Diabetol Int (2016) 7:167–172
DOI 10.1007/s13340-015-0232-0

ORIGINAL ARTICLE

Combination of type 2 diabetes and smoking increases total cancer mortality in Japanese men using competing risk analysis: the Tanno-Sobetsu study

Hirofumi Ohnishi[1,2] · Shigeyuki Saitoh[3] · Hiroshi Akasaka[2] · Tetsuaki Furukawa[2] · Mitsuru Mori[1] · Tetsuji Miura[2]

Received: 20 May 2015 / Accepted: 5 August 2015 / Published online: 25 August 2015

Abstract
Aims We assessed the impact of the combination of type 2 diabetes (T2DM) and smoking on total cancer mortality using cohort data of a general Japanese population.
Methods Of 1908 residents who received health checkups in two towns in 1994, 794 males were included as study participants. Smoking status was defined as three categories: never smoker, ex-smoker and current smoker. Individuals with T2DM were defined as individuals with fasting plasma glucose ≥7.0 mmol/l and/or receiving medication for T2DM. Participants were divided into six groups according to T2DM and smoking status: non-DM (NDM) and never smoker, NDM and ex-smoker, NDM and current smoker, DM and never smoker, DM and ex-smoker, and DM and current smoker groups. All participants were followed up for a maximum of 13 years. We calculated the hazard ratio (HR) using Cox's proportional hazard model and subhazard ratio (SHR) using competing risk regression analyses in each group.
Results During the follow-up period, there were 169 all-cause deaths (62 cancer deaths and 40 CVD deaths). When using Cox regression analysis, HRs were higher in the ex-smoker and current smoker groups than in the never-smoker group, and HRs were also higher in the DM groups than in the NDM groups. When using competing risk analysis, SHRs were almost the same as the HRs of Cox regression analysis (DM and ex-smoker 6.06, DM and current smoker 10.12).
Conclusions The combination of T2DM and smoking is a strong risk factor for total cancer mortality in Japanese men.

Keywords Type 2 diabetes · Smoking · Cancer mortality · Competing risk analysis

Introduction

Type 2 diabetes mellitus has recently been shown to be associated with cancer incidence and mortality [1–8]. Hyperinsulinemia accompanied by insulin resistance, hyperglycemia and chronic inflammation are known to be mechanisms of oncogenesis. Another reason why type 2 diabetes is related to cancer is that individuals with type 2 diabetes are likely to have common cancer risk factors such as obesity, smoking and alcohol drinking. Cigarette smoking is a strong risk factor for various types of cancer [9]. However, the effect of the combination of type 2 diabetes and smoking on cancer mortality is still unclear.

Both type 2 diabetes and smoking are also risk factors of cardiovascular disease [10], and cardiovascular death may preclude the possibility of cancer death due to type 2 diabetes and smoking in later years. Therefore, when assessing the effects of these two risk factors on cancer mortality, cardiovascular death should be considered as a competing risk. In such cases, a competing risk analysis such as the Fine and Gray model is recommended rather than the

✉ Hirofumi Ohnishi
hohnishi@sapmed.ac.jp

[1] Department of Public Health, Sapporo Medical University School of Medicine, W-17, S-1, Chuo-ku, Sapporo, Hokkaido, Japan

[2] Department of Cardiovascular, Renal and Metabolic Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

[3] Department of Basics and Clinical Medicine, Sapporo Medical University School of Health Science, Sapporo, Japan

standard Cox's proportional hazard model for analyzing data [11, 12]. Hence, in the present study, competing risk analysis was used for determining the impact of the combination of type 2 diabetes and smoking on cancer mortality with consideration given to cardiovascular mortality as a competing risk in Japanese males.

Materials and methods

This study was approved by the Ethics Committee of Sapporo Medical University. Written informed consent was obtained from all participants in this study.

Study participants

We recruited participants in the Tanno-Sobetsu Study [13, 14], a study with a population-based prospective cohort design for the present analyses. In two towns, Tanno and Sobetsu, in Hokkaido, Japan, public health nurses in the local government recruited by mail all residents aged 20 years or more for annual medical examinations, including standard blood and urine tests and an electrocardiogram. We explained this cohort study to each resident who was going to receive the health checkup by a face-to-face interview onsite, and we included residents who consented to participate in this study.

In 1994, 1908 residents who were aged 30 years or older received health checkups (794 men and 1114 women). Because there were few individuals with type 2 diabetes and few ex-smokers and current smokers among the females (4.8, 2.2 and 8.8 %, respectively), we included only 794 males as study participants for this analysis.

Measurement items

All participants were examined in the morning after an overnight fast. Body weight and height were measured, and body mass index (BMI) was calculated as body weight divided by the square of body height (kg/m^2). After 5 min of rest, systolic and diastolic blood pressures (SBP and DBP) were measured twice in a sitting position using a mercury sphygmomanometer by a well-trained doctor, and average values were used for analysis. Total cholesterol (TC) and fasting plasma glucose (FPG) levels were measured by venous blood tests. TC and FPG levels were measured by the cholesterol oxidase and hexokinase method, respectively. Information on medical history including use of medications, smoking status and alcohol drinking status was obtained via interviews by public nurses.

In this study, smoking status was defined according to three categories: never smoker, ex-smoker and current smoker. Individuals with type 2 diabetes were defined as individuals with FPG $\geq$7.0 mmol/l and/or receiving medication for type 2 diabetes.

Follow-up

All participants were followed up from 1994 to 31 December 2007, and their vital status and emigration status and cause of death were annually ascertained using residence registry data, death certificates, medical records in hospitals and/or questionnaires. Out-migrate individuals were defined as censored cases at the time of move-out day.

Statistical analyses

To determine the impact of the combination of type 2 diabetes and smoking on cancer mortality, participants were divided into the following six groups: non-DM (NDM) and never smoker, NDM and ex-smoker, NDM and current smoker, DM and never smoker, DM and ex-smoker, and DM and current smoker.

Stata version 12.1 (StataCorp LP, USA) was used for statistical analysis. The significance level in all analyses was set at $p < 0.05$. All numerical values are expressed as mean $\pm$ SD. Dunnett's and Fisher's exact tests were used for examination of intergroup differences compared with the NDM and never-smoker group and for frequency comparison, respectively.

To assess the risk of cancer mortality in each of the six groups, we first calculated the hazard ratio (HR) and 95 % confidence interval (CI) using Cox's proportional hazard model. We then performed competing risk regression analyses because cardiovascular death is considered to be a competing risk event in this analysis. Competing risk regression analyses were conducted using the Fine and Gray method, and the subhazard ratio (SHR), with the NDM and never-smoker group being used as a reference group, was calculated in each group. In multivariate analysis, age, BMI, alcohol drinking and TC level were selected as covariates being confounding factors for cancer mortality.

As a sensitivity analysis, we conducted the same analysis as that described above after excluding events of cancer death within 3 years from baseline.

Results

Baseline characteristics in the six groups according to DM and smoking status are shown in Table 1. Mean age tended to be lower in the current smoker groups than in the never-smoker groups and was significantly lower in the NDM and

Table 1 Baseline characteristics in the six groups according to DM and smoking status

	NDM and never smoker ($n = 185$)	NDM and ex-smoker ($n = 151$)	NDM and current smoker ($n = 393$)	DM and never smoker ($n = 15$)	DM and ex-smoker ($n = 21$)	DM and current smoker ($n = 29$)	p value‡
Age (years)	60.9 ± 11.6	63.6 ± 12.5	57.8 ± 12.5*	65.9 ± 10.6	65.1 ± 11.8	64.7 ± 10.2	<0.001
BMI (kg/m^2)	23.7 ± 2.9	23.6 ± 3.2	23.0 ± 3.1	24.4 ± 2.6	23.3 ± 2.4	24.2 ± 4.0	0.06
SBP (mmHg)	133.7 ± 17.1	136.3 ± 19.2	131.2 ± 18.6	143.3 ± 18.6	142.4 ± 15.2	134.4 ± 19.7	0.003
DBP (mmHg)	79.5 ± 9.2	79.8 ± 9.6	77.6 ± 9.4	77.1 ± 7.5	81.9 ± 9.5	78.5 ± 8.6	0.045
TC (mmol/l)	5.1 ± 0.8	4.9 ± 0.9	4.7 ± 0.8	5.2 ± 0.8	4.9 ± 0.9	4.8 ± 0.9	0.199
FPG (mmol/l)	5.2 ± 0.5	5.4 ± 0.6	5.2 ± 0.6	8.4 ± 3.0*	8.1 ± 2.5*	8.0 ± 3.0*	<0.001
Alcohol drinking							<0.001
Never drinker (%)	31.4	20.5	18.1	33.3	28.6	31.0	
Ex-drinker (%)	5.4	17.2	8.4	6.7	38.1	3.4	
Current drinker (%)	63.2	62.3	73.5	60.0	33.3	65.5	
Medication for hypertension (%)	15.1	21.9	17.6	20.0	14.3	24.1	0.576
Medication for hypercholesterolemia (%)	1.6	0.0	0.8	0.0	0.0	3.4	0.297
Medication on DM (%)	0	0	0	73.3	66.7	69.0	<0.001

Values are expressed as mean ± SD

DM type 2 diabetes, *NDM* non-DM, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *FPG* fasting plasma glucose

* $p < 0.05$, vs. NDM and never smoker, Dunett's test

‡ Analysis of variance (ANOVA) and Fisher's exact test were used for mean comparison and frequency comparison, respectively

current smoker group than in the NDM and never-smoker group. BMI and blood pressure levels tended to be higher in the DM groups than in the NDM groups. Frequency of being an ex-drinker tended to be high in the ex-smoker groups. There were no significant differences in the frequency of medication for DM among the three DM groups.

The mean follow-up period was 11.3 ± 3.6 years, and 8914 person-years were totally observed. During the follow-up period, there were 169 all-cause deaths (62 cancer deaths and 40 CVD deaths). The 62 cancer deaths included 22 lung cancer, 11 gastric cancers, 8 liver cancers, 5 pancreatic cancers, 5 prostate cancers, 3 colorectal cancers and 8 other cancer deaths. Table 2 shows cancer mortality and CVD mortality rates in the six groups. Cancer mortality rates in the ex-smoker and current smoker groups were higher than those in the never-smoker groups both with and without DM. Cancer mortality rate also tended to be higher in the DM groups than in the NDM groups.

Table 3 shows the results of competing risk regression and Cox proportional hazard regression analysis for total cancer mortality. When using Cox regression analysis, HRs after adjustment for several confounding factors were higher in the ex-smoker and current smoker groups than in the never-smoker group, and HRs were also higher in the DM groups than in the NDM groups. HR in the DM and current smoker group was the highest among the six groups. When using competing risk regression analysis, SHRs were almost the same as the HRs of Cox regression analysis.

As a sensitivity analysis, we conducted the same analysis as that described above after excluding events of cancer death within 3 years from baseline (Table 4). Although there were some differences in HRs and SHRs and slightly larger 95 % CIs, the DM and ex-smoker group and the DM and current smoker group showed the same tendency of higher HRs and SHRs as shown in Table 3.

Discussion

The main findings of this study are (1) both type 2 diabetes and smoking status were strong risk factors for all-cause cancer mortality, and the combination of type 2 diabetes and smoking status was a stronger risk than type 2 diabetes alone or smoking status alone; (2) when using competing risk analysis, there were no remarkable attenuations of SHR compared with Cox regression analysis.

There has been an accumulation of evidence indicating that type 2 diabetes is related to cancer morbidity and mortality [1–8], and the American Diabetes Association (ADA) and American Cancer Society (ACS) jointly published a consensus report on the association between

Table 2 Cancer mortality and CVD mortality in the DM and smoking groups

	Number of cancer deaths	Number of CVD deaths	Person-years	Cancer mortality (/1000 person-year)	CVD mortality (/1000 person-year)
NDM and never smoker ($n = 185$)	4	7	2153	1.9	3.3
NDM and ex-smoker ($n = 150$)	10	10	1647	6.1	6.1
NDM and current smoker ($n = 390$)	37	17	4463	8.3	3.8
DM and never smoker ($n = 15$)	1	1	152	6.6	6.6
DM and ex-smoker ($n = 21$)	4	3	206	19.4	14.6
DM and current smoker ($n = 29$)	6	2	293	20.5	6.8

CVD cardiovascular disease, *DM* type 2 diabetes, *NDM* non-DM

Table 3 Competing risk and Cox proportional hazard regression analyses for total cancer mortality among DM and smoking status categories

	Competing risk			Cox proportional hazard		
	SHR	95 % CI	*p* value	HR	95 % CI	*p* value
NDM and never smoker ($n = 185$)	1.00 (ref)	–	–	1.00 (ref)	–	–
NDM and ex-smoker ($n = 150$)	2.42	0.71–8.17	0.157	2.36	0.72–7.74	0.155
NDM and current smoker ($n = 390$)	5.01	1.77–14.21	0.002	4.89	1.72–13.91	0.003
DM and never smoker ($n = 15$)	2.77	0.27–28.42	0.391	2.54	0.28–23.10	0.406
DM and ex-smoker ($n = 21$)	6.06	1.39–26.51	0.017	7.88	1.91–32.55	0.004
DM and current smoker ($n = 29$)	10.12	2.69–38.07	<0.001	10.61	2.99–37.66	<0.001

Both HR and SHR were adjusted for age, body mass index, alcohol drinking and total cholesterol level

DM type 2 diabetes, *NDM* non-DM, *SHR* subhazard ratio assessed by competing risk regression, *HR* hazard ratio assessed by Cox proportional hazard model, *95 % CI* 95 % confidence interval

Table 4 Competing risk and Cox proportional hazard regression analyses for total cancer mortality among DM and smoking status categories after excluding events of cancer death within 3 years from baseline

	Competing risk			Cox proportional hazard		
	SHR	95 % CI	*p* value	HR	95 % CI	*p* value
Non-DM and never smoker ($n = 185$)	1.00 (ref)	–	–	1.00 (ref)	–	–
Non-DM and ex-smoker ($n = 150$)	2.63	0.67–10.35	0.166	2.61	0.68–10.06	0.164
Non-DM and current smoker ($n = 390$)	5.93	1.78–19.74	0.004	5.78	1.75–19.11	0.004
DM and never smoker ($n = 15$)	3.73	0.34–41.40	0.283	3.46	0.35–33.74	0.286
DM and ex-smoker ($n = 21$)	5.81	1.07–31.54	0.041	8.00	1.56–41.03	0.013
DM and current smoker ($n = 29$)	8.64	1.78–41.94	0.007	9.41	2.10–42.06	0.003

Both HR and SHR were adjusted for age, body mass index, alcohol drinking and total cholesterol level

DM type 2 diabetes, *NDM* non-DM, *SHR* subhazard ratio assessed by competing risk regression, *HR* hazard ratio assessed by Cox proportional hazard model, *95 % CI* 95 % confidence interval

diabetes and cancer in 2010 [15, 16]. The Japan Diabetes Society (JDS) and Japanese Cancer Association (JCA) also published a report of the JDS/JCA Joint Committee on Diabetes and Cancer in 2013 [17]. In these two reports, both type 2 diabetes and smoking are common risk factors for cancer, and individuals with DM are recommended to stop smoking. However, the impact of a combination of type 2 diabetes and smoking on cancer is not mentioned in these two reports, and this issue is still unclear because smoking status was likely to have been used as a confounding factor for the relationship between type 2 diabetes and cancer in previous studies. There are a few reports on the interaction of DM and smoking for pancreatic cancer. Two case-control studies showed that the combination of DM and smoking was a stronger risk for pancreatic cancer than DM alone or ever smoking alone [18, 19]. We assessed the interaction between type 2 diabetes and smoking on cancer mortality by using both a Cox model

and a Fine and Gray model into which type 2 diabetes (yes/no), smoking status (current and ex/never) and the interaction term (type 2 diabetes × smoking status) were added as covariates in the analysis before dividing participants into six categories according to DM and smoking status (data not shown). *P* values of the interaction term were 0.489 and 0.678 in the Cox model and the Fine and Gray model, respectively, and we could not find a significant interaction between type 2 diabetes and smoking status. However, the results of this study showed that the highest SHR for all cancer mortality was in the DM and current smokers (Table 3), and this large risk for cancer mortality may enhance the motivation of patients with type 2 diabetes to stop smoking.

Mechanisms of this effect of the combination of type 2 diabetes and smoking on cancer mortality could not be explored in this analysis, but some mechanisms can be considered. Hyperinsulinemia due to insulin resistance [20–22], oxidative stress accompanied by hyperglycemia [23, 24] and chronic inflammation [25, 26] are considered to lead to development and progression of cancer in type 2 diabetes patients. The combination of these various mechanisms and the effect of smoking is easily considered to play a pleiotropic and synergistic role in the development of cancer. As another mechanism of the interaction, a recent meta-analysis [27] showed that the circulating soluble receptor for the advanced glycation end product (sRAGE) was inversely associated with the risk of developing cancer, and smoking status explained some part of the heterogeneity for the association of circulating sRAGE with cancer risk using a meta-regression analysis. The AGE-RAGE system may be related to the synergistic interaction between type 2 diabetes and smoking for cancer mortality.

In this study, when using competing risk analysis, there were no remarkable attenuations in SHRs of the DM and ex-smoker group and the DM and current smoker group compared with the results of Cox regression analysis. One possible reason for this is the change in specific causes of death in type 2 diabetes patients over the past few decades in Japan. The most common cause of death among Japanese patients with diabetes was cardiovascular disease from 1979 to 1989, but cancer death became the most common cause of death in the 1990s with the extension of life expectancy among patients with diabetes [28]. Therefore, the change in specific causes of death among patients with diabetes may have affected the results of this study, which were intended for mortality.

One of the clinical implications of this study is that the impact of the combination of type 2 diabetes and smoking on cancer mortality may help medical staff in the situation of education for patients with type 2 diabetes and a smoking habit. These patients may be motivated to stop smoking by the tenfold higher risk of cancer mortality than for non-DM and never smokers. Another clinical implication is that the results of this study may be useful in education for community-dwelling smokers by public health workers. Smoking is one of the risk factors for future occurrence of type 2 diabetes as well as occurrence of cancer [29, 30]. Community-dwelling smokers, therefore, are at high risk for future occurrence of both type 2 diabetes and cancer. Moreover, if they acquire type 2 diabetes in the near future and become patients with type 2 diabetes who have a smoking habit, their relative risk for cancer mortality might increase from five- to tenfold. This information may help to motivate community-dwelling smokers to stop smoking.

There were several limitations to this study. First, we could not assess cancer morbidity. Therefore, the results mainly reflect the effect of type 2 diabetes and smoking on cancers with high mortality. Second, we could not assess site-specific cancer mortality because of the small number of cancer deaths. To clarify the effect of the combination of type 2 diabetes and smoking for site-specific cancer mortality, further large-scale studies are needed. Third, we could not completely exclude the possibility that cancer-bearing individuals were recruited in this study at baseline. However, that possibility is not high since exclusion of events of cancer death within 3 years from baseline did not significantly change the results (Table 4). Fourth, because of the small numbers of individuals with type 2 diabetes and smokers in women, we could not assess the gender differences in the effect of the combination of type 2 diabetes and smoking on cancer mortality, and further large-scale studies also are needed to clarify gender differences. Fifth, we could not assess treatments for diabetes in detail, but some medications such as metformin [31, 32] may have confounded the results of this study.

In conclusion, the combination of type 2 diabetes and smoking is a strong risk factor for total cancer mortality in Japanese men, and it may motivate smokers both with and without type 2 diabetes to stop smoking.

Acknowledgments No potential conflicts of interest relevant to this article were reported. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent or a substitute for it was obtained from all participants for being included in the study. The authors sincerely thank the public health nurses and staff in the Tanno and Sobetsu Town Offices for their help in the recruitment of study participants and data collection.

References

1. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA. 1995;273:1605–9.

2. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. Diabetologia. 2004;47:1071–8.
3. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97:1679–87.
4. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med. 2006;166:1871–7.
5. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia. 2007;50:1365–74.
6. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer. 2007;121:856–62.
7. Noto H, Tsujimoto T, Sasazuki T, Noda M. Significantly increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Endocrine Pract. 2011;17:616–28.
8. Sasazuki S, Charvat H, Hara A, Wakai K, Nagata C, Nakamura K, et al. Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan. Cancer Sci. 2013;104:1499–507.
9. Humans IWGotEoCRt. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum. 2004;83:1–1438.
10. Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. Diabetes Care. 1999;22(11):1887–98.
11. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. Clin Cancer Res. 2007;13:559–65.
12. Wolbers M, Koller MT, Stel VS, Schaer B, Jager KJ, Leffondre K, et al. Competing risks analyses: objectives and approaches. Eur Heart J. 2014. (**Epub ahead of print 2014/04/07**).
13. Ohnishi H, Saitohi S, Takagii S, Katohi N, Chibai Y, Akasakai H, et al. Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population: the Tanno and Sobetssu study. Diabetes Care. 2006;29:1128–9.
14. Mitsumata K, Saitoh S, Ohnishi H, Akasaka H, Miura T. Effects of parental hypertension on longitudinal trends in blood pressure and plasma metabolic profile: mixed-effects model analysis. Hypertension. 2012;60:1124–30.
15. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33:1674–85.
16. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60:207–21.
17. Kasuga M, Ueki K, Tajima N, Noda M, Ohashi K, Noto H, et al. Report of the Japan diabetes society/Japanese cancer association joint committee on diabetes and cancer. Diabetol Int. 2013;4:81–96.
18. Hassan MM, Bondy ML, Wolff RA, Abbruzzese JL, Vauthey JN, Pisters PW, et al. Risk factors for pancreatic cancer: case–control study. Am J Gastroenterol. 2007;102:2696–707.
19. La Torre G, Sferrazza A, Gualano MR, de Waure C, Clemente G, De Rose AM, et al. Investigating the synergistic interaction of diabetes, tobacco smoking, alcohol consumption, and hypercholesterolemia on the risk of pancreatic cancer: a case–control study in Italy. BioMed Res Int. 2014;2014:481019 (**Epub 2014/04/29**).
20. Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of the insulin–IGF axis. Trends Endocrinol Metab TEM. 2006;17:328–36.
21. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr. 2007;86:s836–42.
22. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004;4:579–91.
23. Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, et al. Oxidative damage to DNA in diabetes mellitus. Lancet. 1996;347(8999):444–5.
24. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324:1029–33.
25. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883–99.
26. Ben-Neriah Y, Karin M. Inflammation meets cancer, with NF-κB as the matchmaker. Nat Immunol. 2011;12:715–23.
27. He L, Bao H, Xue J, Zheng L, Zhang Q, Sun L, et al. Circulating soluble advanced glycation end product is inversely associated with the significant risk of developing cancer: evidence from a meta-analysis. Tumour Biol. 2014;35:8749–55.
28. Hotta N, Nakamura J, Iwamoto Y, Ohno Y, Kasuga M, Kikkawa R, et al. Causes of death in Japanese diabetics: a questionnaire survey of 18,385 diabetics over a 10-year period. J Diabetes Investig. 2010;1:66–76.
29. Willi C, Bodenmann P, Ghali WA, et al. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2007;298:2654–64.
30. Sairenchi T, Iso H, Nishimura A, et al. Cigarette smoking and risk of type 2 diabetes mellitus among middle-aged and elderly Japanese men and women. Am J Epidemiol. 2004;160:158–62.
31. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoS One. 2012;7:e33411 (**Epub 2012/03/27**).
32. Tseng CH. Metformin significantly reduces incident prostate cancer risk in Taiwanese men with type 2 diabetes mellitus. Eur J Cancer. 2014;50:2831–7.