

## Editorial

Commentary on Insinga et al., p. 287

## The Need for Forward-Looking Decision Analyses to Guide Cervical Cancer Prevention

Mark Schiffman

In this issue, Insinga and colleagues estimate the rates of transition from individual, carcinogenic types of human papillomavirus (HPV) infection to histologic cervical intraepithelial neoplasia (CIN). Using HPV typing data from the control arm of a Merck HPV vaccine trial, they estimated the transition rates from type-specific infections to cervical intraepithelial neoplasia grade 1 (CIN1), the histologic diagnosis of acute HPV infections. They observed only a few cases of CIN2, and even fewer of CIN3, the best accepted surrogate endpoint for risk of invasive cervical cancer (1).

Regarding their results, they suggest: "...these data can be especially helpful for policy evaluations of future generation of HPV vaccines." As a snapshot for today, this is certainly correct and virtually all current decision analysis models of cervical cancer distinguish the transition from HPV to CIN1 for the sake of reflecting current practice, suboptimal or not (2).

However, the transition from HPV infection based on molecular testing to histologic CIN1 is not as meaningful as the notion of adjudicated, histologically confirmed diagnoses might imply. Although it is considered a reference standard of disease, histology is functionally just another kind of biomarker. CIN1 is intrinsically an insensitive and nonspecific microscopic sign of acute HPV infection (3). Many types of HPV that do not pose a high (or even any) risk of cervical cancer can cause morphologic CIN1 (4), and there are morphologically identical cases of CIN1 that do not involve HPV at all. There are no definite, reproducible morphologic boundaries between HPV infection and CIN1 (or between CIN1 and CIN2, etc.). For a given cervical HPV infection typed by molecular methods, finding CIN1 is a function of how hard the clinician looks when taking colposcopically guided biopsy samples, how many biopsy samples are taken, and how each pathologist defines the boundaries between different lesional classes. It is not surprising, therefore, that for a woman infected with a particular type of HPV, finding CIN1 histologically raises her risk of subsequent CIN3 only slightly compared with not find-

ing it (5). (It is not valid to include CIN2 with CIN3 as an outcome, as Insinga and colleagues have done, because CIN1 is frequently confused with CIN2.) In contrast, the distinction between the most and least carcinogenic types is much greater in terms of absolute risk of eventual cancer (6).

Insinga and colleagues explain the utility of estimating the transition from HPV to CIN1 as follows:

"Although in some natural history studies, HPV infections and CIN1 lesions are considered as indistinguishable, for health economic studies and other types of policy evaluations the actual diagnoses provided to women in clinical practice are generally preferred whether highly reproducible or not as they will determine quality of life and cost of outcomes for the women."

The authors thereby acknowledge that they are modeling current reality, with its errors, and that their decision analyses are rooted in what is happening today. They are not estimating the cost-effectiveness of current versus ideal strategies. For example, they are not analyzing the impact of making the kind of radical change supported by the natural history data, that is, to treat all HPV infection alike whether or not CIN1 is diagnosed.

One might ask then, what is the role of decision analysis in a rapidly evolving clinical field? Policy makers rely on health decision analysis to guide change. If the starting point of the modeling is acceptance of the *status quo*, it is unclear how we will move forward. At present, cervical cancer prevention is based on frequent, repetitive rounds of cytology screening, with colposcopic biopsies when cytologic results are abnormal (1). We are at the beginning of a clinical practice revolution that is emphasizing vaccination and HPV testing at prolonged intervals, but we do not know how best to make the transition. It seems logical in forward-looking analyses to base health economic studies on our best understanding of HPV and cervical carcinogenesis, that is, to de-emphasize the demonstrably unreliable aspects of morphology-based screening in favor of modeling cervical cancer prevention/early detection on the foundation of the reproducible, major steps in HPV natural history that have been defined during the last 20 years of research.

More generally, what is the impact of basing economic models on current practice if one accepts that current practice is based partly on out-of-date concepts? Decision analysis defines transitional states in a causal pathway, or at least a clinical pathway, from health to death. The transitional states are defined as successive, intermediate

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endpoints in a chain of forward and backward probabilities that can be modeled to predict the value and cost of a proposed preventive strategy. The model is most compelling if the transitional states and probabilities can be defined with minimal error; otherwise, base-case assumptions must be addressed by sensitivity analyses that can alter the conclusions. Even if the answers obtained by the modeling process are not wrong, this wiggle room in health decision analysis when the base-case is "soft" can lead to distrust of the message and even the process.

In contrast to the historical model based on CIN stages, a very simple, HPV-based transitional model is available, in which ambiguous terms and uncertain transitions are removed in favor of biologically distinct causal steps (1). In an HPV-based stepwise model of cervical carcinogenesis, each transition is causally necessary and easily measured. Forward and backward probabilities can be assigned to the transitions on the basis of prospective cohort data. The model does not rely on poorly reproducible transitions such as histologic CIN1 or equivocal cytology called atypical squamous cells of undetermined significance (ASC-US). The causal transitions are as follows: HPV infections are easily transmitted. At any age, most new HPV infections resolve rapidly from within a few months to a few years. Viral persistence past approximately 2 years is associated with gradually increasing risk of diagnosis of precancer, defined stringently as CIN3. If untreated, CIN3 lesions can regress, but some grow superficially for years and can give rise, typically over decades, to invasive cervical cancers.

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Health economic studies of proposed prevention strategies could be conducted on the basis of this evidence-based model rather than a CIN1-CIN2-CIN3 histopathology model. But, to my knowledge, there are no updated cervical cancer prevention models that (a) present a simplified and updated natural history transition state model in which HPV infection takes center stage, (b) fully recognize the lack of sensitivity of cytology and suboptimal accuracy of colposcopic biopsy as a flawed diagnostic standard, and (c) project the impact of vaccines and/or HPV-based screening tests and strategies were we to switch to a new prevention program that highlights adolescent vaccination and long-interval primary HPV screening.

In sum, because the distinction between HPV infection and CIN1 is biologically and prognostically uninformative, it does not make sense to continue to make the distinction. The presence of HPV of carcinogenic types is best defined by a molecular test. More generally, it is worth discussing the interesting question of whether decision analyses should predominantly reflect current health practice or should lead health care. I would argue that for the cervical cancer prevention questions that are facing us right now, we need forward-looking decision analyses to guide us most efficiently.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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