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MED CHECK

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№ 5

Be careful with serious bias in epidemiologic studies

Symptoms after HPV vaccine and "frailty exclusion bias"

Actos (pioglitazone) and bladder cancer: "time-related bias" of a new type

CONTENTS （August 2016, Vol. 2, No. 5）

Epidemiologists and biostatisticians, be honest!

Translated from the editorial in Med Check-TIP (in Japanese) Jan 2016 ; 16 (63)

When new types of substances are introduced into medicine, an unfortunate result is new types of harm from new drugs. In Japan, we have experienced several serious drug disasters, including thalidomide phocomelia/embryopathy, clioquinol-induced SMON (Subacute Myelo-Optico-Neuropathy), chloroquine retinopathy, HIV infection induced by unheated blood products, CJD induced by dried dura mater, and hepatitis C infection induced by fibrinogen and other blood products. In lawsuits against government and/or pharmaceutical companies that resulted from these disasters, causal associations between the drugs and the diseases were established and recognized.

However, more recent drug disasters caused by some products introduced since around 2000 seem to be different from the above cases in that confirmation of causality is very difficult. One example is acute respiratory injury associated with the use of Iressa (gefitinib, an anti-cancer drug for non-small cell lung cancer). Another is harm associated with the use of Tamiflu: sudden death or hypoxic encephalopathy with sequelae from respiratory arrest, and accidental death following abnormal behaviours. HPV vaccine has led to complex and intractable diseases involving the nervous and immune systems, including autoimmune diseases.

A task force headed by epidemiologist Y. Hirota, who was believed to have no conflict of interest with the pharmaceutical company that developed Tamiflu, produced a fraudulent analysis of an epidemiologic survey on the association of Tamiflu use with abnormal behaviors. The Japanese Ministry of Health, Labour and Welfare (MHLW) subsequently adopted this faulty analysis. Although Tamiflu increases incidence of sudden death during influenza, many observational studies that do not correct for time-dependent bias claim that it decreases mortality if used early.

An epidemiologic study published in July 2015, featured in this issue of Med-Check, claims that there is no association between the use of Actos (generic name pioglitazone) and bladder cancer. Professor Brian L. Strom, a world-class pharmacoepidemiologist, is one of the coauthors of this epidemiologic study, which was conducted by Kaiser Permanente. In Kaiser Permanente's latest report, a new analytical method that contains a type of time-related bias is introduced, and the association between Actos and bladder cancer is found to have disappeared.

The article in this issue clearly explains why such a bias was introduced.

The epidemiologic studies that the MHLW used as evidence for the safety of HPV vaccine have many limitations. One mistakenly stated the prevalence of autoimmune disease to be one-20th of its actual usual prevalence. Other studies compared healthy vaccinees with non-vaccinees who may have been more frail as a group (see p17 in this issue). It is known in epidemiologic research that such bias is called "healthy vaccinee effects", or inversely, "frailty selection bias". We call this type of bias “frailty exclusion bias”. In observational studies assessing efficacy and harm by comparing vaccinees with non-vaccinees, this type of bias is normally taken into account.

However, many epidemiologic studies have been published that do not deal with this bias appropriately. Such studies may conclude that even a harmful vaccine is “safe” or “leads to risk reduction”.

The preliminary report on the Nagoya City study of HPV vaccine and symptoms, which was first issued in December 2015, has some serious limitations. One is the neglect of “frailty exclusion bias”. In this study, 88 ~ 90% of girls born in the years 1994 to 1996 were vaccinated; it is therefore possible that frailty may have accumulated in the remaining non-vaccinated 10 ~ 12% .

It is not known whether the investigator who analysed the Nagoya City data omitted “frailty exclusion bias” intentionally or not. However, the conclusions stated in the preliminary report are undoubtedly incorrect, and should not be used to reject causality. This report should not be used to deny the payment of compensation to the victims of HPV vaccine. We strongly call on epidemiologists and biostatisticians to be honest in science.

Symptoms after HPV vaccine:
typical "frailty exclusion bias" in Nagoya City study

Translation from Japanese edition of Med Check-TIP 2016: May (No 65) :62-63

Abstract:

The preliminary released analysis of Nagoya City study which compared the proportion of symptoms among more than 30,000 girls with and without HPV vaccine, reported no link with the inoculation of HPV vaccine. However, the analysis seems having serious biases including “frailty exclusion bias”, “healthy vaccinee effect” or “frailty selection bias”. We discuss the theoretical basis of this type of bias which is frequently missed to be taken into account in epidemiologic studies not only on the effectiveness and safety of vaccine but also on other medications.

Introduction

Nagoya City issued on December 14 2015 a preliminary report on "A survey of HPV vaccination" which was conducted in September 2015 [1]. It is a large scale questionnaire survey to compare symptoms of the girls who were inoculated with HPV vaccine and those of the girls who were not. It was valuable in that about 70,000 girls who were born between 1994 and 2000 living in Nagoya City were included in the survey and about 30,000 of them responded (response rate: 43.4%), including not only those who were vaccinated but also those who were not.

The preliminary report concluded that in a multivariate analysis adjusted by age, none of the 24 kinds of symptoms was reported significantly more frequently in those who were vaccinated with HPV vaccine, and denied the association between HPV vaccine and serious symptoms after the vaccination.

As a response to our inquiry, Nagoya City explained that they would disclose the raw data on the web for an investigation by the third party, but they had never done it yet on early May (**note:** data were disclosed on around 20th June 2016). This report discusses the "frailty exclusion bias", which Nagoya City study overlooked.

The increase of symptoms which cannot be explained by age

For instance, it was estimated that the girls with symptoms such as "difficulty in simple calculation" or "cannot walk normally" among the non-vaccinees would increase for each age by 1.39 times (39%) or 1.38 times (38%) **[4]**. If a proportion of persons with the symptoms increase with age by these ratios, what would be the consequence ? The proportion at the age of 26 would be 30 times higher than that at the age of 15. This estimation is obviously unrealistic. This simply indicates that the analysis methods using age adjustment may be inappropriate.

In Nagoya City survey, HPV vaccine coverage (%) was up to 85 to 90% among those born between 1994 and 1997. It is easily expected that frailty may be accumulated in the remaining 10 to 15 %, who did not receive the vaccine: this is one of the best examples of “frailty exclusion bias”.

One of the major reasons why the proportion of the girls with symptoms was the lowest in those born in 2000 (about 15-year-old) may be because they had the lowest coverage (15%), and not because it was the youngest age group.

Frailty exclusion bias or healthy vaccinee effects

If a person has fever on the day of vaccination, she would be excluded from vaccination. Therefore, vaccinees have better health than the non-vaccinated at the start of comparison. Hence, even if the vaccine has no efficacy nor harmful effect, the result would show that it is effective and safe. This is called “healthy vaccinee effect” **[6,7]** or “frailty selection bias” **[8]** in epidemiology.

We propose to call this type of bias as “frailty exclusion bias” **[9]**. This is a type of selection bias and is usually called “frailty selection bias”. However, it may cause misunderstanding that frail persons are selectively vaccinated while actually, they tend to be excluded from vaccination. This is also commonly called “healthy vaccinee effect”, and it occurs frequently in observational studies on efficacy and safety of vaccines. However, this type of bias is not only important in the assessment of vaccine but also should be taken into account for medications in general **[9]**. An example for the latter is a case-control study claiming the efficacy of rosiglitazone for reducing heart disease **[10]**. A proportion of patients who took rosiglitazone in the control group was

Figure 1: No exclusion of frailty

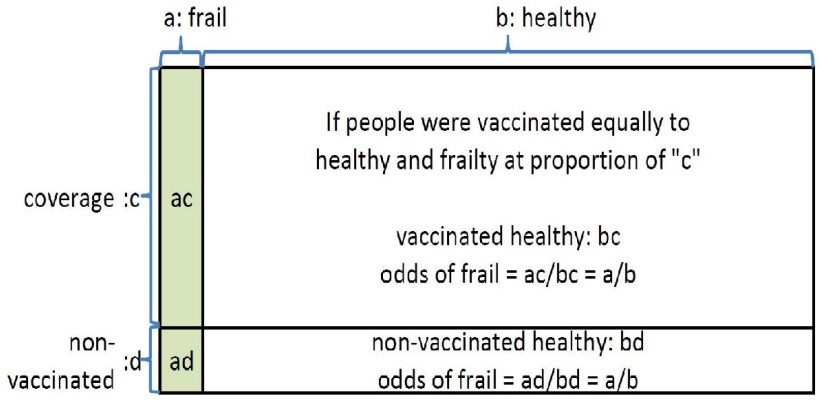
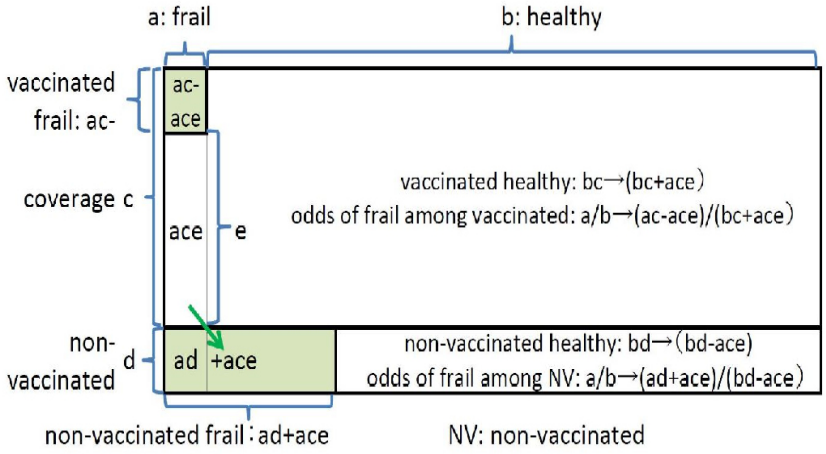


Figure 2: If frail people were excluded from vaccination



higher than 95%, and those who were not prescribed with rosiglitazone probably had heart diseases that contraindicated the drug.

Without considering the "frailty exclusion bias", we cannot assess the harm of the HPV vaccine adequately.

Theoretical basis of the "frailty exclusion bias"

(1) No exclusion

First, we consider the case in which no exclusion of frailty occurs in **Figure 1** under the condition that a vaccine has no beneficial and harmful effect.

Imagine that the proportion of high risk people (the frail) in a population is "a". People are vaccinated by the coverage "c". If the frail (people with high risk) or the healthy are equally vaccinated, and the vaccine does not cause any adverse effects, the odds of the frail is **a/b** for both the vaccinated and non-vaccinated. Hence, the odds ratio of the frail in the vaccinated compared with the non-vaccinated is **1.0**.

(2) In the case with exclusion

If the frail were excluded from vaccination by the proportion of "e", and if the vaccine does not cause any beneficial and harmful effects, odds of the frail is **(ac − ace)/(bc+ace)** among the vaccinated and **(ad+ace)/(bd − ace)** among the non-vaccinated.

Hence, the odds ratio of the frail in the vaccinated compared with the non-vaccinated is **((ac − ace)/(bc + ace)) ／ ((ad + ace)/(bd − ace)).**

Unless "e" is 0, odds ratio of the frail in the vaccinated compared with the non-vaccinated will always be **less than 1.0 theoretically.**

This is the theoretical basis of "frailty exclusion bias", "frailty selection bias" or "healthy vaccinee effect".

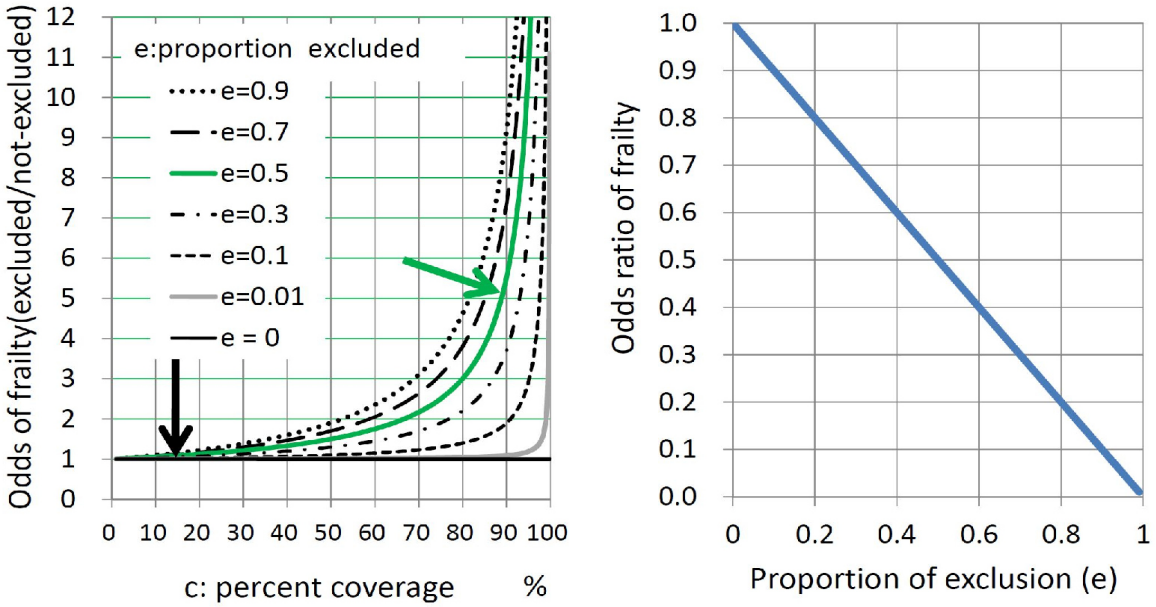
Effect of the frailty exclusion bias

Under the condition in which the vaccine has no beneficial and harmful effects, and a proportion of the frail is 0.001 (0.1%), theoretical odds ratios of the frail in the case where the frail were excluded by "e" compared with the case where the frail were not excluded from the non-vaccinated people is shown by percent coverage (**Figure 3a**). In the **Figure 3a,** various curves for each e (0, 0.01, 0.1, 0.3, 0.5, 0.7 and 0.9) are shown. **Figure 3b** is the

Figure 3: Theoretical effects of frailty exclusion on odds ratio compared with no exclusion (in the condition that vaccine has no benefit or harm)

A. Effect of exclusion in non-vaccinated

B. Effects of exclusion in vaccinated

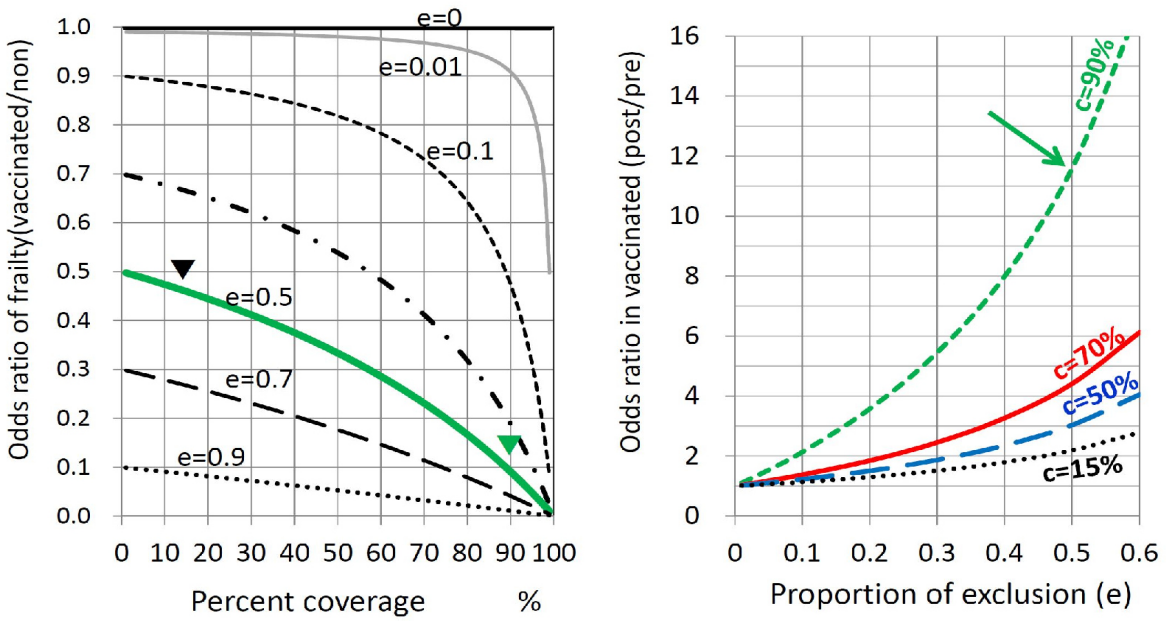


A. If the percent coverage is around 15%, there is little effect of the exclusion bias among the non-vaccinated regardless of exclusion (↓). However, the effect increases greatly when percent coverage increase up to 90% as in the study conducted by Nagoya City; the odds ratio of the frail by exclusion compared with non-exclusion increases greatly (→ in the case when e=0.5, for example). It may be the results of the frailty exclusion bias, which becomes more evident as the coverage increased up to 90% , and not of the effect of the age that the odds ratio of positive symptoms of various birth year groups compared with those born in 2000 increased greatly up to 3.0 to 7.3 in the Nagoya City study.
B: The effect of the exclusion bias on the vaccinated group increases proportionally to the extent of "e" regardless of vaccination coverage.

Figure 4: Theoretical effects of frailty exclusion on odds ratio of vaccinated compared with non-vaccinated (in the condition that vaccine has no benefit or harm)

A: Odds ratio of the frail by the coverage and exclusion

B: Extent of harm to be 1.0 of apparent odds ratio



A. As a result, odds ratio of the frail comparing the vaccinated to the non-vaccinated decreases as the coverage (c) and/or exclusion (e) increase. If c=0.9 and e=0.5, odds ratio may be 0.09 when a vaccine has no beneficial nor harmful effect.
B. Therefore, in order to demonstrate odds ratio of 1.0 when c=0.9 and e=0.5, the vaccine has to induce 11 times more harmful outcomes in the vaccinated than in the non-vaccinated (→). In order to demonstrate apparent odds ratio of 2.0, when c=0.9 and e=0.5, the vaccine has to induce 22 times more harmful outcomes in the vaccinated than in the non-vaccinated.

theoretical odds ratios of the frail in the case where the frail were excluded by "e" compared with the case where the frail were not excluded from the vaccinated people. **Figure 4** is the theoretical odds ratios of the frail in the vaccinated group compared with that in the non-vaccinated group by percent coverage and by "e".

An adjustment by the health status before inoculation is essential

It is essential to adjust odds ratio of the harm of HPV vaccine by the health status before vaccination of the vaccinated and the non-vaccinated in order to get true figures. However, it is not known whether the investigators of the Nagoya City study collected such information for the adjustment. If not, it may be difficult to adjust the health status before inoculation.

However, there are some methods to estimate better the risk of the HPV vaccine by utilizing the collected data.
Because odds ratio of individual positive symptoms in the same stratum of birth year is not affected by age, odds ratios and 95% confidence interval (95% CI) should be calculated by the number of women with positive symptoms (numerators), number of women subjects (denominator) by symptom, by birth year, and by inoculation status.

Because the odds ratio in the stratum of women with least coverage (15%) of inoculation (born in 2000; about 15 years old) may be affected the least by "frailty exclusion bias", we propose to adjust odds ratio of other strata of birth years that have higher vaccine coverage.

Note that "frailty exclusion bias" will not completely disappear by these procedures (**cf. Figure 4-Aand B**).

Conclusion

We strongly request that Nagoya City withdraw the preliminary results and disclose the data so that the third party could analyse them. We also recommend Nagoya City to re-analyse the data appropriately by themselves as soon as possible (Note).

Note: Nagoya City withdrew the interim report and disclosed the raw data as a PDF file on around 20th June, 2016. We are now working on the conversion of the raw data into an excel file for further analysis.

References

1) About Nagoya City, the enforcement of the cervical cancer vaccination investigation, http://www.city.nagoya.jp/kenkofukushi/page/0000076417.html

2)http://www.city.nagoya.jp/kenkofukushi/cmsfiles/contents/0000078/78732/kf271214-k.pdf

3) 2015.12.14 Mayor Takashi Kawamura, Nagoya City press conference https://www.youtube.com/watch? v=X1m5wTR1Rlw&feature=youtu.be

4) Nagoya City. Preliminary report of the survey on the symptoms after HPV vaccine. http://www.city.nagoya.jp/kenkofukushi/page/0000073419.html

5) Satoshi Takano, medical truth of the HPV vaccine, MMJ (Mainichi Medical Journal)2016:12(1): 7-11.

6) Fine PE, Chen RT. Confounding in studies of adverse reactions to vaccines. Am J Epidemiol. 1992; 136(2): 121-35.

7) von Kries R et al Sudden and unexpected deaths after the administration of hexavalent vaccines: is there a signal? Eur J Pediatr. 2005;164:61-9.

8) Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis. 2007 Oct; 7(10): 658-66.

9) Hama R. Do clinical trials and epidemiologic studies support the safety of the human papillomavirus (HPV) vaccine? - A critical review, in Shaw et al edd. "Controversies in Vaccine Safety", Elsevior (in press)

10) Florez H, Reaven PD, Bahn G, Moritz T, Warren S et al. VADT Research Group. Rosiglitazone treatment and cardiovascular disease in the Veterans Affairs Diabetes Trial. Diabetes Obes Metab. 2015;17(10):949-55.

Carcinogenicity of pioglitazone (brand name: Actos)

A critical review on the recently published paper.

Translated synopsis from the Japanese edition of Med Check TIP No 63 (2016) with web supplementary materials.

Abstract:

Pioglitazone (Actos) is an anti-diabetic agent released in December, 1999 in Japan. We warn the harms of this agent since the early stage of marketing. Bladder cancer is one of the serious adverse effects of the agent. The systematic reviews and meta-analysis have shown statistically significant and dose dependent relation. A major new epidemiologic study (a final analysis of Kaiser study) claiming no association has "a time related bias" of new type which we discussed in this synopsis.

Takeda Pharmaceutical has agreed to pay $2.4 billion to settle thousands of lawsuits filed by patients and their family members who said that Actos caused bladder cancer **[1-3]**.

Two new epidemiological studies (one by Kaiser group **[4]** and the other from Europe **[5]**) reported that statistically significant association was not found between Actos and bladder cancer [4,5]. Most media and academia expressed their negative view on the association **[6-9]**. However, the denial of the association seems to be erroneous as discussed below.

Actos is an anti-diabetic agent released in December, 1999 in Japan. We have warned of harmful effects of Actos: on the heart failure, bone disorders and carcinogenesis just after the marketing **[10-12]** and several times subsequently **[14-16, 23]** with the evidence on the pathogenesis **[17-22]** and the results from the animal carcinogenicity test **[14]**.

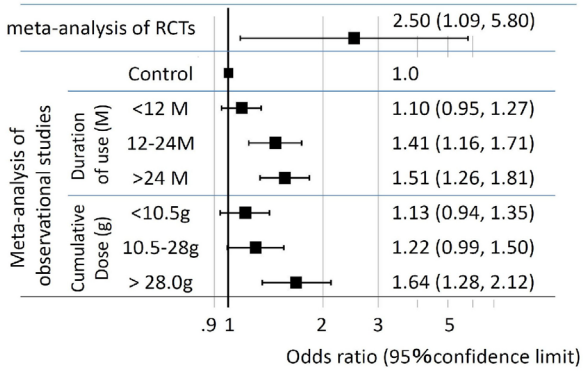
A systematic review and meta-analysis results of five randomized controlled trials as well as a systematic review and meta-analysis results of 13 epidemiologic surveys including the interim-analysis of the Kaiser's study published in 2011 **[24]** have shown statistically significant and dose dependent relation between the risk of bladder cancer and Actos use **[25]** (**Figure 1a**).

As the populations of both newly disclosed epidemiologic studies are far smaller (less than one tenth **[4]** and less than one thirtieth **[5]**) than the total population of those meta-analysed **[25]**, the results of both studies do not affect the overall results "positive association between Actos use and the bladder cancer".

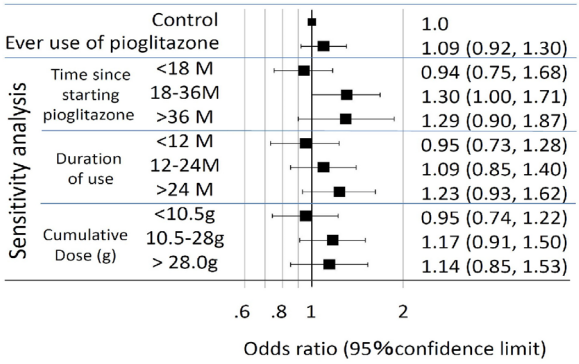
Moreover, we found a different figure in the final report of Kaiser study **[4]** (**Figure 1b**) compared with results of the systematic review and meta-analysis **[25]** (**Figure 1a**). In the

Figure 1: Risk of bladder cancer from pioglitazone use

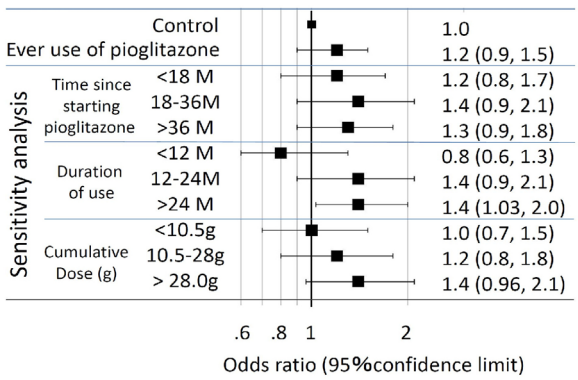
(a) Meta-analysis results [25]



(b) Final report of Kaiser [4]



(c) Interim report of Kaiser [24]



meta-analysis results, the dose dependent increase of bladder cancer risk was observed, and even at the lowest dose, the point odds ratio was more than 1.0 **[25]** (**Figure 1a**), but in the final report of Kaiser study **[4]**, odds ratio was less than 1.0, namely 0.94 or 0.95 (**Figure 1b**). The results from the interim report **[24]** (**Figure 1c**) was intermediate between the meta-analysis results (**Figure 1a**) and the final report **(Figure 1b).**

We investigated the reason why such controversial phenomena were observed; bladder cancer risk of Actos became lower in the final results compared with the interim results, and negative tendency of association was observed in the final results.

We conclude that misclassifications of exposure to Actos yield time-related bias **[26-32]** in the Kaiser study and it became more evident after the observation period was prolonged. This time-related bias is precisely described in the next section.

Actos is a PPAR-γ agonist that regulates fat metabolism, and may affect immune and inflammatory reactions. Consequently, it may have carcinogenicity **[34, 35]**. These biological properties are consistent with the findings from clinical, epidemiological and animal toxicity (carcinogenicity) tests **(Figure 2)**.

On the "time-related bias"

"Time-related bias in observational studies can produce illusory results in favour of the treatment group and may affect both cohort and case-control studies, mostly database studies. They are most often a form of differential misclassification bias and should be recognised as they can be generally avoided by appropriate accounting of follow-up time and exposure status in the design and analysis of such studies." **[26]**

Immortal time bias

Immortal time in epidemiology refers to a period of cohort follow-up time during which death (or an outcome that determines end of follow-up) cannot occur. It is defined in the book Modern Epidemiology (K. Rothman, S. Greenland, T. Lash. 3rd Edition, Lippincott Williams & Wilkins, 2008 p. 106-7) **[26]**.

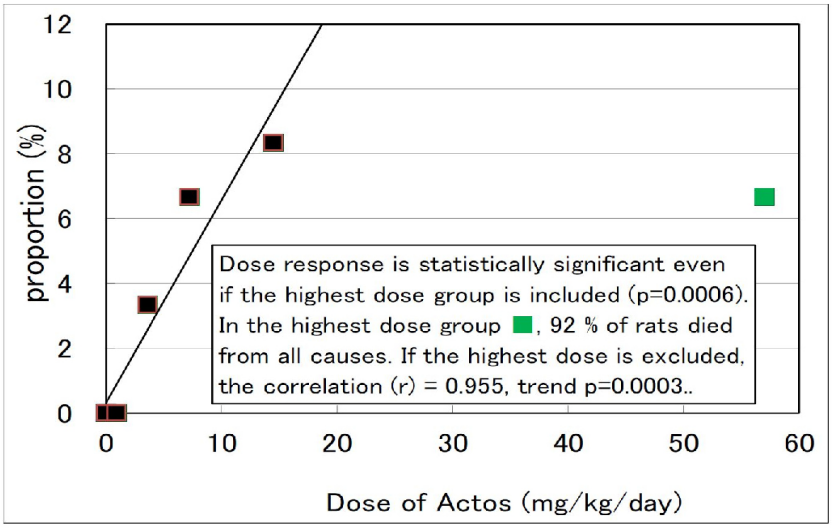
The exposure definition in the methods of Kaiser study:

"Ever use" of pioglitazone and other diabetes medications was defined as "having filled 2 prescriptions for the drug within a 6-month period". Once a patient met the exposure definition, he or she was considered exposed from that point forward.

Figure 3 shows 12 typical individuals by the exposure state of pioglitazone and bladder cancer diagnosis to demonstrate how the immortal time bias results in the final odds ratios, although the Kaiser study conducted so that immortal time bias does not occur.

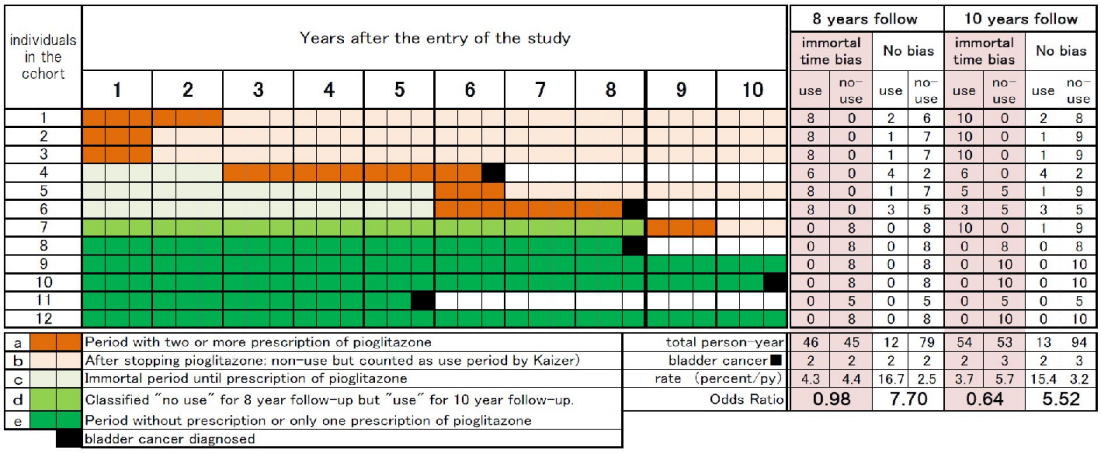
In the **Figure 3**, during the period c (**Case 4-6**) and the period d (**Case 7**) no event occurred. This means that these periods are the immortal time: i.e. a period before Actos being

Figure 2: Actos-dose related increase of proportion of rats with bladder cancer --- from the rats carcinogenicity study for 2 years.



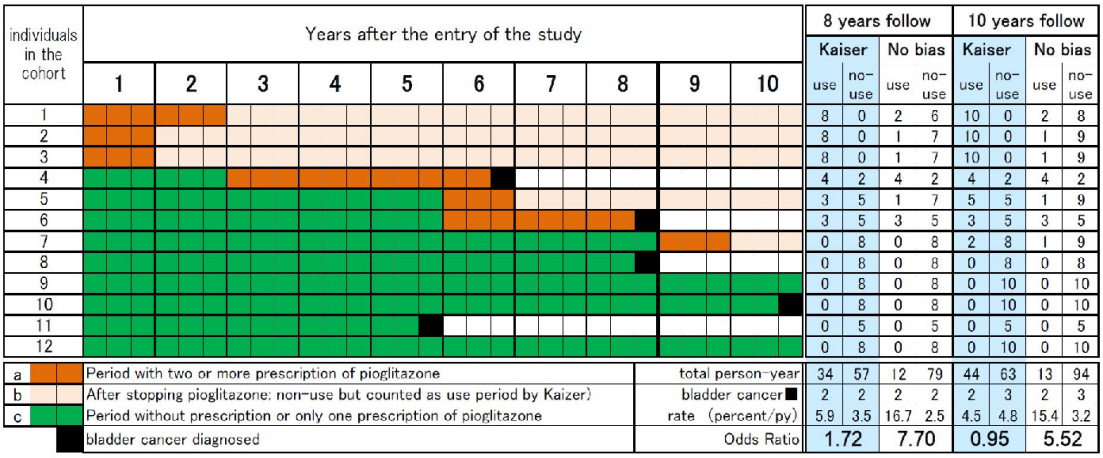
Dose response was statistically significant including the highest dose group. (p=0.0006). All-cause mortality was 40 to 63 % in the control and in the lower dose group of Actos (14.5 mg/kg/day or less). However, all-cause mortality was 91.7% in the highest dose group (57 mg/kg/day). Hence the reason of relatively low incidence of mortality may be derived from the early death caused by the diseases (by Actos) other than bladder cancer.

Figure 3: Theoretical explanation of time related bias including **immortal time bias** in the observational study: Description of 12 typical individuals by the exposure state of pioglitazone and bladder cancer diagnosis



individuals in the cohort	8 years follow				10 years follow			
	immortal time bias		No bias		immortal time bias		No bias	
	use	no-use	use	no-use	use	no-use	use	no-use
1	8	0	2	6	10	0	2	8
2	8	0	1	7	10	0	1	9
3	8	0	1	7	10	0	1	9
4	6	0	4	2	6	0	4	2
5	8	0	1	7	5	5	1	9
6	8	0	3	5	3	5	3	5
7	0	8	0	8	10	0	1	9
8	0	8	0	8	0	8	0	8
9	0	8	0	8	0	10	0	10
10	0	8	0	8	0	10	0	10
11	0	5	0	5	0	5	0	5
12	0	8	0	8	0	10	0	10
total person-year	46	45	12	79	54	53	13	94
bladder cancer ■	2	2	2	2	2	3	2	3
rate (percent/py)	4.3	4.4	16.7	2.5	3.7	5.7	15.4	3.2
Odds Ratio	0.98		7.70		0.64		5.52	

Figure 4:Theoretical explanation of time related bias in **the Kaiser study;** Description of 12 typical individuals by the exposure state of pioglitazone and bladder cancer diagnosis



individuals in the cohort	8 years follow				10 years follow			
	Kaiser		No bias		Kaiser		No bias	
	use	no-use	use	no-use	use	no-use	use	no-use
1	8	0	2	6	10	0	2	8
2	8	0	1	7	10	0	1	9
3	8	0	1	7	10	0	1	9
4	4	2	4	2	4	2	4	2
5	3	5	1	7	5	5	1	9
6	3	5	3	5	3	5	3	5
7	0	8	0	8	2	8	1	9
8	0	8	0	8	0	8	0	8
9	0	8	0	8	0	10	0	10
10	0	8	0	8	0	10	0	10
11	0	5	0	5	0	5	0	5
12	0	8	0	8	0	10	0	10
total person-year	34	57	12	79	44	63	13	94
bladder cancer ■	2	2	2	2	2	3	2	3
rate (percent/py)	5.9	3.5	16.7	2.5	4.5	4.8	15.4	3.2
Odds Ratio	1.72		7.70		0.95		5.52	

prescribed (or in the Kaiser investigation, the time before the second prescription for Actos was issued). The reason why Actos was prescribed in the **Case 4-7** is that an event (bladder cancer) did not occur during these periods.

If an event (bladder cancer) occurred during the period as in the **Case 8, 11**, Actos may not be prescribed after the event. Even if Actos is prescribed, the event during the subsequent period is not used for the analysis.

The odds ratio is 7.7 (eight years follow-up) and 5.5 (ten years follow-up) without bias. However, the odds ratio reversed to 0.98 (eight years follow-up) and 0.64 (ten years follow-up), which are very favourable to the intervention if immortal time bias is not corrected.

In the Kaiser investigation, as in the definition of “exposure”, once the participants are met with the definition of a "user" = “prescribed more than twice within six months", he or she was subsequently considered as “user”, even if Actos was not prescribed after they became a user as the **Case 1-3, 5** and **7**.

In the follow-up study **[33]** conducted after the PROactive study **[22]**, incidence of bladder cancer among Actos non-users was compared between those who received placebo and those who received Actos in the PROactive study. Odds ratio was less than 1 (there is no significant difference) and the positive association between Actos use and bladder cancer disappeared after discontinuation of Actos.

Therefore, if Actos was stopped in the Kaiser study, the participants should be classified as "the non-use group" after that (or at least after one year subsequently). However, the Kaiser study classified them as "the use group" mistakenly.

By using the cases (in the table on **Figure 4**), odds ratios are

calculated at 1.72 (eight years follow-up) and 0.95 (ten years follow-up) if the definition of exposure by Kaiser methods was applied, while the unbiased odds ratios are 7.7 (eight years follow-up) and 5.5 (ten years follow-up).

Because the immortal time bias is avoided in the Kaiser method, the underestimation effect size is reduced compared with that in the **Figure 1**, but still underestimation of risk of bladder cancer by Actos use is clearly shown due to the "time-related bias". This time-related bias should be called "post-exposure bias".

Note that the effect of time-related bias becomes bigger as the observation period becomes longer in both biased methods.

References

1) Takeda Pharmaceutical Company Limited, MediCon. June 2015 http://medical-confidential.com/confidential/2015/06/post-949.html

2) New York Times. Takeda Agrees to Pay $2.4 Billion to Settle Suits Over Cancer Risk of Actos http://www.nytimes.com/2015/04/29/business/takeda-agrees-to-pay-2-4- billion-to-settle-suits-over-cancer-risk-of-actos.html?_r=0

3) Takeda Pharmaceutical Company Limited September 12, 2015 https://www.takeda.co.jp/news/2015/20150912_7126.html

4) Lewis JD, Habel LA, Quesenberry CP, Strom BL, Ferrara A. et al Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons With Diabetes. JAMA. 2015 Jul 21;314(3): 265-77

5) Korhonen P et al. Bladder cancer risk in relation to exposure to pioglitazone among patients with T2DM in the Pan European Multi-Database Bladder Cancer Risk Characterisation Study. Presentation No 169LB, ANDA 75th Scientific Session, Boston, USA, 5-9 June, 2015 http://epidresearch.com/assets/Pioglitazone-Study-News-Release.pdf

6) Pioglitazone Not Significantly Associated With Bladder Cancer--But research reveals association with pancreatic, prostate cancer. Physician's Briefing http://www.physiciansbriefing.com/Article.asp?AID=701540

7) A diabetes resource guide (in Japanese) http://dm-rg.net/news/2015/07/017052.html?pr=dmrg001

8) CareNet (in Japanese): https://www.carenet.com/news/journal/carenet/40411

9) Negative association between Actos and bladder cancer (in Japanese) http://blog.livedoor.jp/fizz_di/archives/1036155095.html

10) Editorial team. "Do not use Actos" Med Check 2001, 1 (1): 36-39.

11) Hama R. Actos may be more harmful than troglitazone (Noscal), TIP "The Informed Prescriber" 2,000:15 (4): 35-40,

12) Hama R. Actos should be banned. TIP "The Informed Prescriber" 2000:15 (10): 107-109.

13) Takeda Pharmaceutical, Summary basis of approval of "Actos: Pioglitazone" 1999

14) Kimoto Y. pioglitazone (Actos) does not improve prognosis of diabetes, but increase heart failure, bladder cancer. TIP "The Informed Prescriber" 2006:21 (1): 3-6. With comments by editorial bord.

15) Hama R. Harm of pioglitazone (Actos). TIP "The Informed Prescriber" 2010:25 (12): 166-168,

16)Hama R and Kimoto Y. Pioglitazone and related agents (including Actos) should be banned TIP "The Informed Prescriber"2011:26 (6): 86-91.

17) Mascitelli L, Pezzetta F. Thiazolidinediones. N Engl J Med 2005; 352: 206.

18) Jiang Y, Jahagirdar BN, Reinhardt RL, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 2002;418: 41-9.

19) Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernick B. Bone is a target for the antidiabetic compound rosiglitazone. Endocrinology 2004;145:401-6.

20) Akune T, Ohba S, Kamekura S, et al. PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. J Clin Invest 2004; 113: 846-55.

21) Schwartz AV, Sellmeyer DE, Feingold KR, et al. Thiazolidinedione use and bone loss in older diabetic adults. Diabetes 2002;51:A237. abstract.

22) Dormandy JA, et al Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005 Oct 8 ; 366:1279-89.

23) Editorial team. Pioglitazone (Actos) was excluded from the reimbursement list in Germany. TIP "The Informed Prescriber"2010:25 (12): 165-166.

24) Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Strom BL. et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care. 2011 Apr; 34(4): 916-22.

25) Turner RM, Kwok CS, Chen-Turner C, Maduakor CA, Singh S, Loke YK. Thiazolidinediones and associated risk of bladder cancer: a systematic review and meta-analysis. Br J Clin Pharmacol. 2014 Aug; 78(2): 258-73.

26) ENCePP Guide on Methodological Standards in Pharmacoepidemiology. http://www.encepp.eu/standards_and_guidances/methodologicalGuide4_2_2_2.shtml

27) van Walraven C, Davis D, Forster AJ, Wells GA. Time-dependent bias was common in survival analyses published in leading clinical journals. J Clin Epidemiol. 2004 Jul; 57(7): 672-82.

28) Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care. 2012 Dec; 35(12): 2665-73.

29) Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol. 2008 Feb 15;167(4): 492-9.

30) A Pharmacoepidemiologic Study on the Relationship between Neuropsychiatric Symptoms and Therapeutic Drugs after Influenza Infection. Pharmacoepidemiology (Japan) 15 (2): 73-92. 2010 https://www.jstage.jst.go.jp/article/jjpe/15/2/15_2_73/_pdf

31) Kubota K Comment. Pharmacoepidemiology (Japan) 15 (2): 93-95. 2010 https://www.jstage.jst.go.jp/article/jjpe/15/2/15_2_73/_pdf

32) Jones M, Del Mar C, Hama R. Statistical and methodological concerns about the beneficial effect of neuraminidase inhibitors on mortality. Lancet Respir Med. 2014; 2(7): e9-e10

33) Erdmann E, Song E, Spanheimer R, van Troostenburg de Bruyn AR, Perez A. Observational follow-up of the PROactive study: a 6-year update. Diabetes Obes Metab. 2014 Jan; 16(1): 63-74.

34) Spiegelman BM. PPARgamma: adipogenic regulator and thiazolidinedione receptor. Diabetes. 1998 Apr?47(4): 50714.

35) Zhang X, Young HA. PPAR and immune system--what do we know? Int Immunopharmacol. 2002 Jul; 2(8): 1029-44

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