SPECIAL ARTICLE

Canadian Association of General Surgeons, the American College of Surgeons, the Canadian Society of Colorectal Surgeons and the American Society of Colorectal Surgeons Evidence Based Reviews in Surgery – Colorectal Surgery

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for the members of the Evidence Based Reviews in Surgery Group

The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients."[1]The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and reading all of the medical literature is impossible for an individual clinician. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so they can determine the validity, reliability, credibility and utility of individual articles, ie, critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis and economics as well as clinical knowledge.

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsor a program entitled "Evidence Based Reviews in Surgery" (EBRS), supported by an educational grant from Ethicon Endo Surgery Inc and Ethicon Endo Surgery Canada. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. EBRS has a module covering topics in colorectal surgery. Each academic year, 6 clinical articles are chosen for review and discussion. The articles are selected not only for their clinical relevance to colorectal surgery, but also to cover a spectrum of methodological issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, quantifying disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the Evidence Based Reviews in Surgery-Colorectal Surgery (EBRS-CRS) Web site. In addition, a listserv discussion is held where participants can discuss the monthly article. Members of the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) can access EBRS-CRS through the Canadian Association of General Surgeons Web site (www.cags-accg.ca), the American College of Surgeons Web site (www.facs.org/education/ebrs.html), the Canadian Society of Colon and Rectal Surgeons (CSRCS) Web site (www.cscrs.ca), and the American Society of Colon and Rectal Surgeons (ASCRS) Web site (www.fascrs.org), All journal articles and reviews are available electronically through the Web site. Surgeons who participate in the monthly packages can receive 6 CME and/or Maintenance of Certification credits by completing an evaluation and a series of multiple-choice questions each month. For further information about EBRS-CRS readers are directed to the CAGS, ACS, CSCRS, and ASCRS Web sites or should email the administrative coordinator, Marg McKenzie, at mmckenzie@mtsinai.on.ca

In addition to making the reviews available through the CAGS and the ACS Web sites, a condensed version of the reviews will be published in the *Diseases of the Colon & Rectum*. EBRS is useful in improving your critical appraisal skills, keeping abreast of new developments in colorectal surgery, and, most importantly, you are able to obtain 6 CME credits each month from anywhere that you have access to a computer. Comments about EBRS may be directed to mmckenzie@mtsinai.on.ca

SELECTED ARTICLE

Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med.* 2011;365:1576–1585

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QUESTION: What is the safety and efficacy of quadrivalent human papillomavirus (qHPV) vaccine against anal intraepithelial neoplasia (AIN) associated with human papillomavirus (HPV) types 6, 11, 16, and 18 infection in men who have sex with men?

DESIGN: This is a multicentered randomized controlled trial.

SETTING: This study spanned 7 countries (Australia, Brazil, Canada, Croatia, Germany, Spain, and the United States).

PATIENTS: Six hundred two men, 16 to 26 years of age, who have sex with men were included.

INTERVENTION: The subjects were randomly assigned to receive qHPV or placebo.

MAIN OUTCOME MEASURE: The primary outcome measured was the prevention of AIN or anal cancer.

RESULTS: The efficacy of the qHPV vaccine against AIN associated with HPV types 6, 11, 16, or 18 was 50.3% (95% CI, 25.7–67.2) in the intention-to-treat population and 77.5% (95% CI, 39.6–93.3) in the per-protocol efficacy population; the corresponding efficacies against AIN associated with HPV of any type were 25.7% (95% CI, −1.1 to 45.6) and 54.9% (95% CI, 8.4–79.1). Rates of AIN per 100 person-years were 17.5 in the placebo group and 13.0 in the vaccine group in the intention-to-treat population and 8.9 in the placebo group and 4.0 in the vaccine group in the per-protocol efficacy population. The rate of grade 2 or 3 AIN related to infection with HPV types 6, 11, 16, or 18 was reduced by 54.2% (95% CI, 18.0–75.3) in the intention-to-treat population and by 74.9% (95% CI, 8.8–95.4) in the per-protocol efficacy population. Similarly, the risks of persistent anal infection with HPV types 6, 11, 16, or 18 were reduced by 59.5% (95% CI, 43.0–71.4) in the intention-to-treat population and by 94.9% (95% CI, 80.4–99.4) in the per-protocol population. No vaccine-related serious adverse events were reported.

CONCLUSION: Use of qHPV vaccine reduced the rates of AIN, including grades 2 and 3, among men who have sex with men. The vaccine had a favorable safety profile and may help to reduce the risk of anal cancer.

COMMENTARY: There are many similarities between cervical cancer and anal cancer. Much of what is known about anal cancer has been previously elucidated through the investigation of cervical cancer. In both cervical and anal cancer, human papillomavirus is the cause in most cases. HPV types 16 and 18 are the primary causal agents, whereas HPV types 6 and 11 are rarely implicated causally by themselves. As in cervical cancer, anal cancer is preceded by high-grade squamous intraepithelial neoplasia. Prevention of cervical intraepithelial neoplasia (CIN) is known to decrease the risk of cervical cancer, and, similarly, prevention of AIN leads to decreased rates of anal cancer. The rates of anal cancer remain low but are rising by 2% per year. It is most common among high-risk groups, which include immunosuppressed patients with solid-organ transplants, patients with HIV, and men having sex with men. The qHPV is currently used to prevent persistent cervical infection with HPV types 6, 11, 16, and 18. It is also beneficial in preventing external genital lesions in men. The use of this vaccine might be valuable, particularly in groups that are at high risk for developing AIN.

This analysis assesses both the safety and efficacy of qHPV in the prevention of AIN associated with HPV types 6, 11, 16, and 18 infection in men who have sex with men. It is a subgroup analysis of a larger trial. This trial is a multicenter randomized controlled trial using computer-generated random allocation of individuals who received an injection of either the vaccine or placebo in the deltoid muscle at 0, 2, and 6 months. This trial was "blinded" to the sponsor (Merck), investigators, patients, monitors, and laboratory personnel until all data had been collected. This blinding gives us confidence that study participants were treated the same with the single exception being the intervention under study. Follow-up was completed in all 602 participants. Baseline characteristics between groups appear to be very similar in terms of potential known confounders, giving us confidence that unknown and unmeasured potential confounders are similarly equally distributed between the study arms. All patients underwent serum serologic HPV testing at day 1 and month 7. In addition, the anal canal was examined at day 1 and months 7, 12, 18, 24, 30, and 36. These examinations included anal swabs for cytologic HPV DNA examination, digital rectal examinations, and standard anoscopy. If an abnormality was detected on examination or by anal cytologic testing (atypia), then the patient underwent high-resolution anoscopy with biopsy of any detected lesions. Adverse events were monitored by using vaccine report cards, which collected data on oral temperatures and any other adverse event noted between days 1 and 15 after vaccine administration.

The a priori primary end point was the efficacy of qHPV in preventing HPV type 6, 11, 16, and 18 related AIN or anal cancer. The end point was determined to have occurred if there was pathology consensus identified AIN (grades 1–3) or anal cancer with detection of HPV types 6, 11, 16, and 18 DNA by polymerase chain reaction assay in a section of tissue adjacent to the AIN or cancer. In the intention-to-treat analysis, prevention of AIN due to any HPV infection was decreased by 25.7% (95% CI, −1.1 to 45.6) and against HPV type 6, 11, 16, and 18 related AIN/cancer was decreased by 50.3% (95% CI, 25.7–67.2). In the per-protocol analysis, prevention of AIN/cancer due to infection with HPV types 6, 11, 16, and 18 was decreased by 77.5% (95% CI, 39.6–93.3).

This study shows that the vaccine is effective in preventing AIN in a high-risk group, decreases rates of persistent infection, decreases infection with HPV, and decreases rates of external genital lesions. The results in the intention-to-treat analysis are somewhat attenuated

as a result of HPV infection with types different than those included in the vaccine (types 6, 11, 16, and 18) and because some people were already infected before immunization. The generalizability (external validity) of these study results for males less than 26 years of age is good. It is possible that the hormonal milieu of females in similar age groups may alter the efficacy of the vaccine in the prevention of AIN; however, given the large experience with this vaccine in young females in the prevention of CIN/cancer it seems highly unlikely that there would be significant differences.

Based on this study and on extrapolation from similar studies of primary prevention of CIN in females, the ideal would be to vaccinate young males and females before the initiation of sexual activity. However, given the low rates of AIN/cancer and the cost of such a massive immunization program, it seems unlikely that such a program will be implemented. However, the vaccine may benefit those identified at an early age to be at high risk. Practically, this would be difficult to undertake. In addition, the vaccine should be made available for purchase to those wishing to be vaccinated.

Further studies should be undertaken. A study independent of industry (although there is no evidence that industry introduced any bias in this trial) that was larger in size with longer follow-up might be able to answer the question as to whether the vaccine can prevent anal cancer. In addition, the success of the vaccination program would likely be realized to a greater extent if it were a trial that included participants not yet sexually active (primary prevention).

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1. Evidence Based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA*. 1992;268:2420–2425.