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Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Rodin D, Burger E A, Atun R, et al. Scale-up of radiotherapy for cervical cancer in the era of human papillomavirus vaccination in low-income and middle-income countries: a model-based analysis of need and economic impact. *Lancet Oncol* 2019; published online May 28. http://dx.doi.org/10.1016/S1470-2045(19)30308-0.

Appendix

1. Disease Input Parameters

1.1. Cervical Cancer Incidence

Population estimates of cervical cancer incidence were extracted from GLOBOCAN for each country and categorized by the 2017 World Bank income group classification system[1], which included 31 low-income countries (LICs), 48 lower middle-income countries (L-MICs), and 49 upper middle-income countries (U-MICs). Projection estimates for 2015, 2020, 2030, and 2035 were available through GLOBOCAN 2012 and linear interpolation was used to estimate incidence in the intervening years. These incidence projections are based on an average growth trend of 3%/year in LICs, 2%/year in L-MICs, and 1%/year for U-MICs due to differences in population forecasts.[2] Our base-case projection of cervical cancer incidence from 2035 to 2072 assumed no changes in these growth rates. This analysis was not updated to the GLOBOCAN 2018 data, which was published in late 2018, as the base case for this analysis is 2015-2035, and the human papillomavirus (HPV) analysis relies on much longer-term projections to 2072.

Although incidence and mortality from invasive cervical cancer have decreased over the last several decades in a number of Western countries, these decreases have been largely limited to the highest resourced countries with well-organized screening programs in place for extended periods of time.[3] In most countries with lower quality or opportunistic screening programs, continued population growth and the expansion of antiretroviral treatment, which has led to increased life-expectancy for women infected with human immunodeficiency virus (HIV), have led to stable or increasing cervical cancer rates. HIV has also been associated with increased risk of acquiring HPV and impaired clearance.[4,5]

1.2. Age Distribution of Cervical Cancer at Diagnosis

The health and economic benefits accrued from radiotherapy scale-up were estimated from the median age of diagnosis in each World Bank income group, which was 50 years of age in LICs and L-MICs and 47 years of age in U-MICs. These ages were derived from the GLOBOCAN 2012 age-specific rates (Table S1).

Table S1. Age Distribution of Cervical Cancer by Income Group, GLOBOCAN 2012

Age (years)	Low-Income Countries	Lower-Middle-Income Countries	Upper-Middle-Income Countries
0-14	0·1%	<0·1%	<0·1%
15-39	21·0%	17·2%	25·6%
40-44	11·1%	12·5%	13·6%
45-49	12·6%	15·3%	13·6%
50-54	13·2%	15·7%	11·8%
55-59	12·2%	13·9%	10·4%
60-64	10·5%	10·2%	7·9%
65-69	8·5%	6·9%	5·5%

70-74	5·6%	4·4%	4·5%
75+	5·6%	3·9%	7·2%

1.3. Radiotherapy Demand and Survival Benefit

Population-level demand for external beam radiotherapy (EBRT) and brachytherapy were estimated based on the proportion of new cervical cancer cases in which they were recommended as the treatment of choice according to evidence-based guidelines and based on evidence that they result in superior clinical outcomes compared to no treatment or compared to other available treatment options.[6,7] These indications were incorporated into the decision trees created by the Collaboration for Cancer Outcomes Research and Evaluation (CCORE) in TreeAge Data software (Williamstown, MA) in which the decision tree branches into progressively more specific patient subgroups where radiotherapy was or was not indicated. This evidence-based estimation method, which is also described in detail in the Global Task Force on Radiotherapy for Cancer Control (GTFRCC) Commission report,[8] has been used for large population estimates in several countries and regions.[9-11]

Patients requiring radiotherapy were counted only once, even if they had indications for radiotherapy at multiple points during their illness, such as at the time of initial diagnosis and then later at the time of recurrence. In our base case analysis, the proportion of all cervical cancer patients who had an indication for external beam radiotherapy (EBRT) was 71% with an average of 21 fractions delivered per patient. The proportion of all cervical cancer patients receiving EBRT with an indication for brachytherapy was 75% with an average of 3 fractions per patient (53% of the total population of cervical cancer patients). The mean number of fractions per treatment course for each radiotherapy indication was modelled. However, if there were two regimens of equal efficacy cited for a cervical cancer indication, we used the lower number in the model.

Radiotherapy benefit was defined as the 5-year overall survival benefit of optimal radiotherapy utilization as in the GTFRCC Commission report.[8] Local control and palliative symptom control benefits were not considered. The population-based benefit was estimated as the proportion of patients with each radiotherapy indication identified in the CCORE decision trees multiplied by the associated incremental survival benefit from radiotherapy for that specific indication and patient population.[12] This method estimated the absolute benefit of external beam radiotherapy and brachytherapy over no treatment for radical indications and over surgery alone for adjuvant indications, and has also been applied in several studies in other disease areas.[13-15] The 5-year population-based incremental overall survival benefit of receiving radiotherapy, when radiotherapy is indicated as the treatment of choice, was estimated to be 17·9%.[16] This radiotherapy benefit was additive to the benefits accrued from surgery and chemotherapy. For patients with stages IB-IIA disease, the addition of concurrent cisplatin provided a 4% increase in overall survival at 2-years and 6% at 5-years compared to radiotherapy alone. For patients with IIB-IVA disease, chemotherapy provided a 4% overall survival benefit at 2- and 5-years compared to radiotherapy alone.[16] After 5 years, patients were assumed to be cured of their disease, but remained at risk from other causes of death.

Sensitivity Analysis:

In a sensitivity analysis, we applied the stage distribution from the 26th FIGO Annual Report[17] to model the effects of more advanced disease on demand for radiotherapy and the associated survival benefit from treatment provision. The stage distribution from the base case analysis and the advanced stage sensitivity analysis is presented in Table 1 of the report. This report contains staging information on 15,081 patients diagnosed between 1999 and 2001, of which 32% were derived from LMIC institutions. Based on this sensitivity analysis, the proportion of patients with an indication for radiotherapy increased to 86% for EBRT, with 79% of all radiotherapy patients also requiring brachytherapy. The 5-year incremental overall population survival benefit from radiotherapy also increased to 33·7%.

2. Radiotherapy Costing Input Parameters

2.1 Model Overview

The GTFRCC used a time-based activity costing model to estimate the capital and operating costs of scaling up radiotherapy capacity to meet the demand for treatment of the top 10 cancers, according to burden of disease, by 2035.[8] The equipment and human resource components of the radiotherapy delivery process were identified and the cost per unit time of supplying this capacity and the amount of time these resources were committed to each activity were estimated. The GTFRCC described a 'nominal' and 'efficient' radiotherapy delivery model, with data inputs based on 2014 vendor quotations, questionnaires, and public databases. The components of the model and the time allocations are described in detail in the description of the costing model in Van Dyk et al (2017)[18] and in the GTFRCC Appendix.[8] These inputs were used for this analysis and adapted to the cervical cancer population. The present analysis discounts the treatment costs over the scale-up period in order to estimate the present value of such policies; therefore, all values are presented in 2015 USD($).

Radiotherapy costing was estimated through a capital cost and an operating cost metric. A capital cost was estimated to account for the additional infrastructure and training investment needed to treat the patient population with the top 10 cancers by incidence by 2035, as defined by the GTFRCC. These capital expenditures reflected upfront costs needed to create the initial capacity, after which time only the operating costs are incurred. This capital cost was calculated on a per-fraction basis for EBRT and for brachytherapy and was apportioned to the net annual increase in cervical cancer patients treated. Operational costs accounted for human resources, maintenance, consumables, and overhead, which was estimated as a factor of 1·2 applied to the total estimated cost.

In the GTFRCC model of overall demand for radiotherapy, the cost per treatment course was estimated with the assumption that 6·7% of all radiotherapy cases in LMICs (LIC 14·05%, L-MIC 9·95%, U-MIC 4·02%) require brachytherapy, which is not congruent with the cervical cancer indications. Consequently, for this cervical cancer-specific analysis we adapted the GTFRCC model to separately estimate the capital and operating costs of EBRT and high-dose rate (HDR) brachytherapy. Brachytherapy capital costs included construction of the brachytherapy suite, HDR afterloader, treatment planning system, applicators, and recovery area. Brachytherapy operating costs encompasses all procedures related to the procedure, including image acquisition, treatment planning and dosimetry, treatment delivery, and quality assurance. Although radiotherapy centres for EBRT are built to treat all cancer patients, rather than a single disease site, best-practice curative radiotherapy for cervical cancer requires a combination of EBRT and brachytherapy to maximize the survival benefit[19] and is one of the primary indications for brachytherapy facilities in LMICs.

2.2 Efficiency Model Assumptions

The efficiency model relied on cost savings achieved through improved operational efficiency (including automation) to treat more patients per hour, longer operating hours and reduced

capital costs through bulk purchasing of equipment, while maintaining high quality and safe treatment.

Bulk purchasing, also known as pooled or aggregated purchasing, refers to the purchasing of large quantities of an item to negotiate lower unit prices with manufacturers. Donors and international agencies such as UNAIDs and UNICEF are often involved in multi-country procurement for LMICs, which increases their negotiating power to drive down the cost.[20] This mechanism is also used by high-income countries for both devices and pharmaceuticals, such as the group-purchasing organizations in the United States, which negotiate on behalf of a group of hospitals,[21] or the Gulf Cooperation Council, which centralizes tender and bidding processes for a group of countries in the region.[22]

Longer operating hours have also been found to reduce costs and improve access to diagnostic imaging in resource-constrained settings. In Canada, long wait-times for magnetic resonance imaging (MRI) scanners spearheaded an effort to increase operating hours of machines. In a 2017 audit by the Canadian Agency for Drugs and Technologies for Health, >50% of MRI scanners operated more than 12 hours per day and >40% operated more than 80 hours per week.[23] Similar practices have been noted in LMICs as well. In a 2013 Harvard Business Review analysis of over 40 hospitals in India that were identified as having innovative models of care delivery, several ran their MRI scanners 24 hours per day, 7 days per week, with some charging lower prices at night when machines were previously unused to incentivize patients to have their scans performed at inconvenient times.[24] These practices, and the resultant higher clinical volumes, contributed to more effective negotiating positions for purchasing related medical supplies and devices.[24] As a result of this experience in diagnostic imaging, the experts on the GTFRCC felt that this was an appropriate scenario to explore for radiotherapy in the efficiency model sensitivity analysis. Given the demand for radiotherapy in LMICs and the current lack of radiotherapy equipment, new programs will inevitably come under pressure to treat as many patients as possible with whatever equipment is available, particularly in the early scale-up period. However, the higher patient throughput associated with longer operating hours will need to be balanced against higher staffing and other operational costs and higher equipment maintenance and service costs.[25]

A growing body of evidence, including studies of real-world practice, have demonstrated how technology innovation, including process and equipment automation, can improve the efficiency of radiation delivery. At Princess Margaret Cancer Centre in Toronto, Canada, automated treatment planning for tangential breast cancer treatment has been the standard treatment technique since June 2009. This process automatically delineates treatment volumes and does not require user interaction once initiated. A review of this process has found that this automated system provides unacceptable treatment plans in less than 3% of cases and allows plans to be developed in an average of 5 minutes and 19 seconds +/- 46 seconds.[26] In the LMIC setting, a collaboration between hospitals in South Africa and the United States has led to the development of a fully automatic treatment planning tool that designs patient-specific treatment plans for locally advanced cervical cancer. This system created a treatment plan for physician review in a median of 11.0 minutes (range, 8·2 to 13·6 minutes).[27] These technologic advances are expected to continue to yield meaningful improvements in treatment efficiency and patient throughput,

allowing more patients to be treated each hour on each machine without compromising quality or safety.

3. Economic Benefits

In the GTFRCC Commission, the net present value (NPV) of radiotherapy investment was determined from a macroeconomic perspective by multiplying the net annual life-years gained through radiotherapy scale-up by the average GDP per capita in each World Bank Income region. Due to the initial capital investment required to invest in radiotherapy technology and the need for appropriate multidisciplinary care and ancillary services, increasing coverage and capacity of radiotherapy is typically through government funding commitments and decisions are incorporated into national cancer control plans. Macroeconomic returns are therefore important indicators for evaluating return on investment. This relationship between reductions in mortality and economic growth in LMICs has been well-established over the last 25 years and subsequently applied in multiple disease areas to make decisions on funding allocation at the national and international level. Our model assumes that women under age 70 years who are cured of cervical cancer would return to the workforce and productively contribute to the economy. We recognize that not all women will formally work following treatment, and this may represent an upper bound on their labour force participation.

Strictly examining the effects of healthy life years gained on national income accounts, however, fails to recognize the important contribution that women who are curatively treated for their cervical cancer can make to the economic wellbeing of their country.[28] The traditional human capital approach underestimates the full scope of women's economic contributions because it does not assign a value to unpaid activities.[29] As cervical cancer uniquely affects women, we sought to recognize and value women's domestic and caregiving contributions. Several studies quantified the financial value of these informal contributions and we applied the methodology described in the *Lancet* Women and Health Commission to the human capital impact estimates on GDP. It is important to note that this does not account for joint activities that are typically considered domestic work and that do not directly contribute to health (cooking, cleaning, sourcing clean water, etc.).

We used the average annual value of home-based unpaid work related to health care[30] calculated for each income group region and inflated to 2015 values and added this value to the amount generated through national income accounts. The average wage was determined by the *Lancet* Women and Health Commission using the proxy good method in which the time spent on caregiving was valued at the same level as the closest comparator in the paid labour force (e.g. nurse, nanny).[28] Based on 2010 GDP per capita and inflated to 2015 USD($), the average wage was $52 for LICs, $229 for L-MICs, and $428 for U-MICs. This value was multiplied by the life-years gained from being curatively treated for cervical cancer in the setting of radiotherapy scale-up, compared to a scenario of no-scale-up. To calculate the total human capital return on investment, this amount was added to the economic return gained through effects on national income accounts (the traditional human capital approach). Evidence suggests that women are responsible for a large proportion of unpaid household and caregiving work that is performed in addition to their paid work. For this reason, we have included both metrics in our human capital estimates. This unpaid work represents 9%, 11%, and 6% of the economic benefit that has been calculated in LICs, L-MICs, and U-MICs, respectively.

The 2013 *Lancet* Global Health 2035 Commission recognized the general limitations of the human capital approach and applied a full-income metric to broadly account for non-market productivity as well as the intrinsic value that countries place on the potential for increased life expectancy. This concept of "full income" was first introduced in Gary Becker's 1965 household model as also significantly contributing to a country's economic output. To capture the full scope of methodologic efforts used in the literature to estimate the effects of improved health on macroeconomic productivity, we also applied this metric to quantify radiotherapy's benefits. As in the GTFRCC, this was modelled using the value of a statistical life year modifier of 2·3 (USD) in LMICs.[31] The modifier was applied by multiplying the product of the annual net life years and the average GDP per World Bank Income region by 2·3.

4. HPV Carcinogenesis Modelling

4.1. Reduction in cervical cancer cases after Human Papillomavirus (HPV) vaccination

The primary cause of cervical cancer is persistent infection with high-risk HPV genotypes. Previously published studies on the effects of HPV vaccination on the burden of invasive cervical cancer typically estimate the number of cases or life years saved following HPV vaccination introduction.[32-34] This information is essential for evaluating the cost-effectiveness of population-based public health vaccination strategies in which the benefits may take several decades to accrue. However, the significant lag time (often decades) for carcinogenesis after HPV infection makes such analyses less informative for health system financing over defined budgetary cycles. For this reason, our model-based analysis estimates the annual reduction in cervical cancer incidence as a consequence of HPV vaccination using previously published HPV vaccination effectiveness parameters. We used the parameters defined as the "best case" analysis in the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model, which assumed that the entire cohort of 12-year-old girls in every GAVI-72 country (in this case, in all low- and middle-income countries) is vaccinated from 2014[33] We evaluated this strategy over a short-term time horizon (2015 to 2035) to converge with the Global Health 2035 commission and the GTFRCC commission report, as well as over an extended period from 2015 to 2072 at which point our first vaccinated cohort would be 70 years of age.

Age-specific 2012 cervical cancer incidence rates were extracted from GLOBOCAN [35] for each country. GLOBOCAN provides incidence rates for 10 age groups, and the incidence within a given age bracket was assumed to be equally distributed among the intervening years. We then modelled the reduction in the annual cervical cancer incidence relative to GLOBOCAN projections (Figure 1) based on the following parameters:

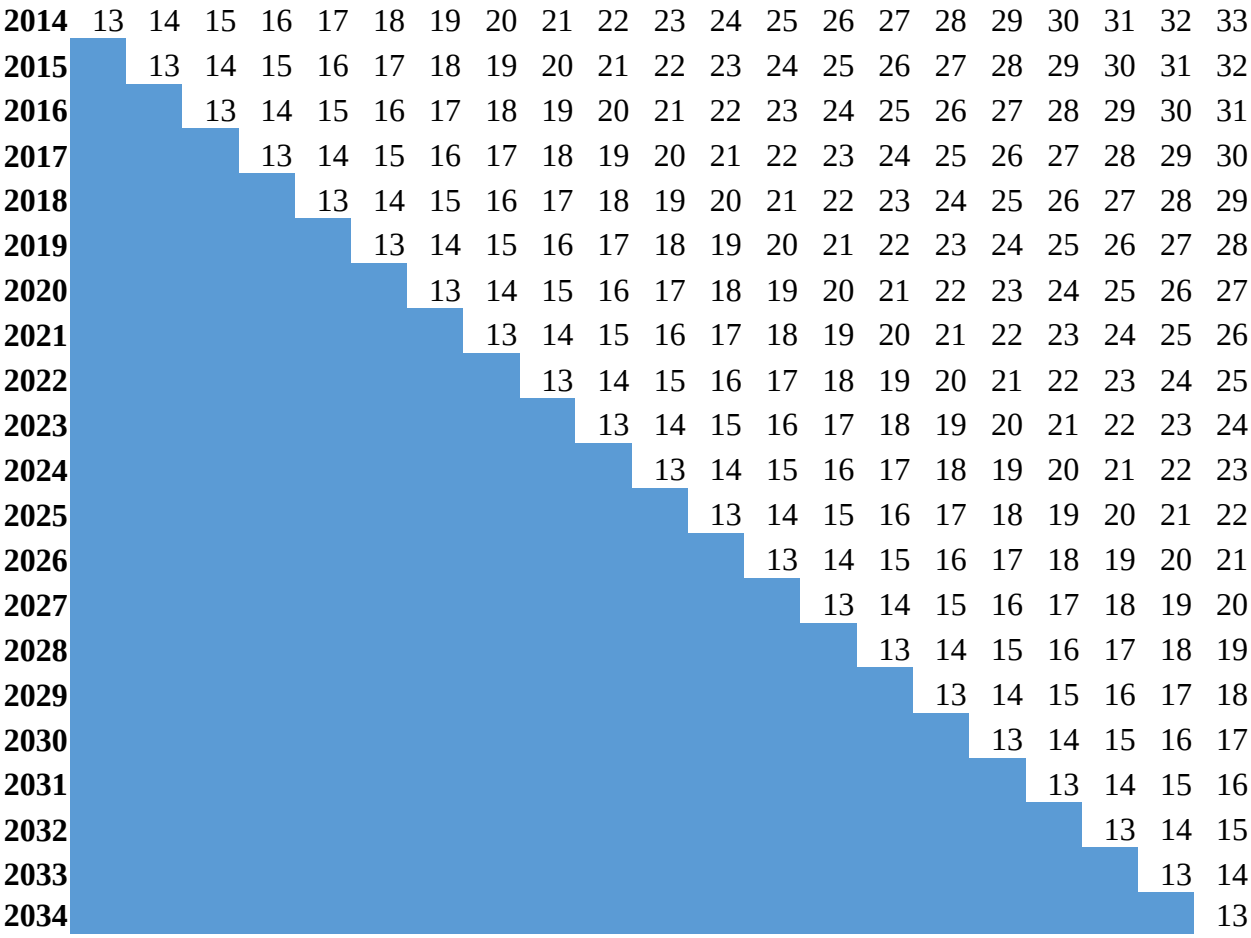
$c(i) = x(i) * p(i) * v1 * v2$

where,
c(i) = annual number of cases eliminated after vaccination introduction at age (i)
x(i) = annual number of projected cases at age (i)
p = proportion of cases attributable to HPV 16/18
v1 = vaccine efficacy against HPV 16/18
v2 = 3-dose HPV vaccine coverage prior to sexual debut

As in the PRIME model, we assumed 100% efficacy against HPV strains 16 and 18, which was responsible in the model for 75% of cases worldwide, and a three-dose schedule coverage rate of 75%. Over this timeframe, women from unvaccinated cohorts and those in later cohorts who were not effectively vaccinated remain at risk of developing the disease. A variety of coverage scenarios, defined as completion rates of the two- or three-dose vaccination schedules, have been employed in earlier modelling studies[36] and a 70% completion rate has been determined to be the threshold for optimum cost-effectiveness of immunization programs.[37] The impact of improvements in general health system performance and cervical cancer screening practices over time were not specifically evaluated (i.e., non-vaccine-based interventions were assumed to remain constant),

but the data used on stage at diagnosis in our base case analysis is from a country (Australia) with a well-developed screening program (alternative stage distribution assumptions used in sensitivity analysis).

Figure 1. Cumulative Ages of Vaccinated 12-Year-Old Females, 2015-2035



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