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REPRODUCTIVE HEALTH

Cancer of the cervix: Early detection and cost-effective solutions

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ABSTRACT

Cervical cancer is known to be a preventable disease through the detection of cervical cancer precursors, historically using cytology of the cervix as the primary screening test. Over 85% of cervical cancer cases and deaths occur in low-resource countries. Alternatives to cytology have been investigated with the strongest possibilities being visual inspection with acetic acid (VIA) and HPV DNA testing. HPV DNA testing has been shown in randomized trials to be significantly more sensitive for the detection of cervical cancer precursors than either cytology or VIA. In this paper we argue that prevention really does cost less than cure, or that prevention and treatment of cancer costs less than no prevention, in effect just treatment, of cancer. The true cost savings of prevention will include a more difficult assessment of the socioeconomic savings associated with longer, healthier lives for women in their prime who have a major role in supporting their families.

1. Introduction

Globally there were 14 million new cases of cancer and 8 million cancer-related deaths in 2012 [1]. This database reveals that breast and cervical cancer are among the most common incident sites of cancer in women, representing over one-third of the total. Among women, breast cancer has a substantially higher incidence (43.3 per 100 000) than any other cancer, representing 25.2% of all cancers diagnosed in females [2].

In Sub-Saharan Africa, the incidence of cervical cancer is equivalent to breast cancer, each constituting approximately one-quarter of the total burden (Figs. 1 and 2). The incidence and mortality rates for cervical cancer in Sub-Saharan Africa are 34.8 and 22.5 per 100 000 respectively—the highest of any world region. In Sub-Saharan Africa, cervical cancer is the most common cause of cancer death in women (23.2% of the total) [3]. Cancer of the breast and cervix kill more women than any other forms of cancer in all low-resource regions of the world [4]. Sixty-two percent (n = 57 318) of women in Sub-Saharan Africa diagnosed with cervical cancer died compared with 50% (n = 47 583) of women with breast cancer [5]. Over 85% of incident cases and deaths from cervical cancer occur in low-resource countries where the initiation and/or maintenance of cervical cancer screening programs have proved impossible [5]. Weak healthcare systems, lack of financial and human resources, competing health needs, war and civil strife, and widespread poverty have prevented many governments from supporting cervical cancer prevention programs.

2. Secondary prevention

While historically cervical cytology has been the mainstay of secondary prevention and, where successfully implemented, has had a major impact on reducing the incidence of and mortality from cervical cancer, the demands of the test are too complex for many low-resource countries. The past 15 years has seen a surge in studies designed to find alternative tests to cytology, specifically to allow point-of-care testing to enable women to be screened and treated in a single visit, without the necessity for complex and expensive laboratory investigations as well as colposcopy and histological examination.

In low-resource countries, these studies have focused mainly on using visual inspection with acetic acid (VIA) and testing for DNA of high-risk types of HPV, so-called HPV DNA testing. Cross-sectional studies of VIA initially were quite reassuring and most studies demonstrated relatively high sensitivity, but low specificity and positive predictive value. Sauvaget et al. [6] performed a meta- analysis of 26 studies of VIA performed in low- and middle-income countries. Overall, VIA had a pooled sensitivity of 80%, specificity of 92%, a positive predictive value of 10%, and a negative predictive value of 99% for the detection of cervical intraepithelial neoplasia (CIN) 2+. In all of the studies, VIA was performed in asymptomatic women who all underwent confirmatory testing; however, there were inconsistencies among the studies.

In longitudinal studies however, Denny et al. [7] in a randomized controlled trial of 6555 unscreened women aged 35–65 years of age showed that the sensitivity of VIA for high-grade precursors was around 48% when women were followed for 36 months. By contrast the sensitivity of HPV DNA testing for high-risk types (using Hybrid Capture 2; Qiagen, Gaithersbury, MD, USA) was consistently higher than either

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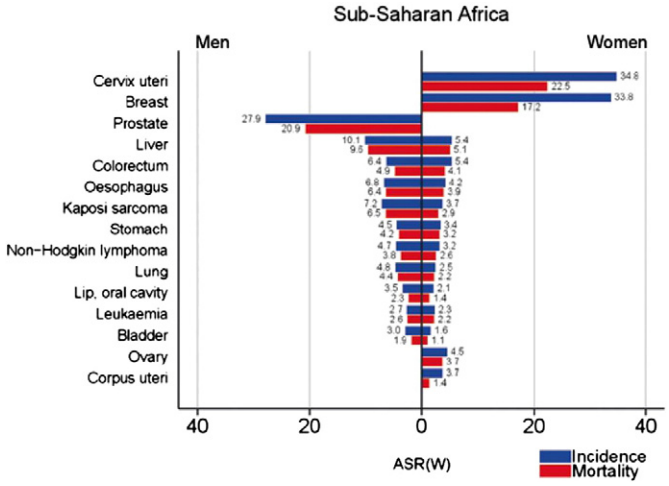

Fig. 1. Sub-Saharan Africa. Estimated age-standardized (World) cancer incidence and mortality rates (ASR) per 100 000, by major sites in men and women, 2012. Reproduced with permission from: Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Pineros M, et al., eds. Cancer incidence in five continents, Vol. X (electronic version). Lyon: IARC; 2013. Accessed 24 September 24, 2014.

cytology or VIA and had a sensitivity of 86% for high-grade cervical cancer precursors over a 36-month follow-up period. Further, for every 100 women screened, the HPV screen-and-treat strategy eliminated 4.1 cases of CIN 2 or greater compared with VIA-and-treat, which eliminated 1.8 cases.

In another landmark study, Sankaranarayanan et al. [8] performed a cluster randomized trial of 131 746 women aged 30–59 years who were randomly assigned to one of four groups: HPV testing; cytological testing; VIA; or standard of care that involved no screening as the control group. The incidence rate of cervical cancer stage 2 or higher and death rates from cervical cancer were significantly higher in the cytological, VIA, and control groups compared with the HPV testing group. Furthermore, the age-standardized incidence rate of invasive cancer among women who had negative test results on cytological or VIA testing was more than four times greater than the rate among HPV-negative women.

These data suggest that primary screening with HPV DNA, followed by treatment will be associated with a significant reduction in cervical cancer and cervical cancer precursors. HPV DNA testing is a

Table 1
Cost of treating cervical cancer among Medicaid beneficiaries in North Carolina, USA.[a]

	Stage 0	Stage I	Stage II–IV A	Stage IV B
12-month cost, US $	6347	32 255	46 681	83 494

[a] Source: Subramanian et al. [15].

laboratory-based test and current commercially available tests are not affordable in low-resource countries. The ideal test for HPV DNA detection would provide a result at the time of examination and screening—a point-of-care test. Such a test has recently become available, the GeneXpert test (Cepheid; Sunnyvale, CA, USA), which can provide a result within one hour. Clinical trials in a screen-and-treat setting are soon to be established.

?twb=0.27w?>There is currently a great deal of research on using HPV DNA testing as either a primary screen or as an adjunct to cytology in women over 30 years of age. Ronco et al. [9] reported on 176 464 women aged 20–64 years who participated in four randomized trials in Sweden, the Netherlands, England, and Italy. Women were randomly assigned to HPV-based (experimental arm) or cytology-based (control arm) screening and were followed for a median of 6.5 years during which 107 invasive cervical cancers were identified. Detection of invasive cancer was similar in the two arms in the first 2.5 years of follow-up but was significantly lower in the HPV screening arm. Further, the cumulative incidence of invasive cervical cancer in women with a negative screening test at entry was double in the control versus the experimental arm. These four trials showed that HPV testing provides 60%–70% greater protection against invasive cervical cancer compared with cytology and the authors recommend initiation of HPV-based screening from age 30 years and to extend the screening intervals to 5 years.

While many studies have focused on the characteristics of screening tests, the programmatic issues often pose the strongest barriers to successful screening. WHO began a demonstration project called "Prevention of cervical cancer through screening using VIA and treatment with cryotherapy" [10], which recruited 19 579 women from September 2005 to May 2009 from six countries in Africa (Madagascar, Malawi, Nigeria, Uganda, Tanzania, and Zambia). Overall, 11.5% (n = 1980) of women screened were VIA positive and 1.7% (n = 326) were found to be suspicious for cancer. Of the 1980 women with positive VIA, 87.7% (n = 1737) were eligible for cryotherapy and 60.9% (n = 1058) underwent cryotherapy, 34.6% (n = 601) were lost to follow-up, and 4.5% (n = 78) did not undergo cryotherapy.

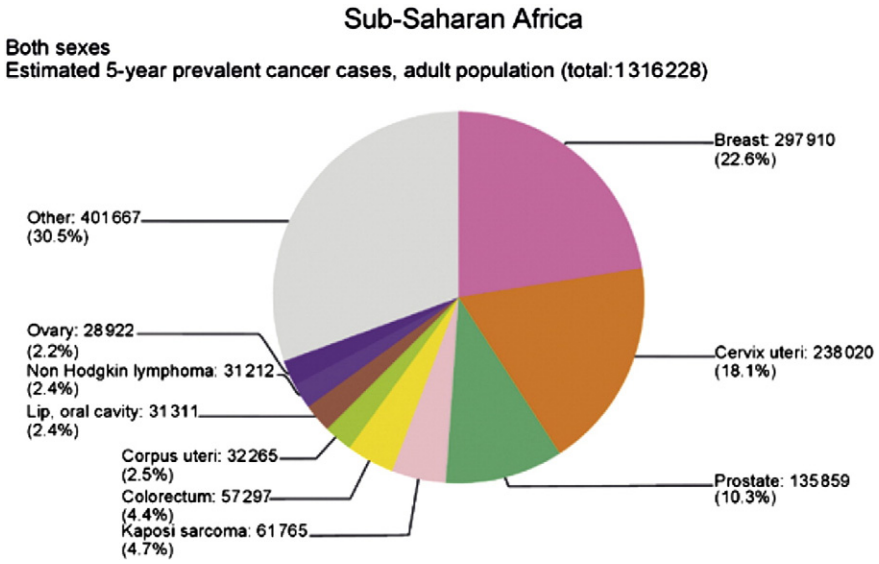

Fig. 2. Sub-Saharan Africa. Estimated cancer five-year prevalence proportions by major sites, in both sexes combined, 2012. Reproduced with permission from: Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013;132(5):1133–45.

Table 2
Cost of treating all cervical cancer cases in Taiwan, 2002–2010.[a]

	Stage 0 (n = 17 701)	Stage I (n = 6236)	Stage II (n = 2987)	Stage III (n = 1157)	Stage IV (n = 716)
Expected life-years lost	–	6.3	11.6	12.7	18.6
Lifetime costs, US $	1316	7020	10 133	11 120	10 015

[a] Source: Hung et al. [16].

Of those undergoing cryotherapy, just under 40% (n = 243) had the procedure performed on the same day as screening. Furthermore, around 50% of women treated returned for their follow-up visit one year later.

Of the 326 women with possible cancer, only 29.4% (n = 96) were investigated, of whom the majority—79 women—were confirmed to have cancer, and 77 received treatment. There was no information on 70.6% (n = 230) of women with a cervix suspicious for cancer. These data underscore that there are no quick fixes to screening programs, even using a low technology accessible test such as VIA. Despite huge effort, the coverage rate of the target populations was way below what was anticipated, there was significant loss to follow-up, and poor uptake of same day treatment. Furthermore, the majority of women with a cervix suspicious for cancer were not investigated. Some of the reasons for the lack of investigation of these women were lack of access to pathology services or inability to pay for pathology services.

3. Cost-effectiveness

It is perhaps intuitive to think that cancer prevention programs (vaccination and screening) are cost-effective, yet relatively few countries have implemented them. Data audits and predictions are reported variously as cost-effectiveness, cost-benefit, and cost-utility. These terms differ according to the index of measurement chosen (cost per life year saved, cost per dollar of intervention, cost per years saved, and quality of life adjusted years saved) and the interested reader is referred to the recent overview by Subramanian [11].

In 2010, cervical cancer accounted for over 7 million disability-adjusted life years lost [2]. If cervical cancer prevention programs had been implemented globally it has been estimated that between 10 and 230 million dollars and almost 1 trillion dollars in value of a statistical life (VSL) would have been saved [12,13]. In the present paper we argue that prevention really does cost less than cure, or that prevention and treatment of cancer costs less than no prevention, in effect just treatment, of cancer. The true cost savings of prevention will include a more difficult assessment of the socioeconomic savings associated with longer, healthier lives for women in their prime who have a major role in supporting their families. This wider cost will not be addressed here, largely because of the lack of valid information [11] and because it may have less impact on healthcare budget holders than tangible resources savings.

Sankaranarayanan (personal communication, December, 2014) described a model that compares three approaches to the management of cervical cancer:

(A) Prevention by vaccination and screening with treatment of pre-cancer cases plus treatment of cancer surgically and with radiotherapy.
(B) Screening and treatment of pre-cancer plus early cancer.
(C) Diagnosis and treatment of symptomatic cancer patients without any preventive program.

A recent study at Harvard estimated a cost saving between groups A and C ranging from 54% to 65% in different WHO regions and a cost saving between 32% and 38% for groups A versus B [14].

Clearly the cost of treating cervical pre-cancer and cancer will be greater in an adequately resourced country. But does the relative difference in treating cancer at different stages prevail between adequately resourced and poorly resourced countries? Directly comparable figures are not easily available. Tables 1 and 2 show the costs in regions at different ends of the income spectrum and demonstrate a stark relative difference in the cost of treatment at different stages. These comparisons are likely to underestimate the true cost as they do not include the socioeconomic costs; however, they do show a consistent cost saving of well over 50% when comparing the treatment of pre-cancer to late stage disease, whether in Taiwan or the USA.

Taiwan introduced cytology screening in 1995 and despite an increase in population there has been a 43% decline in cervical cancer incidence between 2002 and 2009 [16,17]. Again the cost savings of this reduction (approximately US $42.2 million) is likely to be a conservative cost savings estimate (Fig. 3).

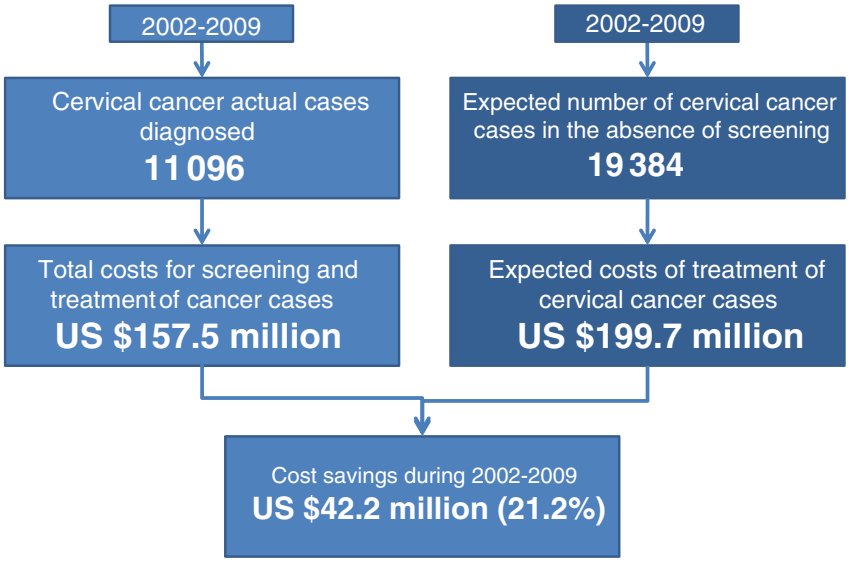

Fig. 3. Projected cost savings following introduction of cervical cancer screening in 1995 in Taiwan.

Table 3
Estimated costs of cervical cancer treatment and follow-up care in public hospitals in India.[a]

Stage	Number of cases	Estimated one-year costs (direct medical costs, treatment plus follow-up care) and indirect costs (transportation, food and stay during treatment, lost wages), US $	Total costs, US $
I (radical hysterectomy with bilateral pelvic lymphadenectomy)	12 284 (assumed to be 10% of annual burden)	2127	26 128 068 (26.1 million)
II, III, IVA (external beam therapy 45–50.4 Gy 25–28 fractions, with midline shielding after 36 Gy, 5–6 sittings of high-dose rate brachytherapy to a total of 25–30 Gy to point A, and 5–6 weekly concurrent chemotherapy with cisplatin 40 mg/m^2 beginning on day 1 of radiotherapy)	110 560	3439	380 215 840 (380.2 million)
IV B	12 284 (assumed to be 10% of annual burden)	3111	36 987 124 (37.0 million)
Follow-up visits of prevalent cancer cases	1.5 million visits	50 per visit	75 000 000 (75 million)
Total estimated costs of cervical cancer care per year			518 331 032 (518.3 million)

[a] R. Sankaranarayanan, personal communication, December, 2014).

Perhaps the most useful country data to study come from India, which has the world's largest burden of cervical cancer (122 844 cases per annum, 67 477 deaths per annum, and 1 125 960 prevalent cases at five years [18]. Table 3 details the estimated one-year costs of cervical cancer treatment in public hospitals in India (Sankarayarayanan; personal communication, December, 2014). If India were to introduce HPV vaccination and two-visit HPV screening (assuming 70% coverage), Diaz et al. [19] estimated a reduction in lifetime cancer risk of 63% in the context of the Indian healthcare environment. In Fig. 4, an estimation of the cost savings has been made were India to introduce a three-dose vaccination of 12-year-old girls and a single round of HPV screening at age 35 over the next 30 years. As is shown in the Fig. 4, there would be a marginal reduction in cost if prevention were introduced (vaccination and one-off HPV screening at 35 years of age) but a massive reduction in costs (over US $6 billion) after 30 years of the prevention program. This may seem a long time to wait; however, even in the first 30 years of the prevention program the costs do not increase, but rather decrease, albeit marginally. Again these estimates are conservative. The cost of vaccination, especially if bought in bulk at a national level and of screening is likely to reduce, whereas the cost of treatment of later-stage disease may well increase.

The assessment of cost will be different from the perspective of a gynecologist to that of a national healthcare budget holder. Although eliminating surgical and radiotherapy costs from a hospital makes immediate sense to the caring doctor, it might have little influence on a healthcare budget if the surgical and radiotherapy resources are so limited that they will be used up by other diseases once freed from cervical cancer needs. However as more and more diseases are prevented, ultimately healthcare resources should reduce overall.

Health economics are perceived very differently between low- and high-income countries, and priorities will depend not just on the relative cost of prevention versus cure but also on the absolute cost of any intervention and the impact of that intervention on other health resources in that region. If the absolute cost of preventing cervical cancer is not affordable then it will not happen. It is hoped that the cost of vaccination and HPV testing will plummet over the coming years.

Conflict of interest

Lynette Denny has received honoraria for appearing on various speaker forums on HPV vaccination for GlaxoSmithKline and Merck and has received research funding from both organizations. Walter Prendiville has no conflicts to declare.

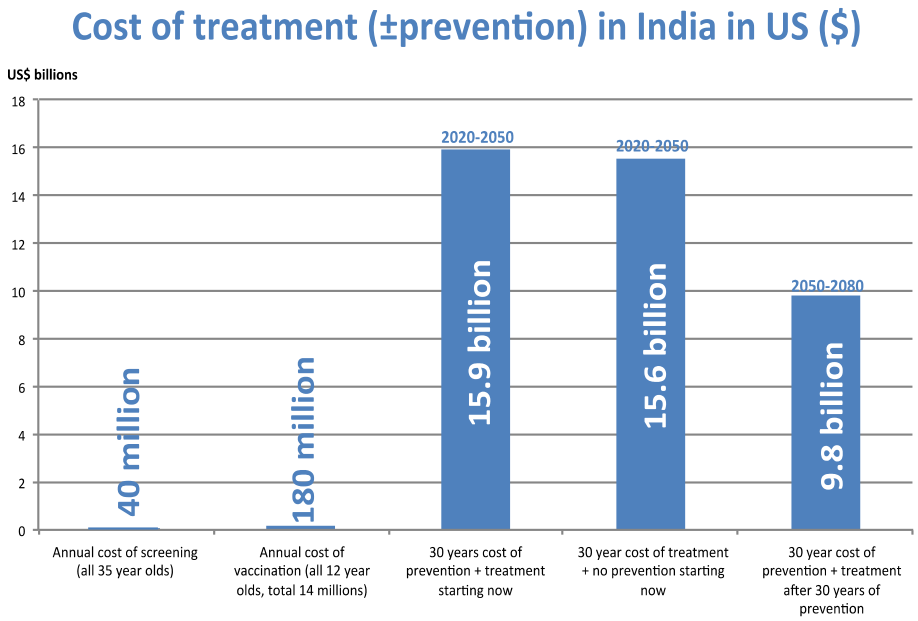

Fig. 4. Cost of treatment (± prevention) in India in US dollars.

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