diabetes Mellitus [9]

The hazard ratio, which differs from a relative risk in that it is the relative risk ratio plus the factor of the time of occurrence (in this case the time of the study), of 1.13 for total cancer indicates that the risk of cancer among those with type 2 diabetes was 1.13 times the risk of cancer among those without type 2 diabetes in the course of the study which last through December 31 2013. This is significant with a 95% confidence interval of 1.07 to 1.19 [table 2]. The increased risks of certain site-specific cancers were most significant in cancers of the pancreas, liver , and female breast among the participants. Hazard ratios and 95% confidence intervals for each one were 1.86 (1.43, 2.41), 1.51 (1.29, 1.76) and 1.21 (1.01, 1.47), respectively. Thus, the disease rate to incident cancer of these three cancers was higher among those with T2DM during follow-up. It is important to note that the female breast confidence interval starts at almost 1, meaning this is extremely close to including the null hypothesis.

Colorectal cancer had conflicting outcomes based on the source of T2DM diagnosis. The cancer hazard ratio for physician-identified type 2 diabetes was 0.91 (0.73, 1.13 95% CI), versus the hazard ratio of 1.44 (1.18, 1.77 95% CI) when screen-detected. Higher random blood glucose levels (higher than 5.6 mmol/L) of participants who were not diagnosed with type 2 diabetes prior to the study showed significant positive association with total cancer risk, specifically with cancers of liver, stomach, and female breast cancer. Table 3 shows the significant p-value of less than or equal to 0.02 for each of these outcomes.

The essential criterion of temporality necessitates that the exposure or causal factor of interest precedes the outcome, which is clearly met by this study. Given that the end points of interest were measured from a separate source a year or more later than the initial screen, sufficient time between exposure and outcome is established.

Table 3: Association Between Random Blood Glucose Level and Risk of Incident Cancer Among Participants Without Prior Physician-Diagnosed Type 2 Diabetes, China Kadoorie Biobank Study, 2004–2013[a]

Type of Cancer	Random Blood Glucose Level							
	≤5.5 mmol/L	5.6–6.9 mmol/L			≥7.0 mmol/L			*P* for Trend[b]
	(No. of Events)	No. of Events	HR[c]	95% CI	No. of Events	HR[c]	95% CI	
All cancers	7,263	6,020	1.07	1.04, 1.11	3,057	**1.20**	1.15, 1.25	<0.001
Esophagus	712	577	1.14	1.02, 1.27	299	1.15	1.00, 1.31	0.56
Stomach	918	763	1.08	0.98, 1.20	423	**1.25**	1.11, 1.41	0.01
Colon and rectum	757	664	1.05	0.95, 1.17	366	1.23	1.08, 1.40	<0.01
Liver	789	629	1.11	0.99, 1.23	379	**1.44**	1.27, 1.63	<0.001
Lung	1,478	1,211	1.06	0.98, 1.14	593	1.11	1.01, 1.22	0.08
Female breast[d]	606	524	1.05	0.93, 1.18	253	**1.30**	1.11, 1.51	0.02

Abbreviations: CI, confidence interval: HR, hazard ratio.
a Participants with prior physician-diagnosed diabetes (*n* = 15,881) and no data on random blood glucose level (*n* = 8,111) were excluded from the analysis, and the total sample size was 484,900.
b *P* values for trend were from a likelihood ratio test comparing the model with random blood glucose as a continuous variable to the model without random blood glucose.
c The model stratified by the sex, age (5-year intervals), and study area of the study population. Results were adjusted for education, parental history of cancer, body mass index, cigarette smoking, alcohol drinking, and physical activity.
d For women only (*n* = 285,448). The model stratified by the age (5-year intervals) and study area of the study population. Results were adjusted for education, parental history of cancer, menopausal status, body mass index, cigarette smoking, alcohol drinking, and physical activity.

Table 3: Higher Random Blood Glucose Levels of subjects not previously diagnosed for T2DM by a physician show association with Incident Cancer. Data summary from China Kadoorie Biobank Study, 2004–2013 [10]

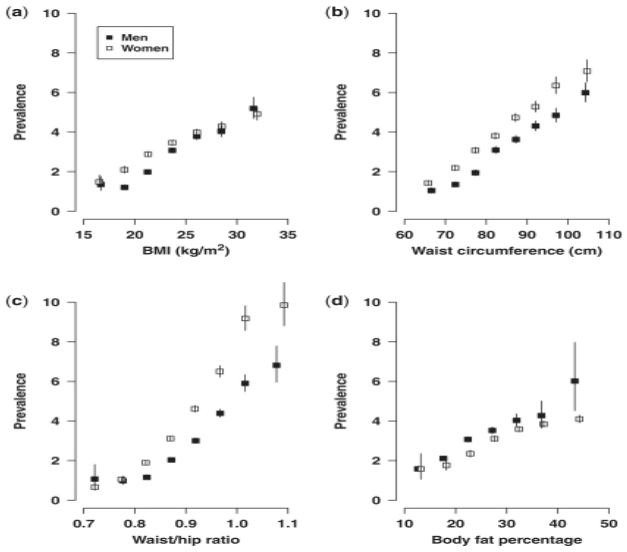
The results of blood sugar levels of 7.0 mmol/L or higher among participants not previously diagnosed for the exposure showed greater risks for all cancer types in response as compared to those whose sugar levels were below this range, as seen in table 3. Participants with prior diagnosis, meanwhile, had greater positive association between incident cancers in proportion to time since diagnosis, except in the case of liver cancer which had higher association among those

diagnosed within 5 years from baseline versus earlier. Besides the exception, the dose-response relationship is evident in all other cases, in support of the study's original hypothesis of causal association between prevalence of type 2 diabetes and incident cancer.

Confounders, Bias, and adjusting for noncomparability

As depicted in table 1, several covariates were measured by the researchers of the original study, including but not limited to sex, age, household type, BMI, menopausal status for females, smoking, drinking, physical activity level, and parental history of cancer. Spearman correlation analysis was applied to confirm these data between baseline and their subsequent surveys for quality control [11]. Sex, age, geographic areas, education level, parental history, BMI, smoking, drinking and exercise since showed association with prevalence of diabetes and were also independently considered as causal factors of various cancers; these were examined as being potential confounders.

The images below depict BMI as a confounding covariate between type 2 diabetes and cancer .



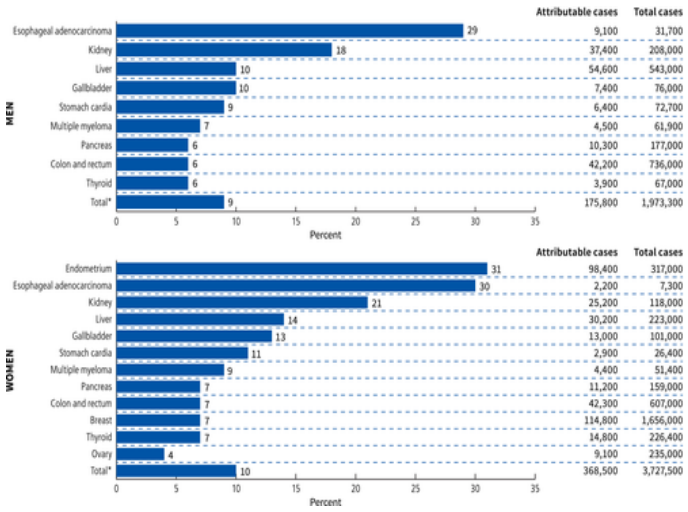


Figure 3 [12]
Associations of different measures of adiposity with self-reported diabetes at baseline. Prevalence of diabetes vs (a) BMI, (b) waist circumference, (c) waist/hip ratio, (d) body fat percentage after adjustment for age and area. Solid boxes denote men and open boxes denote women. Vertical line indicates 95% confidence interval (CI)

Figure 4 [13]
Proportions and Numbers of Cancer Cases Attributable to Excess Body Weight (Body Mass Index ≥ 25 kg/m2) by Sex and Cancer Type in 2012. *Total percentage is calculated among the excess body weight–related cancers listed in the figure rather than among all cancers.

Demographic confounders such as age (intervals of 5 years), sex and study area were controlled by direct standardization in analysis phase, with base study population as the standard. To further

reinforce comparability in results, a second model was built and analysis was stratified by controlling for parental history of cancer, educational level, body mass index, smoking, alcohol drinking, and physical activity. For women, the menopause stage was considered a confounder for breast cancer and was stratified for analysis. Hepatitis infections and non-alcohol associated diseases of the liver which are prevalent in China, were also potential confounders between diabetes and liver cancer. The study was adjusted by using association analysis and sub-group analysis for the two confounders.

As figures 3 and 4 indicate, higher levels of body mass index being associated with increase in type 2 diabetes exposure and cancer outcomes would result in overestimating the measures of association between the exposure and the outcome in a positive direction. Meanwhile, positive associations between postmenopausal stage with T2DM and breast cancer also resulted in over-estimated crude hazards ratio of 1.24 versus the adjusted HR of 1.21 [table 2], even if by an insignificant amount.

Since all observations of association between T2DM and cancer types were homogenous when controlled for above mentioned confounders, results showed comparability in the overall study outcome.

There was some evidence to suggest that potential sources of selection bias could have affected the internal validity of the study, although that selection bias was accounted for. The exposure of interest, T2DM, was pooled into one group despite being characterized in two ways: screen-detected and physician diagnosed. There could have been differences in the way a physician might have diagnosed T2DM with how the study detected T2DM, potentially having different thresholds for characterization or different criteria. There was also potential risk of incorrect recall where individuals may have incorrectly been placed into an exposure or non-exposure group. However, the recall bias was accounted for because every participant was screened and those who had an RBG level of 7.8–11.0 mmol/L went through the screen-detection procedure for T2DM regardless of prior physician diagnosis.

The sample population aptly captures the source population. Permanent residents of China between the ages of 35 and 74 from 100–150 rural villages or urban residential committees in 10 diverse regions (5 rural counties and 5 urban districts) across China were captured. Given the large population size and the heterogeneity of the sample, the study was pretty successful in achieving an accurate sample.

Given this was a longitudinal cohort study in which follow-up was post-hoc defined by national morbidity registries, the accuracy of the outcome hinges on the reliability of those data sources. Since outcome was defined as death or morbidity by incident cancer, loss-to-follow up would imply that an unobserved outcome may not have been accurately recorded in the registry or that an unobserved outcome meant that a patient was still alive. There may have been inaccuracies in the study results due to misclassification of participants in these ways.

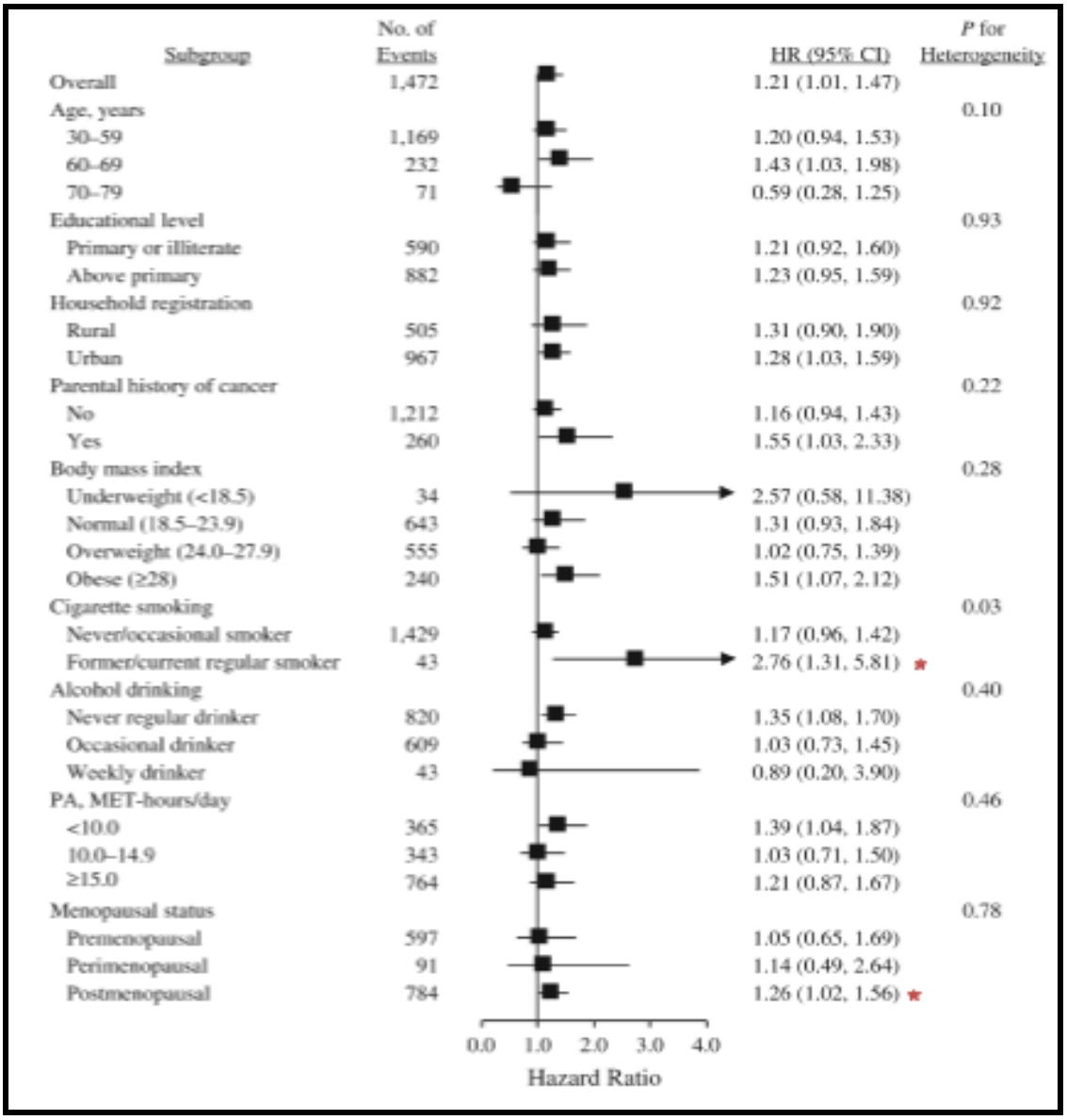
In this research, several precautions were taken to avoid misclassification. First, as the primary exposure of interest was T2DM, blood spot tests for measurement of blood glucose level were conducted on all the participants to reduce misclassification of exposure/non exposure group. Besides, the devices for measurement were regularly calibrated with quality control solutions to effectively avoid poor measurement of exposure.Second, other than prior physician diagnosed T2DM, the researchers also included screen detected T2DM to exposure group so that recall bias and social desirability bias can be effectively reduced. Third, in the stage of follow up, the cause of death information was coded by trained staff blinded to baseline information, which helps prevent some investigator bias.

Although many precautions were taken to avoid misclassification, we can see that misclassification could still be a problem. For example, for prior physician-diagnosed T2DM participants, it is possible that scales for T2DM in different districts are different, so some participants who were not really T2DM patients were misclassified as T2DM patients. In this case, the misclassification would be classified as non-differential and the result would be biased toward the null. Another scenario that may result in misclassification is that the screen-detecting can not efficiently differentiate Type I diabetes and Type II diabetes. In this case, some participants who were defined as T2DM patients through screen-detecting may have type I diabetes instead of T2DM. This would be a non-differential misclassification and push the result toward the null**.**

Effect Measure Modifiers and Generalizability

Interaction was observed for site-specific liver and breast cancers and T2DM when analysis was strata-specified for age in liver cancer, and menopausal status and smoking status for breast cancer, along with BMI measure being a confounder as well as discussed earlier. The crude measures for hazard ratios (HR) were 1.51 for liver cancer and 1.21 for breast cancer. For liver cancer, strata-specific HR was highest among age group 35- 59 yrs (HR and CI: 1.79 and 1.44, 2.23), versus HR of 1.14 (0.87, 1.50) for 60 - 69 years and 1.56 (1.10, 2.22) for 70 - 79 years of age. Thus, age is an effect modifier on multiplicative scale, modifying the association between T2DM and liver cancer further away from the null in subgroups 35-59 years and 70 - 79 years, while lowering the HR in subgroup 60 -69 years in comparison to the crude measure.

Figure 5. Female breast cancer and type 2 diabetes mellitus, with adjusted hazard ratios (HRs)



Source: China Kadoorie Biobank Study, 2004–2013 [14]

There was a significant difference between strata-specific HRs for breast cancer by BMI, menopausal status and smoking status (figure 5). Post-menopausal women showed higher positive association with breast cancer, with HR of 1.26 (CI 1.02, 1.56) as compared to perimenopausal and premenopausal women, with HRs of 1.14 (CI 0.49, 2.64) and 1.05 (CI 0.65, 1.69), respectively. Association between exposure and outcome was also statistically different among subgroups based on smoking status, with HR among smokers being 2.76 (CI 1.31, 5.81) as compared to non-smokers with HR 1.17 (CI 0.96, 1.42). Thus, smoking status and menopausal status both being causal partners of T2DM in the outcome of breast cancer, indicate that the true association between

the exposure of type 2 diabetes and breast cancer can be accurately identified when subjects are classified into these subgroups.

Overall all, this study was conducted in a scientific and objective way. The finding in this study demonstrates a robust and reliable link between diabetes and incident cancer in the Chinese population.The main strengths of this study includes the nature of prospective cohort study, the large enough sample size(508892 persons), geographic diversity of sampling(sampled from 100-150 rural villages or urban residential committees in 10 diverse regions across China), completeness of data collection , stringent ascertainment, and follow up mechanisms, and a high retention rate.The study incorporated multiple methods to avoid bias during design phase, and made exhaustive analysis into different type of cancers.

However, the study also has certain limitations. First, since new T2DM cases (previously undiagnosed diabetes) found at baseline were detected only on the basis of RBG level, case misclassification might have been possible. Second, the present study was not able to examine the association between T2DM and less common cancers, such as cancers of the prostate, bladder, cervix, and endometrium, that are thought to be associated with diabetes. Third, the study was not able to address the association between severity of T2DM and the onset of cancer to provide additional support for our findings. Fourth, the study did not examine the associations between T2DM and the exact subtypes of certain cancers (e.g., esophageal cancer and breast cancer). Fifth, screening can potentially influence the detection of certain cancer types, such as cancers of the cervix, esophagus, female breast, and colon and rectum. The differential use of cancer screening may confound the association between diabetes and cancer. We did not have information on cancer screening for this cohort of Chinese and thus could not control for its impact. However, it is unlikely that people with and without diabetes chose different cancer screening approaches in China during the followup period.

The study was started 15 years ago, the techniques for T2DM diagnostic back then were not as accurate as what the technique scientists developed nowadays. If we were to replicate this study, we could use a leading edge way to detect T2DM to reduce potential misclassification. Second, we would go deeper to study not only the association between T2DM with the most common cancers, but pay more attention to its association with less common cancers, such as prostate cancer, bladder cancer, cervix cancer and endometrial cancer, because according to some studies, those type of cancers may have association with diabetes[15, 16].

The generalizability of this research study is strong, but there are some clear limitations. The large sample size captured in the study demonstrates a solid distribution of variability across socio-economic status, gender, age, BMI, susceptibility to cancer, and various other categorical variables. Many key confounding variables that could relate to cancer onset were sufficiently distributed across the T2DM exposure and non-exposure groups. However, the study, by design, was focused on a Chinese population, where similarities among participants may not generalize well to the same aged-individuals in different countries. There could be many significant factors that

would produce different results in different demographic populations. For example, this predominantly Chinese sample group may contain genetic similarities, food and diet similarities, and cultural similarities around exercise and food consumption. These similarities might bias the results in a particular direction that may not be true in sample populations with different genetics, diets or cultural habits around lifestyle. Another, less important, factor that contributes to generalizability is age. While this study captures a large age range in its sample population, it does not have great coverage of the elderly population (80+), which is likely to develop cancer and is a good candidate sample group to be part of the study.

Ultimately, the study was solid with a decent generalizability. Countries with similar cultures and diets may find good generalizability to their populations, but countries with significant differences may see different results. While age is an important factor in cancer risk, the elderly population above 80+ is not well captured in this study, which is likely a high-risk population for cancer (the outcome of interest). While it extends well within the Chinese population, this study, therefore, may not be that generalizable to the whole world. Further research may need to be investigated that assesses confounders of T2DM like genetics and diet.

Conclusion

This study by Pan et al. was successful in providing evidence of association between T2DM and incident cancer among Chinese adults, specifically cancers of the liver, pancreas, and female breast cancer. They were able to successfully show a positive causal link between type 2 diabetes or presence of high RBG levels with onset of various cancers, which was coherent with the findings from similar other western studies.

Due to the nature of large data size, consisting of 508,892 participants from over 150 various villages and urban residential communities in China, the study was able to well establish strong causal association. Temporality was evident, given that the end points of interest were measured from a separate source a year or more later than the initial screening for diabetes in 2004 to 2008. Information on morbidity was collected from established disease registries, and the national health insurance system during the follow-up period through the end of 2013. There was also an element of biological gradient evident, given the strength of association based on blood glucose levels.

Any change in public health practice or policy in China as a result of this study was not evident in the report, although the potential for such impact is necessitated based on the statistical reports of exposure prevalence and cancer risk. Since undiagnosed diabetes is high in the country, proper and timely diagnosis might impact the quality of lifestyle due to earlier intervention and management. Public health practice related to prediabetic management might even be able to prevent the onset of exposure of interest.

As a follow-up, how might the results of the study be affected by a broader population of the country, and in comparison to other regions of the country? What might contribute to any differences in exposure and disease between them, and maybe even between other countries might be of further interest to pursue and compare, given that both diabetes and cancer are significant contributors to the burden of disease in China and worldwide. Close monitoring and diagnosis of T2DM for early detection of onset-cancers might aid in cancer prevention. Therefore, it might be beneficial to conduct large-scale trials to establish such evidence in order to make such practices cost-effective.

Before you finish, please be sure to document all outside resources and describe the contributions each of your group members made to the CourseWorks page and oral presentation.

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