Would we oppose a federal policy that could prevent 70% of childhood cancers? The 400 Canadian women who die of cervical cancer every year[4] suffer unbearable pain and loss of function and form. Their dignity slips away as the disease progresses and treatment fails. Pelvic exenteration, a heroic act by gynecologic oncologists to rescue patients with locally advanced disease, is among the most gruesome and complex of all surgical procedures and is psychologically devastating. No economic analysis can assign a proper value to a procedure that causes so much suffering, or to an initiative that would allow patients to avoid it.

Eppur si muove.

Eduardo L. Franco MPH DrPH
Alexandra de Pokomandy MD
Andrea R. Spence MSc
Ann N. Burchell MSc
Helen Trottier PhD
Marie-Hélène Mayrand MD MSc
Susie Lau MD
Department of Epidemiology, Biostatistics and Occupational Health
McGill University
Montréal, Que.

Competing interests: None declared for authors de Pokomandy, Spence and Lau. Eduardo Franco has received occasional lecture or consultation fees from Merck Frosst, GlaxoSmithKline, Roche and Gen-Probe. Ann Burchell has received speaker fees from Merck Frosst. Helen Trottier has served as a paid consultant for and has received travel assistance from GlaxoSmithKline Biologicals. Marie-Hélène Mayrand has received consulting and lecture fees from Merck Frosst, Pfizer, Roche and GlaxoSmithKline.

REFERENCES

1. Lippman A, Melnychuk R, Shimmin C, et al. Human papillomavirus, vaccines and women's health: questions and cautions. *CMAJ* 2007;177:484-7.
2. Franco EL, Cuzick J, Hildesheim A, et al. Chapter 20: Issues in planning cervical cancer screening in the era of HPV vaccination. *Vaccine* 2006;24 (Suppl 3):S171-7.
3. Burchell AN, Richardson H, Mahmud SM, et al. Modeling the sexual transmissibility of human papillomavirus infection using stochastic computer simulation and empirical data from a cohort study of young women in Montreal, Canada. *Am J Epidemiol* 2006;163:534-43.
4. Canadian Cancer Society, National Cancer Institute of Canada. *Canadian cancer statistics 2007*. Toronto: National Cancer Institute of Canada; 2007. Available: www.ncic.cancer.ca/vgn/images/portal/cit_8675111l4/21/40/183595043ocw_2007stats_en.pdf (accessed 24 Oct 2007).

DOI:10.1503/cmaj.1070120

I read the commentary by Abby Lippman and colleagues on vaccination against HPV,[1] and I was disturbed by the authors' statement about the scientific merit of the "handful of randomized controlled trials of sufficient quality to qualify for systematic review." Unfortunately, the authors failed to elaborate on what they believe to be the limitations of these trials, the results of which were published in prestigious peer-reviewed journals such as *Lancet*, *New England Journal of Medicine* and *Vaccine*.[1-4]

The trials, which involved 50 000 girls and women aged 9–26 years, were designed and conducted in 30 countries with the utmost scientific rigour. The results provide level 1 evidence of the immunogenicity, safety and efficacy of GlaxoSmithKline's Cervarix and Merck Frosst's Gardasil for at least 5 years after vaccination. The excellent quality of these randomized controlled trials led to the approval of Gardasil for use in girls and women aged 9–26 years in over 80 countries, including Canada.[5] The only explanation I can envision for the authors' statement concerning the scientific merit of the trials is that they might have misinterpreted the methodology and statistical analyses detailed in the research papers published to date on the trials' results.

It is regrettable that Lippman and colleagues failed to recognize the scientific significance of the tremendous efforts and dedication of the hundreds of investigators around the world, including myself, who have been actively involved in Merck Frosst's and GlaxoSmithKline's randomized controlled trials. We, the investigators, consider the discovery and manufacture of prophylactic HPV vaccines to be the greatest milestone in cervical cancer prevention since the introduction of the Pap smear 50 years ago.

Alex Ferenczy MD
Professor of Pathology and Obstetrics and Gynecology
Jewish General Hospital and McGill University
Montréal, Que.

Competing interests: Alex Ferenczy has received consultant and speaker fees, as well as honoraria and travel assistance, from Merck USA and Merck Frosst Canada.

REFERENCES

1. Lippman A, Melnychuk R, Shimmin C, et al. Human papillomavirus, vaccines and women's health: questions and cautions. *CMAJ* 2007;177:484-7.
2. Harper DM, Franco EL, Wheeler CM, et al; HPV Vaccine Study Group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomized control trial. *Lancet* 2006;367:1247-55.
3. Garland SM, Hernandez-Avila M, Wheeler CM, et al; FUTURE I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356:1928-43.
4. Ault KA; Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like particle vaccine on risk of cervical intraepithelial neoplasia grade 2/3 and adenocarcinoma in-situ: a combined analysis of four randomised clinical trials. *Lancet* 2007;369:1861-8.
5. Bryan FJ, Esser MT, Sings HL, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer* 2006;95:1459-66.

DOI:10.1503/cmaj.1070123

A recent meta-analysis in *CMAJ* about prophylactic vaccination against HPV reported a reduction in the frequency of high-grade cervical lesions caused by vaccine-type HPV strains compared with control groups: Peto odds ratio 0.14 (95% confidence interval [CI] 0.09–0.21) from combined per-protocol analyses and 0.52 (95% CI 0.43–0.63) from modified intention-to-treat analyses.[1] The magnitude and statistical significance of the difference between per-protocol and modified intention-to-treat analyses speak to the issues involved in translating efficacy to effectiveness.

Even more uncertainty abounds when translating results from the controlled settings of randomized trials to the real world. As most cases of cervical cancer occur in women who have not undergone preventive Pap smear screening, an enhanced public health program, possibly with mandatory screening and improved educational initiatives, may well attain health benefits equal or superior to those attainable with a generalized vaccination program, with better cost-effectiveness. This, of course, remains to be studied.

Although Lisa Rambout and colleagues provide a clear justification for their use of surrogate end points,[1] the use of such outcomes does mandate a word of caution. Here lessons learned in cardiology 30 years ago may be pertinent. The association of premature ventricular beats with adverse outcomes fol-