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H.pylori eradication may shorten life span

CONTENTS （April 2015,Vol. 1, No. 1）

Editorial

An independent drug bulletin for medical practice

Translated from the original editorial in the Japanese edition of Med Check-TIP #57 (Jan 2015)

New drugs with new modes of action are continuously being developed. Most of the current biggest-selling pharmaceutical products have been marketed in the last 20 years. If these drugs actually benefit health, they will be good for people. However, the development of drugs which prolong life and/or improve patients' quality of life (QOL) has been rare since 1990.

Sometimes, pharmaceutical companies may distort preclinical and clinical data of their products to make them appear attractive. The Diovan scandal in which data was falsified is just the tip of the iceberg. In the case of Tamiflu, Iressa, HPV vaccine and Actos (pioglitazone), the pharmaceutical companies manipulated data to show these drugs are effective and safe. Since the advent of the 21st century, this type of data manipulation has become more common. SGLT-2 inhibitors are such a type of drug developed and introduced in medical practice based on questionable efficacy and safety data. Financial incentives from the pharmaceutical industry have influenced the evaluation of medicines by such parties as the researchers (or medical societies/associations), regulators, public organizations including World Health Organization (WHO), the media and medical journals.

The role of drug bulletins in Japan is very important, as prescribers and public alike are inundated by a flood of information which is often heavily influenced and distorted by the pharmaceutical industry. "The Informed Prescriber" (TIP: founded in 1986) for professionals and "Med Check, Save Lives" (founded in 2001) targetting general public have provided evidence based rational information which meets the needs of professionals and the general public. This is possible, because they are completely independent: i.e. free from advertisement, funding or any other assistance from industry.

The Japanese edition of this bulletin "**Med Check - The Informed Prescriber**" or "**Med Check-TIP**" started in January 2015 as a single drug bulletin integrating the two abovementioned bulletins. Although aimed primarily at professionals, we endeavour to produce articles that can be understood by people and the media.

We will take a critical look at new products and with critical evaluation. We will show some of the drugs essential to medical practice. Metronidazole (issue #57) and methadone (# 58) are two examples.

Valuable information that cannot be obtained from any other source will be provided in the new bulletin "**Med Check-TIP**". Despite criticizing substandard products for the past 30 years, we have never been sued by a pharmaceutical company. This is because we concientiously and thoroughly investigate the evidence of efficacy and harm by assessing clinical evidence as well as animal experiments including toxicity studies and epidemiological studies. When we notice that important data is unpublished, we ask the pharmaceutical companies to disclose the data and have it analyzed independently. The Tamiflu case is one such example, where we have uncovered evidence of increased brain toxicity.
(http://doi.wiley.com/10.1002/14651858.CD008965.pub4)

Policy makers and regulatory authorities should be obligated to disclose drug approval dossiers to protect public health, as demanded by the Cochrane statement.
http://www.cochranelibrary.com/editorial/10.1002/14651858.ED000035

We provide information that is completely independent of the pharmaceutical industry.

It is important for the bulletin to be read by as many people as possible in order to improve medical practices for the common good. We welcome feedback from readers, as it can improve the bulletin qualitatively and quantitatively.

We need ***your*** help and support in spreading the word on our bulletin "**Med Check-TIP**".

SGLT-2 inhibitors:

Unacceptable products -- can we call these "medicines"?

Why such toxic agents are touted as "medicines"? Excerpted from Med Check TIP 2015; 15 (#57); pp. 3-7.
Various concerns were expressed before approval. Excerpted from Med Check TIP 2015; 15 (#58); pp. 35-36.
ipragliflozin, tofogliflozin, tabaglyflozin, luseogliflozin, canagliflozin and empagliflozin

Introduction

Six new hypoglycemic agents in one class of product, SGLT-2 inhibitors were marketed with buzzwords like "new mechanism of action" in recent one year (between April 2014 and February 2015) in Japan. The endpoint of agents which target chronic diseases such as diabetes mellitus must be "prolongation of life" and/or improvement in "quality of life (QOL)" (Table 1**[1]**) .

However, like other hypoglycemic agents, SGLT-2 inhibitors were not adequately endpoint tested before approval but merely by indirect surrogate endpoints such as "reduction of fasting glucose level" and "reduction or of "per cent glycosylated hemoglobin (HbA1c)." **[2-6]** Even disease specific incidence and/or mortality due to such complications as cardiovascular and/or cerebrovascular incidence/ mortality were not investigated among patients in long term randomized controlled trials.

The mechanism of action of SGLT-2 inhibitors is the lowering of blood glucose level by inhibiting glucose reabsorption via renal tubules and by excreting glucose through urine. They do not lead to the improvement of glucose metabolism but only act to lower blood glucose level.

Leading Japanese diabetologists warned the public of the harmful effects of SGLT-2 inhibitors, not once but twice soon after marketing: saying "Harmful effects of SGLT-2 inhibitors that we were concerned about became reality."**[7]** The concerns with SGLT-2 inhibitors included (1) serious hypoglycemia, (2) dehydration, (3) ketoacidosis, (4) thromboembolism including cerebrovascular diseases, (5) urinary tract/genital infections, (6) serious cutaneous complications such as Stevens-Jonson syndrome.

Abstract of Med Check TIP 2015; 15 (#57); pp. 3-7.

These clinical problems that were revealed just after the marketing of SGLT-2 inhibitors, but which were easily predictable in the preclinical stage of these products included:
1) that SGLT-2 receptors exist not only in renal tubule cells, but in virtually all cells, e.g. the central nervous system**[8,9]**.
2) Even if SGLT-2 inhibitors selectively inhibit SGLT-2 receptors, a high concentration of SGLT-2 inhibitors in the intestinal tract may also inhibit SGLT-1 receptors in the intestines.
3) Non-observable adverse effect level (NOAEL) was not determined for most of the products in the toxicity tests.
4) Death, arterial mineralization (calcification) **[10]**and pheochromocytoma increased dose-dependently **(figure 1, figure 2a and figure 2b).**
5) Although a patient died due to acute chronic pyelonephritis with increased urine volume related to a SGLT-2 inhibitor, the agent was considered safe according to the manufacturer's claim, namely "these are the consequence of pharmacological action of SGLT-2 inhibitor" concluding "it is not a toxic sign of the SGLT-2 inhibitor."

As a result, the regulator concluded the SGLT-2 inhibitor "is safe for use in practice."

Table 1. Strength of endpoints
(ranked in descending order) **[1]**

A.Total mortality (or overall survival)
Comment: the most important and is the most easily defined and least subject to investigator bias.
B-1. Cause-specific mortality
Comment: more subjective than total mortality, more subject to investigator bias in its determination. It may also miss important effects of therapy that actually shorten overall survival.
B-2 Cause-specific morbidity (or in combination with B-1) *a
Comment: similar as above (B-1)
C. Carefully assessed quality of life *b.
D. Indirect surrogates
1) Disease-free survival
2) Progression-free survival
3) Tumour response rate
4) Scales and other measures *a

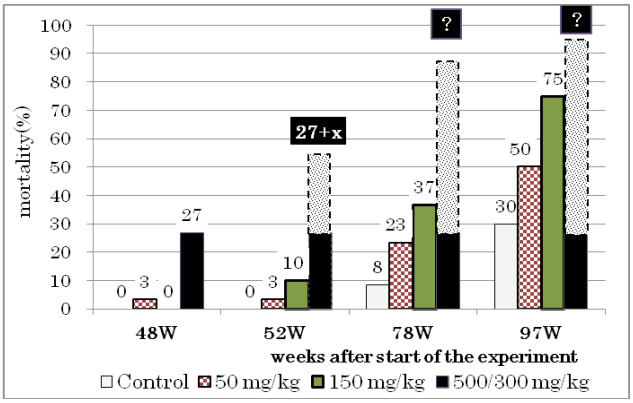
Source: Based on a hierarchy from the US National Cancer Institute web site (http://www.cancer.gov/cancertopics/pdq/levels-evidence-adult-treatment/)
***a:** Added by the manual's editors, to make it more applicable to other diseases and interventions.
***b:** If "carefully assessed quality of life" is combined with overall survival, the combined endpoint could be classified as A-2.(simplified from ref **[1]**)

Abstract of Med Check TIP 2015; 15 (#58); pp. 35-36.

By mid-February 2015, the number of deaths related to the use of SGLT-2 inhibitors increased to 17 patients in total. It was revealed in the authorized documents that all problems warned againts by diabetologists just after marketing were well known during the clinical trials and were presented during the discussion on approval of SGLT-2 inhibitors by drug regulators. In other words, the following problems were already known in all SGLT-2 inhibitors before their marketing commenced **[2-6]**: **(1)** severe hypoglycemia, **(2)** urinary tract and genital infections, **(3)** pollakiuria and polyuria, **(4)** dehydration, disruption of body electrolyte balance, weight loss, **(5)** incease of ketone body , **(6)** adverse effect on bone

"Med Check" #44 and #45 (currently only available in Japanese) provide more information on **principles of diabetes treatment** including the **assessment** of **diabetic drugs** other than SGLT-2 inhibitors. A condensed version can be found under **"Plain Language Summary"** on **p.13**.

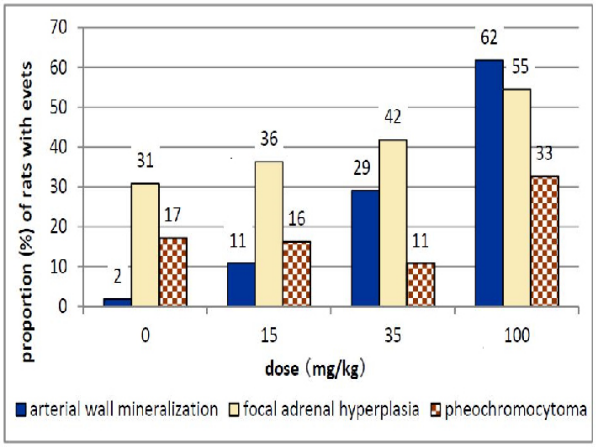
Figure1 : Mortality in mice carcinogenicity study (ipragliflozin, male)



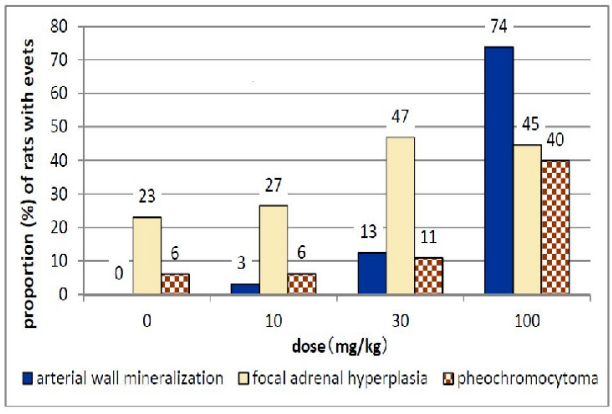
N=60 for each dose group. Chi square for linear trend was significant (P<0.0001) at 52w with the assumption of 16 deaths (similar to that at 48 w in the highest dose groups. The results at 78W and 97W, for trend were p=0.002 and p<0.0001 without including the highest group. Mortality in the lowest group (50 mg/kg) was significantly higher than control group both at 78w (OR=3.35; 95% CI: 1.12 to 10.0, p=0.0244) and at 97w (OR= 2.33, 95%CI; 1.10 to 4.93, p=0.0253). Hence, safe dose in which deaths do not occur was not determined in this toxicity study.

Figure 2 Dose-related findings in the rat carcinogenicity study

(a) tofogliflozin



(b) canagliflozin



concentration, (7) cardiovascular risk, and (8) malignant tumours.

Renal, hepatic and gastrointestinal adverse reactions were also observed for some products. Potential harm to the central nervous system is predicated on the fact that nerve cells have SGLT-2 receptors with signs and symptoms of neuropsychiatric toxicities being observed in animal toxicity tests. Toxicities may be problematic especially in the elderly.

Although carcinogenicity was not aparent in the animal experiments excepting an increase in adrenal pheochromocytoma, clinical trials of dapagliflozin showed that cancers in all sites were observed more frequently with statistical significance in the dapagliflozin group (25/5936) compared to the control group (4/3403): odds ratio 3.59 (95% CI: 1.25 to 10.34, p=0.011). Increases in breast cancer (12 vs 2) and bladder cancer (5 vs 0) were especially noted.

In the trials of other SGLT-2 inhibitors such as ipragliflozin, luseogliflozin and canagliflozin, cancers were reported more frequently in the active arms than in the control groups: odds ratio was 1.1 for canagliflozin and 4.3 for ipragliflozin (not statistically significant).

Bladder cancer may increase in predisposed patients through stimulation from persistent inflammation in the bladder with long-term bladder expansion due to increased urinary volume.

In conclusion, all problems of SGLT-2 inhibitors revealed just after marketing were already known before approval. Even if the fasting glucose level and HbA1c are improved, neither improvement in metabolism nor in prolongation of life is expected in diabetic patients by SGLT-2 inhibitors.

SGLT-2 inhibitors should be banned. We strongly recommend physicians not to prescribe them.

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Methadone :Limited use:

Useful only in opioid rotation with special precautions

Translated as synopsis from Med Check TIP 2015; 15 (Mar; #58); 27-30.

Synopsis:

Methadone hydrochloride ("methadone", brand name: Methapain)[1] was first synthesized in Germany in 1937. It was approved in the United States in 1947 as an opioid. Vincent Dole et al. reported in 1964 that it was useful as an alternative therapy for patients with drug addiction [2]. It subsequently came into worldwide for the treatment of patients with drug addictions [2].

After methadone was approved as a strong analgesic in the United States, it subsequently was approved in many countries since around 1990. In Japan, methadone did not start to be marketed until March 2013, after it was finally approved in September 2012

Methadone has a high affinity to an opioid μ receptor similar to common opioids including morphine [1]. In addition, it acts as an antagonist to N-methyl-D-aspartate (NMDA) receptor [1]. Because of the latter effect, it is used as one of the most important medicines in the "opioid rotation therapy" for the patients who do not respond to and/or have become tolerant to common opioids such as morphine or oxycodone [4]. It will be a boon to patients who suffer from refractory pain if used appropriately. However, it could easily induce serious harm including respiratory arrest and/or lethal arrhythmia with an overdose if not used appropriately. It is well known that there have been many fatalities [5,6].

Due to the characteristic pharmacokinetics of methadone, dose adjustment may be difficult. In order to prevent serious harm induced by methadone, it is essential for prescribers to know pharmacokinetics and interactions of methadone well, and to carefully consider the clinical conditions of the patients.

For switching from morphine or oxycodone to methadone, 3DS method (3 days switch method) is superior [16].

Supplement to the synopsis:

Serious clinical condition resulting in death: Respiratory suppression and lethal arrhythmia

Pathophysiologic conditions resulting in death from methadone overdose include respiratory suppression and lethal arrhythmia. In order to prevent these deaths, prescribers should be aware of the risk factors which exacerbate these conditions so that they can be avoided.

Risk factors that could exacerbate **respiratory suppression** are: old age, liver dysfunction, sleep apnea syndrome, concomitant substances (including alcohol use, benzodiazepines and antidepressants), excessive-dose and/or rapidly increased dose of methadone.

The risk factor that could exacerbate **lethal arrhythmia** (Torsades de Pointes) are: female gender, electrolyte abnormality (e.g. low potassium and magnesium levels), history and complication of heart diseases (especially heart failure), bradycardia, diabetes, QT prolongation, concomitant use of drugs that prolong QT time (e.g. antiarrhythmic agents, neuroleptic, tricyclic antidepressants, cilostazol, azithromycin, moxifloxacin and oseltamivir).

Characteristic Pharmacokinetics of Methadone

Methadone is metabolized by CYP3A4 and CYP2B6 and is able to self-induce these enzymes. The elimination half-life is reduced after longer periods of use. Conversely, during the early phase of commencement, the elimination half-life of methadone is long. Hence, the risk of accumulation is higher in the initial phase, extra caution is necessary especially during the first 4 to 6 days after initial use.

Interaction is associated with the followings: methadone is metabolized by **CYP3A4** and **CYP2B6**, and it is one of the substrates of **p-glycoprotein**.

Azole-based antifungal agents and macrolide derived antibiotics raise the blood level of methadone by CYP3A4 antagonists. The paroxetine raises blood level of the methadone by CYP2D6 antagonists. Rifampicin, phenytoin and carbamazepine induce metabolising enzymes, promote the metabolism of methadone, and reduce blood level.

Because p-glycoprotein inhibits absorption via the gastrointestinal tract and is an efflux transporter at the blood-brain barrier to prevent increasing methadone levels in plasma and in the brain, p-glycoprotein antagonists such as cyclosporine or clarithromycin may increase methadone levels.

The clinical condition of high risk patients:

Renal failure: Dose reduction and prolongation of the interval of dosing are recommended in patients suffering from renal failure. Methadone in the system is largely unaffected by haemodialysis or peritoneal dialysis.

Liver damage: Because the prolongation of the elimination half-life is reported in patients with severe liver damage, methadone use should be avoided in them. The use of methadone is restricted even in patients with mild to moderate liver disease.

Elderly people: Because renal, hepatic, cardio-pulmonary, and other physiological conditions including neurological functions, are all reduced, careful management is essential, especially to prevent respiratory failure or fatal arrhythmias.

Conversion methods in opioid rotation:

Two methods are available for rotation from other opioids to methadone. One is the **SAG** method (Stop And Go method: discontinue previous opioids, and start methadone promptly).

The other is the **3DS** method (3 Day Switch method: tapering previous opioids for three days and gradually increasing methadone).

Moksnes et al.**[16]** compared these two methods for the first time in a prospective randomized controlled trial. Thirty-five participants with cancer who had been taking relatively high-doses of morphine or oxycodone were divided into two groups with each placed on one of the two switching methods. The SAG method was used in 16 patients (average dose was 900 mg/day of equivalent oral morphine dose), and the 3DS method was used in 19 patients (average dose was 1,330 mg/day). More patients withdrew due to serious adverse events in the SAG method group: six serious adverse events including two deaths due to myocardial infarction and pulmonary embolism occurred in the SAG group. On the other hand, only one adverse event occurrence was reported in the 3DS group. The odds ratio was 10.8 (p=0.0318). In addition, in the SAG group, pain management was poorer than that in 3DS group **[16]**. It should be concluded that the 3DS method is superior to SAG method both in terms of treatment adherence and pain management.

No "Plain Language Summary" is available for this drug, because this is a very specialized drug highly restrictive use in patients.

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H. pylori eradication may shorten life span

Gastric cancer risk decreases, but, incidence of *C. difficile* infections and pneumonia increases

Abstract:

Proton pump inhibitor (PPI) usage increases the risk of *Clostridium difficile (C. difficile)* infections. Underlying factors for this phenomenon include the high prevalence of asymptomatic *C. difficile* carriage, and vacuolar proton pump (V-ATPase) inhibition in every eukaryotic cell by PPI resulting in cell function impairment. Efficacy of *H. pylori* eradication in asymptomatic carriers needs to be evaluated by weighing potential benefits against any detrimental effects including increased infection risk and taking overall long-term survival rates into account. Meta-analysis of long-term randomized controlled trials (RCTs) showed decreasing gastric cancer incidence and non-significant increases in all-cause mortality in the *H. pylori* eradicated group vs. the non-eradicated. Hence, *H. pylori* should not be eradicated in otherwise healthy carriers.

Introduction

The need of metronidazole use has been increasing due to recent rises in *C. difficile* infections **[1a]**. However, the continuous use of metronidazole induces neuropathy (both peripheral and central) dose-dependently **[1b]**. Increases in *C. difficile* infections are attributable to the use of proton pump inhibitors (PPIs) **[2]**.

We reviewed the mechanisms behind increased *C. difficile* infections in the context of PPI usage and its long-term outcomes including overall survival rates.

The following points will be discussed:

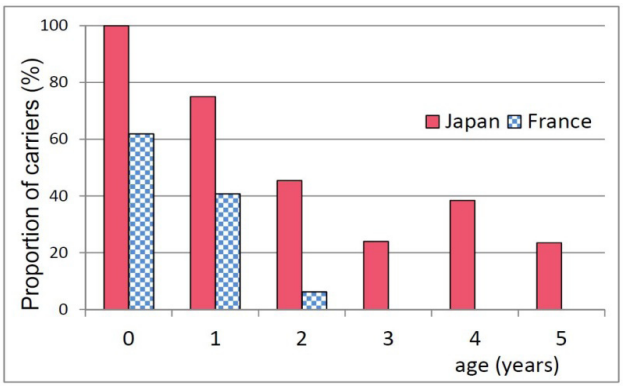
(1) Natural history of *C. difficile* infections
(2) *C. difficile* infection risk factors: including PPI, antibiotics and anticancer agents
(3) Effects on overall survival rates in long-term RCTs
(4) PPI inhibits proton pump activity in gastric parietal cells and V-ATPase in systemic cells
(5) Mechanism behind increased mortality risk

(1) Prevalence of *C. difficile* carriage is high

Prevalence of asymptomatic *C. difficile* carriage in neonates is lower than that in mothers. However, 100 % of affected infants were infected during the first 12 months after birth and prevalence fell subsequently **[3]** (**figure 1**). In France, a year-long monthly follow-up study involving 10 healthy infants to determine the incidence of intestinal *C. difficile* colonization was conducted. **[4]**. All subjects became infected with *C. difficile* during the first 6 months after birth **[4]**. A cross sectional study revealed that the prevalence of asymptomatic carriage fell to 6% in 2 year old infants, the same level as in adults **[4]** (**figure 1**). The prevalence of asymptomatic carriage of *C. difficile* in Japanese infants is significantly higher than in French infants: odds ratio (OR) = 7.1 (95% CI: 2.5, 19.9, p=0.0002).

The prevalence of *C. difficile* colonization among Japanese adults is reported as 7.6%, which is comparable to that in other countries **[5]**. It is reported **[9]** that the prevalence of *C. difficile* colonization among patients with recent inpatient healthcare exposure is at least double (7%–17%) that of patients without inpatient healthcare exposure (3% –7%).

Figure 1. *C. difficile* carriage in infants: trends by age (Comparison: Japan and France)



Note: French study includes a 36.2-month old child in 2-year old group. Pooled odds ratio (POR) using data of 0-year olds, 1-year olds, and 2 year olds is 7.1 (95% CI: 2.5, 19.9, p=0.0002).

(2) PPI increases CDAD incidence two- to seven fold

Use of gastric acid antagonist drugs such as PPI, Histamine-2 antagonists (H_2-bl) and sucralfate was reported as a ***C. difficile* associated diarrhea** (CDAD) risk factor in a 1994 case-control study **[10]**. However in this study, no risks associated with the breakdown of gastric acid antagonists were reported. In 2003 (a case-control study) **[11]** and 2004 (a case-control and a cohort study) **[12]**, PPI was reported as an independent risk factor for CDAD. Since 2008, some similar reports and several meta-analyses followed **[13-16]**.

Among these, the meta-analysis by Deshpande et al **[14]** is most reliable because case-control studies and cohort studies were meta-analysed separately. Pooled odds ratio (POR) of PPI for CDAD was 1.78 (95% CI: 1.41, 2.25, p<0.0001) using cohort studies and 2.22 (1.82, 2.70, p<0.0001) for case-control studies.

In a study by Dial et al **[12]**, analysing the risk of CDAD among long-term PPI users (6 months or more), the hazard ratio (HR) was 6.9 (95% CI: 2.3 to 20.8, p=0.0001), compared to 3.1 (95% CI: 1.7 to 5.6, p=0.0001) for any duration of PPI

use. (**Table 1**) Recurrent CDAD risk associated with PPI use calculated using the data of Dial et al. **[12]** was very high: OR = 16.8 (**Table 1**).

PPI, antibiotics and anticancer drugs constitute independent risk factors **[11]**. When antibiotics and PPI were combined, the OR was 5.4. When all three factors were combined, OR was 43.2 **[11]**. (**Table 1**)

H_2-blocker exposure was also revealed as a risk factor for CDAD by meta-analysis **[17]**: POR was 1.44 (1.22-1.70).

Table 1: ***C. difficile*** **infection risk factors**

ref.	risk factors	odds ratio (OR)		p value
		OR	(95% CI)	
12	PPI use (any duration of use)	3.1	(1.7, 5.6)	0.0001
	PPI use >= 6M	6.9	(2.3, 20.8)	0.0001
	PPI (recurrent CDAD vs non-CDAD)	16.8	(3.7, 76.5)	<0.0001
11	PPI+antibiotics vs no risk factor	5.4	(2.2, 13.2)	
	PPI+antibiotics+anticancer vs non	43.2	(5.7, 330.4)	

CCAD: *C. difficile* associated diarrhea, CI: confidence interval

Table 2: Gastric cancer incidence and mortality, cancer mortality (all sites) and all-cause mortality (source: RCT with longest follow up duration [19])

outcomes		adjusted hazard ratio (HR)		p value
		HR	(95%C)I	
gastric cancer	incidence	0.61	(0.38, 0.96)	0.032
	mortality	0.67	(0.36, 1.28)	0.22
mortality	cancer (all sites)	0.97	(0.68, 1.39)	0.89
	all-cause	1.14	(0.90, 1.46)	0.28

(3) Possibility of higher PPI-associated all-cause mortality risk

A meta-analysis of RCTs reporting among the long-term (4 to 15 years) outcomes after *H. pylori* eradication was reported **[18]**. In this study, gastric cancer incidence decreased with pooled relative risk (RR) at 0.66 (0.46, 0.95). However, the eradication group showed a non-significant increase in all-cause mortality compared with the placebo (untreated) group: pooled OR = 1.10 (0.89, 1.37). To date, long-term outcomes after *H. pylori* eradication in asymptomatic carriers have been reported primarily in Asian subjects.

The results from an RCT with a long-term follow-up (15 years) **[19]** showed non-significant increases of adjusted HR for all-cause mortality rates in the eradicated group: 1.14 (0.90, 1.46, p= 0.28). In populations with low gastric cancer mortality, all-cause mortality risk may be higher.

(4) The proton pump is essential to maintain the normal functions of many cells

The vacuolar (H+)-ATPases (V-ATPases or "vacuolar proton pumps") are ATP-dependent proton pumps responsible for both acidification of intracellular compartments and, for certain cell types, proton transport across the plasma membrane **[8]**. Intracellular V-ATPases function in both endocytic and intracellular membrane traffic, the processing and degradation of macromolecules in secretory and digestive compartments, the coupled transport of small molecules such as neurotransmitters and ATP as well as the entry of pathogenic agents, including envelope viruses and bacterial toxins. V-ATPases are present in the plasma membrane of renal cells, osteoclasts, macrophages, epididymal cells and certain tumour cells where they are important for urinary acidification, bone resorption, pH homeostasis, sperm maturation and tumour cell invasion, respectively. PPI inhibits not only the proton pump of gastric parietal cells (H+/K+ATPase) but also V-ATPases **[7]**.

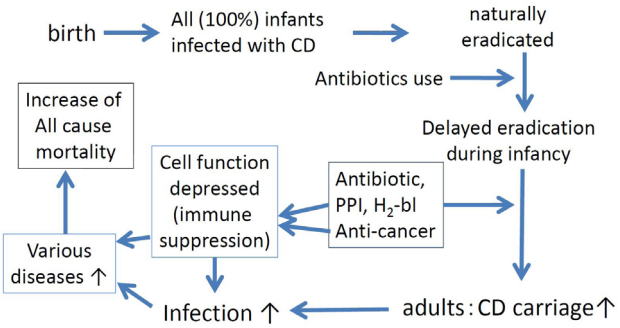
As a result, PPI inhibits immune response and inflammation during infections or in situations where tissue repair is necessary. It could affect bone metabolism as well as neurological and renal functions, among others. **[7, 8]**.

(5) Mechanisms behind increased mortality risk

Increases in all-cause mortality after *H. pylori* eradication using PPI may be related to the mechanisms that inhibit vacuolar proton pumps which is present in every cell and has an important role in maintaining the functions of each cell.

Based on above-mentioned examination results, we propose a hypothesis on the natural history of *C. difficile* infections and the effects of medical intervention as shown in **figure 2**.

Figure 2
A hypothesis on the natural history of CD infections and the effects of medical intervention



CD: *C. difficile*, PPI: Proton pump inhibitor, H_2-bl: H_2 blocker

In practice

Asymptomatic *H. pylori* carriers should not be eradicated. We strongly recommend against repeated eradication regimens. It is necessary for prescribers to only use PPI for short-term treatment of peptic ulcers (6 weeks for duodenal ulcer and 8 weeks for gastric ulcer) as recommended in the labeling of PPIs. Long-term outcomes of combination regimens combining PPI and non-steroidal anti-inflammatory drugs (NSAIDs) for rheumatoid arthritis or low-dose aspirin for prevention of thrombotic diseases have never been assessed for all-cause mortality, the strongest endpoint of treatment **[see p3 Table 1] [a]**.

We recommend against long term use of PPI for reflux oesophagitis or non-erosive gastroesophageal reflux.

[a]: *One patient in the lansoprazole group (n=62) succumbed to pneumonia after a stroke in a randomized controlled trial with 123 participants in both groups and followed for one year [20].*

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Harm of HPV vaccine:

Latest information and examination of epidemiological studies

Abstract: According to the latest pharmacovigilance data, the incidence of serious adverse reactions to HPV vaccine is 3.2% per year (3,200 cases per 100,000 person-years). This is similar to the incidence rate of serious adverse events within 1.2 years after the first vaccination (annual rate of 2.8%) reported in randomized controlled trials (RCT) for Cervarix. In Cervarix RCTs, the excess incidence of serious reactions, autoimmune diseases and death after 3.4 years compared with reactions from 1.2 to 3.4 years was respectively calculated to be 4,000 patients, 630 patients and over 100 deaths per 100,000 person-years. These might also occur in Japan. The epidemiological surveys from Europe and North America that Japan's Ministry of Health, Labour and Welfare (MHLW) used as evidence for safety of the vaccine have flawed methodologies. One study confused prevalence with incidence, and the other two have serious risk of bias attributable to the "healthy vaccinee effect". While there is no evidence yet confirming that HPV vaccination decreases the incidence of and mortality from cervical cancer, assuming that the vaccine could halve cervical cancer mortality, the expected maximum benefit would be 2.0 deaths per 100,000 person-years. Hence, the harm experienced to date is overwhelmingly greater than the benefit expected.

Introduction

The NPO Japan Institute of Pharmacovigilance (NPOJIP) has repeatedly discussed the harmful effects of HPV vaccine in the Informed Prescriber (TIP) **[1-4]**, "Med Check" **[5-9]** and the "On-line Med Check" **[10]**. In 2014, reports of diseases with intense symptoms appeared one after another. They were so severe that experts on neurologic intractable diseases, childhood collagen diseases and fibromyalgia unanimously stated that they had never seen such serious diseases before **[11]**. As of September 2014, more than two hundred such serious cases had been reported **[12]**.

Although the MHLW withdrew its active recommendation after 14th June 2013, it denied the causality of HPV vaccination in the subsequent onset of severe symptoms, and

has not retracted the "Psychosomatic Reaction Theory **[13]**." Moreover on the association with autoimmune diseases, the MHLW has not overturned its conclusion that the vaccine is safe **[13]** by referring to several epidemiological studies **[14-17]**.

This review primarily examines the problems found in the epidemiological studies that the MHLW uses as a basis for determining the safety of the vaccine. In addition, it introduces the result of the latest analysis of serious adverse reactions, and compares the harms with the possible maximum benefit of HPV vaccination. We also respond to some criticisms **[18]** on the method of analysis we employed previously, and discuss that the MHLW and HPV vaccination advocates have little evidence to support their claim.

No need to compare incidence of serious reactions with lifelong mortality: One year for mortality is enough

We first published an article assessing the potential benefits and harms of HPV vaccines in April 2013 **[1] (See a brief description on p 13).** Some criticisms to our article appeared subsequently. Of these, Kinugasa **[18]** criticised our methods of analysis. He point out that we used annual mortality instead of lifetime mortality that is higher by several orders of ten than the former making it fundamentally flawed.

After the active recommendation of the vaccine was withdrawn, serious reactions became apparent even long after HPV vaccine administration. The article concerned **[1]** was written before the active recommendation was withdrawn, and at that time, approximately 800 cases of serious reactions had been reported out of 2,600,000 persons vaccinated with HPV vaccine (30 cases per 100,000 persons). Serious reactions after inoculation disclosed by the MHLW include reports both from pharmaceutical companies and directly from doctors. The MHLW limited the reporting of events to those that occurred within 30 days of inoculation. In fact, cases involving serious reactions occurring later than one month were extremely rare (0.5% of the cases reported). Therefore, data on cases with adverse reactions should have been collected even beyond one year after inoculation.

On the other hand, there is no evidence yet to prove that HPV vaccines reduce the incidence of cervical cancer fatalities. Even if we assume that the vaccine can cut the incidence of cervical cancer in half, the expected decrease will only be 2.0 per 100,000 person-years. In order to balance the benefits and the serious reactions within one month after inoculation, the potential benefit must be 0.2 per 100,000 person-years (one-twelfth of the annual maximum preventable mortality). It is not necessary to compare the frequency of serious adverse reactions to HPV vaccine with lifelong cumulative cervical cancer mortality.

Annual incidence of serious reaction is 3.2% in Japan:

Meanwhile, since the active recommendation was retracted in June 2013, it has become well known that the vaccine might induce serious harms even long after inoculation. Out of 217 persons who were vaccinated with Cervarix between 1st August and 30th September 2013 (after the harms became well known), four cases of serious reactions were reported by 31st March 2014 **[13b]**. Since the four cases of serious reactions were reported during an average seven-month follow-up period, the annual incidence amounts to 3.2% (95% CI: 0.9-7.9), which means 3,200 per 100,000 person-years. Assuming that the maximum expected annual preventive effect is 2.0%, the incidence of serious reactions to the vaccine is more than 1,500 times higher.

This finding (3.2% per year) is almost equivalent to the annual incidence of serious adverse events within 1.2 years (2.8%; 95%CI: 2.6-3.1) in Cervarix RCTs **(figure** on p11**) [supplementary references]**. The excess incidence or excess mortality of serious adverse events, autoimmune diseases, and death after 3.4 years over those from 1.2 to 3.4 years in Cervarix RCTs are about 4,000, 630 and more than 100 deaths per 100,000 person-years respectively. Considering these findings, serious reactions might occur after 3.4 years at similar incidence rates also in Japan.

Four years have passed since the first marketing of Cervarix in November 2010. After the active recommendation was canceled and serious reactions to HPV vaccine become well known, autoimmune disease, dysfunction in brain and/or serious neuropathy occurring long after inoculation have begun to be reported. As it is very likely that serious adverse reactions would occur in the future, those who were vaccinated should be under close monitoring.

Epidemiological studies on HPV vaccine and autoimmune diseases:

Japan's MHLW states "No evidence for causality between the HPV vaccine and known autoimmune diseases such as rheumatoid arthritis and SLE was evident in cases involving extensive pain or motor disturbance."

This is based on the following five epidemiological studies: a systematic review of RCTs **[14]**, Siegrest's paper **[15]**, Gee' s paper **[16]**, Arnheim-Dahlstrom's paper **[17]** and Institute of Medicine of the National Academies (IMNA) report. Kinugasa **[18]** based his argument only on the Arnheim-Dahlstrom article. This review examines these published articles except for the IMNA report which remains unpublished..

a) Safety cannot be proven by RCTs of two vaccines that used problematic adjuvant (preparation) in both the active and control groups:

The MHLW remarked on the result of the systematic review and the meta-analysis **[14]** that there was no difference in risk of adverse events between the vaccinated and control groups. However, in all RCTs examined in the systematic review, potentially harmful adjuvants or adjuvanted products were used as the control: alum adjuvant for Gardasil and alum adjuvanted hepatitis-A vaccine for Cervarix. Therefore, even though there was no difference in harm between the two groups, it may be too early to conclude that the vaccine is safe. Because the incidence of adverse events fluctuates significantly over time **[4,6]**, it may be reasonable to consider that the adverse effects of HPV vaccine are in part due to adjuvants.

As the harms of adjuvants are also discussed in other papers **[2,8,9]**, this review does not do so in detail. The problems of epidemiological studies that claim the safety of the vaccine are described in the following sections.

b) A study that confused prevalence with incidence:

Siegrist et al. **[15]** calculated the "frequency" by using the number of health insured females aged 9-18 and 19-30

years old as a denominator and the number of persons who consulted a doctor (outpatient, emergency and hospitalization) at least once in 2005 as a numerator. The MHLW estimated the expected number of patients with autoimmune diseases in 3,300,000 vaccinated persons. For example, as multiple sclerosis occurred one per 100,000 person-years in the Siegrist study, the MHLW calculated that 30 cases are expected to occur in 3,300,000 persons inoculated with HPV vaccine in Japan.

However, the "frequency" Siegrest et al. showed is not the "incidence" (or newly occurred disease among certain population within a certain period of time). Their frequency is the "prevalence" (or a proportion of persons having a disease among certain population at a certain point in time). Since autoimmune diseases do not easily remit, prevalence is 10-30 times higher than incidence in general. For instance, in the case of multiple sclerosis, the ratio of prevalence to incidence in various countries is about twenty on average **[19]**. This shows that the "frequency" Siegrist et al. reported cannot be the "incidence" of autoimmune diseases and cannot be compared with autoimmune diseases that newly occur after inoculation of the vaccine.

According to Siegrist et al., 11 out of approximately 215,000 women aged 9-18 years old consulted a doctor for multiple sclerosis/optic neuritis once or more in the study year. As the prevalence is 5.1 per 100,000 person-years, the incidence is assumed to be approximately 0.25 per 100,000 person-years. It is lower than the incidence of multiple sclerosis for the women of the same age group in general population (1 to 5 per 100,000 person-years) **[7]**. For one month, it can be converted to 0.021 per 100,000 person-months or 0.7 per 3,300,000 person-months.

Incidence of multiple sclerosis among Japanese is lower than one-tenth that in the West **[19-20]**; thus, it is very low. Therefore, even a single case of onset might signify high incidence. Two cases of optic neuritis, four ADEM, one multiple sclerosis, and one demyelinating central nerve disorder have already been reported after HPV vaccination **[13]**. Optic neuritis often signal the onset of multiple sclerosis, and at least one case of ADEM is reportedly uncured and possibly developing into multiple sclerosis. Demyelinating central nerve disorder and multiple sclerosis are almost synonymous. This means that the incidence is extremely high with three serious cases that may possibly be multiple sclerosis. Moreover, in Gardasil RCTs, incidence of multiple sclerosis was **14.7** per 100,000 person-years **[4,7]**, which is approximately sixty-times that in Siegrist's study.

c) Healthy vaccinee effect is not considered

The MHLW argues "There is no significant increase of risks," referring to Gee's article. The fundamental flaw of Gee and Arnheim-Dahlstrom is that they do not correct substantial confounding bias caused by the "healthy vaccinee effect" **[21, 22]**. People usually prone to fever and infection tend to avoid vaccination. Hence, non-vaccinated people are sicklier than vaccinated people and autoimmune diseases often follow infection. Therefore, even if high incidence of autoimmune diseases is observed among vaccinated people, it will simply be offset by the diseases in sickly non-vaccinated people. This is **the "healthy vaccinee effect."**

In the Gee article, selection criteria for the control group are not clearly stated. This alone is enough to make the study unreliable. Additionally, it is likely that outpatients who consulted for any reasons other than vaccination were selected for the control group. This means that the control group included many patients with infections, increasing the incidence of autoimmune diseases at the start of follow-up. Therefore, they are unsuited as a control group of healthy vaccinated people.

Arnheim-Dahlstrom et al. **[9]** conducted a follow-up study of approximately one million girls aged 10-17 years old between 2006 and 2010, utilizing a database in Sweden and Denmark. Some 300,000 girls received at least one dose of Gardasil (average 2.35 doses), and were observed for 180 days after inoculation. After adjusting for their age, educational background of parents, and the year of inoculation, incidences of fifty-three kinds of neurological disorders, autoimmune diseases and venous thrombosis were analyzed, and the risk ratio with the control was calculated. As a result, among twenty-nine diseases analyzed, twenty-three autoimmune diseases appeared in five or more vaccinees. Of these, there was no significant difference for 20 diseases, but the incidence was significantly higher in the Gardasil group for three diseases, namely Behcet's disease (risk ratio 3.37), Raynaud's disease (risk ratio 1.67) and Type I diabetes mellitus (risk ratio 1.29).

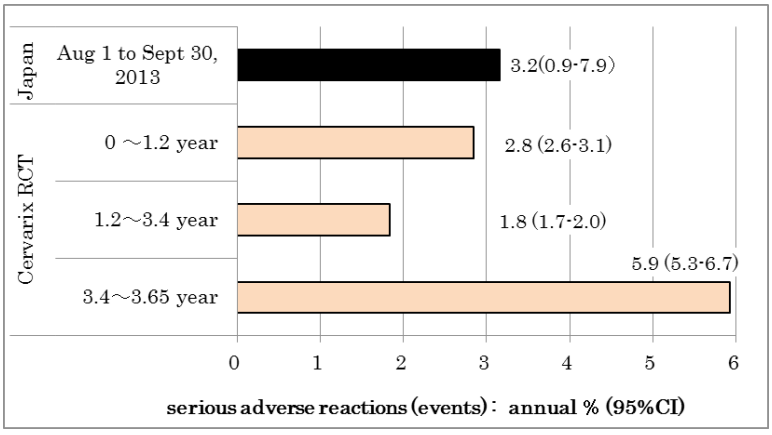
In the case of influenza vaccination, vaccinees were less prone to influenza infection than non-vaccinated people. After adjusting for the usual health conditions of children, there is no difference in incidence of influenza at all between the vaccinated and the non-vaccinated **[22]**. This is another example of the "healthy vaccinee effect". It is also true for the elderly.

As mentioned above, the causal relation between HPV vaccine and autoimmune diseases cannot be denied based on epidemiological studies on the incidence of autoimmune diseases in various countries in Europe and North America.

Adjuvant lacking tissue-injury cannot be an effective adjuvant:

Kinugasa **[17]** assumes that many epidemiological surveys

Figure: Incidence of serious reactions (events) after Cervarix: Japan* vs RCT



*Spontaneous serious adverce reaction reports in Japan

deny the causal relation between the harm and inoculation of adjuvant, referring to two studies [23, 24].

The case control study of DeStefano et al. [23] investigated the relation between demyelinating central nerve disorder such as multiple sclerosis and adjuvanted vaccine, and concluded that there was no significant difference in the vaccine users between cases with demyelinating diseases and the control group. However, this study also did not consider the healthy vaccinee effect (it was not mentioned in the discussion). Jefferson et al. [24] conducted a meta-analysis of eight RCTs or quasi-RCTs in a systematic review of the effect of vaccine with or without adjuvant. All trials were low in quality: the longest follow-up period was six weeks (one trial), and two trials followed up patients for only 24 hours after inoculation. Sustained pain observed in people who received adjuvanted vaccine was approximately two times more than that in control (odds ratio 2.05 [95%CI: 1.25-3.38]). Long-term harms have never been investigated.

Harm of adjuvants was discussed in detail in **TIP** [2] and **Med Check** [8, 9]. In brief, aluminum adjuvant acts as an adjuvant when it first injures tissues especially injected intramuscularly. White blood cells accumulate to repair injured tissue, phagocyte aluminum and die releasing DNA. Although unbound DNA is easily digested by DNase, protein-bound DNA becomes stabilized and acts as a real adjuvant to enhance innate immunity. If DNA and/or MPL (monophosphoryl lipid A), a very strong adjuvant derived from salmonella endotoxin (lipid A) in Cervarix is also stabilized by binding with aluminum nano-particles, they act as ligands of TLR-4 from which innate immune reactions start.

Vaccination with Cervarix is predicted to provide long-term persistence with high antibody titre for up to 20 years [25]. This is induced by HPV virus-like protein particles bound to aluminum nano-particles and MPL remaining in tissues for a long time. Hence, it can well be predicted that not only antibody production would persist but also other excessive immune responses would persist via innate immunity stimulated by long-term persisting virus-like particle-adjuvant complex in various tissues including the central nervous system.

Conclusion:

As the harms of HPV vaccine became well known, many serious adverse reaction cases were reported long after injection including unprecedented "severe reactions", which were completely new even to specialists in neurology and collagen disease of childhood. Because the risk of autoimmune disease is estimated to be several hundred-times higher and even the excess fatalities higher than the maximum expected preventable cervical cancer death risk by several orders of ten; so, the harms are definitely unacceptable. The MHLW and the manufacturers should admit the causality of the HPV vaccine in serious adverse reactions as soon as possible. HPV vaccine should be withdrawn from the market and all women inoculated with HPV vaccine should be followed up.

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Harm/benefit comparison in our first analysis [ref.1]

For the comparison between the reported proportion of serious adverse reactions among innoculated HPV-vaccinees and preventable cervical cancer deaths, we wrote as follows: Among 599 serious adverse reaction reports, 95% occurred within a week and only three (0.5%) occurred after one month or later. Reported proportion of serious reactions to Gardasil and to Cervarix were 9 to 11 and 26 to 29 per 100,000 persons inoculated respectively. On the other hand, maximum preventable cervical cancer deaths attributable to HPV vaccine were expected 1.5 per 100,000 person years in Japan (mortality is standardized by the world population). The former are about 6 to 9 times and 17 to 23 times higher respectively.

Plain Language summary

SGLT-2 inhibitors: inacurate to call these"medicines"

What is diabetes? What is insulin?
What is the target of treatment?

Diabetes is **NOT** a simple disease in which blood sugar (glucose) levels increase. It is a disease in which insulin secretion decreases or work poorly. As a result, various organ failures might occur without adequate management but, a long normal life is still possible if the disease is properly managed. Insulin is excreted from the pancreas and is essential for the body to work, because it maintains the metabolism of various nutrients such as sugars (carbohydrate), lipids and proteins. Hence, if the amount of insulin excretion decreases, the human body cannot utilise nutrients properly. Unutilised sugar increases in the blood and various symptoms occur: excessive thirst, overeating, drinking too much water, confusions and other mental impairment, etc. Blood vessels and nerves are damaged. Various organs such as the eye (especially the retina), kidney and heart deteriorate after a long period of time, over several years or dozens of years.

Treatment of diabetes does **NOT** simply aim to "normalize the blood sugar levels……" but "**to normalize the metabolism** of nutrients and to prolong life, preventing various complications." **DO NOT CONFUSE** them.

An adequate amount of nutrients especially fats and proteins necessary for one's physical constitution (height) and activity is essential to maintain a healthy body and a healthy mind.

Insulin needs to be secreted especially when one eats carbohydrates (sugars). Hence, a low carbohydrate diet may decrease the need for insulin to be secreted and this is good for patients with lowered insulin secretion. Adequate exercise is always good for health. If one cannot achieve good blood glucose level through a low carbohydrate diet with adequate exercise, insulin therapy may be necessary.

Other medicines for diabetes such as sulfonylureas, metformin, alfa-glucosidase inhibitors, which delay absorption of sugars, and other newly developed oral or injectable hypoglycemic agents have not been proven to prolong the life of diabetics. These are of little use and harmful to health. Insulin is the only medicine needed by diabetics. However, even insulin can induce cancer.

SGLT-2 inhibitors are newly introduced agents for diabetes and are used for lowering blood sugar by impairing the activity of kidneys to reabsorb sugar. These medications lower blood glucose but may increase dehydration, leading to stroke, increased urinary tract infections (bladder and kidney), life-threatening skin disease and cancer. You should avoid SGLT-2 inhibitors.

"Pylori" removal may shorten life

Proton pump inhibitors (PPIs) are drugs which reduce acid in the stomach by inhibiting proton (hydrogen ion) pump activity in the acid excreting cells. These drugs are used to treat stomach and duodenum ulcers for short periods (8 weeks for stomach ulcers and 6 weeks for duodenum ulcers).

These drugs are also used to remove bacteria called "*pylori*" from the stomach to prevent stomach and duodenum ulcers , and stomach cancer.

However, PPIs increase infection from other bacteria. One of the most important of these bacteria is called *Clostridium difficile (C. difficile)* which can cause serious enteritis, a sometimes fatal condition. One of the reasons why this type of serious infection occur is because many people have *C. difficile* without exibiting symptoms, Moreover, PPIs inhibit not only the proton pump action in stomach cells but also another type called vacuolar proton pump (V-ATPase) which exists in almost all cells of the body and has an important role to maintain normal cell functions. Inhibition of the latter type of proton pump may impair functions of various cells, such as renal, bone, sperm and immune cells which are important for acidification of urine, bone resorption, sperm maturation and for adequate PH maintenance.

The benefit of removal of "*pylori*" in healthy carriers has to be weighed against the harmful effects including increased risk of infection and decide whether it may prolong life or not. Long-term well controlled clinical trials have shown that removal of "*pylori*" in healthy carriers decreased gastric cancer incidence, but tended to increase all-cause mortality compared with the control group.

If you have "*pylori*" in your stomach without gastric or duodenal ulcers, "*pylori*" should not be removed by PPIs.

Harm of HPV vaccine:

Epidemiologic studies do not probe safety

Two HPV vaccines (Cervarix and Gardasil) have been marketed in Japan since 2010. More than 3 million girls were inoculated with HPV vaccines prior to the withdrawal of a recommendation for inoculation by the Japan's Ministry of Health, Labor and Welfare (MHLW) in May 2013.

Incidence of serious adverse reactions to Cervarix was 800 among 2.6 million girls inoculated (one in 3000 before withdrawal of the recommendation), while the incidence increased to 3.2% per year after the retraction, using the latest data (3,200 cases per 100,000 person years or one in 30 per year). This is similar to the frequency of serious adverse events within 1.2 years after the first vaccination (annual rate of 2.8%) reported in a well-controlled clinical study of Cervarix. In this study, annual incidence of serious reactions, autoimmune diseases and death after 3.4 years comparing with those between 1.2 and 3.4 years was estimated as 4%, 0.63% and more than one per thousand respectively. These incidence rates may also occur in Japan.

The epidemiologic surveys that the MHLW used as evidence of safety have serious flaws in their methodologies. One study confuses incidence *(newly occurred disease among a certain population within a certain period of time)* with prevalence *(a proportion of persons having a disease among a certain population at a certain point of time)*. The other two studies have a serious bias known as the **"healthy vaccinee effects"**. Those vaccinated are usually healthier than those non-vaccinated, because the latter group avoid vaccines due to health problems.

While there is no evidence yet that HPV vaccine decreases mortality from cervical cancer, if we assume that the vaccine could cut the cervical cancer mortality by half, the expected maximum benefit would be 2.0 less deaths per 100,000 person-years. Hence, the harm experienced is overwhelmingly greater than the expected maximum benefit.

We strongly recommend avoiding HPV vaccine.

MED CHECK

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