

Review of

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

By Judy Wilyman MSc

Judy Wilyman often refers to herself as a PhD candidate or researcher. She has also referred to her publication in The British Journal of Ecological Medicine conference proceedings from 2011 available at www.ecomed.org.uk/wp-content/uploads/2011/09/6-wilyman.pdf.

I thought that as someone who has reviewed a number of scientific articles and conference abstracts, I could use this experience to review Ms Wilyman’s paper.

It is usual practice to outline the message of the paper that is being reviewed so I will begin by noting that Ms Wilyman’s article makes the following points;

1. Not everyone with HPV gets cervical cancer
2. Not all cervical cancers are positive for HPV
3. Vaccines have only been shown to reduce precancerous lesions not cervical cancer itself
4. Testing for HPV is fallible
5. There is no systematic long term surveillance of vaccine safety
6. The Gardasil vaccine used dubious marketing

I will deal mainly with points 1 and 2 as these are a recurring theme throughout the article. As a scientist I don’t think I want to get into whether Gardasil marketing was good, bad or indifferent and will leave that to The Gruen Transfer. Evidence from my own research suggests that points 3, 4 and 5 are incorrect and at the end of the article I will use an example to briefly cover how I came to these conclusions.

To even pick out the major points of Ms Wilyman’s paper was quite difficult as the paper does not appear to have gone through any review or vetting process as evidenced by a lack of co-authorship. I don’t think I have even seen an abstract or paper by a PhD student which didn’t include the name of the supervisor as a co-author. It is probably worth noting that Ms Wilyman does not include any academic affiliation which again is unusual as she is normally very forthright about undertaking her PhD at Wollongong University. Errors in grammar, spelling, referencing and structure also make it difficult to identify key points of Ms Wilyman’s argument.

When I read an article the first things I look at are the references, the figures, and the methods section. Since this appears to be a review article rather than a piece of original research there is no methods section. A review article is where an author will examine the other publications in their area of interest and try and collate the relevant information to give the reader an overview of the topic.

This paper contains 29 references for a main text of over 5,500 words. This is a very low rate of referencing for a review article (I wrote a review article at the beginning of my PhD and it was just under 4,300 words long and contained 99 references, <http://www.ncbi.nlm.nih.gov/pubmed/17168836>).

Anyway, I looked at the references in detail to get an idea of what Ms Wilyman considers important sources and found that of that 29 references only 18 were from journal articles. The remaining references included 3 books, 4 government reports, a notorious anti-vaccine article written for a law review (critiqued at <http://www.sciencebasedmedicine.org/index.php/when-you-cant-win-on-science-invoke-the-law-2/#more-12610>) and 4 websites including 2 anti-vaccination sites; sanevax.org and vaccineinfo.net. So just to be clear, 5,500 words and 18 journal references, this is roughly 1 reference per page (or 300 words).

It is probably worth noting that Ms Wilyman has included two appendices for this article which appear to be focused on reviewing the 1995 paper published by Bosch and colleagues (Journal of the National Cancer Institute, 1995, Vol 87 No 11) but as that paper was 17 years ago and the scientific community has moved well past it in terms of evidence I won't spend any more time on these appendices.

This paper contains 4 figures, three cited as being from Parkin and colleagues (Global Cancer Statistics, 2005, Vol 55; 74) and one from Bosch and colleagues.

The first figure (Bosch et al.) shows that HPV strains 16 and 18 (those contained within the vaccine) are present in between 60 – 75% of cervical carcinomas.

I believe the message of this figure is that most cervical cancers contain HPV and most of the time it is strains 16 and 18.

The next two figures appear to be little tables created in Microsoft Excel. I went back to the source paper and initially couldn't work out how Ms Wilyman got these figures. It started to make sense when I realised that Ms Wilyman had simply taken all the incidence/mortality data from the low end of the scale and labelled it from "Developed countries" and all the high incidence/mortality data and labelled it "Developing Countries". This data is from Parkin and colleagues and they explicitly state in their paper which countries/regions they classify as developed or developing. Northern Africa, China and Western Asia are classified as "Developing countries" by Parkin and colleagues but the mortality data (9.8, 3.8 and 2.9 per 100,000 respectively) could only fit into what Ms Wilyman has categorized as "Developed countries" in Figure 3. I cannot see how this is anything other than a clear misrepresentation of Parkin and colleagues work.

The final figure is from Parkin and colleagues and shows that developed countries have lower incidence and mortality from cervical cancer. Interestingly Parkin and colleagues mention that, prior to screening, cervical cancer rates were over twice as high in developed countries, but we will come back to that later.

So the summation of the figures is that generally developed countries have less cervical cancers but that the majority of these cancers contain HPV strains 16 and 18. I hope that is the message Ms Wilyman was trying to get across.

Ok so references, figures and methods have been dealt with, now for the main text. As I said earlier at nearly 6,000 poorly constructed and edited words it is difficult to get a clear idea of what Ms Wilyman is saying but I cut straight to her "Discussion" and "Conclusion" in which she gives a summary of the paper.

Ms Wilyman begins with the statement “There are many serious ethical and scientific concerns regarding the promotion of HPV vaccines to the public”. She then spends a great deal of time talking about the two major strains of HPV in the vaccine (16 and 18). She notes that the vaccines only guard against a few strains (although she does not remind the reader that two of these strains, 16 and 18, are present in 60 – 75% of HPV positive cancers), and the vaccine was promoted as 98% effective but this was only true if the women getting the vaccine were not infected with strains 16 and 18 beforehand. Ok I have to pause here. The vaccine is to prevent someone getting HPV 16 or 18; if they have strains 16 or 18 before they get the vaccine it won't protect them from getting those strains. However Ms Wilyman does note that even in women with HPV 16/18, the vaccine has an efficacy of 44%. Ms Wilyman also mentions that screening programs are safe and cost effective, and I think that is a good point to make and very well supported by her references. However she then makes several broad sweeping statements with no supporting references.

It is at this point that I nearly gave up this review. However I am a blue collar scientist and am not afraid of hard work so I shall continue.

There is a series of dot-points midway through the article in which Ms Wilyman presents a list of reasons why the HPV 16 and HPV 18 strains are not predictive of carcinoma. I have no doubt that since what appears to be a reasonable percentage of women who test positive for HPV 16 or 18 don't get cervical cancer there are other factors involved. However this long list of other factors suggested by Ms Wilyman does not clearly address the issue which is simply “If I don't have HPV 16 or 18 does this reduce my risk of cervical cancer”. It is this question that the HPV vaccine is focused on. I think perusal of Ms Wilyman's list of points is very telling of how she frames her argument and the tools she uses to support it. This list title and dot points from Ms Wilyman's article are in bold.

The Evidence for an Etiological Association with Environmental and Lifestyle factors

1. HPV infection with any strain is not sufficient to cause cervical cancer.

- OK but is the lack of HPV infection enough to protect a woman against cervical cancer. This argument is the same as “All women have a cervix but not all women get cervical cancer”. I would argue that the lack of a cervix however does protect you very well against cervical cancer. For ease of reading feel free to replace cervix with HPV (or prostate if you want to look at it from the male point of view).

It is also worth noting at this time that Ms Wilyman often mentions HPV infection rates but since the strains of HPV that are most connected to cervical cancer and included in the vaccine are strains 16 and 18 I feel it may have been clearer if the infection rates of just HPV 16/18 were also given.

2. Approximately eighty percent of women are infected with HPV yet ninety percent of these HPV infections do not lead to cancer or warts.

- See Point 1, especially in reference to the difference all HPVs and strains 16 and 18.

3. HPV 16 is identified as the pre-dominant sub-type in all countries with HPV yet cervical cancer rates vary significantly between countries.

- Ok now remember a little while back when the author that contributed most of Ms Wilyman's figures (Parkin and colleagues) noted that the introduction of screening tests reduced the incidence of cervical cancer? Ok so if you find pre-cancerous lesions and can treat them then the incidence of cervical cancer goes down. Not surprisingly, developed countries generally have better screening programs and medical treatment. I wouldn't think of arguing that HPV alone causes cervical cancer but I think that the evidence suggests that a lack of HPV, especially strains 16 and 18 does put you in a much lower risk group.

4. Developed countries had the same high rate 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.

- Parkin and colleagues said "There have been quite substantial declines in cervical cancer incidence and mortality, most clearly observed in Western countries where there are well-developed screening programs." This again goes back to the point that pre-cancerous lesions can be identified and treated prior to becoming cancerous at a much higher rate in developed countries.

5. There is an increased risk of cervical cancer with an increased number of sexual partners.

- This suggests that more exposure to HPV increases risk of cervical cancer? In fact the document Ms Wilyman cites (a WHO report) states "Additional studies among young women show a positive trend between increasing numbers of recent sexual partners and increasing prevalence of genital HPV infection"

6. Prostitutes have four times greater chance of getting cervical cancer even when detection of the HPV sub-types is similar to controls.

- This is referenced to a paper by Gitsch et al., (Genitourin Med, 1991, Vol 67; 478). Essentially the paper demonstrated that prostitutes had a four-fold higher rate of cervical cancer (as Ms Wilyman stated), however she neglected to mention that the authors state "However, typing of HPV DNA revealed a more frequent infection rate with so called "high risk" HPV-types 16/18 in prostitutes compared with the control group."

7. Condoms can reduce the risk of cervical cancer four fold.

- Again reduced risk of HPV exposure, reduced risk of cervical cancer. See point 5.

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.

- This piece of information appears to be from Parkin and colleagues (Ms Wilyman must really like this article as it cited 13 times and it contributed to three out of four figures). Ms Wilyman states that China has a low rate of cervical cancer, and when compared with Eastern Africa it is true, however China still has nearly twice the incidence rate of Australia/New Zealand. I think it is great that cervical cancer incidence is going down but if a vaccine can be given to reduce it by a further 70% (see point 11 below) then this could reduce the number of cervical cancer deaths from approximately 25,000 per year (3.8 per 100,000 x a population of roughly 0.65 billion females) to

7,500. This is obviously a very simplistic calculation but a reduction in cervical cancer deaths of 17,500 per year in a country with a “low rate” still sounds like a good outcome.

9. Bosch and colleagues highlight that the sensitivity of new molecular biology techniques confirm the plausibility of HPV infection as the pre-cursor event leading to cervical cancer. However, a pre-cursor event is not predictive of cancer if the majority of cases do not progress to cancer.

- This point was dealt with back at number 1.

10. Some scientists still claim 5 – 10% of tumours are not associated with any HPV DNA.

- The flip side to this statement is that 90 – 95% of cervical cancers are associated with HPV.

And finally

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

- If you can give a vaccine that is 98% effective in preventing infection with the two strains of HPV that are linked to 70% on cervical cancers why wouldn't you do it? Ms Wilyman appears to be dabbling in something we call the Nirvana fallacy, basically if something doesn't work 100% of the time it is worthless. I also think that there is a large amount of data available on the accuracy of HPV tests on cancers (a PubMed for “HPV detection methods cancer”, only allowing human clinical trials gave 124 results) and that the evidence suggests that these numbers are reasonably accurate.

Throughout her article Ms Wilyman points out what she regards as incomplete evidence (e.g. Gardasil manufacturers only report on U.S. adverse events), then draws on notoriously unreliable evidence (VAERS reports) and also mentions two of the anti-vaccine movements pet hates; that vaccines are tested by the companies that develop them and that they are not tested against “inert placebos”. All of these points provide support for the notion that Ms Wilyman is not investigating whether HPV vaccines are safe and effective but is trying to frame data in such a way to support her philosophy.

In an effort to let the part tell the whole (as Paul Kelly said) I will use a specific example of what appears to be Ms Wilyman's bias.

Ms Wilyman states that “There has been no systematic, active, long term surveillance of the adverse events resulting from this vaccine (Gardasil) since it was marketed five years ago (in 2006)”, please note words in brackets are my clarifications.

I went to PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) added “Gardasil” to the search term, then added “human”, clinical trials” and only looked at data prior to 2011 when Ms Wilyman wrote her paper. I found 20 articles; the first one I opened was from Block and colleagues (Pediatr. Infect. Dis. J. Feb 2010 Vol 29 p95). The authors describe “the safety of the human papillomavirus (HPV)-6/11/16/18 vaccine using updated clinical trial data (median follow-up time of 3.6 years) and summarize up to 3 years of post-licensure surveillance.”

So in summary Ms Wilyman's article

- Ms Wilyman cites a number of references in a selective fashion and omits key information that supports the use of a HPV vaccine targeting strains 16 and 18
- Ms Wilyman appears to be at the disadvantage of not having adequate supervision (as evidenced by the lack of proof reading and review of this paper). Her current supervisor Professor Brian Martin does not have any qualifications in the biological sciences and a quick PubMed search does not reveal any peer reviewed biological research. I think that Ms Wilyman would benefit from having a supervisor that could provide experience and guidance in the fields of virology, immunology, or epidemiology as her research appears to be into these three areas.
- Ms Wilyman does not provide an accurate review of the area of study (the case for and against HPV vaccines) and she appears to cherry pick evidence to support her hypothesis without giving a reasonable overview of the current literature

I would just like to finish with the conclusion from Block and colleagues in 2010 (cited earlier).

“Based on review of post-licensure safety information, the benefits of vaccination to prevent the majority of genital tract precancers and cancers continue to far outweigh its risks.”

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