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The pathogenesis of human Papillomavirus (HPV) in the development of cervical cancer: are HPV vaccines a safe and effective management strategy?

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Abstract

Human Papillomavirus (HPV) infection has been linked with cervical cancer. Some medical professionals see it as the determining causal agent and therefore promote vaccination as an effective prevention strategy. However, the biological plausibility of a causal theory requires that the incidence of the causal agent varies with the incidence and mortality of the disease. Yet the incidence and mortality of cervical cancer do not vary with the incidence of infection with HPV strains 16 and 18; the strains covered by the HPV vaccine. Though HPV infection is a necessary precursor to most cervical cancer, most high-risk HPV infections (with one of 15 or more high-risk strains) do not progress to cervical cancer and HPV infection with any strain is not sufficient on its own to induce cervical cancer. This evidence supports the conclusion that environmental and lifestyle factors are a determining cause in conjunction with HPV in the progression to cervical cancer.

Clinical trials for the HPV vaccine did not attempt to observe the vaccine preventing any cervical cancer. Instead the trials looked for pre-cancerous lesions in women 16 – 26 years of age. This was an inadequate surrogate for cervical cancer because studies show that most lesions in this demographic clear quickly without requiring treatment. Preventing infection from HPV strains 16 and 18 also assumes these women will not get cervical cancer from infection with one of the many other high risk strains that are prevalent. Therefore the decision to use an HPV vaccine to prevent cervical cancer was based upon circumstantial evidence: assumptions. HPV vaccines have been promoted to women on selective information. This vaccine is an HPV vaccine not a cervical cancer vaccine. There is inconclusive evidence it will reduce any cervical cancer and the long-term risks of using this vaccine have not been determined.

Keywords

safe, vaccines, cancer, cervical, strategy, development, hpv, management, effective, human, pathogenesis, papillomavirus

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Judy Wilyman MSc

Abstract

Human Papillomavirus (HPV) infection has been linked with cervical cancer. Some medical professionals see it as the determining causal agent and therefore promote vaccination as an effective prevention strategy. However, the biological plausibility of a causal theory requires that the incidence of the causal agent varies with the incidence and mortality of the disease. Yet the incidence and mortality of cervical cancer do not vary with the incidence of infection with HPV strains 16 and 18; the strains covered by the HPV vaccine. Though HPV infection is a necessary precursor to most cervical cancer, most high-risk HPV infections (with one of 15 or more high-risk strains) do not progress to cervical cancer and HPV infection with any strain is not sufficient on its own to induce cervical cancer. This evidence supports the conclusion that environmental and lifestyle factors are a determining cause in conjunction with HPV in the progression to cervical cancer.

Clinical trials for the HPV vaccine did not attempt to observe the vaccine preventing any cervical cancer. Instead the trials looked for pre-cancerous lesions in women 16 - 26 years of age. This was an inadequate surrogate for cervical cancer because studies show that most lesions in this demographic clear quickly without requiring treatment. Preventing infection from HPV strains 16 and 18 also assumes these women will not get cervical cancer from infection with one of the many other high risk strains that are prevalent. Therefore the decision to use an HPV vaccine to prevent cervical cancer was based upon circumstantial evidence: assumptions. HPV vaccines have been promoted to women on selective information. This vaccine is an HPV vaccine not a cervical cancer vaccine. There is inconclusive evidence it will reduce any cervical cancer and the long-term risks of using this vaccine have not been determined.

Background

Cervical cancer has been studied worldwide for a century and a half and during this time many lifestyle and environmental factors have been implicated in its etiology 1. However, by 1995 the discovery of new hybridization technology led Bosch et al to claim "infection with HPV 16 and 18 is predictive of carcinoma and independent of other factors" 2. In 2006, Munoz et al declared human papillomavirus (HPV) Type 16 and 18 to be the determining cause of cervical cancer 3. These researchers stated "the causal role of human papillomavirus in all cancers of the uterine cervix has been firmly established biologically and epidemiologically" 3. This led to the release of a new vaccine to prevent HPV infection in the same year. It was promoted to the public as a vaccine that prevents cervical cancer 4, 5.

At this time it was known that HPV infection on its own was not sufficient to cause cervical cancer 1, 6, 7. Several co-factors had been identified as necessary for the progression of normal epithelial cells to carcinoma. Whilst there is still doubt about the identity of some co-factors, those that are confirmed are: multiple partners for the male and female, presence of HPV plus other viruses (for example HPV + Herpes Simplex Virus Type 2), prostitution, sex without a condom/microbicides, low socioeconomic status (poor hygiene/sanitation/nutrition conducive to sexually transmitted diseases), immunosuppression, smoking, oral contraceptives 1, 6, 7.

In addition, the plausibility of a causal theory, such as that put forward by Bosch et al, requires that the incidence and mortality of a disease varies with the factors implicated in the cause of the disease 8. It also requires evidence that the disease develops only in cases where the virus is present 8. The

strongest evidence for proving that HPV 16 and 18 are the central etiological factors in cervical cancer worldwide would be a correlation between the incidence of HPV 16/18 worldwide and the incidence and mortality of cervical cancer worldwide 8. This evidence would be strengthened by performing long-term prospective studies investigating biological and environmental factors that might operate in conjunction with HPV infection and would provide empirical evidence of the cause of cervical cancer 8. This is because these studies would include the correct follow up period or latent period between the initiation of the cancer and its development many years later 8, 9. In the case of cervical cancer this period has been estimated at about ten to twenty-five years 4, 9, 10.

However, long-term prospective studies to determine the causality of cervical cancer have not been done 11. The pharmaceutical companies (manufacturers of the vaccine) that sponsored the trials for HPV vaccines decided long-term studies would be too costly due to the latent nature of the disease 11. In 1995 it was claimed that HPV DNA could be found in the majority of carcinomas 2. Prior to 1995 the detection of HPV DNA in different tissues had been unreliable and the sensitivity of the results varied with different technology 12. However, in 1995, it was being claimed that 'new molecular biology techniques were truly sensitive and specific' 13.

These new techniques were used to re-analyse the Bosch et al, study that claimed 93% of tumors contained HPV DNA 14. As a result it was concluded that 99.7% of tumors contained HPV DNA 14. In other words, the basis for the claim that HPV is found in the majority of carcinomas was founded on a new technique for detecting HPV DNA that was promoted as being 'truly sensitive and specific'.

In 2003, it was stated that the role of HPV infection in the cause of cervical cancer was established and the World Health Organisation (WHO) was encouraged to test HPV vaccines as a preventative for cervical cancer; but not by observing actual cases of the disease 11. It was decided that a surrogate for cervical cancer would be appropriate 11. The clinical trials for the vaccine used the occurrence of pre-cancerous lesions in women 16 -26 years of age as the end-point for cervical cancer. This end-point was used as a surrogate for proving the efficacy of the vaccine against cervical cancer in an age-group that rarely gets cervical cancer 4, 11.

So despite evidence that co-factors are required for the progression of normal cells to cancer and despite a lack of definitive evidence supporting the claim that HPV 16/18 are necessary and sufficient to cause cancer, the HPV vaccine was promoted to all women as an effective preventative method. In the following sections the validity of the claims that have been made about HPV vaccines are examined from an historical perspective of etiology.

The Incidence of HPV Worldwide

There are over 100 HPV sub-types that have been identified and 40 of these are known to infect the genital tract 3. Most strains of HPV are common and harmless, however there are at least 20 types associated with cervical cancer: 14 of these are considered carcinogenic and these include HPV -16, -18, -31, -33, -35, -39, -45, -51, -56, -58, -52, -26, -53, -66 2. These types are frequently found in cervical cancer and are classified as 'high-risk' HPV's 2. Other types such as HPV -6, -11, -42, -43 and -44 are rarely associated with cervical tumors and they are classified as low risk HPV types 2 .

High rates of genital HPV infection are sustained in all communities throughout the world even in groups that do not have a high partner exchange 6. As there are striking differences in the rate of cervical cancer globally, it has been postulated that the more 'high-risk' HPV types may be associated with higher rates of cervical cancer 6. The prevalence of HPV sub-types varies between communities but the prevalence of HPV 16 and 18 does not correlate to regions with a high risk for cervical cancer 15. High-risk sub-types are found in both developed and developing countries yet women in developing countries have a much greater risk of cervical cancer than woman in developed countries 16.

Some similarities in the distribution of HPV sub-types have been found in invasive cervical carcinomas across regions 17. HPV 16 was found to be the dominant strain in all countries (51% of cases) and HPV 18 found consistently in 10-14% of cases 17. This led Clifford et al to claim that HPV 16 and 18 are

found in approximately 70% of all ICC cases 17. Trends were also noticed in the prevalence of other strains 2, 17.

Figure 1 illustrates a summary of the trends observed in the distribution of HPV sub-types in carcinomas globally:

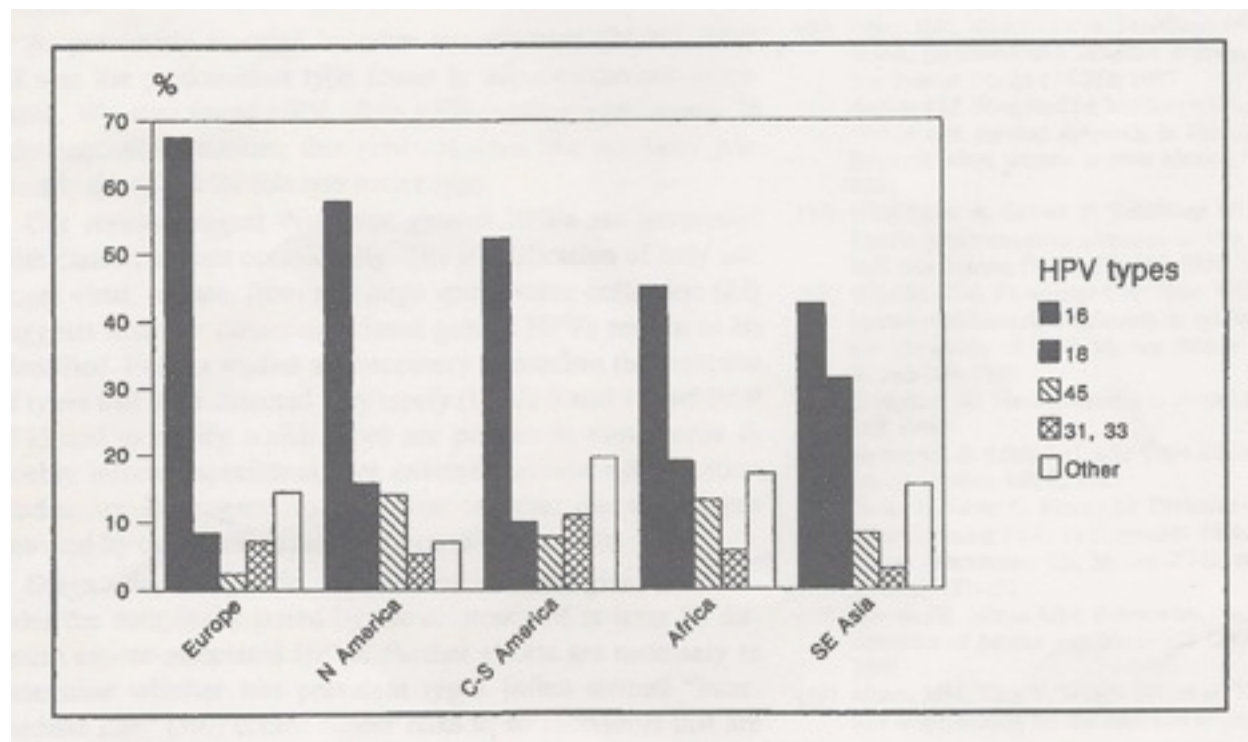


Figure 1: HPV type-specific prevalence by Geographic Region. Bosch FX, Manos M, Munoz N, Sherman M, Jansen A, Peto J, Schiffman M, Moreno V, Kurman R, Shah K, International Biological Study on Cervical Cancer (IBSCC), 1995, Prevalence of Human Papillomavirus in Cervical Cancer: a Worldwide Perspective, Journal of the National Cancer Institute, Vol.87, No.11

The study by Clifford et al claimed two thirds of ICC was associated with HPV 16 and 18, yet these two strains are not more prevalent in developing countries where the incidence of cervical cancer is highest 17. The prevalence of HPV 16 was higher in America, Australia and Europe: the developed countries where the risk of cervical cancer is considered to be low 16. More than 16 high-risk HPV sub-types are prevalent in all countries both in regions where the rates of cervical cancer are considered high and where they are considered low 17. These sub-types include 45, 31, 33, 58, 39, 59 and 52 2, 17. This trend can be observed in Figure 1.

Clifford et al state that heterogeneity in the distribution of high-risk HPV subtypes in different populations should be taken into account when developing screening tests and predicting the effect of vaccines on the incidence of HPV infection 15. The observed distribution of high-risk HPV sub-types led Clifford et al to conclude a vaccine against HPV 16 and 18 may prevent a larger proportion of ICC in the developed countries than in the developing countries 17. If this vaccine does not target the burden of cervical cancer in the developing countries then it cannot claim to protect the population against 70%

of cervical cancer. This statement was made the year before the vaccine was introduced into developed nations and indicates there was no certainty of the effectiveness of this vaccine against cervical cancer.

In addition, the claim by Clifford et al that HPV 16 and 18 are present in approximately 70% of ICC cases needs to be examined with respect to the limitations of the study. The cases included in this analysis were not representative of the burden of ICC worldwide 17. The study was under-represented by cases from Africa and Asia which together represent 64% of cervical cancer cases and over-represented by cases from Europe and North Africa that represent 20% of cervical cancer 17.

Another factor which puts doubt on this claim is the variation in the methods used to detect HPV in the different studies that were included in the meta-analysis. The Clifford et al study combined the results of 85 studies that used only Polymerase Chain Reaction (PCR) -based assays to identify HPV DNA 17. However, not all PCR primer sets enhance HPV sub-types with the same sensitivity and this puts uncertainty on the validity of the results of the meta-analysis 17.

An example of the variation in results obtained by using different PCR assays was the Bosch et al 1995 study. This study used MY09/11 polymerase chain reaction assay to detect HPV in 1000 tumors 2. HPV was found to be prevalent in 93% of the tumors using this technique 2. However, when a different detection method was applied it was found that HPV was prevalent in 99.7% of cervical carcinomas 14. This allowed the researchers to conclude ‘a virtual absence of HPV-negative cancers (in 1000 tumors) implies that effective prophylactic vaccination might eliminate cervical cancer worldwide’: even though the 1000 cases were not representative of the global risk of cervical cancer 14. Appendix 1. This claim led to the trial of an HPV vaccine to prevent cervical cancer even though the International Agency for Research on Cancer (IARC) states case series can only provide suggestive results and can never serve as a basis for causal inferences 6.

The Correlation between the Risk of HPV Infection and the Risk of Cervical Cancer Worldwide

The incidence of HPV infection in women worldwide is approximately 80 %, vastly greater than the incidence of cervical cancer 16. The lifetime risk of cervical cancer before the age of 64 is 0.8 % in a developed country and 1.5% in a developing country 16.

Figure 2 illustrates the variation of risk between developed and developing nations.

Developed Countries per 100,000 women	Developing Countries per 100,000 women
0 - 14.5	0.5 - 44

Figure 2: Incidence of Cervical Cancer Worldwide. *Parkin DM, Bray F, Ferlay J, Pisani P, 2005, Global Cancer Statistics 2002, CA: A Cancer Journal for Clinicians, 2005; 55; 74-108*

In developed countries the risk of cervical cancer is considered very low 16. For example, in Australia the incidence of cervical cancer is 6.9 /100,000 women and the death rate is 1.9/100,000 women 11. Australia has one of the lowest rates of incidence and mortality from cervical cancer in the world: 99% of Australian women will not be affected by cervical cancer in their lifetime 11. In Australia, indigenous women have twice the risk of developing cervical cancer and the mortality rate is four times that of non-indigenous women 11. In general Aboriginal communities in Australia are poorer communities and a high incidence of cervical cancer is associated with these conditions 18. This variation of risk between

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indigenous and non-indigenous women indicates the significance of environmental and lifestyle factors in the etiology of this disease.

In contrast, the risk of cervical cancer in developing countries is considered to be high 16. In the 60's and 70's, developed countries had similar rates of cervical cancer to developing countries today 16. China has also seen a dramatic decline in the incidence of cervical cancer from 17.8 per 100,000 women in 1985 to 6.8 in 2002 16. Developed countries have had improved living standards and greater access to screening programs and condoms since the 1960's. In addition, the incidence of HPV infection is similar between all countries but the incidence of cervical cancer is not 6. This also supports the theory that lifestyle and environmental risk factors act in conjunction with HPV infection to cause cervical cancer.

It should be noted that the mortality rates for cervical cancer are lower than incidence rates 16.

Figure 3 illustrates this difference.

Developed Countries per 100,000 women	Developing Countries per 100,000 women
0 - 10	10 - 34

Figure 3: Mortality Rates for Cervical Cancer Worldwide. *Parkin DM, Bray F, Ferlay J, Pisani P, 2005, Global Cancer Statistics 2002, CA: A Cancer Journal for Clinicians, 2005; 55; 74-108*

A comparison of the incidence and mortality rates for cervical cancer between countries is illustrated in Figure 4 (below). This graph shows that mortality rates are lower than incidence rates for cervical cancer and this disease is a much higher risk in developing countries than developed countries. The difference in the risk of cervical cancer between countries has not been emphasised to women in the education campaigns for this disease.

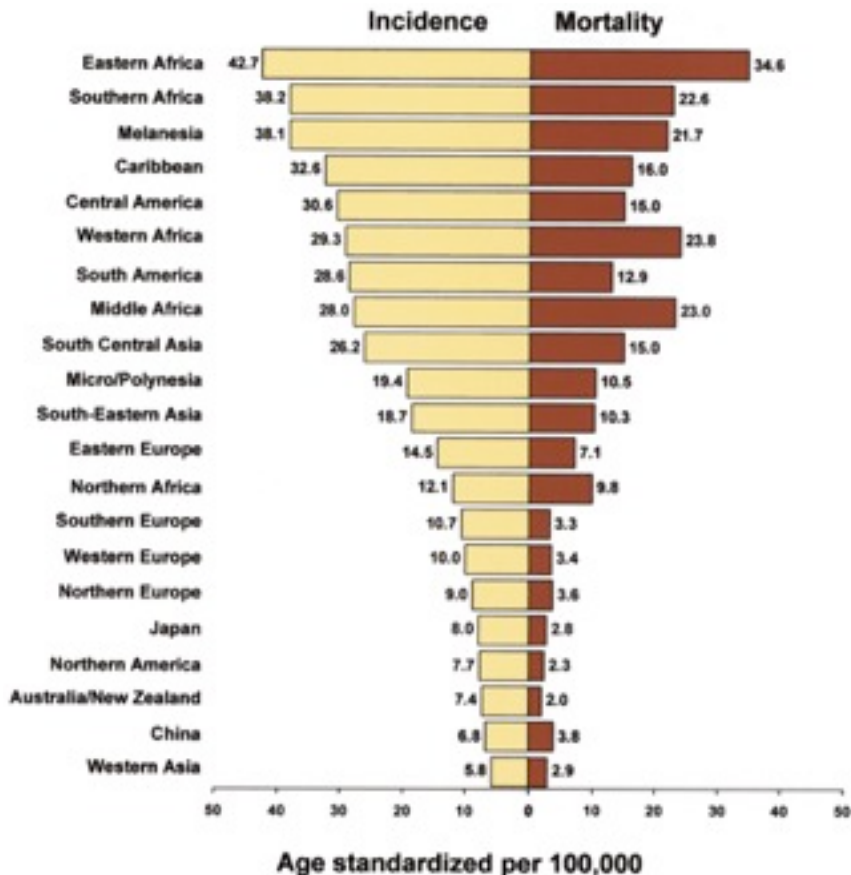


Figure 4: Age-standardized Incidence and Mortality Rates for Cervix Uteri Cancer. *Parkin DM, Bray F, Ferlay J, Pisani P, 2005, Global Cancer Statistics 2002, CA: A Cancer Journal for Clinicians, 2005; 55; 74-108*

Analysis of the evidence for HPV as the determining cause of cervical cancer

HPV are a group of viruses with strong epitheliotropic properties; that is, they have a strong affinity for epithelial cells 19. Epithelial cells normally harbor the virus and 80% of women are infected with HPV during their lifetime 19. Therefore a significant association between HPV and invasive cervical cancer (ICC) is expected 19. In 1989 it was unclear whether HPV was a passenger virus in carcinoma development or whether it played a causal role in the progression to ICC 19. The overall evidence in 1989 pointed to a multi-factorial cause of cervical cancer as other determinants consistently emerged as independent risk factors in epidemiological investigations 20.

The conclusion that HPV is the determining causal factor in cervical cancer development has been based upon the research by Bosch et al investigating the worldwide prevalence of HPV in 1000 cervical cancer tumors 2.

Epidemiologists claim there is a “highly statistically significant association between HPV and the development of cervical intraepithelial neoplasia (CIN) grade 2 or 3 with persistent CIN 2/3 and with development of cervical cancer” 1. Carcinogenicity of HPV 16 and 18 is supported by experimental evidence that proteins of these viruses interfere with the functions of cellular regulatory pathways 6.

However, Walboomers et al state “whilst persisting infection of the cervix with high-risk HPV is necessary for the development of cervical cancer, it is certainly not sufficient” 14.

There would be strong evidence for HPV as the main independent cause of cervical cancer if the majority of cases of infection with HPV 16 and 18 progressed to cervical cancer. But they do not. The Australian Government states cervical cancer is a rare outcome of high-risk HPV infection and this is supported by the International Agency for Research on Cancer (IARC) 6, 7. In addition, it would be expected that the incidence and mortality of cervical cancer would vary with the incidence of HPV 16 and 18 across the globe if these strains are the determining cause of most cervical cancer. We have already observed that there is no correlation between the incidence of cervical cancer and incidence of high-risk HPV sub-types, including HPV 16/18, so it is necessary to examine the influence of lifestyle and environmental factors as co-factors in cancer development.

The Evidence for an Etiological Association with Environmental and Lifestyle factors

For many decades public health scientists have used the epidemiological triangle, consisting of host, agent and environment, to assist in determining the etiology of infectious disease 8. This model of causality has been revered as “one of the fundamental public health concepts of disease causality and well suited to determining the cause of infectious diseases” 8.

Whilst an agent must be present for an infection to occur, other factors, such as the characteristics of the environment and the host, also play a role in determining whether events progress to an active case of the disease 8. This public health fact and the evidence cited here show that the claim by Bosh et al (1995) that “infection with HPV 16 and 18 is predictive of carcinoma and independent of other factors” is false 2. Evidence for this conclusion is summarised below:

1. HPV infection with any strain is not sufficient to cause cervical cancer 7.
2. Approximately eighty percent of women are infected with HPV yet ninety percent of these HPV infections do not lead to cancer or warts 6, 7.
3. HPV 16 is identified as the pre-dominant sub-type in all countries yet cervical cancer rates vary significantly between countries 16.
4. Developed countries had the same high rates of cervical cancer in the sixties and seventies as the developing countries today but this was reduced by changes in environmental and lifestyle factors and the introduction of screening 16.
5. There is an increased risk of cervical cancer with an increased number of sexual partners 6.
6. Prostitutes have a four times greater chance of getting cervical cancer even though the detection of HPV sub-types is similar to controls 21.
7. Condoms can reduce the risk of cervical cancer four-fold 9.
8. China had a high rate of cervical cancer in 1985 but this was reduced to a low rate by 2002 without the use of a vaccine 16.
9. Bosch et al highlight that the sensitivity of new molecular biology techniques confirm the plausibility of HPV infection as the pre-cursor event leading to cervical cancer 2. However, a pre-cursor event is not predictive of cancer if the majority of cases do not progress to cancer.
10. Some scientists still claim 5-10% of tumors are not associated with any HPV DNA 1, 22.

11. It is postulated that HPV 16 and 18 are present in possibly 70% of tumors but it has not been proven 15. This statistic is dependent upon the detection methods used and still leaves 30% of cervical cancer unprotected by the vaccine.

The use of Pre-cancerous Lesions in the Determination of Efficacy for the Vaccine

The WHO consultation group used four key features to suggest that observing the frequency of pre-cancerous lesions (the virological endpoint of persistent HPV infection) in young women was a useful endpoint for testing a vaccine against cervical cancer 11. These features were:

1. They are obligate precursors of cervical cancer
2. They are closely associated in temporal sequence to the development of invasive cervical cancer
3. They are associated with a high risk of development of invasive cervical cancer (ICC)
4. Reductions in incidence or treatment are shown to result in a reduction in risk of invasive cervical cancer.

The first three statements above are only true when the environmental and lifestyle risk factors (listed above) are also present 1, 6, 7. Yet the clinical trials for this vaccine did not select participants for these risk factors 23. The fourth statement needs to be qualified because cervical cancer is a rare outcome of high-risk HPV infection and there are many high-risk subtypes 6, 7. There is no evidence that just targeting HPV 16/18 will result in a significant reduction in the risk of cervical cancer. In order to suggest that this vaccine will be effective in reducing the burden of cervical cancer, it must be demonstrated that there is a correlation between the worldwide incidence of HPV 16 and 18 and mortality from cervical cancer. This has not been demonstrated.

Pre-cancerous lesions were chosen as the end-point for cervical cancer based upon two assumptions 11:

1. The first assumption is that pre-cancerous lesions in this age group most often lead to cancer 23. This assumption is incorrect. Pre-cancerous lesions in this age group are most often cleared quickly by the immune system 7, 10. It is also known that pre-cancerous lesions can persist for a lifetime without giving rise to cervical cancer 7.
2. The second assumption underpinning these clinical trials is that preventing strains 16 and 18 from infecting women will prevent some cervical cancer. However, the prevention of strains 16 and 18 from infecting provides an opportunity for one of the many other high-risk HPV types to infect; there are about 20 of these 6. The Australian health department confirms that resolved infection with a high-risk HPV does not protect against other high-risk types 7.

The two assumptions described above confirm that using the occurrence of pre-cancerous lesions, in 16-26 year olds, was an inappropriate end-point for cervical cancer development. This is because the relationship between HPV infection at a young age and development of cervical cancer 20 to 40 years later is unknown 24. In addition, the fact that HPV of all sub-types is found in high frequency among women with normal cervixes indicates that on its own HPV is not predictive of cancer 15.

Ninety percent of HPV infections have no clinical consequences at all: there is no development of genital warts or progression to cervical cancer 6, 7. In 1990, Pfister noted 'no papillomavirus is able to induce cancer right away and fully on its own' (p.6, 12). Carcinomas usually develop only after primary lesions persist for several months/years, which indicates that additional events are needed to trigger malignant growth 12.

Efficacy of the HPV Vaccine

The trials investigating the efficacy of HPV 16/18 vaccine in preventing cervical cancer observed that women, 16-26 years old, who were given the vaccine, had fewer pre-cancerous lesions than women who were not given the vaccine 23. However, this result was dependent upon the protocol of the study group 23. A significant reduction in pre-cancerous lesions was only observed in the study group that had not been infected with HPV 16/18 at baseline 23.

The health department states that the HPV vaccine does not prevent HPV infection (16 and 18) which was already present at the time of vaccination 7. The trials demonstrated only 44% efficacy in the study group that was infected with HPV 16/18 at baseline 25. Previous sexual activity is the main reason for infection with HPV 7. In other words, you are still susceptible to cervical cancer if you were infected with HPV 16/18 prior to vaccination. This would be a large percentage of the population if HPV 16/18 are the dominant sub-types, as scientists are claiming.

Since the vaccine was marketed in 2006 there has been no screening for HPV sub-types prior to vaccination so there is no conclusive data on the effectiveness of this HPV vaccine in preventing pre-cancerous lesions in a demographic that rarely gets cervical cancer. Currently the only clinical trials that have been performed for this vaccine were funded by the manufacturers of the vaccine 23.

The manufacturer of HPV vaccines claims the drug prevents “high-grade disease” based on its ability to prevent pre-cancerous lesions in women 16-26 years of age 23. High-grade disease was measured by the presence of pre-cancerous lesions that were graded CIN 2 or 3 10, 23. These types of lesions were thought to be the immediate precursors of cervical cancer when the trials were performed in 2000-2004 23. However, new guidelines regarding the natural history of cervical cancer were introduced in Australia in 2005 which indicated scientists no longer believed this to be the case 7.

Previously, the guidelines for the treatment of cervical cancer implied a progression from CIN 1, CIN 2 and CIN 3 to cancer 7. The new belief is that “rather than an inevitable linear progression towards cancer, most precursor HPV infections (CIN 2 and 3) acquired by women resolve without medical intervention” 7.

If CIN 3 does change into invasive cancer the time frame for this to happen averages between 8.1 to 12.6 years 10. Yet the longest follow up study of the HPV vaccine during the clinical trials was only 4 years 10, 23. In addition, “the vast majority of women (16-26 years of age) clear or suppress HPV to levels not associated with CIN 2 or 3 (high-grade disease) and for most women this occurs promptly” 10. Raffle et al state that modeling data from the United Kingdom suggests that eighty percent of high-grade intraepithelial abnormalities will regress without intervention (as cited in 7).

Therefore, the correct assumption is that pre-cancerous lesions in this age-group are not an indication that cervical cancer will develop from a high -risk HPV infection. The clinical trials do not provide conclusive evidence that a reduced number of pre-cancerous lesions in women 16-26 years of age (even if not previously infected with HPV 16/18) will reduce the incidence of cervical cancer in older women: the age groups with the highest incidence of cervical cancer. The only conclusive evidence obtained from the clinical trials in this age group was that the drug prevents infection from two out of many strains of high-risk HPV's identified in cervical cancer cases. It was assumed that fewer pre-cancerous lesions in the vaccinated group indicated a reduction in cervical cancer cases in older women, but the evidence discussed above suggests otherwise.

Promotion of Benefits and Risks of the Vaccine

In 2006 when the HPV vaccine was licensed and marketed to females, the phase 3 clinical trials had not been completed 25. In other words, the benefit and duration of this vaccine against cervical cancer had not been established. The promotional campaigns for this vaccine were funded by the vaccine manufacturer and promoted through professional medical associations in America 26. This arrangement was established to ensure that the public received education about this vaccine from a

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trusted source 26. The pharmaceutical companies supplied the medical associations with ready-made presentations and letters to promote Gardasil® as a preventative for cervical cancer: even though the data was incomplete and it was primarily a guard against HPV viruses 25. Much of the promotional material did not address the complexity of the issues surrounding the vaccine and did not provide balanced advice regarding the risks and benefits of the vaccine 26.

By promoting the vaccine as a preventative for cancer, instead of a sexually transmitted infectious disease, the HPV vaccine was placed in the non-communicable disease category thus enabling the manufacturer to avoid public health officials who would have scrutinized a high-risk vaccination campaign 26. In addition, a law was passed in the United States in 1986 that permits vaccine manufacturers the right not to disclose known risks of vaccines to parents and guardians 27. It states “manufacturers bear no liability for giving, or failing to give, accurate or complete information to those vaccinated, and have only to provide relevant information to doctors, who must give patients CDC Vaccine Information Statements. 49” (as cited in 27).

The effectiveness and duration of this vaccine against cervical cancer were unknown in 2006 yet Gardasil® was named the pharmaceutical “brand of the year” for building a ‘market out of thin air’ 26. In 2008 worldwide sales reached \$1.4 billion 26. This was an HPV 16/18 vaccine being promoted as a cervical cancer vaccine to females aged 9 -26; even though it had not been tested in females under 15 years of age 5.

Many adverse events to HPV vaccines were reported during the two and a half years following the licensure of the vaccine 5. The US Centers for Disease Control (CDC) and the Food and Drug Administration (FDA) operate the US Adverse Events Reporting System (VAERS) 5. This is a voluntary, national, passive surveillance system set up to monitor the adverse events to vaccines; it enables manufacturers, health professionals and patients to report adverse reactions 5.

Although an analysis of the postlicensure safety surveillance data for the HPV vaccine has been performed, the analysis only included adverse event data from the US 5. This is despite Gardasil® being licensed in many foreign countries 5. The decision to use only American data was justified on the grounds that US data offers more complete information and is more feasible for follow up studies for medical review 5. Slade et al state 70% of the adverse event reports in their analysis came from the manufacturer 5. Of these reports, 90% did not provide sufficient identifying information to allow medical review of the individual cases 5. As a result of this failure in the system, VAERS data cannot be used to infer causal associations between vaccines and adverse events 5. This also nullifies the stated reason for excluding adverse event data from foreign countries, as the majority of the data did not permit medical review. This shows an absence of rigorous surveillance and analysis of adverse events which is essential in determining the safety of the vaccine.

The adverse events reported to VAERS included hypersensitivity, anaphylaxis, Guillaine-Barre syndrome, transverse myelitis, pancreatitis, venous thromboembolic events, seizures, deaths and pregnancy abnormalities 5. An accurate comparison of adverse events, including congenital abnormalities and spontaneous abortion after vaccination, cannot be made from the clinical trials because an inert placebo was not used 25. The manufacturer funded clinical trials used the adjuvant, aluminum, as the placebo in the unvaccinated group 25: a chemical known to be linked with serious adverse events 28. Therefore, the safety data provided by the clinical trials is inadequate.

In addition, adverse events were only monitored for 15 days after the administration of the vaccine 25. An accurate picture of the harmful events of a vaccine must be obtained from a systematic, prospective, long-term assessment of adverse events 5. Since 2006 there have been 94 deaths and 21,634 adverse events reported to VAERS 29. Of these events 4,386 have resulted in permanent damage 29. The VAERS statistics are believed to represent only one-tenth of the population damaged by the vaccine as this is a passive reporting system 5. There has been no systematic, active, long-term surveillance of the adverse events resulting from this vaccine since it was marketed five years ago.

The evidence cited above illustrates there was no requirement for the manufacturer to prove this vaccine was safe and effective before it was marketed to women.

Discussion

There are many serious ethical and scientific concerns regarding the promotion of HPV vaccines to the public. The lack of correlation between cervical cancer mortality and infection with high-risk HPV sub-types indicates that lifestyle and environmental factors play a significant role in the progression of HPV infection to carcinoma. HPV vaccines have been promoted to women as a cervical cancer vaccine when in fact they guard against only two of many HPV sub-types. They have also been promoted to women before the efficacy and safety profile has been established.

Scientists used an inappropriate surrogate to determine the efficacy of HPV vaccines against cervical cancer. The observation of pre-cancerous lesions in an age group that rarely gets cervical cancer, and in which these lesions mostly clear without leading to cervical cancer, was not an adequate measure of the possible reduction in cervical cancer incidence. This is particularly the case when many other HPV sub-types can infect and cause cervical cancer. There were known risk factors for this disease yet the clinical trials did not select the study group for these risk factors. Women have been misled by the claim that the vaccine is 98% effective when this result was only obtained for the study group that was not infected with HPV 16/18 prior to vaccination. The reality is that many women will already be infected with HPV 16/18, as it is a common infection, and efficacy in this group was only 44%.

The health department admits that screening for high-risk HPV infection would identify a very large number of women but only a few of these are at risk of cervical cancer 7. Taking a drug to prevent infection from HPV 16 and 18 results in a similar situation - the majority of the women on the drug would not be at risk of cervical cancer. Many of the pre-cancerous lesions identified in cervical cancer screening and included in the incidence rates for cervical cancer, will remain sub-clinical throughout life and would otherwise have gone unnoticed 16.

Vaccinating the majority of women for an infectious disease that is mostly asymptomatic can expose the population to more harm than good. Screening programs are a safe and cost-effective measure of reducing this disease and women still need to be screened after vaccination 7. It is time to question the cost-benefit of exposing women to the potential harm of a vaccine when cervical cancer was reduced to low levels in developed nations before a vaccine was introduced.

Conclusion

It can be claimed that HPV infection is a necessary precursor to most cervical cancers but if most HPV infections do not progress to cervical cancer then a vaccine against two strains of many high-risk HPV subtypes will not be beneficial to the majority of women.

HPV vaccines have been promoted to women as a cervical cancer vaccine without any definitive evidence they will prevent cervical cancer. In addition, no long-term systematic surveillance has been implemented to establish the safety of the vaccine over the 5 years it has been used. It is clear that government policy decisions and the marketing of vaccines have not been based on the best available scientific evidence. This is detrimental to the health of the population and needs to be addressed in order to maintain trust in the institutions that are supposed to protect public health.

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Appendix 1: The Limitations of the Bosch et al, 1995 Study.

Whilst Bosch et al, 1995, claim their international study of 1000 tumors confirms the role of HPV's as the central etiological factor in cervical cancer worldwide, their evidence does not explain why there is a higher risk of cervical cancer in developing nations than developed nations. They claim that "HPV prevalence was remarkably homogenous among the countries' 2. The statement that HPV's are the central etiological factor in cervical cancer development relies upon detection methods being 'truly sensitive and specific' and ignores the epidemiological evidence that indicates co-factors are necessary to initiate cancer development.

The limitations of this study are listed below:

1. This study only included 10 of 18 regions for which cervical cancer incidence has been recorded
2. It did not include Asia and India which have very high rates of cervical cancer
3. In each country the size of the study is limited and the cases cannot be claimed to be representative.
4. The results alter according to the method of detection used. For example, analysis of the 66 HPV- negative specimens using additional HPV detection methods (eg. other primers) alters the number of negative tumors to fewer than 5%.
5. In the final analysis HPV-negative results were only accepted from specimens with adjacent, confirmed tumor tissue. 'This was to avoid false-negative results'. However, by doing this the researchers were influencing the result.
6. The researchers state that their prevalence estimate of 93% maybe slightly inflated because the only restrictions for HPV-positive specimens were diagnostic confirmation and PCR sufficiency.
7. Whilst it is stated that all HPV detection was carried out by one expert laboratory and by one histological reviewer, it would be important for the results to be confirmed by another reviewer to ensure there is agreement. This is because there is subjectivity in the interpretation of the result. The study does not state that the results were checked by an independent researcher.

The primary researchers involved with these studies have links to industries that profit from vaccines 2, 14, 3, 13.

Appendix 2: The Strength of Evidence for HPV types in Cervical Carcinomas

Despite the significant evidence illustrating environmental and lifestyle factors are implicated in the etiology of this cancer, Bosch et al, stated in 1995 that epidemiological studies have shown that the association of genital human papillomavirus with cervical cancer is “strong, independent of other risk factors and consistent in several countries” 2. This contradicts all the evidence of previous epidemiological studies. Prior to 1995 most scientists were claiming a multifactorial etiology for cervical cancer. At this time, Bosch et al, realized it was necessary to show that HPV is present in all cases of cervical cancer in order to prove that HPV is the main factor in cancer etiology. So they set out to conduct an international study of HPV sub-types in invasive cervical cancer 2. The aim of this study was to characterize the distribution of HPV types in cervical cancer in different geographical regions. They state “this is essential to the development of vaccination strategies to curb the burden of cervical cancer” 2. So even though HPV was not always found in carcinomas and the geographical distribution of HPV sub-types had not been mapped Bosch et al, were carrying out this research with the aim of developing a vaccine.

Prior to this study it was believed that HPV DNA rates in tumor specimens were about 60-90% 13. By 1995 it was believed that the filter in situ hybridization technique used to identify HPV DNA in epidemiological studies in the eighties had inadequate specificity and sensitivity 13. There was of great concern regarding the variation in laboratory methods with different levels of specificity and sensitivity for detecting HPV DNA 13. Therefore a new biological technique was used in the Bosch et al study that was believed to be highly specific and sensitive. This was polymerase chain reaction (PCR) protocol based on consensus primers flanking a relative conserved region in the L1 gene of HPV 13. This technique is also called MY09/11 13. They concluded from their study that new molecular biology techniques are ‘truly sensitive and specific’ and they believed their result confirmed the plausibility of HPV infection as the pre-cursor event leading to cervical cancer 2.

This claim has been made based upon a biological test and the IARC states case series can only provide suggestive results and can never serve as a basis for causal inferences 6. A claim of causality based on PCR tests ignores the influence of host characteristics and environmental factors that are known to influence pathogenesis. Bosch et al, (1995) state “more than 35 distinct HPV types are known to infect the genital tract complicating the detection and distinction of these agents” 2. This must be taken into account when assessing the reliability and specificity of the tests.

The Bosch et al, (1995) study tested nearly 1000 tumors and the negative-HPV tumors were re-tested using different methods 2. It was found that HPV DNA could be detected in “separate portions from the same specimen, which raised the prevalence to 93% and even higher - “to 95% on re-analysis with PCR using primers” 2, p.780. Franco believes that the article by Bosch et al, 1995, can be viewed as a critical contribution to our understanding of the etiology of cervical cancer. He says ‘traces of HPV were detected in 95% of all cervical cancers’ 13. On this basis he claims that ‘HPV infection might turn out to be the first cause of a human cancer shown to be a necessary one’- even though this evidence is dependent upon the detection method used and still leaves 5% of tumors without evidence of HPV infection 13.

The sub-types of HPV have been found in the following frequencies globally - HPV 16 (50%) of cases, HPV 18 (12%), HPV 45 (8%) and HPV 31(5%) 2. Prevalence of these types also varied geographically.

On the evidence of the Bosch et al study, Franco questions the existence of cervical cancers that are induced by carcinogenic routes other than HPV infection 13. He suggests HPV free cancers might be reflecting loss of the HPV genome as the disease progresses. This is speculation. Rather than accepting that it’s possible some tumors are induced by factors other than HPV, he suggests researchers will have to demonstrate that “failure to detect HPV DNA is not due to insufficient sensitivity” of the test 13. Franco has taken the position that an absence of HPV genome is not because there is an absence of HPV genome but rather a loss due to disease progression and he is assuming the HPV was there in the

first place. This is interpreting the results to produce the desired outcome. It is not evidence-based science.

In addition, if HPV DNA is found in organs and tissues where it is not expected to be found he claims “researchers will have to prove that “an occasional HPV-tissue association is not due to insufficient specificity or contamination” 13. Again Franco is providing an explanation for the unexpected result to fit in with the desired outcome.

Franco states earlier in his article that “an easily diagnosed viral infection as the pre-cursor event leading to cervical cancer calls for action on 2 fronts:

1. primary prevention by immunisation against HPV and
2. secondary prevention by cytology screening with testing for cervical HPV infection.

It would appear that the researchers were pre-empting the result in order to find evidence to support the preventative measures they would like to implement: vaccination programs.