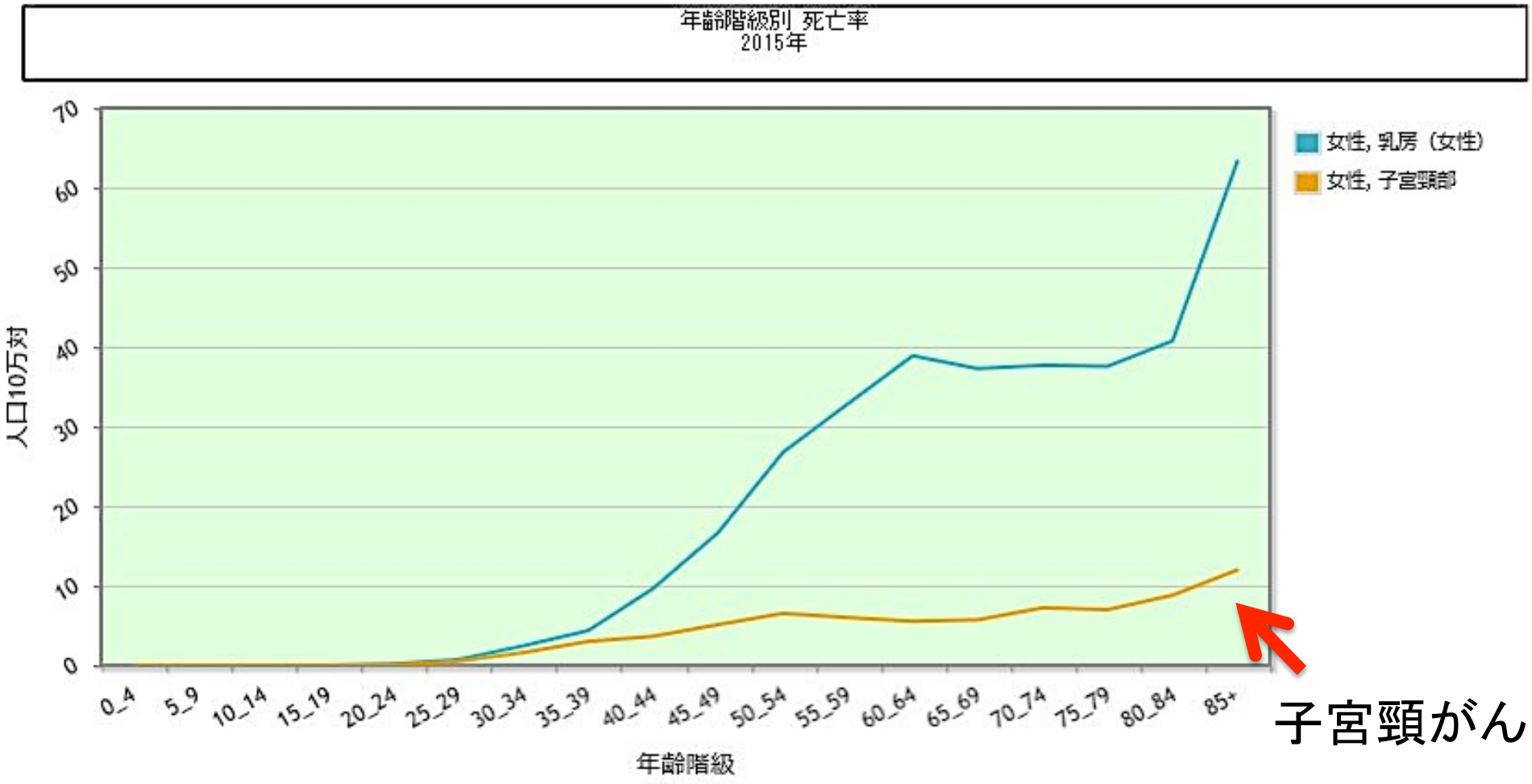
2019/12/8
第31回日本生命倫理学会

子宮頸がんの罹患・死亡は「ワクチン接種」によって予防すべきか。

打出　喜義（金城大学）

子宮頸がんの死亡率は
乳がんの1／5程度

年齢階級別死亡率の子宮頸がんと乳がんとの比較



子宮頸がん

資料：国立がん研究センターがん対策情報センター「がん登録・統計」
Source：Cancer Information Services, National Cancer Center , Japan

女性内外性器がんの死亡率(人口十万対)

乳房＞卵巣＞頸部＞体部

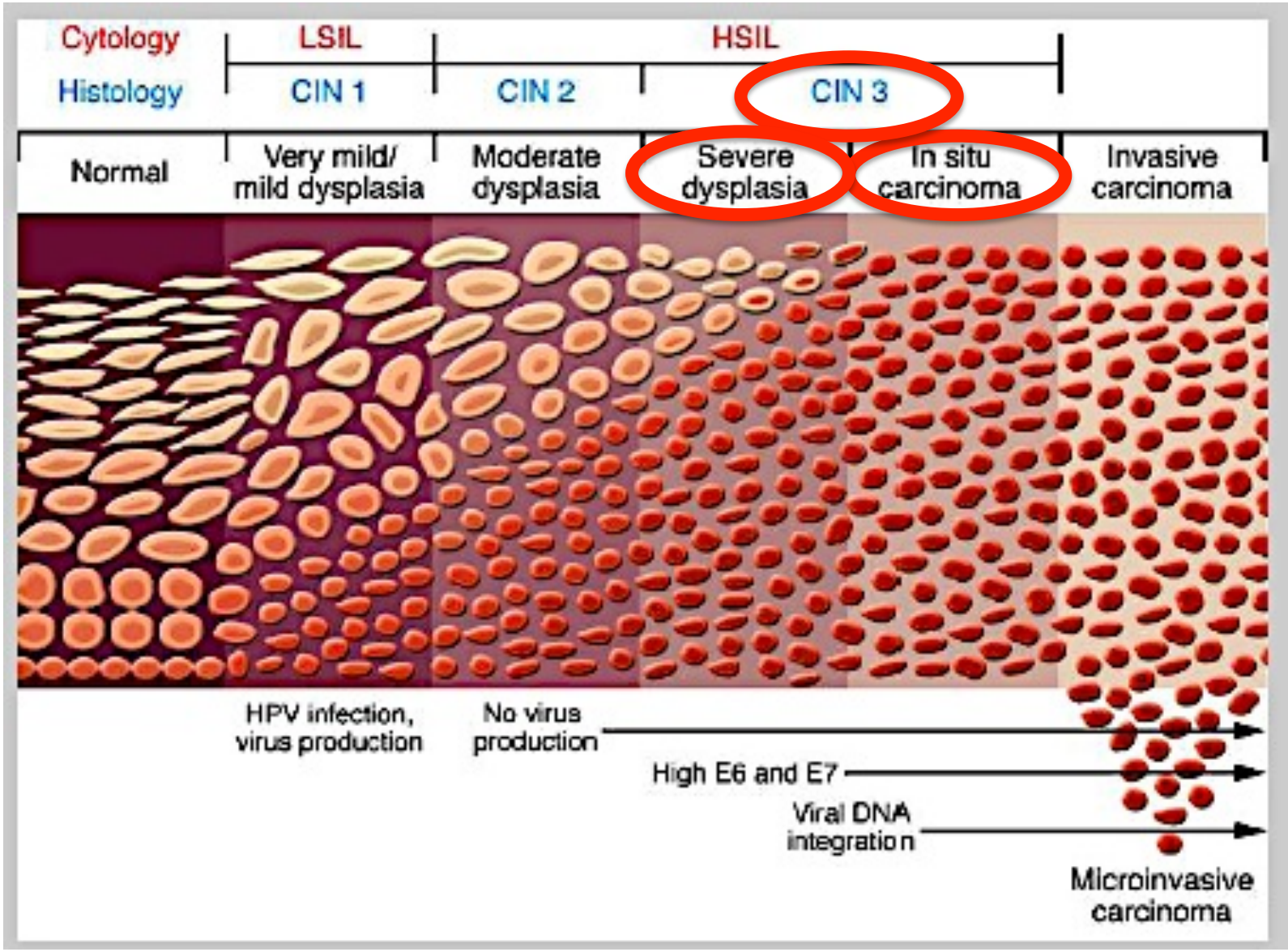
22.3　7.4　4.4　3.9

子宮頸部上皮内がんの罹患率は過大に言われる

なぜなら

異形上皮も上皮内がんとして報告されているから

○ 子宮頸がんになるまで


Cytology
LSIL
HSIL
Histology
CIN 1
CIN 2
CIN 3
Normal
Very mild/
mild dysplasia
Moderate
dysplasia
Severe
dysplasia
In situ
carcinoma
Invasive
carcinoma
HPV infection,
virus production
No virus
production
High E6 and E7
Viral DNA
integration
Microinvasive
carcinoma

子宮頸がんの罹患・死亡は

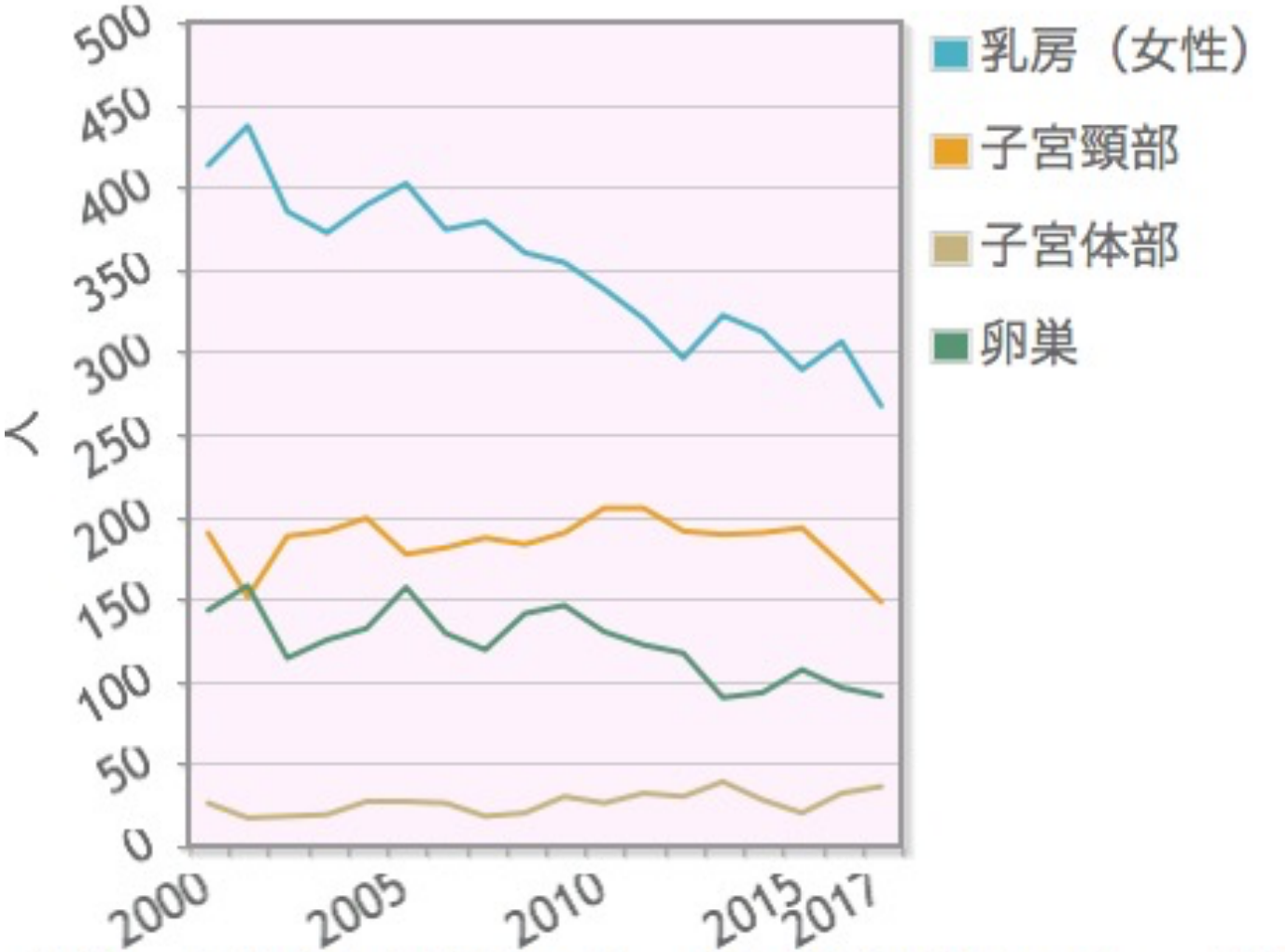
- 女性部位別死亡率で見ると、子宮頸がん**死亡率**はそれほど高くはない

1.	大腸	(36.5)
2.	肺	(33.0)
3.	膵臓	(26.3)
4.	胃	(24.2)
5.	乳房	(22.3)
6.	肝臓	(14.5)
7.	胆嚢・胆管	(14.0)
8.	悪性リンパ腫	(8.6)
9.	卵巣	(7.4)
10.	腎など	(5.4)
11.	白血病	(5.2)
12.	子宮頸部	(4.4)

人口１０万人対

- 子宮頸がんの**罹患**に「上皮内がん」までを含めると実態よりも**罹患率**は多くなりすぎる

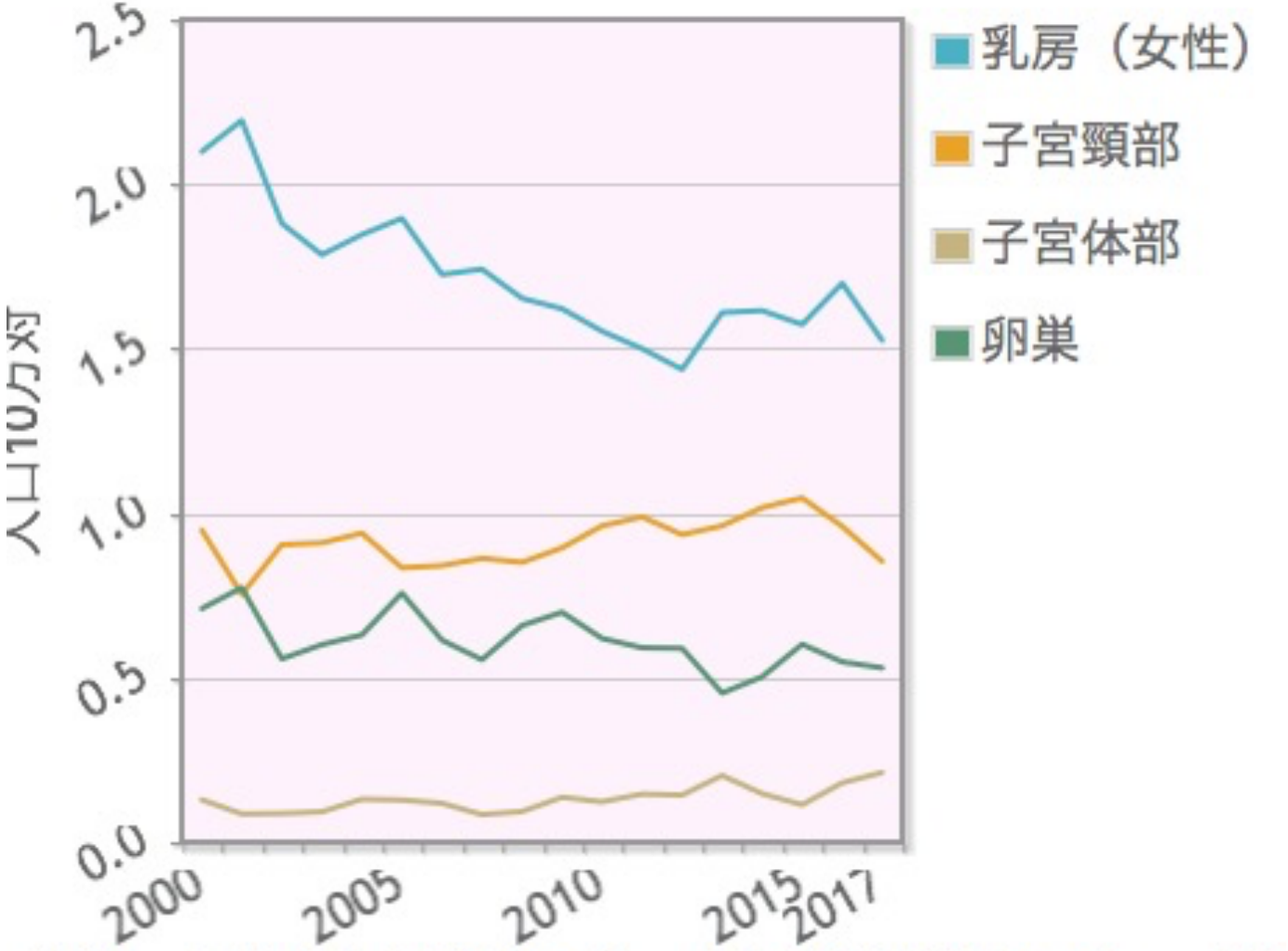
AYA世代のこの１０年の死亡数



資料：国立がん研究センターがん対策情報センター「が
Source：Cancer Information Services, National Cancer C

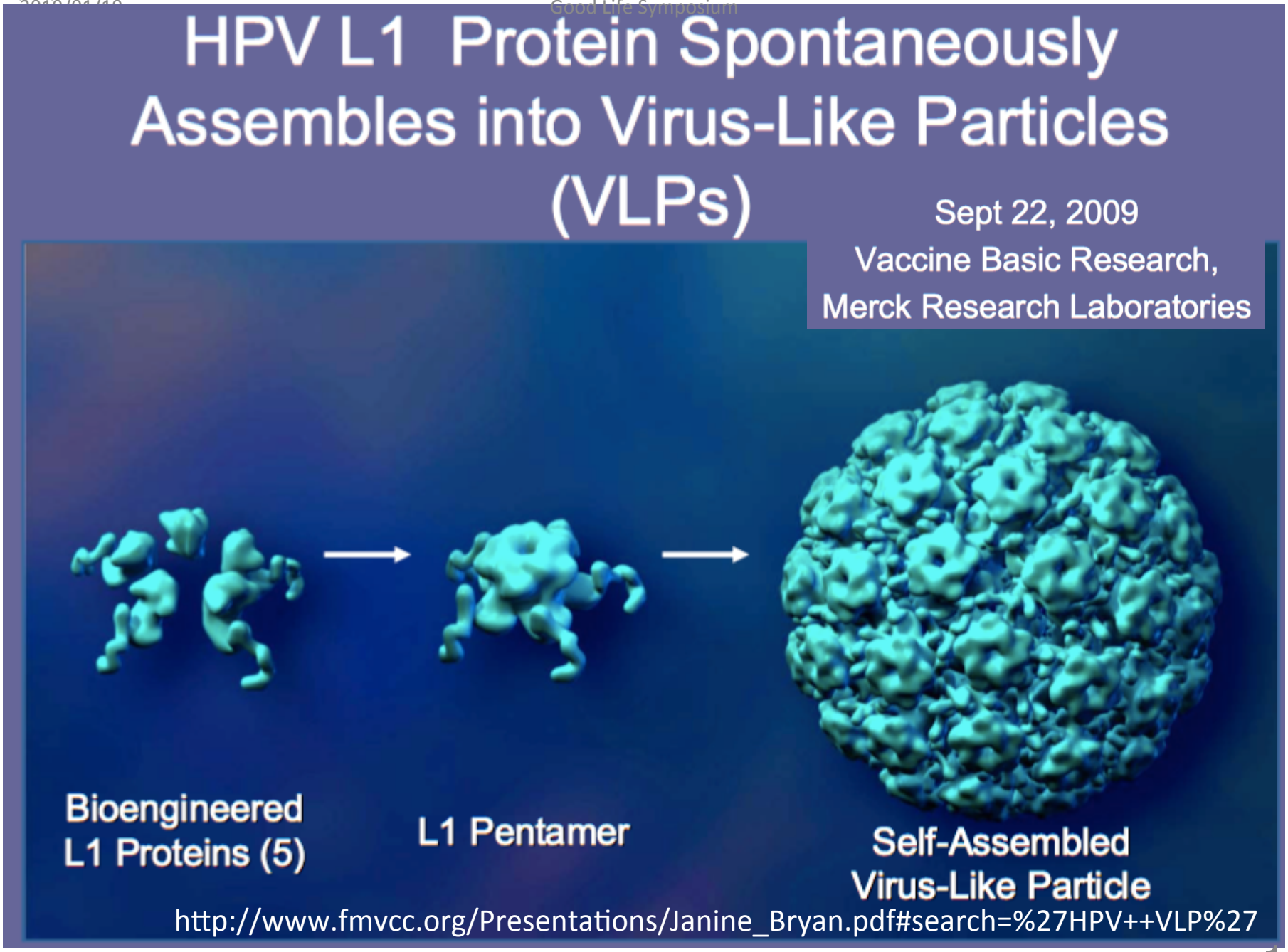
部位別 年齢調整死亡率 年次推移
［女性，15–39歳］

AYA世代のこの１０年の死亡率



資料：国立がん研究センターがん対策情報センター「が
Source：Cancer Information Services, National Cancer C

HPVワクチンの製造方法


HPV L1 Protein Spontaneously Assembles into Virus-Like Particles (VLPs)
Sept 22, 2009
Vaccine Basic Research,
Merck Research Laboratories
Bioengineered L1 Proteins (5)
L1 Pentamer
Self-Assembled Virus-Like Particle
http://www.fmvcc.org/Presentations/Janine_Bryan.pdf#search=%27HPV++VLP%27

卵　©竹内浩二

成熟幼虫　©竹内浩二

イラクサギンウワバ
Trichoplusia ni
チョウ(鱗翅)目ヤガ科

アブラナ科ではキャベツ、ハクサイ、ブロッコリー、コマツナなどで発生する。他にキク科、ウリ科、シソ科、ナス科など広く食害する。

蛹(撮影で繭を破ったところ)
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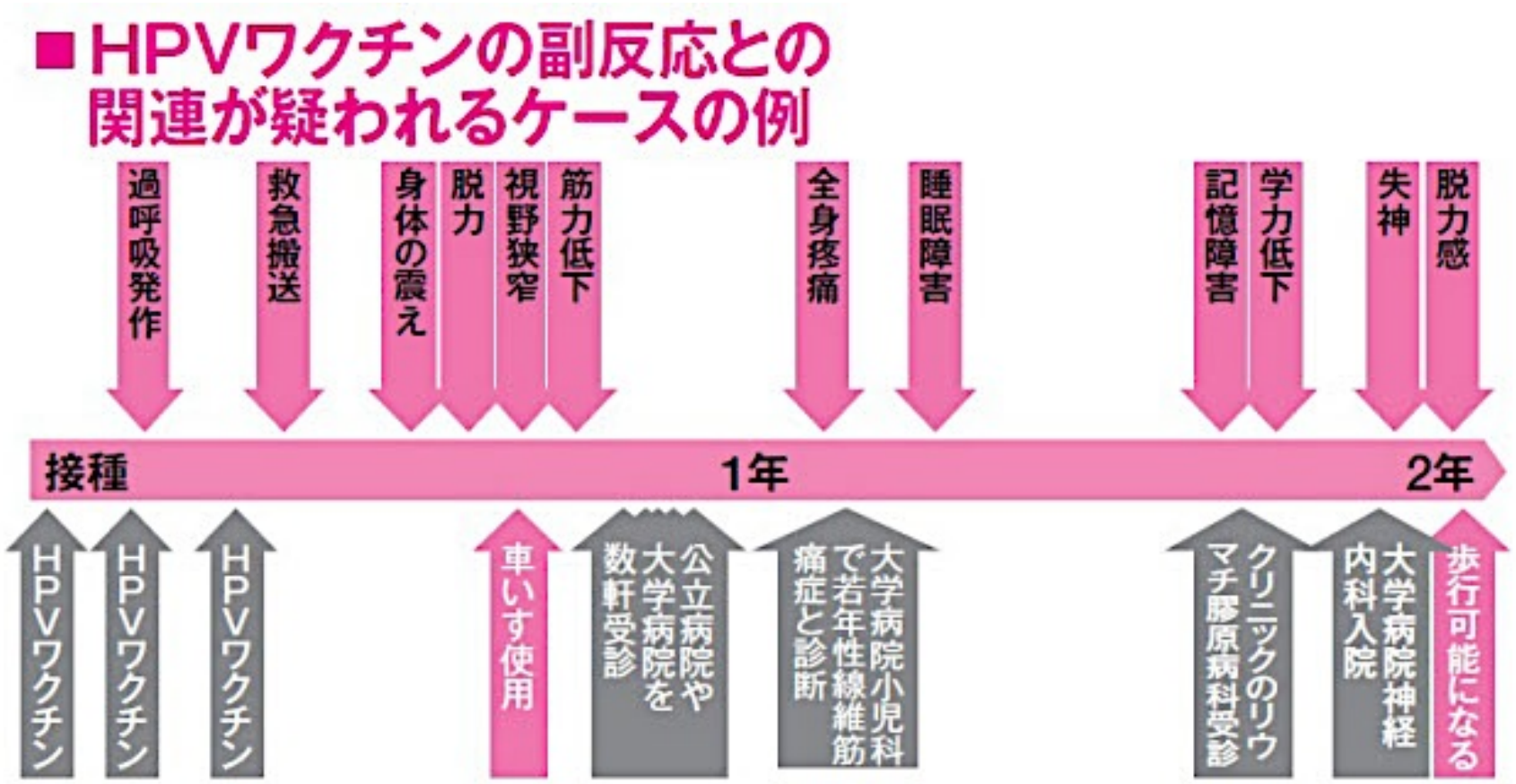
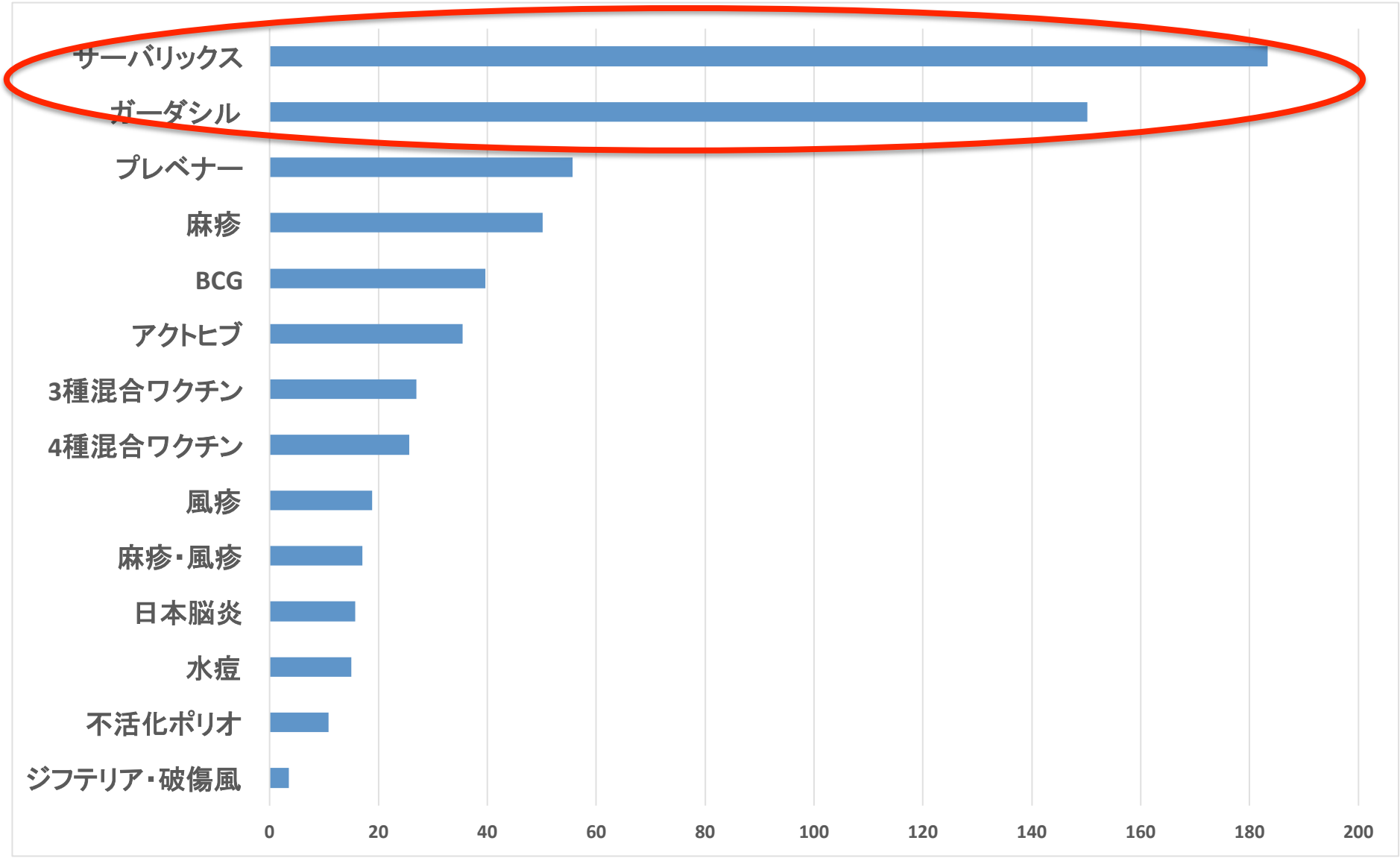
HPVワクチンに副反応はないのか



研究チーム内で治療した44例の1例で、急性型と遅延型の症状が出た14歳女性のケース。原因が分からず病院を転々としたが、ステロイドホルモンや免疫抑制剤で症状が改善した

日本におけるHPVワクチンと他のワクチンの重篤副作用の比較

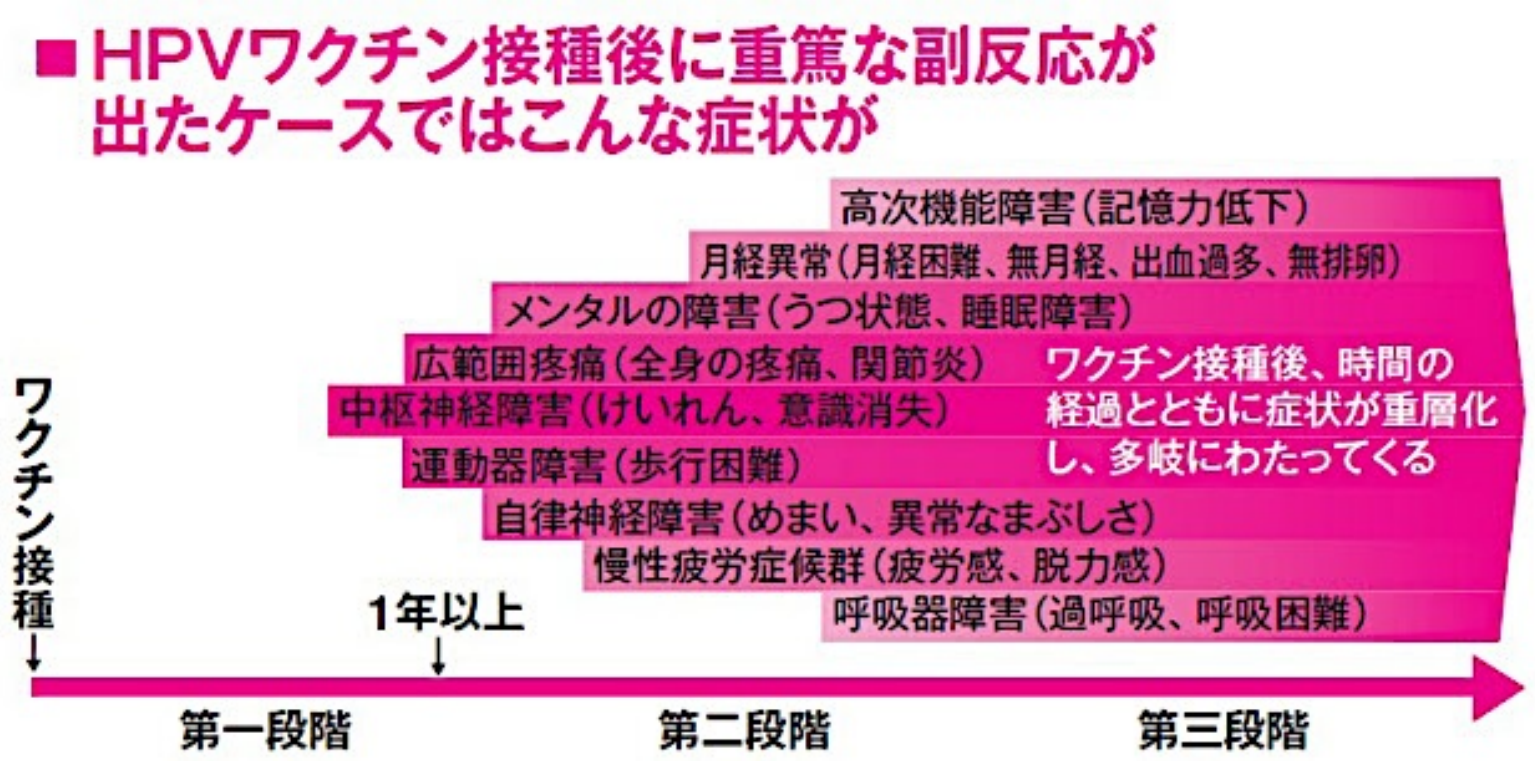


＊データは「ヒトパピローマウィルス（HPV）ワクチン接種推進に向けた関連学術団体の見解」に対する意見書より引用 http://www.yakugai.gr.jp/topics/topic.php?id=922

日本経済新聞 11月13日 木曜日

子宮頸がんワクチンの副反応、新病態の可能性も

2014/11/13 6:30



重篤なケースでは、ワクチン接種後、1年以上たってから意識消失、月経異常、歩行困難、記憶力低下など複数の症状が並行して起こっていた（資料提供：西岡所長）

HPVワクチンに長期にわたる重篤副作用多い理由(私見)

① HPVとヒトのタンパクとの相同性

② HPVワクチンにより高い抗体価が長期に持続する

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

From HBV to HPV: Designing vaccines for extensive and intensive vaccination campaigns worldwide

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[b] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer 5265601, Israel

２０１６年

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Keywords:
HBV/HPV vaccines
Peptide crossreactivity
Autoimmune reactions
Peptide uniqueness concept
Safe and effective vaccines

ABSTRACT

HBsAg and HPV L1 proteins – the HBV and HPV antigens utilized in current vaccines – share amino acid sequences with human proteins such as cardiomyopathy-associated protein 5, titin, protein-arginine deiminase, E3 ubiquitin-protein ligase RNF19A, bassoon, G-protein coupled receptor for fatty acids, insulin isoform 2, and mitogen-activated protein kinase kinase kinase 10, *inter alia*. Many shared peptides are also part of immunopositive epitopes. The data 1) support the possibility of crossreactions between the two viral antigens and human proteins that, when altered, may associate with neuropsychiatric, cardiovascular and metabolic diseases such as multiple sclerosis, amyotrophic lateral sclerosis, diabetes, and sudden death; 2) confirm the concept that only vaccines based on sequences unique to pathogens might nullify potential crossreactivity risks in vaccination protocols.

６０

抗原決定基（エピトープ）

A：アラニン
R：アルギニン
N：アスパラギン
D：アスパラギン酸
C：システイン
P：プロリン
S：セリン

Heptapeptide[a]	Strain[b]	Human proteins[c]
VPKVSGL	16	FBSL. Fibrosin-1-like protein
VSGHPFL	6	EZH1. Histone-lysine N-methyltransferase EZH1
VTSDSQL	18	OR4D2. Olfactory receptor 4D2
VYSPSPS	18	RPGP2. Rap1 GTPase-activating protein 2
GDTVPQS	18	Q4W4Y1. Dopamine receptor interacting protein 4

ドーパミンは神経伝達物質の一つで、人格、運動、動機づけなど、極めて重要な脳機能を担っています。加えて、**統合失調症や注意欠陥多動性障害(ADHD)**などの精神疾患とも深く関わっています。

抗原抗体反応＝免疫反応

抗原として抗体に認識されるのは、Ll タンパク全体ではなく、その表面の特定の部位である。

そこで抗体に認識される部位を、**抗原決定基**あるいは、**エピトープ**と呼ぶ。

http://www.tmd.ac.jp/artsci/biol/textlife/immunology.htm

ウイルスの
抗原決定基が
ヒトのそれと
分子相同性が
あった場合

http://www.tmd.ac.jp/artsci/biol/textlife/immunology.htm

http://www.tmd.ac.jp/artsci/biol/textlife/immunology.htm

ＨＰＶタンパクのアミノ酸配列
（抗原決定基）が
ヒトタンパクのそれと相同する

↓

ＨＰＶ抗体がヒトタンパクに付着

↓

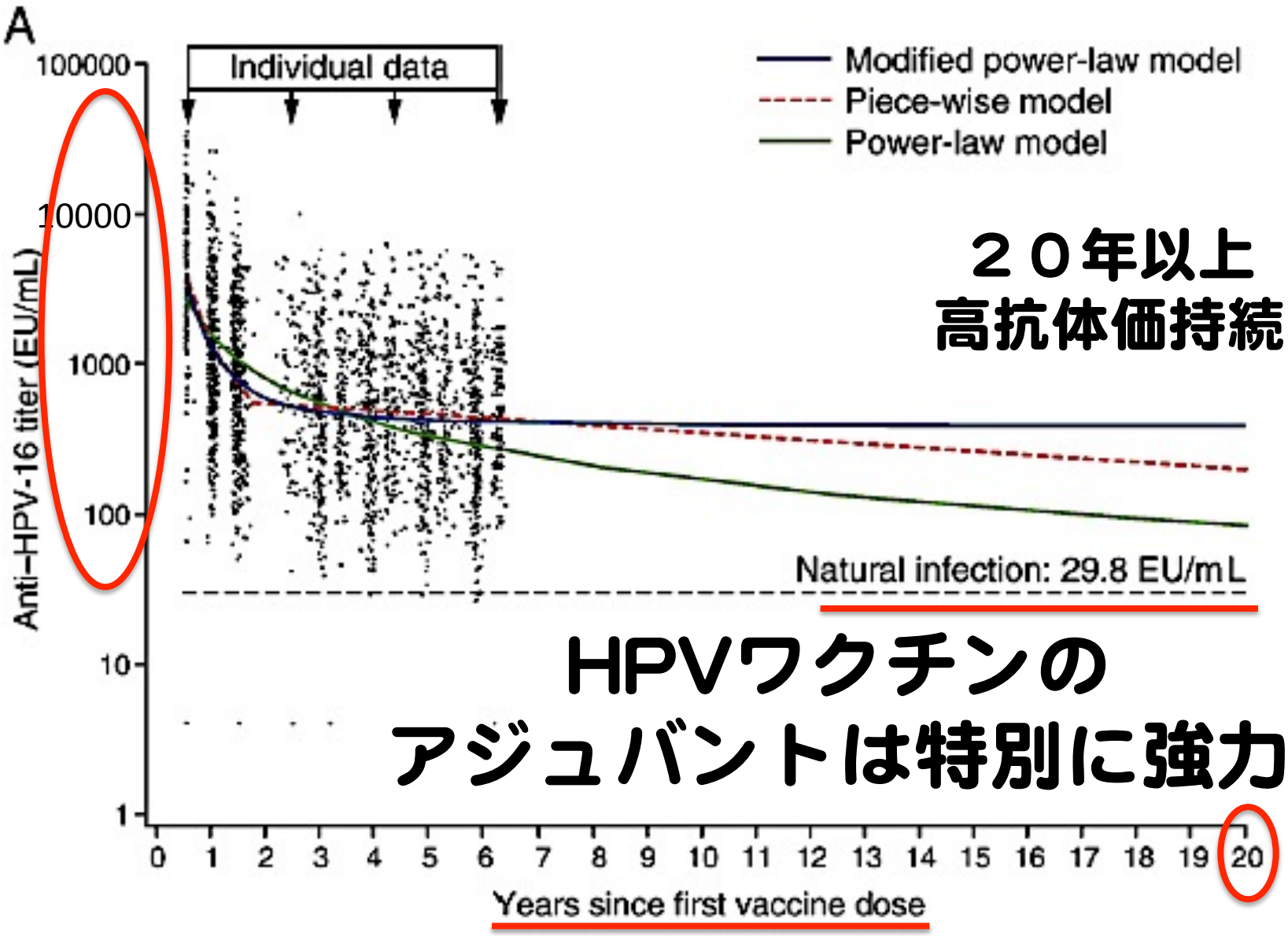
そのタンパクが担う機能に
障害発生の可能性

副反応発生の可能性

HPVワクチンに長期にわたる重篤副作用多い理由(私見)

① HPVとヒトのタンパクとの相同性

② HPVワクチンにより高い抗体価が長期に持続する

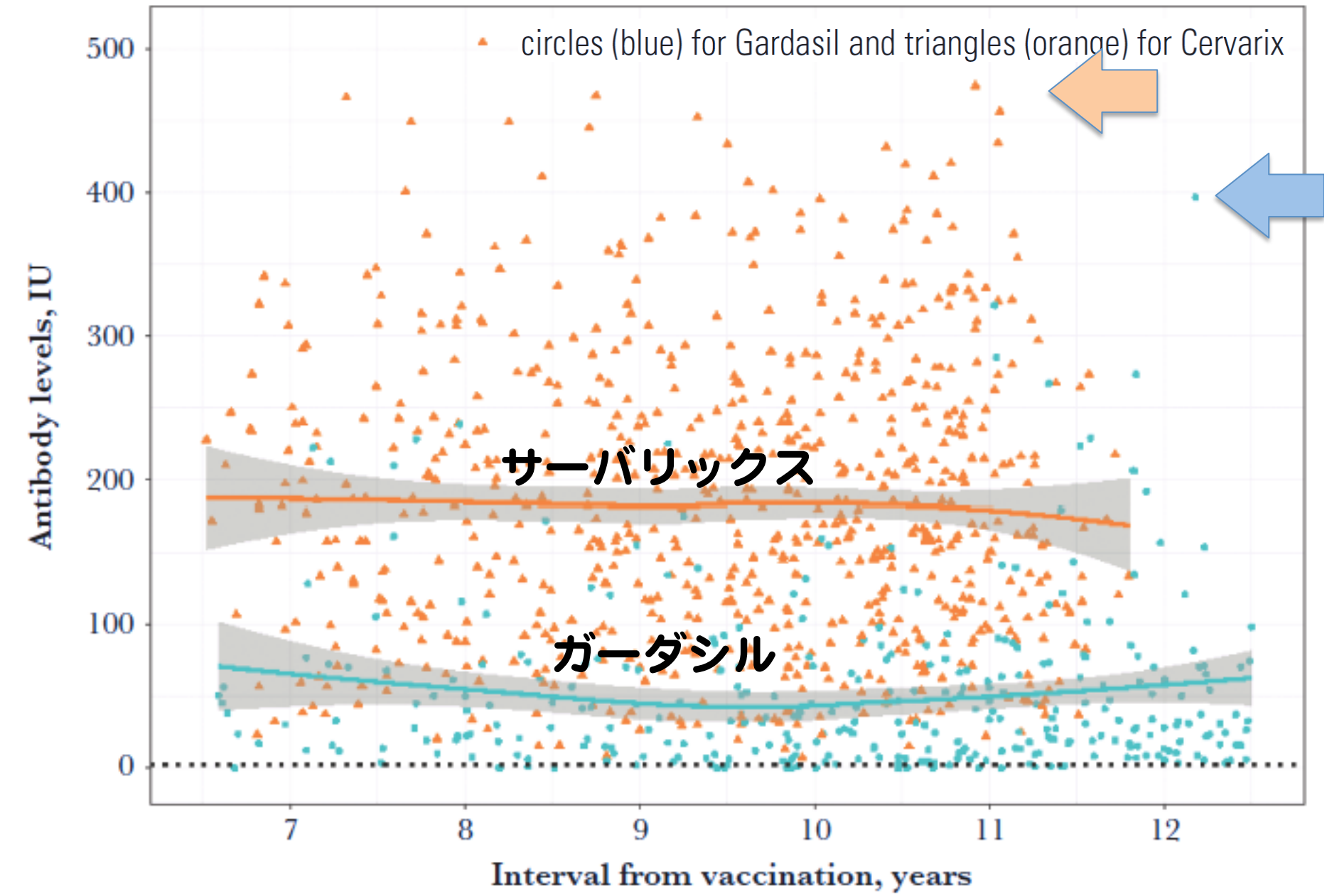


２０年以上
高抗体価持続

HPVワクチンの
アジュバントは特別に強力

M.-P. David et al. / Gynecologic Oncology 115 (2009) S1–S6

The Journal of Infectious Diseases® 2019;219:582–9



http://cancerinfo.tri-kobe.org/index.html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検
印刷用ページ
Powered by
がん情報サイト Cancer Information Japan
寄附・協賛のお願い
PDQ®がん情報要約
PDQ®臨床試験検索
PDQ®がん用語辞書
薬剤情報
お知らせ
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Cancer Information Summaries
最新の研究成果に基づいて定期的に更新している、
科学的根拠に基づくがん情報の要約です。
目次
医療専門家向け
概要
証拠の記述
本要約の変更点
（03/01/2019）
子宮頸がんの予防（PDQ®）
原文更新日：2019-03-01
翻訳更新日：2019-05-22
最新版（NCIサイト）
英語版
患者様向け

子宮頸がんのリスク増加の十分な証拠を有する因子

- ヒトパピローマウイルス（HPV）
- 免疫抑制
- 若年時の性的行為および性的パートナー数の多さ
- 多妊多産
- 経口避妊薬の長期使用
- タバコ煙曝露
- ジエチルスチルベストロール（DES）曝露

（かつて流産防止などに用いられた合成女性ホルモン）

子宮頸がんのリスク減少の十分な証拠を有する因子

- 性的禁欲
- 性交中のバリア避妊具の使用
- Pap検査によるスクリーニングおよび HPV DNA検査によるスクリーニング
- HPVワクチン接種

HPVワクチン有効性を証明する有名な論文

Lancet 2009; 374: 301–14

Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women

J Paavonen, P Naud, J Salmerón, C M Wheeler, S-N Chow, D Apter, H Kitchener, X Castellsague, J C Teixeira, S R Skinner, J Hedrick, U Jaisamrarn, G Limson, S Garland, A Szarewski, B Romanowski, F Y Aoki, T F Schwarz, W A J Poppe, F X Bosch, D Jenkins, K Hardt, T Zahaf, D Descamps, F Struyf, M Lehtinen, G Dubin, for the HPV PATRICIA Study Group

医の倫理の基礎知識　2018年版

ディオバン事件
―研究者と企業の倫理

桑島　巖

臨床研究適正評価教育機構理事長

http://dl.med.or.jp/dl-med/doctor/member/kiso/h12.pdf

Lancet 2007; 369: 1431–39

Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study

*Seibu Mochizuki, Björn Dahlöf, Mitsuyuki Shimizu, Katsunori Ikewaki, Makoto Yoshikawa, Ikuo Taniguchi, Makoto Ohta, Ta[illegible]mada, Kazuhiko Ogawa, Kiyoshi Kanae, Makoto Kawai, Shingo Seki, Fumiko Okazaki, Masayuki Taniguchi, Satoru Yoshida, Naoko [illegible]for, Jikei Heart Study group**

Summary

Background Drugs that inhibit the renin–angiotensin–aldosterone system benefit pa[illegible]s a[illegible]for or with ex[illegible]ng cardiovascular disease. However, evidence for this effect in Asian populations is scarce. We [illegible]d to investigate whether addition of an angiotensin receptor blocker, valsartan, to conventional [illegible]vascular treat[illegible] was effective in Japanese patients with cardiovascular disease.

Methods We initiated a multicentre, prospective, randomised contro[illegible] trial of 30[illegible]panese patients, aged 20–79 years, (mean 65 [SD 10] years) who were undergoing conventional [illegible]tment for hy[illegible]ension, coronary heart disease, heart failure, or a combination of these disorders. In addition to con[illegible]nal treatm[illegible], patients were assigned either to valsartan (40–160 mg per day) or to other treatme[illegible] without angi[illegible]or blockers. Our primary endpoint was a composite of cardiovascular morbidity and [illegible]nalysis was b[illegible]ntention to treat. The study was registered at clintrials.gov with the identifier NCT00133328.

Findings After a median follow-up of 3·1 years (range 1–3·9) th[illegible] endpoint was recorded in fewer individuals given valsartan than in controls (92 *vs* 149; abso[illegible]21·3 *vs* 3[illegible]er 1000 patient years; hazard ratio 0·61, 95% CI 0·47–0·79, p=0·0002). This difference was[illegible]ly at[illegible]utable to[illegible]er incidences of stroke and transient ischaemic attack (29 *vs* 48; 0·60, 0·38–0·95, p=0·0[illegible]angina p[illegible]oris (19 *vs*[illegible]0·35, 0·20–0·58, p<0·0001), and heart failure (19 *vs* 36; 0·53, 0·31–0·94, p=0·029) in[illegible]give[illegible]in the control group. Mortality or tolerability did not differ between groups.

Interpretation The addition[illegible]sartan to co[illegible]onal treatment prevented more cardiovascular events than supplementary conventio[illegible]trea[illegible]. These benef[illegible]annot be entirely explained by a difference in blood pressure control.

Lancet 2007; 369: 1431–39

See Comment page 1407

*Members listed at end of article

Division of Cardiology (Prof S Mochizuki MD, Prof M Shimizu MD, K Ikewaki MD, M Yoshikawa MD, I Taniguchi MD, M Ohta MD, T Yamada MD, K Ogawa MD, K Kanae MD, M Kawai MD, S Seki MD, F Okazaki MD, M Taniguchi MD, S Yoshida MD), **and Division of Diabetes, Metabolism, and Endocrinology** (Prof N Tajima MD), **Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; and Institute of Medicine, Department of Emergency and Cardiovascular Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden** (B Dahlöf MD)

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m_seibu@jikei.ac.jp

Introduction

Cardiovascula[illegible]rders a[illegible]e leading cause of mortality worldwide,[1] a[illegible]e exp[illegible]d to continue to increase with general ageing[illegible]world's [illegible]ulation and rapid socio[illegible]ic cha[illegible]in the[illegible]loping world. Hence, or[illegible]mmacot[illegible]cardiovascular disease is [illegible]ntly n[illegible]ed, in ad[illegible]n to lifestyle changes, to [illegible]vide [illegible]matic relief and long-term protection. [illegible]ost common cause of coronary he[illegible]isease and heart failure in Japan, and cereb[illegible]ular disease is more prevalent in the Japanese populati[illegible]n in western societies.[2] Angiotensin II has a well defined role in the pathogenesis of hypertensive left ventricular hypertrophy, stroke, coronary heart disease, and heart failure.[3–5] Over the past decade, several clinical trials have shown the benefits of treatments that specifically block the renin–angiotensin–aldosterone system. Angiotensin receptor blockers were originally targeted at hypertension, but also benefit patients with a range of diseases[6–15] and reduce the incidence of new onset type II diabetes.[7,11,16]

Direct implementation of available evidence into clinical practice in Japan might not be warranted by the available data, since responses to drug intervention and its clinical consequences might differ between ethnic groups. Clinical trials of angiotensin receptor blockers on end-organ damage in Japanese patients show cardiovascular benefits, but because of shortcomings such as small sample sizes and observational data, these results are not conclusive and cannot be directly translated into clinical outcomes.[17–21] Thus, further large-scale Japanese clinical trials are needed.

We aimed to implement a large-scale clinical trial to investigate the effect of control of blood pressure (to a target of less than 130/80 mm Hg) with an added angiotensin receptor blocker, valsartan, compared with conventional treatment in a large Japanese population that was representative of the cardiovascular continuum of disease.[22] Our hypothesis was that treatment with valsartan would yield additional protective benefits, compared with conventional treatment, beyond those attributable to control of blood pressure.

Conflicts of interest

DD, GD, FS, KH, and TZ are employees of GlaxoSmithKline Biologicals. DD, GD, FS, and KH own stock in GlaxoSmithKline Biologicals, and GD holds a relevant patent. All investigators at study clinical sites were funded through their institutions to do the study protocol. FYA, SG, ML, TFS, CMW, and BR have received funding through their institutions to do other HPV vaccine studies for GlaxoSmithKline Biologicals or Merck, or both. CMW has also received funding through her institution from Roche Molecular Systems to do HPV genotyping studies. FXB, XC, SG, DJ, PN, WAJP, BR, JS, TFS, AS, and JCT have received consulting fees in the past 3 years. DA, FXB, XC, HK, PN, JP, BR, TFS, SRS, AS, and JCT have received honoraria, paid expert testimony, or travel grants from GlaxoSmithKline Biologicals. S-NC, JH, UJ, GL declare that they have no conflicts of interest.

24/27 (89%)

Acknowledgments

This study (NCT00122681/580299/008) was funded by GlaxoSmithKline Biologicals. We thank study participants and their families. We wish to dedicate this report to Minnamaija Kekki, a subinvestigator for this study, who sadly passed away.

HPVワクチンの Benefitを示す 有名論文の 著者らにも 利益相反がある

討論して頂きたい課題

- ✓ 医療情報の正誤判断は一般人に可能か
  - → 不可能なら誰がどうすれば良い
    - → プロフェッショナリズムとは

- ✓ 健常人への医療介入の是非
  - → 医療で「病」を予防すべきか、できるか
    - → 「死」への取り組みは医療で可能か

- ✓ HPVワクチン接種推進派X慎重派
  - → その間の対立構造は解消できないのか
    - → 何が対立構造を作っているのか