Is the current evidence sufficient to warrant dietary recommendations for our patients who ask the simple question, “How can I keep my cancer from coming back”? We agree with an American Cancer Society expert panel that advises colorectal cancer survivors “to maintain a healthy weight, participate in regular physical activity, and eat a well-balanced diet consistent with guidelines for cancer and heart disease prevention” (19). Although not definitive regarding the impact on colorectal cancer recurrence, the convergence of clinical observations and biology provides a compelling justification to test hypothesis-driven interventions in prospective randomized clinical trials. These interventions should include behavioral modifications [eg, dietary modification, exercise (20)] as well as more traditional pharmacologic approaches that target pathways involved in glucose metabolism. The report by Meyerhardt et al. (6) reminds us that the epidemiologist is an essential member of the translational science team in oncology. Ongoing interdisciplinary interactions between epidemiologists, laboratory investigators, and clinical scientists promise to improve understanding of host–tumor interactions and expand the evidence that will help us address our patients’ “simplest” queries and improve their outcomes.

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Human Papillomavirus Vaccines for Cervical Cancer Prevention: Translating Possibility Into Reality

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In this issue of the Journal, Van de Velde et al. apply a mathematical model, “HPV-ADVISE” (human papillomavirus agent-based dynamic model for vaccination and screening evaluation), to project anticipated reductions in the incidence of HPV-associated cancers.
accomplishable through widespread HPV vaccination in Canada (1). Based on vaccination of 70% of 12-year-old girls with currently available bivalent and quadrivalent vaccines, they project that it will take approximately two decades to halve the incidence of cervical precancerous lesions and four decades to halve the incidence of cervical cancer. Under optimistic assumptions, future implementation of a nonavalent vaccine would only further augment cervical cancer prevention by approximately 5% over 70 years compared with existing vaccines, reflecting the fact that infections with HPV 16 and HPV18, the most oncogenic viruses, are already covered. HPV-ADVISE incorporates several widely validated, context-specific, epidemiologic assumptions about the natural history of HPV disease, concepts of herd immunity, and newer data on the cross-genotype protection by HPV vaccines. Although it does not tackle economic (cost) considerations, the model refines and adds to previous evidence on population-level effectiveness of vaccination in preventing and reducing HPV-associated diseases in general and cervical cancer in particular. However, the power of the model rests upon the accuracy and future stability of its assumptions in wealthy nations, and, as the authors acknowledge, the generalizability of the model is narrow.

Worldwide, millions of women harbor chronic, persistent HPV infections, which put them at risk for the development of cervical cancer. In the absence of expanded interventions, cervical cancer will continue to be among the major cancer-related killers of women worldwide, particularly in less-developed regions. The International Agency for Research on Cancer estimates that more than 530,000 women were newly diagnosed with cervical cancer and more than 280,000 died of the disease in 2008 (2). The International Agency for Research on Cancer projects that by 2030 more than 94% of the more than 770,000 cases of cervical cancer and more than 98% of the more than 432,000 cervical cancer–related deaths globally will occur in less-developed regions of the world (Figure 1) (2). Cumulatively, over the next two decades, 10 to 14 million women may develop cervical cancer, and 5 to 8 million women may die of the disease unless prevention efforts are expanded. On the background of limited resources, fledgling and overburdened health systems, and competing priorities for disease prevention and control, the costs and complexities of current HPV vaccine delivery strategies present daunting challenges for scaling up coverage in less-developed regions. Although multiple initiatives seek to address cost and implementation challenges for global HPV vaccination, prospects for achieving success in the developing world remain tentative without technological breakthroughs, expanded financial resources, and alleviation of the broader societal impacts of poverty.

Vaccination has led to the eradication of smallpox and the near-elimination of poliomyelitis (3). Smallpox and polio shared characteristics that rendered them more amenable to control than HPV through a combination of comparatively affordable vaccination and effective surveillance programs in the context of general public health improvements. The example of universal childhood vaccination against hepatitis B virus leading to declining rates of hepatocellular carcinoma in adults provides an analogy for the control of cancer through vaccination (4). Still, the challenges posed for universal vaccination against HPV to eliminate cervical and other HPV-related cancers are unique.

HPV is a ubiquitous sexually transmitted infection, with three of four individuals harboring at least one or more HPV genotypes at some point in their lives. To maximize effectiveness of prophylactic HPV vaccines, vaccination of girls just prior to the median age of sexual initiation is usually prioritized. However, the durability of protective anamnestic responses beyond a decade post-vaccination is undefined. Unfortunately, the pivotal multicentric HPV vaccine trials underrepresent countries in Asia and Africa with high case burdens of cervical cancer (5,6). Differences in HPV epidemiology (eg, differences in genotype spectrum), immune response (eg, impact of malnutrition on serologic response), sexual behaviors (eg, earlier or later age at sexual debut), and other prevalent infections (eg, human immunodeficiency virus) between these settings and the industrialized world pose challenges for extrapolating current evidence about HPV vaccine effectiveness to the regions at greatest need for cervical cancer prevention. Furthermore, several other issues related to vaccine implementation and administration remain to be fully answered, including effectiveness of less than three doses (7), future need for booster doses, and optimization of timing in relation to other childhood or adolescent vaccines.

HPV vaccination will likely become increasingly important in global cervical cancer control; however, efforts to prevent cervical cancer among women already infected with HPV remain critical (8). Implementing cytology (Pap) screening has proven challenging in less-developed regions despite its proven effectiveness in wealthy nations. HPV testing holds promise for identifying women at risk if low-cost and rapid HPV assays are made implementable (9). Management of women testing positive for HPV poses complexities, but visual inspection–based screening may be useful for triage for treatment or referral (10). Screening infrastructures may double as effective systems of surveillance for monitoring the downstream impact of HPV vaccination. Treatment of cervical precancer, which is still largely surgical, presents formidable challenges, particularly with respect to applying ablative (eg, cryosurgery) or excisional (eg, loop electrosurgical excision) treatments that need specialized expertise and equipment. Accordingly, the development of therapeutic vaccines (or combined prophylactic and therapeutic vaccines) and chemopreventive options for persistent HPV infection or cervical precancerous lesions are important, if inadequately pursued, areas of research.

HPV vaccination provides the scientific and public health community an unprecedented opportunity to reduce the burden of cervical cancer. However, implementation of cervical cancer prevention will require a strong global commitment and innovative collaborative approaches, including efficient strategies that dovetail with infrastructures established through other global health initiatives (11). Cervical cancer continues to affect some of the most underprivileged women, rarely a vocal constituency. The real challenge is to best direct primary or secondary prevention approaches for such women to maximize impact and make cervical cancer control a reality, not just a possibility.
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