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MINIREVIEWS

Burden of gynaecological cancers in developing countries

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Abstract

Approximately 1:4 of all cancers in women in developing countries (excluding non-melanoma skin cancer) is a gynaecological cancer. The gynaecological cancer burden in developing countries is huge primarily due to the high incidence and mortality of cervical cancer. Cervical cancer accounts for over 60% of the gynaecological cancer burden in developing countries despite being preventable by current technologies. This is due to the absence of effective nationally organized screening programmes in most developing countries. Institution of such programmes, therefore, has the potential to dramatically reduce gynaecological cancer burden in these countries. Subsidized human papilloma virus (HPV) vaccine and HPV typing as well as cheap screening techniques such as visual inspection aided with acetic acid hold the key to effective prevention of cervical cancer in these countries. This is because a significant proportion of patients in developing countries are unable to access and avail themselves of the few available preventive, diagnostic and treatment services because of poverty. Although, advocacy and the political will to invest in the development of human resources and healthcare infrastructure appear critical to gynaecological cancer control and reducing the burden of disease in many developing countries, the proposition assumes that resources are truly available for this investment. This may not be true. Many developing countries rely on foreign aids for developmental programmes and these aids have dwindled significantly with the current global economic meltdown.

Key words: Gynaecological cancer; Cancer burden; Cancer mortality; Cancer morbidity; Cancer prevention

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INTRODUCTION

Emerging global trend in the burden of cancer

Cancer is the second leading cause of death and disability worldwide, behind only heart disease[1]. More people die from cancer every year than human immunodeficiency virus (HIV), tuberculosis and malaria combined[1-4]. Contrary to about three decades ago when cancer was more prevalent in the developed world, the burden is shifting significantly to the developing countries. According to estimates by the International Agency for Research on Cancer (IARC), in 2008, 53% of the 12.7 million new cases of cancer and 63% of the 7.6 million cancer deaths occurred in developing countries[3]. Three decades earlier, developing countries accounted for a mere 15% of global cancer burden[4]. A recent report based on the IARC/GLOBOCAN 2002 world cancer statistics estimated that by the year 2020, about 10.25 million new cases of cancer would be diagnosed in the developing countries compared to 5.94 million in the developed countries[1]. This trend is quite disturbing for many reasons including the fact that it will, no doubt, compound the already existing

formidable health and human developmental challenges posed by poverty, weak economies and high prevalences of communicable diseases in developing countries.

Explanations given for the increasing burden of cancer currently observed in developing countries have been based largely on epidemiological data and empirical observations. Reasons often cited include a shift in developing countries to Western lifestyle and behaviors such as cigarette smoking, low fiber/high fat diets and less physical activity[5]; high prevalence of immunosuppressing conditions such as malnutrition, tuberculosis and HIV[6]; high prevalence of oncogenic infections such as hepatitis B virus, HIV, hepatitis C virus, human papilloma virus (HPV), *Helicobacter pylori*[5]. We observe that it is also possible that increasing health awareness in these countries has facilitated resort to orthodox medical care resulting in more persons with cancer reporting to hospitals for care, rather than seeking care from herbalists and other forms of alternative health care. Whether the increased documentation of cancer in developing countries is due to actual increase in disease incidence or reporting bias, cancer has become a new challenge to the health systems in developing countries.

Definition of operative concepts

Developing countries: For the purpose of this review, the term developing countries refers to countries classified by the World Bank as middle and low income countries in their classification of economies in 2009[7]. These countries had gross national income per capita of USD 12 275 or below[7]. Developing countries are by no means homogenous with respect to all indices of development. However, they are generally characterized by low standard of living (including poor access to health care, poor sanitation, poor access to safe drinking water and poor nutrition); underdeveloped industrial base and low human development index (including low level of literacy, low life expectancy, high infant and maternal mortality)[8]. They include most countries of sub-Saharan Africa, South and South East Asia, Latin and South America.

Burden of cancer: For the burden of cancer, the epidemiological definition of the burden of cancer as described by Sankaranarayanan *et al*[9] was used in this review. For economic burden, the economic definition described by Kim *et al*[10] was adopted. Accordingly, the epidemiological indices of burden of gynaecological cancer used in this review include cancer incidence, mortality and case fatality while the economic definition involves the economic cost of the cancer (including medical costs, nonmedical costs and the cost due to loss of productivity)[9,10].

Sources of data

The information contained in this review were obtained through electronic literature search conducted in major data bases including PubMed, Medline, EMBASE, Scopus, Cochrane database and central register of controlled trials using the following search terms individually and in combination: gynaecological cancer, cancer in developing countries, burden of gynaecological cancer, cancer, cancer burden, cancer in sub-Saharan Africa, South Asia, Latin America, South America, the Caribbean, economic burden of cancer, cervical cancer, ovarian cancer, corpus cancer, vulval cancer, vaginal cancer, choriocarcinoma. All relevant peer-reviewed English language articles and publications were identified, retrieved and reviewed. We also obtained further articles by reviewing the bibliographies of the relevant published documents obtained in the primary search of databases. In addition to these, we consulted the website of the IARC for the current version of the GLOBOCAN world cancer statistics.

Aetiology of gynaecological cancers

In view of the importance of causative factors to any disease burden, it is appropriate to review the aetiological basis of gynaecological cancers. Gynaecological cancers include cancers of the ovary, fallopian tube, uterine body, cervix, vagina and vulva as well as choriocarcinoma which primarily come under the care of gynaecologists and gynaecological oncologists. This review excludes breast cancer because it comes under the specialty of general surgery in most developing countries.

Gynaecological cancers can be epidemiologically grouped into two with respect to aetiology. On the one hand are cervical, vaginal and vulvar cancers which share similarities, first in having known premalignant stages before the development of invasive cancer and secondly in their link with high risk human papilloma virus infection. Chronic infection with this virus is now known to induce premalignant changes in epithelial cells ultimately leading to cancer after several years[11-13]. Human papilloma virus is a sexually transmitted disease. For cervical cancer, the relationship to HPV and the presence of a recognizable premalignant stage of the disease called cervical intraepithelial neoplasia (CIN) provide multiple planks for preventive efforts[14-17]. Several co- factors are known to modify the effect of chronic HPV infection in the causation of cervical cancer and these include high parity, prolonged use of oral contraceptive pills, multiple sexual partners, cigarette smoking and early age at sexual debut[11]. Vaginal and vulvar cancers are also known to evolve through premalignant phases called vaginal intraepithelial neoplasia and vulvar intraepithelial neoplasia respectively, but screening for these stages in the population is not currently recommended[18-20].

On the other hand are ovarian, Fallopian tube and corpus cancers which do not have any known infective aetiology. Most cases of ovarian cancer occur spontaneously although genetic predisposition is responsible for ovarian cancer in 10% of cases[21]. These hereditary ovarian cancers are associated with inherited germ line mutations in the *BRCA-1* and *BRCA-2* genes as well as the Lynch type 2 gene associated with hereditary non-polyposis colorectal cancer[21]. Epithelial ovarian cancer is associated with a number of risk factors including a

family history of ovarian cancer, old age, postmenopausal status and use of hormone replacement therapy[21]. Ovarian cancer has been traditionally thought to occur more in developed countries due to the higher prevalence of these epidemiological risk factors[22]. However, it would appear that with recent global cancer estimates, the trend may be reversing[1].

On its part, corpus cancer refers to cancer of the uterine body and is mainly endometrial cancer although rarely uterine sarcoma (leiomyosarcoma) may occur. Endometrial cancer is the third commonest gynaecological cancer in developing countries[1,2]. It is a hormone-dependent cancer and is associated with several epidemiological risk factors, the most significant of which include unopposed estrogen, sedentary lifestyle and obesity[23,24]. Endometrial cancer is thought to evolve through a premalignant stage called endometrial hyperplasia but the natural course of progression from endometrial hyperplasia to endometrial cancer is not clearly understood.

BURDEN OF GYNAECOLOGICAL CANCERS

General overview

The burden of gynaecological cancers in developing countries appears huge. In these countries, gynaecological cancers account for 25% of all new cancers diagnosed among women aged up to 65 years compared to 16% in the developed world[25]. According to a recent report, developing countries accounted for 820 265 cases (77.7%) of global estimates for new cases of the commonest gynaecological cancers including cervical, corpus and ovarian cancer in 2009[1]. This constituted 12.1% of the 6.8 million cases of cancer in developing countries[1]. This review intends to explore the pattern, magnitude and significance of the current burden of gynaecological cancers in developing countries.

Specific gynaecological cancers

Cervical cancer: Cervical cancer is the commonest gynaecological malignancy in developing countries where organized screening programmes do not exist[1,3]. According to the IARC, there were 453 531 cases of cervical cancer in developing countries in 2008 representing 89% of global estimates[3]. Also 273 000 deaths occur worldwide every year due to cervical cancer out of which 83% occur in developing countries[26]. Case fatality rates of cervical cancer are quite high in these countries with case fatalities up to 60% reported[1]. Conversely in developed countries where nationally organized screening programmes exist, cervical cancer is not as common and case fatality rates are as low as 32%[1]. About 80%-95% of cervical cancers are squamous cell carcinoma[9].

Across different regions of the world, developing countries individually report heavy burdens of high incidences and mortality from cervical cancer. The highest incidence rates are found in Sub Saharan Africa, Latin America and the Caribbean, South Central and South East Asia[9]. A report from Nigeria gave the incidence of cervical cancer as 25/100 000 per year which translates to a disease burden for an estimated 32 million women in 2005 to about 8000 cases per year[27]. A recent hospital based study in Lagos Nigeria showed that, overall, cancer was the leading cause of death among gynaecological inpatients and that cervical cancer contributed over 44% to all gynaecological mortality[28]. South and South East Asia are thought to experience over 200 000 new cases of cervical cancer yearly (more than one-third of the global burden)[26]. Age-adjusted cervical cancer mortality rates exceed 15 per 100 000 in most developing countries, with rates as high as 35/100 000 in East Africa[9]. A nationwide survey in India published recently evaluated the cause of 122 429 deaths in 1.1 million randomly selected homes across the country between 2001 and 2003: cervical cancer made the highest contribution to cancer deaths among women at 17.5%[29]. In Latin America and the Caribbean, Haiti, Nicaragua and Bolivia had the highest mortality due to cervical cancer with rates of 40, 28 and 22 percent respectively[26]. The very high mortality rates of cervical cancer in developing countries are due to the fact that most patients present at advanced clinical stages of the disease, and to the fact that a significant proportion of patients do not receive or complete prescribed courses of treatment due to deficiencies in treatment availability, accessibility, and affordability[9].

Ovarian and adnexal cancers: Fallopian tube cancers and extra ovarian primary peritoneal cancers are considered along with ovarian cancer because their biology and clinical characteristics are similar to ovarian cancer[9]. Over 80% of cases of ovarian cancer are epithelial in origin[22,30,31]. Ovarian cancer is the second commonest gynaecological cancer in developing countries[9]. It accounts for 18.8% of all gynaecological cancers in developing countries and 28.7% in developed countries[9]. Recent estimates indicated that of 240 476 cases of ovarian cancer in 2009, 155 835 (64.8%) occurred in developing countries compared to 84 641 in developed countries[1]. Accounts that ovarian cancer is commoner in developed countries than in developing countries may not, therefore, be supported by the most current estimates. Ovarian cancer has a case-fatality rate of 59.2% in developing countries which is similar to the 54.8% in developed countries[1]. The high case fatality rate of ovarian cancer is primarily due to the fact that the disease only becomes manifest in advanced stages of the disease[30,31].

Corpus cancer: Corpus cancer is commoner in developed countries than in developing countries[23]. In 2009, there were 236 643 cases worldwide out of which 113 486 occurred in developing countries representing approximately 48% of the global burden[3]. Low incidences less than 4/100 000 are found in South Asia and Africa[9]. More than 90% occur in women aged 50 years and above[9]. It has a more favorable prognosis than Ovarian and Cervical cancers with 5-year survival rates around

70% in developing countries[9].

Vaginal cancer: Vaginal cancer is rare and constitutes less than 2% of gynaecological cancers worldwide[9]. Of 13 200 cases globally in 2002, 9000 (68%) occurred in developing countries[9]. Incidence rates do not exceed 0.8/100 000 in any region of the world[9]. Case fatality rate in developing countries is 44.7% compared to 15.4% in the developed world[1]. More than 75% of cases occur in women older than 60 years[9].

Vulva cancer: This constitutes 3% of gynaecological cancers worldwide[9]. In 2002, there were 26 800 cases out of which 11 100 (41.4%) occurred in developing countries[9]. Incidence rate is less than 1/100 000 in developing countries[9]. More than 50% are seen in women over 70 years and more than two-thirds occur in the labia majora[9].

Choriocarcinoma: This represents 0.6% of all gynaecological cancers[9]. Approximately 5800 cases occurred worldwide in 2002 out of which 5400 (96.4%) occurred in developing countries[9]. Incidence rates are highest in South East Asia where rates of (0.43-1.7)/100 000 are quoted compared to 0.04/100 000 in Africa and Europe[9].

ECONOMIC BURDEN OF GYNAECOLOGICAL CANCERS

The economic burden of gynaecological cancers can be discussed at the level of individual patients and their families as well as the level of health systems and government. Accurate estimation of the actual economic burden of gynecological cancers in developing countries is difficult because studies on the economic burden of gynaecological cancers in these countries are scanty. A few cross-sectional studies document the socio-economic impact of cervical cancer on individuals and families in some developing countries. Arrossi *et al*[32] in Argentina and Ohaeri *et al*[33] in Nigeria studied the socioeconomic and psychological impact of cervical cancer. The study in Argentina found that the socioeconomic impact of cervical cancer was considerable and that it had negative consequences on treatment compliance[32]. It found that "in addition to facing pain, disability and fear of death, cervical cancer patients had to deal with increased treatment related expenses, loss of employment and consequent income, and changes in household responsibilities"[32].

At the level of government and health systems, studies on the cost of cancer care and control are also scanty. A report based on calculations extrapolated from a study in Korea suggests a huge unmet need for funding of cancer care in developing countries. According to the report, the cost of new gynaecological cancers in developing countries in 2009 totalled USD 1.087 billion[1]. This pales into insignificance when compared to the USD 11.913 billion spent in developed countries[1]. The report clearly shows a huge funding gap in developing countries compared to developed countries[1]. Africa which represents 15% of global population contributes 6.4% of new cancer cases and accounts for a mere 0.3% global cancer costs[1].

DISCUSSION

From the foregoing, it is clear than the burden of gynaecological cancer in developing countries is huge. Contending with this challenge demands two vital planks of intervention: generation of representative and accurate data on cancer and the introduction or scaling up of preventive programmes and early detection of cancer through increased funding by all stakeholders.

Population data on cancer from developing countries are prone to inaccuracies. For instance the IARC relies on data from population-based cancer registries to estimate cancer incidences and mortality globally. Such registries are available in only 5% of developing countries - in parts of the developing world where cancer registries exist, they are either regional or hospital registries[9]. In many countries of the developing world, data do not exist at all[9]. For such countries, estimates are usually made from neighbouring countries. Variations in validity and extent of data from different countries are therefore unavoidable and the actual burden of cancers may be more or less than current quoted figures. Inaccurate data militates against accurate planning of policies and programmes for cancer care and control. It is therefore advocated that the establishment of population based cancer registries be made a priority policy for cancer control in developing countries.

Gynaecological cancer incidences are either be expressed as an absolute number of cases per year which reflects the load of new patients diagnosed in a region or group, or as a rate in terms of number of new cases per 100 000 per year which represents the average risk of developing the disease in a population. Whichever way it is expressed, recent estimates of gynaecological cancer incidences in developing countries show that as much as 64% of the gynaecological cancer burden is due to cervical cancer[3]. Cervical cancer control, therefore, holds the key to the reduction in overall gynaecological cancer burden in developing countries. With an estimated case-fatality rate of 55.1%[1], cervical cancer is also the major contributor to gynaecological cancer mortality in developing countries.

Cervical cancer is preventable and curable in the very early stages of the disease. Fortunately, it has a very well known natural history characterized by a long pre-malignant phase which provides a good opportunity for preventive interventions. And among all gynaecological cancers, cervical cancer offers the greatest potential for prevention, early detection and cure[9]. Evidence from the developed world shows that the high incidences of cervical cancer in developing countries are due to lack of or inadequate/inefficient existing screening programmes[34,35].

The central role of HPV infection in the etiology of cervical cancer has led to the introduction of the HPV vaccine and HPV detection and typing in cervical screen-

ing[36,37]. Already HPV vaccine is licensed for use in many developing countries, although the cost of the vaccine makes it generally unaffordable. In Nigeria, for instance, it costs the equivalent of USD 100.00 for a course of trivalent HPV vaccine - a country where over 70% of the population live on less than USD 1.0 per day. On its part, HPV detection and typing also require expensive equipment and highly skilled manpower that are not generally available in developing countries. Thus like cytology screening which requires a great input of human and material resources to sustain, nationally organized preventive programmes using HPV vaccine and detection may prove just too expensive for developing countries[38].

It would appear therefore, that cervical cancer control in developing countries will require active scaling up of cheaper screening techniques such as visual inspection with acetic acid which has similar CIN detection rates compared to HPV testing and cervical cytology[3]. Subsidizing the cost of HPV vaccine and HPV DNA testing by governments of these countries will go a long way to make them affordable to individuals. It has been suggested that linking testing or screening to treatment (screen and treat) without recourse to colposcopy or sophisticated laboratories would potentially prevent cervical cancer in large numbers of women in developing countries[15,39,40].

In the case of ovarian cancer, the burden in developing countries appears to be rapidly evolving with recent estimates suggesting a greater burden than in developed countries[1]. Except in about 10% of cases, ovarian cancer tends to occur spontaneously. The key to control of ovarian cancer appears to be early detection and treatment at the very early stages when cure may be theoretically possible[13].

Screening for ovarian cancer has been evaluated recently by several large randomized controlled trials using assay of CA125 and transvaginal ultrasound[41-43]. Results of the prostate, lung, colorectal, and ovarian cancer screening trial in the United States already published in 2011 suggest that whereas screening may decreases the stage at detection[44] and thereby decrease case - specific mortality; it may not decrease disease specific mortality[45]. The methodological flaws in these conclusions have however, been raised in a recent publication[46] and the world awaits the publishing of the final results of the UKCTOCS trial in 2015 to draw a conclusion as to whether ovarian cancer screening decreases mortality from the disease.

Endometrial cancer is the third commonest gynaecological cancer in developing countries. In order to be proactive in addressing the current and future burden of this cancer in developing countries, the risk factors that are modifiable such as obesity, sedentary lifestyles and use of unopposed estrogen/estrogen agonists have to be actively discouraged[47,48]. Population screening for endometrial cancer is not yet recommended[24] although early detection with transvaginal ultrasound scan using measurement of endometrial thickness in symptomatic women is practised in developed countries[49]. Such practice requires provision of ultrasonography and hysteroscopic facilities and manpower which are not yet freely available in developing countries.

The burden of vaginal and vulval cancers is small. Currently no evidence exists to support any screening tests[50] although their association with HPV provides a window of opportunity for preventive interventions through HPV vaccination or typing. The task for developing countries in mounting early treatment or primary preventive interventions will be similar to the challenges faced with cervical cancer.

In conclusion, there is a high incidence and mortality from gynaecological cancers in developing countries due primarily to the failure of these countries to mount effective nationally organized screening programmes for cervical cancer. A huge unmet need for funding for cancer care and control exists in these countries. "The human right to life, to prevention of suffering, and to education are all key rights linked to improving the control of cervical cancer in resource poor parts of the world"[51]. The resources needed to provide adequately for gynaecological cancer care in many developing countries demands that increased funding is critically needed[52]. Scaling up of cheap sustainable and effective preventive interventions against cervical cancer will potentially decrease the burden of gynaecological cancer in developing countries. Nationally organized HPV vaccination and low cost screening programmes subsidized by funding from governments and donor agencies are key to this intervention.

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