Inequalities in Human Papillomavirus (HPV)–Associated Cancers: Implications for the Success of HPV Vaccination

Marc Brisson, Mélanie Drolet, Talía Malagón

Correspondence to: Marc Brisson, BSc, MSc, and PhD, Centre de recherche du CHU de Québec, Hôpital Saint-Sacrement, 1050 Chemin Sainte-Foy, Québec, Canada, G1S 4L8, (e-mail: marc.brisson@uresp.ulaval.ca).

In this issue of the Journal, Jemal et al. (1) present trends in cancer incidence and mortality in the United States, with a focus on human papillomavirus (HPV)–associated cancers. The authors show encouraging results, with decreasing trends in overall cancer death rates and stable cancer incidence rates across all racial/ethnic groups. The results are strikingly different for HPV-associated cancers, with increasing incidence of oropharyngeal and anal cancers and inequalities in the burden of cervical and other anogenital cancers across socioeconomic status (SES) and racial/ethnic groups. These results are particularly relevant given the recent implementation of HPV vaccination, which offers tremendous promise of reducing the overall burden of HPV-related diseases and inequalities.

The results from Jemal et al. (1) are consistent with other studies in the United States and abroad that have shown that lower SES and being black or Hispanic is associated with higher cervical cancer incidence and mortality (2,3). These inequalities are most often explained by differences in screening participation and treatment due to factors such as access to health care and health-seeking behavior (4–11) (Figure 1). However, despite being the main risk factor for HPV infection, sexual behavior is often overlooked when explaining inequalities in HPV-associated cancers (Figure 1). The sexual behavior determinants that are likely to be important for HPV infection (and thus related cancers) can be classified into individual- and population-level risk factors (12–15). Individual-level risk factors include age at sexual debut and lifetime number of partners. Population-level risk factors include the presence of highly sexually active core groups, sexual mixing patterns between risk groups and degree of partnership concurrency (16–22). Studies have shown differences in individual-level risk factors between racial/ethnic groups and SES. For example, lower age at sexual debut, which is strongly associated with riskier sexual behavior (23–26) and increased risk of HPV infection/disease (27), has been associated with black race and low SES (28–31). Studies suggest that individual-level risk factors cannot solely explain inequalities in the prevalence of sexually transmitted infections in the United States and that population-level factors may be a more important

Figure 1. Conceptual framework of the different pathways linking sociodemographic characteristics, human papillomavirus (HPV) vaccine uptake, and HPV-related cancers.
determinant of inequalities (18,30,32). For example, there is evidence that black and white Americans have different mixing patterns (13). Blacks are more likely to mix disassortatively by sexual risk (e.g., more mixing between high-risk and low-risk groups), a mixing pattern that facilitates a more efficient spread of sexually transmitted infections (12,13). Such differences in population-level risk factors by race may explain why, in the United States, HPV prevalence is sixfold higher among blacks with one lifetime partner.

Figure 2. Associations between state-level human papillomavirus (HPV) vaccination coverage, sexual activity, cervical screening participation and socio-economic status. A) Three-dose HPV vaccination coverage levels and proportions of adolescents reporting four or more sexual partners in their lifetime, by state. B) State-level socioeconomic status, 3-dose HPV vaccination coverage levels, Pap testing prevalence, and proportions of adolescents reporting four or more sexual partners in their lifetime, by state. Three-dose HPV vaccination coverage levels are reported for adolescent girls in the 2010 National Immunization Survey (NIS)-Teen who were born during the period from January 1992 to February 1998. Girls may have received either quadrivalent or bivalent human papillomavirus vaccine (Source: 2010 NIS-Teen Vaccination Coverage, Department of Health and Human Services, Centers for Disease Control and Prevention, 2011). Proportion of adolescents reporting four or more sexual partners in their lifetime, by state, is reported for girls and boys in 9th through 12th grades in 2009 (Source: Centers for Disease Control and Prevention, Youth Risk Behavior Surveillance System (28)). State-level socioeconomic status represents the proportion of adolescents (girls and boys aged 13 to 17 years) living below poverty level. Poverty status was based on 2010 US Census poverty thresholds [Source: 2011 NIS-Teen Vaccination Coverage, Department of Health and Human Services, Centers for Disease Control and Prevention, 2011]. Pap testing prevalence is reported as the percentage of women aged 21 to 65 years with intact uteri who received a Pap test in the previous three years in 2010 (Source: Behavioral Risk Factor Surveillance System Public Use Data Tape 2010, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2011, as presented in Jemal et al. (1)).
than among whites with one lifetime partner, whereas the prevalence is similar across racial/ethnic groups among individuals with six or more lifetime partners (33).

Failure to reach high HPV vaccination coverage among key subgroups with low future screening participation and/or high-risk sexual behavior may result in substantially lower population-level effectiveness and may increase inequalities in the burden of HPV-associated cancers. Overall, HPV vaccination coverage is low in the United States, with lower coverage in states with low cervical screening participation (1) and higher sexual activity (Figure 2A). Such ecological associations are likely to be occurring at the individual-level because of shared sociodemographic determinants of HPV vaccine uptake, screening participation, and sexual behavior. Jemal et al. (1) show that HPV vaccination coverage is lower among girls living below the poverty level who are uninsured and have low parental education level. In addition, higher state-level poverty is associated with lower HPV vaccination coverage, lower cervical screening participation, and higher sexual activity (Figure 2B). On the positive side, no substantial differences are reported for vaccine uptake by race/ethnicity (1).

The impact of the above findings on overall HPV vaccination effectiveness and inequalities is difficult to predict because of the nonlinear dynamics produced by herd immunity. Depending on vaccination coverage, herd immunity has played a key role in the failure and success of vaccination programs and in reducing or increasing inequalities through “spillover” effects between population subgroups (34–36). For example, moderate vaccination coverage in Greece resulted in an important increase in congenital rubella syndrome through herd immunity-induced shifts in the age at infection (36,37). On the other hand, high vaccination coverage has led to the virtual elimination of inequalities in the incidence of vaccine-type invasive pneumococcal disease by race and SES in the United States (incidence per 100,000 population decreased from 25.8 among blacks and 11.5 among whites to 1.6 among blacks and 0.9 among whites (38)). In Australia, at 70% coverage, females-only HPV vaccination has substantially reduced anogenital warts not only among female cohorts targeted for vaccination (>90% reduction) but also among young heterosexual men (>80% reduction) and older heterosexuals of both sexes (39,40). Such high levels of direct protection and herd immunity are very promising for population-level effectiveness against HPV-associated cancers and reductions in inequalities in countries with high HPV vaccination coverage. However, in countries where HPV vaccination coverage is low, inequalities in HPV-associated diseases may increase, even if vaccine uptake is equal across SES and racial/ethnic groups. This is because HPV vaccination may produce lower effectiveness (lower herd immunity) within subpopulations that have individual- and/or population-level sexual risk factors that facilitate a more efficient spread of sexually transmitted infections (higher reproductive number, R0) (41).

In the United States, high vaccination coverage has been traditionally reached when immunization is required for school entry. HPV vaccine is not covered by such school mandates. Encouragingly, HPV vaccination coverage is increasing because of a variety of public health programs (1). In addition, routine HPV vaccination of boys has been recommended by the Advisory Committee on Immunization Practices (ACIP) (42), in part, to improve overall herd immunity. However, if the sociodemographic determinants of HPV vaccine uptake are the same for girls and boys, then vaccinating boys may not help resolve inequalities because of assortative mixing by race/ethnicity and SES (43,44). Therefore, important efforts should continue to focus on increasing coverage in girls because it has been predicted to be the most efficient strategy to ensure optimal population-level vaccine effectiveness (43,45).

HPV-associated disease incidence and mortality are disproportionately high among individuals with lower SES and among blacks and Hispanics. To fulfill the full potential of HPV vaccines, vaccination coverage must be high not only at the population-level but also within the populations with the greatest need. Finding effective methods of increasing vaccine uptake is a key priority for HPV-related public health research in the United States.

References
HER2-Directed T-Cell Receptor–Mimicking Antibody: A “Me Too” or an Example of Novel Antitumor Aggressive Mimicry?

Giampaolo Bianchini, Luca Gianni

Correspondence to: Luca Gianni, MD, Department of Medical Oncology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milano, Italy (e-mail: gianni.luca@hsr.it).

Targeting the erbB2 receptor protein (HER2) has been one of the most successful stories of oncology drug therapy in the past 10 years. HER2 overexpression or gene amplification is a “driver” alteration to which approximately 20% of breast cancers are resistant to which approximately 20% of breast cancers are

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