テーマI

「子宮頸がんワクチン」導入の裏側

今年4月から定期接種となった子宮頸がんワクチンによって、
各地の女子中高生に深刻な副反応被害が起こっています。
このワクチンは

海外の論文等でどのように評価されているのか

接種時に十分な説明がなされているのか

利益相反や費用対効果はどうなっているのか

等を含め、ワクチンやクスリに関する情報開示の問題点を探る

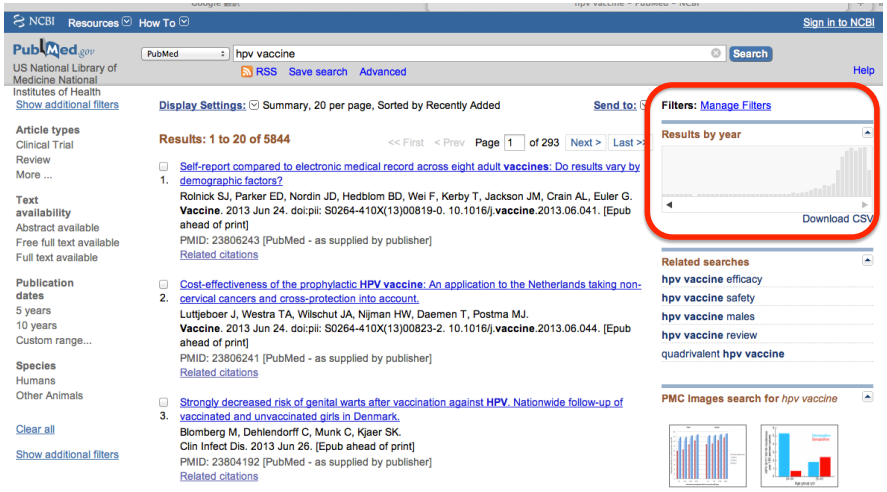
○**打出喜義**　（産婦人科医師、金沢大学附属病院講師）
○**隈本邦彦**　（科学ジャーナリスト、 江戸川大学教授
薬害オンブズパースン会議）

海外の論文等でどのように評価されているのか

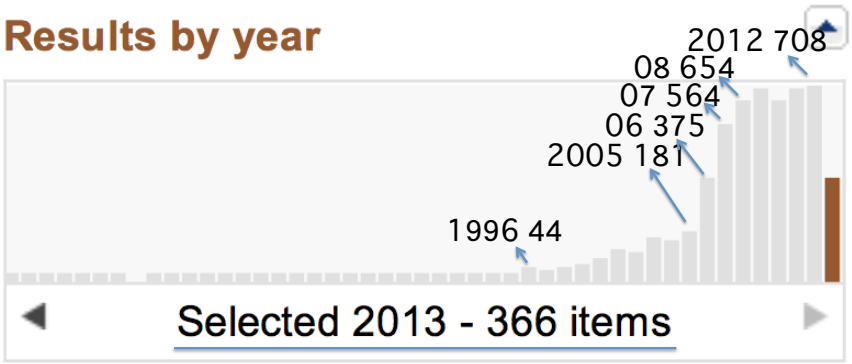
海外論文紹介

海外論文検索

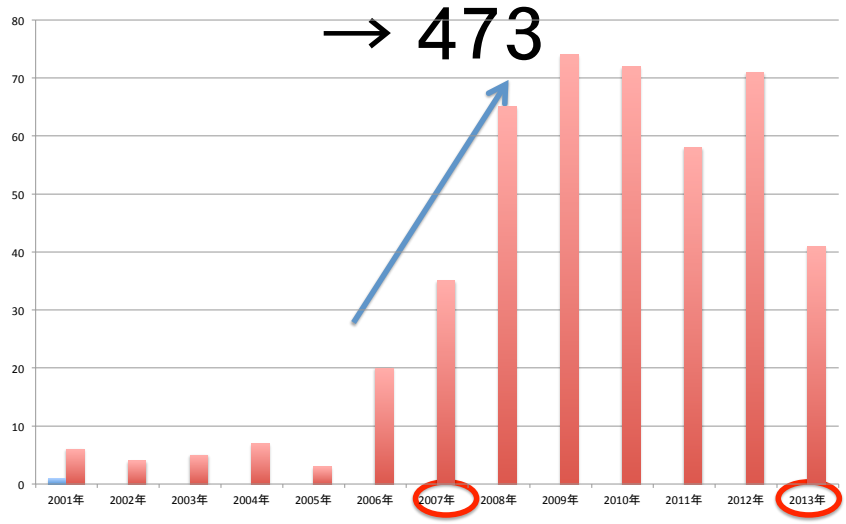
HPV vaccine → 5844



HPV vaccine (5844)



HPV vaccine safety



2007

35論文の殆どが安全

HPV vaccination

A paradigm shift in public health

Aust Fam Physician. 2007 Mar;36(3):106-11.

HPV vaccination - a paradigm shift in public health.

May J.

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Jenny May
BMed(Hons), FRACGP, FACRRM, is an academic and rural general practitioner, University Department of Rural Health Northern NSW, University of Newcastle, New South Wales. jenny.may@hnehealth.nsw.gov.au

Summary of important points

- The quadrivalent HPV vaccine (Gardasil) protects against HPV types 6, 11, 16 and 18.
- HPV types 16 and 18 cause 70% of cervical cancer cases and 50% of high grade cervical abnormalities.

Conflict of interest: Jenny May is a member of CSL Ltd's GARDASIL® Advisory Board.

Original article J Adolesc Health. 2007 Jun;40(6):564-71.

Immunization of Early Adolescent Females with Human Papillomavirus Type 16 and 18 L1 Virus-Like Particle Vaccine Containing AS04 Adjuvant

Court Pedersen, M.D., Sc.D.[a], Tiina Petaja, M.D.[b], Gitte Strauss, M.D.[c], Hans C. Rumke, M.D.[d], Airi Poder, M.D.[e], Jan Hendrik Richardus, M.D., Ph.D.[f], Bart Spiessens, Ph.D.[g], Dominique Descamps, M.D.[g], Karin Hardt, Ph.D.[g], Matti Lehtinen, M.D., Ph.D.[b], , , Gary Dubin, M.D.[h], HPV Vaccine Adolescent Study Investigators Network

CONCLUSIONS: These findings suggest that HPV vaccination during early adolescence is generally safe, well tolerated, and highly immunogenic. The observed higher antibody titers in the group 10-14 years of age are likely to result in longer antibody persistence. Overall, these data support the implementation of prophylactic HPV vaccination in this age group.

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[g] GlaxoSmithKline Biologicals, Rixensart, Belgium
[h] GlaxoSmithKline Biologicals, King of Prussia, Pennsylvania

Acknowledgments

The authors acknowledge the GlaxoSmithKline Biologicals HPV Vaccine Adolescent Study Investigators Network: Denmark, Carsten Sand, MD; Estonia, Lee Tammemae, MD; Finland, Sari Tanus, MD; Greece, Andreas Constantopolous, MD, George Creatsas, MD, Florentia Kanakoudi, MD, PhD; Russia, Natalia Ilina, MD, Vladimir Tatochenko, MD, PhD, D Med Sci, Olga Alikova, MD, PhD, and Natalia Melekhova, MD, PhD.

This study 580299/012 was funded and coordinated by GlaxoSmithKline Biologicals, Rixensart Belgium. We also would like to acknowledge and thank all clinical study site personnel who contributed to the conduct of this trial. GlaxoSmithKline Biologicals Clinical study support: Protocol development, Christian Van Hoeck, MD; Scientific writing protocol preparation, Frederic Geurts, PhD; Statistical contributions: Celia Barberousse, MSc, GlaxoSmithKline Biologicals Rixensart Belgium; Toufik Zahaf, PhD, GlaxoSmithKline Biologicals Rixensart Belgium; Technical writing assistance in manuscript preparation: Scientific Therapeutics Information, Inc, Springfield, NJ; Susan Wieting, BSc, GlaxoSmithKline Biologicals, Rixensart, Belgium.

Lancet 2007; 369: 2161 –70

Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial

*Jorma Paavonen, David Jenkins, F Xavier Bosch, Paulo Naud, Jorge Salmerón, Cosette M Wheeler, Song-Nan Chow, Dan L Apter, Henry C Kitchener, Xavier Castellsague, Newton S de Carvalho, S Rachel Skinner, Diane M Harper, James A Hedrick, Unnop Jaisamrarn, Genara A M Limson, Marc Dionne, Wim Quint, Bart Spiessens, Pascal Peeters, Frank Struyf, Susan L Wieting, Matti O Lehtinen, Gary Dubin, for the HPV PATRICIA study group**

24人　　HPV PATRICIA study group

Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial

*Jorma Paavonen, David Jenkins, F Xavier Bosch, Paulo Naud, Jorge Salmerón, Cosette M Wheeler, Song-Nan Chow, Dan L Apter, Henry C Kitchener, Xavier Castellsague, Newton S de Carvalho, S Rachel Skinner, Diane M Harper, James A Hedrick, Unnop Jaisamrarn, Genara A M Limson, Marc Dionne, Wim Quint, Bart Spiessens, Pascal Peeters, Frank Struyf, Susan L Wieting, Matti O Lehtinen, Gary Dubin, for the HPV PATRICIA study group**

Summary

Background The aim of this interim analysis of a large, international phase III study was to assess the efficacy of an AS04 adjuvanted L1 virus-like-particle prophylactic candidate vaccine against infection with human papillomavirus (HPV) types 16 and 18 in young women.

Methods 18 644 women aged 15–25 years were randomly assigned to receive either HPV16/18 vaccine (n=9319) or hepatitis A vaccine (n=9325) at 0, 1, and 6 months. Of these women, 88 were excluded because of high-grade cytology and 31 for missing cytology results. Thus, 9258 women received the HPV16/18 vaccine and 9267 received the control vaccine in the total vaccinated cohort for efficacy, which included women who had prevalent oncogenic HPV infections, often with several HPV types, as well as low-grade cytological abnormalities at study entry and who received at least one vaccine dose. We assessed cervical cytology and subsequent biopsy for 14 oncogenic HPV types by PCR. The primary endpoint—vaccine efficacy against cervical intraepithelial neoplasia (CIN) 2+ associated with HPV16 or HPV18—was assessed in women who were seronegative and DNA negative for the corresponding vaccine type at baseline (month 0) and allowed inclusion of lesions with several oncogenic HPV types. This interim event-defined analysis was triggered when at least 23 cases of CIN2+ with HPV16 or HPV18 DNA in the lesion were detected in the total vaccinated cohort for efficacy. Analyses were done on a modified intention-to-treat basis. This trial is registered with the US National Institutes of Health clinical trial registry, number NCT00122681.

Findings Mean length of follow-up for women in the primary analysis for efficacy at the time of the interim analysis was 14·8 (SD 4·9) months. Two cases of CIN2+ associated with HPV16 or HPV18 DNA were seen in the HPV16/18 vaccine group; 21 were recorded in the control group. Of the 23 cases, 14 (two in the HPV16/18 vaccine group, 12 in the control group) contained several oncogenic HPV types. Vaccine efficacy against CIN2+ containing HPV16/18 DNA was 90·4% (97·9% CI 53·4–99·3; p<0·0001). No clinically meaningful differences were noted in safety outcomes between the study groups.

Interpretation The adjuvanted HPV16/18 vaccine showed prophylactic efficacy against CIN2+ associated with HPV16 or HPV18 and thus could be used for cervical cancer prevention.

Introduction

The necessary role of oncogenic human papillomavirus (HPV) infection in cervical cancer provides an opportunity to reduce disease burden through prophylactic vaccination.[1,2] HPV types 16 and 18 account for 70% or more of cases of cervical cancer worldwide.[3] Up to 15 oncogenic HPV types contribute to cervical cancer and several are members of either the A7 (HPV18, 39, 45, 59, 68, 70, and 85) or A9 (HPV16, 31, 33, 35, 52, 58, and 67) papillomavirus species.[4,5]

An HPV16/18 L1 virus-like-particle candidate vaccine (GlaxoSmithKline Biologicals, Rixensart, Belgium), adjuvanted with 3-O-desacyl-4′-monophosphoryl lipid A and aluminium hydroxide (AS04), has shown complete prevention of 12-month persistent infections with the combined endpoint of HPV16 infection, HPV18 infection, or HPV16 and HPV18 co-infection (HPV16/18), and associated combined cervical intraepithelial neoplasia (CIN grades 1, 2, and 3) in fully vaccinated young women who were seronegative for HPV16 and HPV18 and negative for any cervical oncogenic HPV DNA at study entry.[6] High efficacy has been shown through 4·5 years of follow-up, together with sustained levels of antibodies against HPV16 and HPV18.[6] The vaccine has also shown evidence of cross-protection against incident infection with HPV45 and HPV31, two non-vaccine HPV types that are phylogenetically related to HPV16 and HPV18,[4] which together with HPV16 and HPV18, account for about 80% of cases of cervical cancer worldwide.[3]

www.thelancet.com Vol 369 June 30, 2007　　2161

Interpretation

The adjuvanted HPV16/18 vaccine showed prophylactic efficacy against CIN2+ associated with HPV16 or HPV18 and thus could be used for cervical cancer prevention.

Conflict of interest statement

JP has received research grants from Merck & Co and GlaxoSmithKline through the University of Helsinki to do clinical trials of HPV vaccines, and has received consulting fees or lecture fees from both companies. BS, PP, FS, SLW, and DJ are employees of GlaxoSmithKline (Rixensart, Belgium). PP owns shares in GlaxoSmithKline. FXB is on steering committees for Merck and Sanofi Pasteur MSD, is an external adviser for GlaxoSmithKline, and has received travel funds or honoraria from GlaxoSmithKline, Merck, Sanofi Pasteur MSD, and Digene. His research unit is involved in vaccine trials organised by GlaxoSmithKline, Merck, and Sanofi Pasteur MSD. PN is a GlaxoSmithKline investigator on HPV development trials. CMW has received funding for HPV vaccine trials from Merck & Co and GlaxoSmithKline. S-NC has served on advisory boards for GlaxoSmithKline. XC has acted as a consultant or received travel grants from GlaxoSmithKline and Sanofi Pasteur MSD and has received research grants from GlaxoSmithKline and Merck & Co. SRS received honoraria for the GlaxoSmithKline Biologicals (Australasia) Cervical Cancer Working Party and has received travel grants from GlaxoSmithKline Biologicals (Australasia). DMH has received financial support from Merck and GlaxoSmithKline for clinical trial support, advisory board participation, and speaking fees. JAH has received research funding from GlaxoSmithKline. WQ has received financial support for diagnostic services in the field of HPV testing from GlaxoSmithKline. GD is a full-time employee of GlaxoSmithKline (King of Prussia, PA, USA). GAML, MD, NSdC, DLA, HCK, UJ, MOL, and JS declare that they have no conflict of interest.

2013

41論文のうち17–2

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

Beliefs, behaviors and HPV vaccine: Correcting the myths and the misinformation☆

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[b] Louise Granofsky-Psychosocial Oncology Program and Lady Davis Institute for Medical Research, Jewish General Hospital, 4333 Cote Ste-Catherine Rd., Montréal, Quebéc, H3T1E4, Canada
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Conclusion: Most fears related to HPV vaccine are more related to myth than reality. In the absence of major health policy initiatives, such as those implemented in Canada, the U.K., and Australia, a multi-level, multi-faceted approach will be required to achieve high rates of HPV vaccination. It will be essential to focus on the education of health care providers regarding indications for HPV vaccination and approaches to communicating most effectively with parents and patients about the safety and benefits of vaccination and the risks associated with non-vaccination.

Conflicts of interest

Two of the authors (GDZ and NWS) are investigators on investigator-initiated grants funded by Merck and Co. GDZ is a recipient of an unrestricted program development grant from GlaxoSmithKline. WAF has received speaker fees, educational, and unrestricted research grants from Merck Canada. ZR has received a fee for consulting with Merck on behavioural science issues. Author SP has no conflicts of interest to report.

Safety and Immunogenicity of Human Papillomavirus-16/18 AS04-Adjuvanted Vaccine: A Randomized Trial in 10–25-Year-Old HIV-Seronegative African Girls and Young Women

Papa Salif Sow,[1,2,a] Deborah Watson-Jones,[3,4,a] Nancy Kiviat,[5] John Changalucha,[4] Khardiata Diallo Mbaye,[1] Joelle Brown,[3,4,6] Kouro Bousso,[1] Bazil Kavishe,[4] Aura Andreasen,[3,4] Macoumba Toure,[1] Saidi Kapiga,[4,7] Philippe Mayaud,[3] Richard Hayes,[7] Marie Lebacq,[8] Marjan Herazeh,[8] Florence Thomas,[8] and Dominique Descamps[8]

[1]CHU Fann, Service des Maladies Infectieuses, Dakar (Fann), Senegal; [2]University of Dakar, Senegal; [3]Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom; [4]Mwanza Intervention Trials Unit-National Institute for Medical Research, Mwanza, Tanzania; [5]University of Washington, Department of Pathology, Harborview Medical Centre, Seattle, Washington; [6]Department of Epidemiology, University of California, Los Angeles, California; [7]Faculty of Epidemiology and Population Health, London School Hygiene and Tropical Medicine, London, United Kingdom; and [8]GlaxoSmithKline Vaccines, Wavre, Belgium

Conclusions. The HPV-16/18 AS04-adjuvanted vaccine was highly immunogenic and had a clinically acceptable safety profile when administered to healthy HIV-seronegative African girls and young women.

Financial support. GlaxoSmithKline (GSK) Biologicals SA was the funding source and was involved, with the investigators, in all stages of the trial conduct and analyses. GSK Biologicals SA also took charge of all costs associated with the development and publishing of the present manuscript. Additional financial support for D. W. J. came from the Wellcome Trust, UK. Additional financial support for P. M. at the London School of Hygiene and Tropical Medicine was provided through the UK's Department for International Development (DFID)–funded Knowledge Programme on HIV/AIDS and sexually-transmitted infections, and the Research Programme Consortium on Research and Capacity Building in Sexual and Reproductive Health and HIV in Developing Countries of the London School of Hygiene and Tropical Medicine. The views expressed herein are those of the authors and do not necessarily reflect the official policy or position of DFID. R. H. and S. K. received grant support from the UK Medical Research Council.

Potential conflicts of interest. D. W. J., J. C., J. B., B. K., and A. A. have received grant funding from GlaxoSmithKline (GSK) Biologicals SA; P. M. has received grants from GSK Research & Development; M. L., M. H. (consultant from the contract research organization Chiltern), F. T., and D. D. are currently employed by the GlaxoSmithKline group of companies; F. T. and D. D. also have stock ownership in the GlaxoSmithKline group of companies. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

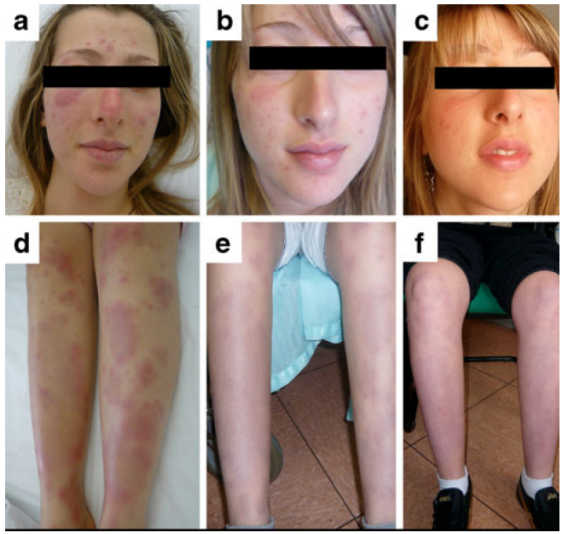


Fig. 1 Multiple erythematous cutaneous lesions of the face and lower limbs of patient number 3, occurring 8 days after the first dose of Gardasil™ (**a**–**b**), 1 week later in course of steroid therapy (**c**–**d**) and 1 month later (**e**–**f**)

Clin Rheumatol
DOI 10.1007/s10067-013-2266-7

ORIGINAL ARTICLE

Human papillomavirus vaccine and systemic lupus erythematosus

Mariele Gatto · Nancy Agmon-Levin · Alessandra Soriano · Raffaele Manna · Ramit Maoz-Segal · Shaye Kivity · Andrea Doria · Yehuda Shoenfeld

In summary, based on the current data, a causal link between HPV vaccination and onset or relapse of SLE is plausible. Therefore, although for most patients, the benefits of immunization outweigh its risks, clinicians must be aware of the odds for an autoimmune disease onset or exacerbation following HPV vaccination.

Disclosure: none.

Wilyman *Infectious Agents and Cancer* 2013, 8:21
http://www.infectagentscancer.com/content/8/1/21

INFECTIOUS AGENTS AND CANCER

REVIEW Open Access

HPV vaccination programs have not been shown to be cost-effective in countries with comprehensive Pap screening and surgery

Judy Wilyman

Competing interests
The authors declare that she has no competing interest.

Acknowledgments
I would like to acknowledge the support and guidance of Professor Brian Martin from the University of Wollongong in researching and writing this article and helpful comments from the referees. I would also like to thank Eva Vanamee for sounding some ideas.

包括的に子宮頸がん検査と手術が行なわれている国ではHPV予防接種プログラムの費用対効果は示されていない

背景情報

- HPV感染は、共同因子がなければガンには進展しない
- ガーダシル第三相試験は 2003 年に開始 2007 年に終了したが、販売されたのは 2006 年
- HPVワクチン費用対効果算出には、ある仮定を含む

頚がんの頻度と死亡率

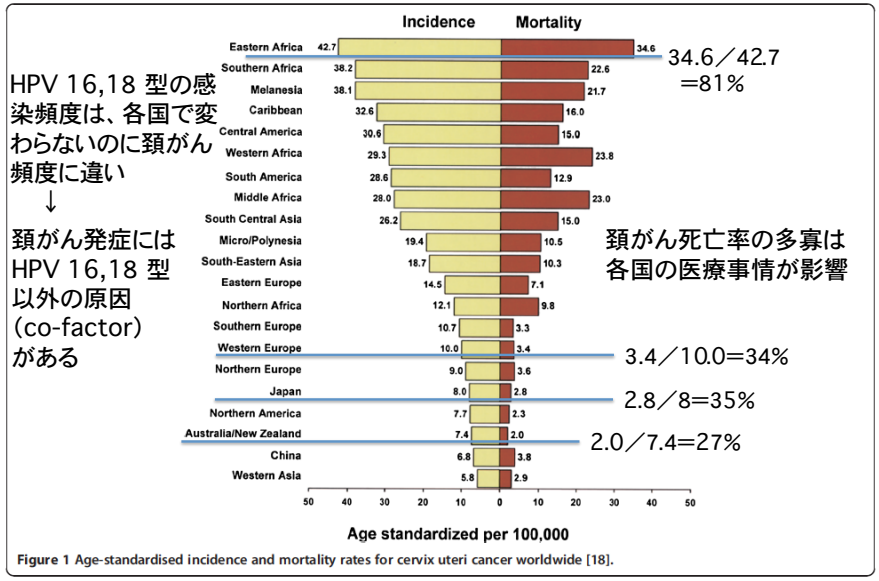


Figure 1 Age-standardised incidence and mortality rates for cervix uteri cancer worldwide [18].

HPV 16,18 型の感染頻度は、各国で変わらないのに頚がん頻度に違い
↓
頚がん発症にはHPV 16,18 型以外の原因（co-factor）がある

34.6／42.7 =81%

頚がん死亡率の多寡は各国の医療事情が影響

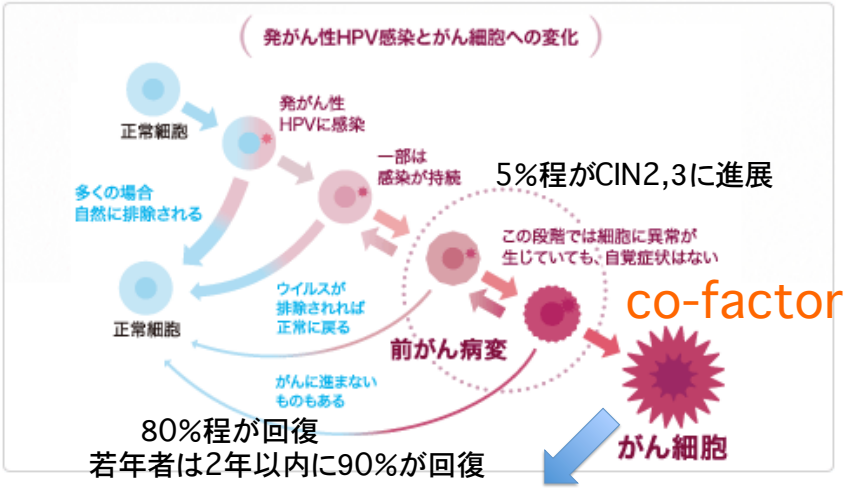
3.4／10.0=34%

2.8／8=35%

2.0／7.4=27%

図：子宮頸がんになるまで

http://allwomen.jp/factor/hpv.html

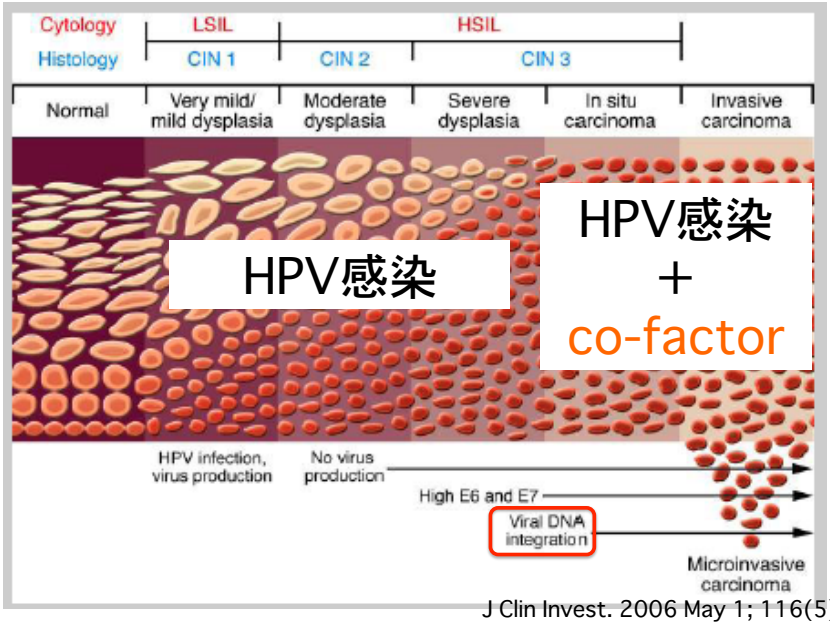


5%程がCIN2,3に進展

co-factor

80%程が回復
若年者は2年以内に90%が回復

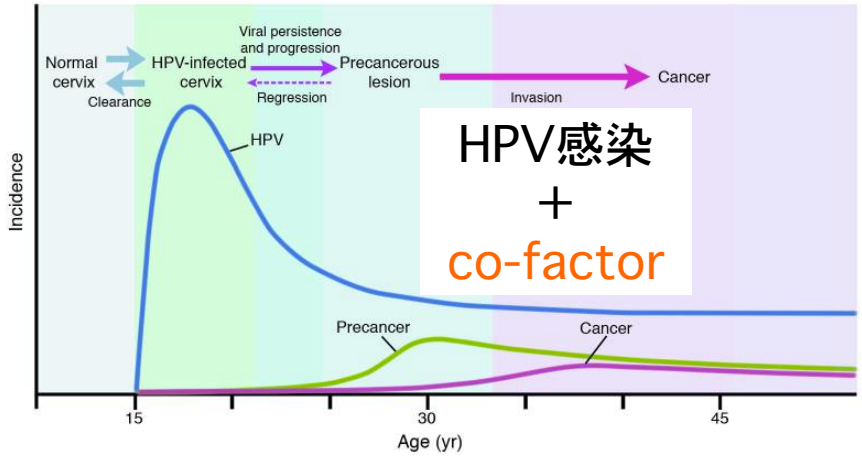
20%程が進行がんに進展（～5年～30年）



J Clin Invest. 2006 May 1; 116(5)

co-factor

a) Multiple partners for the male and female
b) Presence of HPV plus other sexually transmitted viruses
c) Prostitution [21]
d) Sex without a condom/microbicides [13] p.9
e) High parity > 3 children
f) Low socioeconomic status: poor hygiene/sanitation/ nutrition conducive to sexually transmitted diseases
g) Immunosuppression
h) Smoking
i) Long-term oral contraceptive use
j) older age



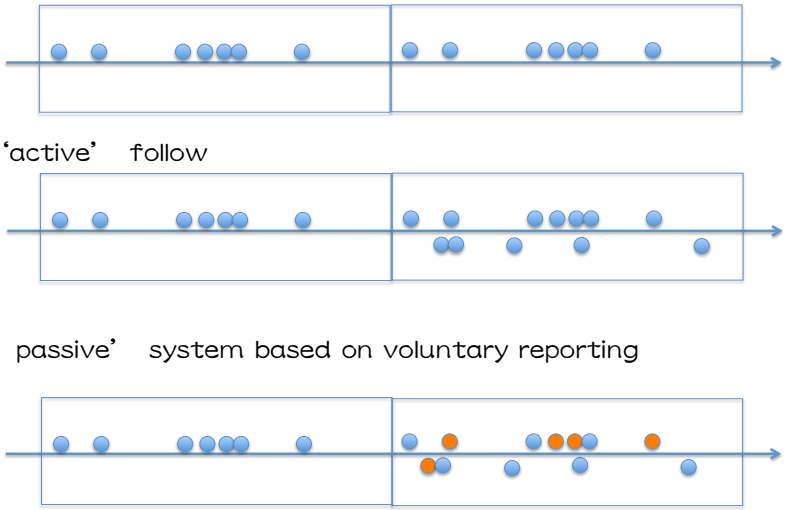
J Clin Invest. 2006 May 1; 116(5)

The safety of HPV vaccines

Slade et al. (2009) also indicate that 68% of the adverse reports for the HPV vaccine in their analysis came from the manufacturer: Merck and Co [31].

Of these reports, almost 89% did not provide sufficient identifying information to allow medical review of the individual cases.
As a result, the US Centers for Disease Control and Prevention (CDC) vaccine adverse events and reporting system (VAERS) cannot be used to infer causal associations between vaccines and adverse events [32].

'passive' system based on voluntary reporting
not an 'active' follow



The surveillance system is severely limited

I. It is a passive system
→ events are underreported.

II. Not all reported events are systematically validated.

III. Inconsistency in the quality and completeness of reported data.

IV. Reporting biases.

Evaluating the cost-effectiveness

費用対便益を算出するには沢山の仮定が要る
→ 各国で事情が異なってくる

Received September 2, 2009, and in revised form December 25, 2009.
Accepted for publication December 27, 2009.
(*Int J Gynecol Cancer* 2010;20: 385–392)

Cost-Effectiveness Analysis of Prophylactic Cervical Cancer Vaccination in Japanese Women

Ryo Konno, MD, PhD, Toshiyuki Sasagawa, MD, PhD,† Takashi Fukuda, PhD,‡ Georges Van Kriekinge,§ and Nadia Demarteau§*

Conclusions: The implementation of a CC vaccination in Japan could reduce the CC burden in a very cost-effective manner for women up to 45 years.

Impact of Vaccination on Clinical Outcomes

The impact of vaccination on incidence and mortality of CC was estimated as follows:

Vaccination of 100% of a single cohort of 12-year-old girls (n = 589,000) would reduce the number of cancer cases by 73.1% (from 5097 CC cases without vaccine to 1373 CC cases with the vaccine) and the number of CC-related mortality by 73.2% (from 1762 CC deaths without vaccine to 473 CC deaths with the vaccine).

This study was supported by a grant from GlaxoSmithKline K.K Japan. R. Konno received research and travel grants and honoraria for courses and conferences from GlaxoSmithKline Japan, Merck Japan, and Qiagen Japan. He is a member of the Advisory/Expert Board at GlaxoSmithKline Biologicals. This study was also supported by GlaxoSmithKline Biologicals, where authors Van Kriekinge and Demarteau are currently employed.

Currently the benefit of the vaccine against the burden of cervical cancer in developed countries is unknown and there are risks of injury and death that have not been accurately determined.

HPV vaccines are not demonstrated to be safer or more effective than Pap screening combined with surgical procedures. Hence it follows that implementing broad HPV vaccination programs is not cost-effective in countries where regular Pap screening programs are available and will still be required.

HPV vaccines in vaccination programs in these countries are offering uncertain benefits in reducing the burden of cervical cancer and may cause more harm than good due to the lack of investigation of their long-term safety.

頚がんの頻度と死亡率

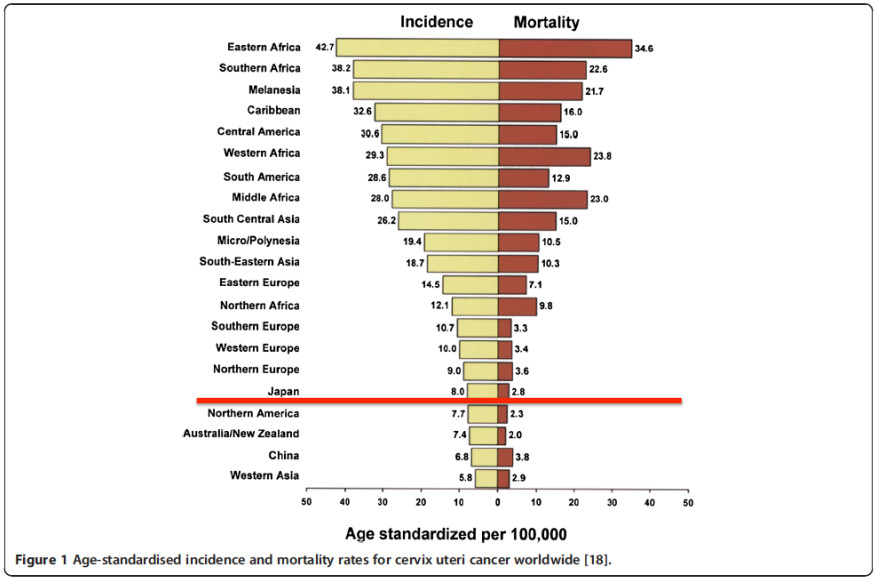


Figure 1 Age-standardised incidence and mortality rates for cervix uteri cancer worldwide [18].

地獄への道は
善意の小石で
敷き詰められている

ご清聴
ありがとうございました