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Original Research

Evaluation of the natural history of cancer of the cervix, implications for prevention. The Cancer Risk Management Model (CRMM) – Human papillomavirus and cervical components

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ABSTRACT

The Cancer Risk Management Model (CRMM) initiative of the Canadian Partnership Against Cancer offers policy makers a tool for making decisions regarding prevention and screening for their particular landscape.

The cervical cancer component of CRMM is complex because the development of cervical cancer depends on HPV infection and has to take account of the fact that individuals must come in contact with one another for HPV to spread. Two tightly coupled models were built, one for the infectious spread of HPV (CRMM-HPV), and the other for the pathway from infection to disease onset, progression, screening, treatment, and mortality (CRMM-Cervical). This paper provides an overview of methods and functionality for CRMM components which simulate vaccination, screening, HPV incidence, disease progression, and cancer incidence.

CRMM-HPV is a continuous-time, interacting-agent, Monte-Carlo microsimulation model that simulates sexual networks and HPV transmission. Six HPV groups (6, 11, 16, 18, other non-carcinogenic, other carcinogenic) and two vaccination types (bivalent, quadrivalent) were modeled. Input parameters include demography, sexual debut, partnership formation/separation and virus transmission, clearance, natural immunity. CRMM-HPV provides a 100-year projection of impacts of vaccinations on HPV infections. Results were scaled to reflect the Canadian population aged 10+ in 2011.

Various vaccination scenarios can be compared by altering vaccination program design (target age, sex, program years, participation rate, vaccine type), vaccine efficacy, duration of protection and previous vaccination status. These parameters enable users to explore impacts of various scenarios such as targeting various age groups, adding boys, and booster and catch-up programs.

Introduction

Canada shares with Finland and the United States the distinction of an 80% reduction in mortality from cancer of the cervix as a result of the application of cytology screening [1]. However, in contradistinction to Finland, this has been achieved following a very substantial investment in resources, largely because of the generally accepted view that screening should begin soon after the initiation of sexual activity, and be annual. In contrast, in the organized program in Finland women age 30–59 are screened every five

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years. Detailed analysis of Canadian data has pointed to the rarity of cervix cancer and the lack of effectiveness of cytology screening in young women [2,3]. A working group of the International Agency for Research on Cancer concluded that screening should not begin until age 25 or more [4].

Canada was one of the first countries to initiate screening with cervical cytology. The first program began in British Columbia in 1949 [5] and programs gradually extended across the country. In the mid 1970s, it was shown that the extent of the reduction in cervical cancer mortality was dependent on the intensity of screening [6], and a succession of national Task Forces recommended several measures to increase the effectiveness and efficiency of screening by introducing fully organized programs [7–9]. As the response of the provinces and territories to these recommendations was patchy, a pan-Canadian Cervical Screening Network was initiated in 2004 to foster collaboration and support for the recommendations.

The Canadian Partnership Against Cancer initiated its Cancer Risk Management Model (CRMM) initiative during its first 5-year mandate [10]. The initial priorities were the development of a microsimulation model to evaluate the future burden of cancer in Canada, focusing on areas where it was felt progress could be made. The first two disease-specific models completed were on lung and colorectal cancer [11,12]. In view of the major investment in screening for cancer of the cervix in Canada it was decided that a model for cervical cancer could provide input into the development of policies for organized screening and dovetail into the policy of promoting vaccination of teenage girls against human papillomavirus (HPV) types 16, 18, 6 and 11, initiated in Canada in some provinces in 2007 (Nova Scotia, Ontario and Prince Edward Island), others in 2008 (Alberta, British Columbia, Manitoba, New Brunswick, Quebec, Saskatchewan) and the North West Territories and the Yukon in 2009.

Cancer of the uterine cervix is unique among cancers as it has a single necessary cause, infection with an oncogenic human papillomavirus (HPV) [13]. Such infection is not sufficient for cancer to occur. Other co-factors including parity, smoking, oral contraceptive use, and possibly other infections of the female genital tract, interact in various combinations with the necessary cause to induce the development of cancer. However, the considerable amount of information now available on HPV prevalence, HPV infection by age, and the extent to which such infections become persistent or are cleared by natural immune mechanisms make it possible to model HPV infection and the incidence of cervical cancer, as well as its occurrence via preclinical precursors. It is also possible to estimate the likely cost-effectiveness of different approaches to vaccination against HPV infection, screening and treatment.

The cervical cancer model in CRMM is more complex than the lung and colorectal cancer models [11,12] because the development of cervical cancer depends on HPV infection and individuals must come in contact with one another for the disease to spread. For cervical cancer two coupled models were built, one for the infectious spread of HPV within a population, including the effects of vaccination (CRMM-HPV) and the other for the pathway from infection to disease onset, progression, screening, treatment, and mortality (CRMM-Cervical). This approach allowed the simulation of large interacting populations without sacrificing detail and accuracy in disease progression, screening, treatment, costs, mortality from cervical cancer, and other cause mortality.[1]

CRMM-HPV is an interacting agent model which simulates the process of HPV transmission through sexual interactions in a dynamic network of male–female partnerships, accounting for evolving sex and age-dependent patterns of partnership formation, dissolution, and duration. Detailed HPV infection rates from this simulation are then input into CRMM-Cervical to initiate infections in the isolated simulated individuals in that model. CRMM-Cervical models subsequent cervical precursor lesion incidence and progression in infected individuals. CRMM-Cervical is a non-interacting agent model which simulates treatments, health and economic impacts, and evaluates the impact of different approaches to vaccination, screening, and treatment. Processes which do not involve interaction between individuals are modeled identically in CRMM-HPV and CRMM-Cervical. These include sexual debut, vaccination, HPV clearance, natural immunity, and infection persistence.

The present paper describes the assumptions for CRMM-HPV, their validation and the methodology applied in developing the resultant model; and the results of incorporating this natural history model into CRMM-Cervical to simulate the effects of HPV vaccination.

Materials and methods

The CRMM, a web-based microsimulation tool, was used to create customized Canadian population-based scenarios that model infection and clearance of HPV and progression/regression through pre-clinical cervix cancer states and ultimately to invasive cervical cancer.

Data to populate the model has been obtained from published and unpublished sources. A working group on cervical cancer (the present authors) was established, and a series of consultations were held with national and international experts. The development work was largely performed by SG and the Statistics Canada team.

CRMM-HPV was developed along similar lines to that of van de Velde et al. [16]. The features of CRMM-HPV include:

- Non-sexually active individuals enter the simulated population at 10 years of age. The model represents an open stable population where the rate of entry into the population balances age and sex-specific Canadian death rates.
- Both stable and casual sequential monogamous partnerships are modeled. Girls and boys are assigned a sexual activity level and become sexually active at a given age by fitting the model to empirical data on sexual debut. Once sexually active, single females form new partnerships at a rate based on age and level of sexual activity. The male partner is chosen from the single male population based on age, activity level, and onset of male sexual debut. Stable partnerships dissolve at rates based on female age and sexual activity level.
- The model represents the transmission and natural history of HPV types 16 and 18 separately, as well as a composite category consisting of all other high-risk HPV types. Low risk HPV types 6, 11, and a composite category of remaining low risk types are also represented.
- The probability of HPV transmission from an infected individual to his/her susceptible partner is modeled per sex act. Consequently, the probability of transmission per partnership is age and level of sexual activity-specific, as it depends on the frequency of sex acts per unit time and the duration of the partnership.
- Virus natural history is modeled to incorporate multiple viral types, per-act transmission and clearance of HPV, natural acquired immunity and persistent infection.
- The duration and the degree of the vaccine effectiveness can be specified by the user, as well as other characteristics of the vaccination program such as targeted ages, sex, and program roll-out.

[1] CRMM-HPV and CRMM-Cervical are freely available. Interested users can access the models through: www.cancerview.ca/cancerriskmanagement after completing a straightforward sign-up process.