WOMEN'S REPRODUCTIVE HEALTH IN TRANSITION: THE OVERLAPPING CHALLENGE OF BREAST AND CERVICAL CANCER

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Substantial improvements have been achieved in reducing the mortality of women from infectious diseases and from complications of pregnancy and childbirth. The emerging disease burden, primarily associated with chronic and non-communicable diseases, requires a new approach that maintains an expanded focus on reproductive health. The evolution over time and across countries of the two leading causes of cancer death in women – cancer of the cervix and of the breast, both associated with maternal and reproductive health – poignantly illustrates how low- and middle-income countries are faced with the challenges of responding to a complex burden of disease that demands both prevention and treatment interventions and falls most heavily on the poor. This paper combines global, cross-country and historical time-series data from a selection of countries to describe the cancer transition for women. The equity issues are presented using sub-national, time series data for Mexico that illustrate the dual burden of women's cancers in poorer states where women continue to face high rates of both cervical and breast cancer. The protracted and polarized nature of the women's cancer transition is emblematic of the equity imperative of meeting the challenge of cancer globally and closing divides between rich and poor. The findings highlight the need to develop integrated programmes and policies that consider both treatment and prevention, underpinned by a life cycle approach to effectively respond to the burden of cancer faced by women globally. Integration with maternal and reproductive health interventions is the effective strategy to meet the emerging challenges to women's health of chronic and non-communicable disease.

Substantial improvements have been achieved in reducing deaths among women from infectious diseases and from complications of pregnancy and childbirth. Although maternal mortality levels and infection-associated causes of death continue to be unacceptably high, non-communicable (NCD) causes now dominate the burden of disease in low- and middle-income countries.[1,2] For women, some 65% of all deaths globally are due to NCDs, many of which occur during childbearing age.[3]

The complexity of the health challenges that face girls and women in resource-constrained settings provides a compelling case – on health, equity and economic grounds – for adopting a life cycle approach. Applying this approach implies taking advantage of the range of opportunities to

invest in the health of a woman at each stage in her life through appropriate preventive, supportive, curative and palliative interventions.[4,5]

The emerging disease burden, primarily associated with chronic diseases and NCDs, requires a holistic approach to women´s health that maintains a focus on reproductive and maternal components, while extending the reach of programmes and policies beyond reproduction to encompass the health challenges that are faced by women over their lifespan.[4] The impressive gains in the life expectancy of women and recent improvements in maternal mortality rates[6,7] will be seriously undermined if emerging health issues affecting women are not addressed.

In line with the suggestions of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases,[8] much of the recent literature on NCDs in low- and middle-income countries has focused on opportunities for risk factor reduction and primary prevention – arguing correctly that these represent key and cost-effective opportunities to prevent future disease.

However, there is an emerging discourse, some encompassed in the WHO Action Plan for the Prevention and Control of NCDs 2013–2020,[9] that argues for incorporating necessary and effective treatment interventions – with one of the key diseases of concern being breast cancer.[10-16] This broader approach takes advantage of the many instances where treatment-related interventions are appropriate in the low- and middle-income country context. Many treatments for cancer, for example, are relatively inexpensive as they use off-patent medications for curative intent. Further, the risk-factor-only focus has stifled efforts to develop appropriate treatment guidelines in accord with the needs and financial capacity of each country and has thus ignored the opportunities to reduce the costs of treatment by developing innovative approaches to deliver medicines and other life-saving care.[17-19]

The response to the emerging challenge of chronic disease and NCDs in low- and middle-income countries has been inadequate. Cancer, and especially cancer in women, is a case in point. Recent studies have coined the term "cancer divide" to refer to the concentration of risk factors, incidence of preventable cancers, stigma, uncontrolled pain, and death and disability from treatable cancers in low- and middle-income countries as well as amongst the poor in both low- and middle-income countries and in high-income countries.[20]

The evolution over time and across countries of the two leading causes of cancer death in women – cancer of the cervix and of the breast, both associated with reproductive health – poignantly illustrates how low- and middle-income countries are faced with the equity challenges of responding to both the preventable and treatable aspects of disease.[21] Trends in women's cancers also highlight the equity imperative of meeting the challenge of cancer globally and closing divides between rich and poor. Further, the focus on these cancers recognizes the specific risks to women associated with their role in reproduction, and highlights the need for dedicated actions, particularly because diseases specific to women often receive delayed and lower quality care and are neglected in other health agendas, especially in low- and middle-income countries, where gender inequities are most pronounced.[21]

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This paper presents cross-country global data, historical data from specific countries and within-country data from Mexico to illustrate the cancer transition for women. The analysis focuses on the equity imperative of meeting the challenge of both diseases in the context of protecting and promoting the health of women over the life cycle. The first part describes the cancer transition as part of the epidemiological transition. The next section introduces the data used in the paper, followed by a discussion of the empirical results.

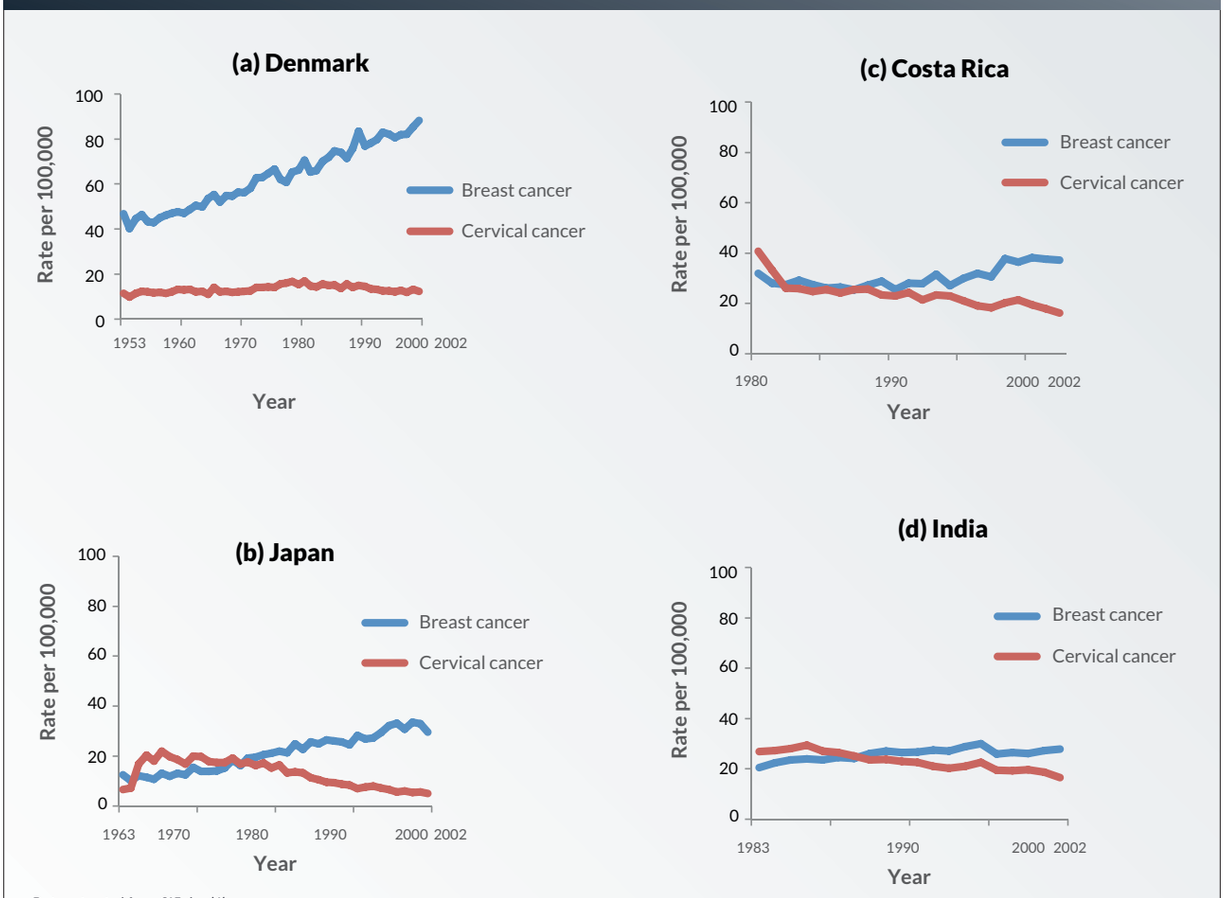
The findings highlight the need to develop integrated responses that consider and include both treatment and prevention interventions. They also indicate the importance of framing the challenges of the cancers of women within a life cycle approach that considers the risks of disease at different stages of their lifetimes.

Cancer transition

The epidemiological transition was originally put forward by Omran.[22] The decline in the incidence of communicable, reproductive and nutritional diseases and a rise in that due to NCDs and injury have been demonstrated empirically, most recently by the 2010 Global Burden of Disease Study (GBD).[1]

The GBD shows a global decline in communicable, maternal, neonatal and nutritional causes of death from 34.1% in 1990 to 24.9% of deaths in 2010.[1] By contrast,

Figure 1: **Trends in the incidence of breast and cervical cancer in selected populations: (a) Denmark, 1953–2002; (b) Osaka, Japan, 1963–2002; (c) Costa Rica, 1980–2002; (d) India (combined data from 2 population-based registries in Chennai and Mumbai, India), 1983–2002**



Data extracted from CI5plus (1)

deaths from NCDs rose sharply and consistently and now account for two out of every three deaths in the world. By 2010, approximately 54% of all DALYs were due to NCDs, compared to 35% from communicable, maternal, neonatal and nutritional disorders, and 11% due to injuries.[2]

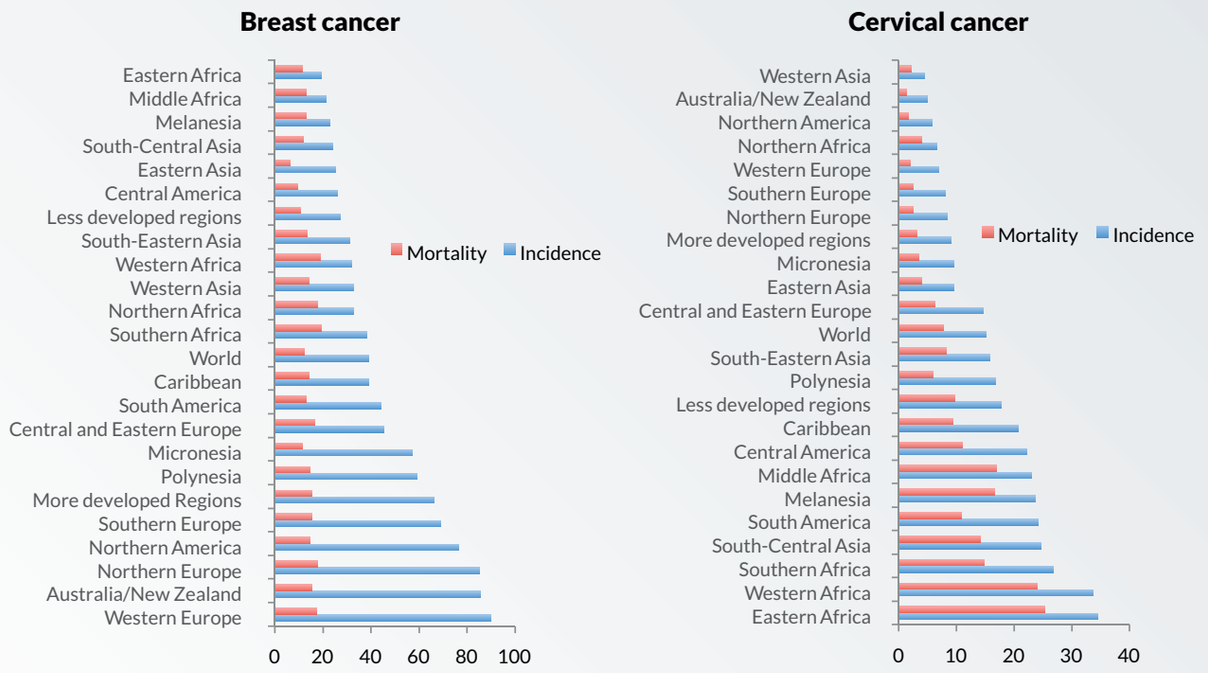
These shifts in the burden of disease have been particularly strong in low- and middle-income countries and the pattern of epidemiological transition facing these countries has been characterized as polarized and protracted.[23] These countries face the backlog of mortality and morbidity from infectious diseases and conditions associated with poverty and underdevelopment, together with an increasing burden of chronic disease and NCDs and injury.[23]

A cancer transition has also been documented. Overall cancer mortality has risen 38%[3] and incidence is projected to rise at twice the rate estimated for high-income countries.[24] The term "cancer transition" is used to describe a decline in wealthier parts of the world of many cancers of infectious etiology and a rise in cancers with no known connection to an infectious agent.[24] There are exceptions such as hepatocellular carcinoma which is increasing in high-income countries such as the Unites States due in part to alcohol consumption and Hepatitis B infection.[25-27] Although there is no specific relationship between the patterns across types of cancers or notion of competing risk – i.e. reductions in the burden of one type of cancer does do not necessarily leave large groups of populations at risk of other cancers – infection-associated cancers are emblematic of the overall decline in communicable, reproductive and nutritional causes of death, while increases in incidence and death from other cancers parallel the rise in NCDs.

The cancer transition tends to be associated with the socioeconomic development of populations both across and within countries and can also be characterized as polarized and protracted. Analogous to the overall epidemiological transition in low- and middle-income countries, several cancers are increasingly *only of* the poor, but these are *not the only* cancers faced *by* the poor.[20]

Cancers of women are illustrative of this transition. Cervical cancer, which is infectious in origin, is now and will

Figure 2: Incidence of, and mortality from, breast and cervical cancers by World region, 2008



Data extracted from GLOBOCAN (4) International Agency for Research on Cancer. GLOBOCAN 2008. Cancer incidence, mortality and prevalence worldwide in 2008. Available from: http://globocan.iarc.fr/

continue to be even more so as coverage of the HPV vaccine progresses, a disease that kills women living in poverty. The burden of breast cancer, by contrast, falls on women at all levels of income, yet the probability of death is greater if the woman is poor.[20] As is evident from Figure 2, while the incidence of breast cancer is several times higher in countries of high income, mortality rates are similar indicating that fatality is much higher in low- and middle-income countries.

Further, and particularly due to the relatively young age distributions of populations, a large group of young women face these cancers in low- and middle-income countries. Although the incidence of breast cancer typically increases with age, as a fraction of all women within this age group, it is twice as common in women under age 50 – often the primary custodians and caregivers of families including young children – in low- and middle-income countries as it is in high-income countries.[5,28] A recent study comparing four Latin American countries to the United States and Canada found similar results.[29] This generates a particular set of challenges related to maternal health and reproduction.

Data and methods

We use data from several sources – global cross-sectional data, historical data from a sub-set of countries and sub-national data from Mexico – to demonstrate the cancer transition for women by comparing mortality rates for cervical and breast cancer.

The global cross-sectional data are age-adjusted (to the world standard population) rates for the year 2008 extracted from GLOBOCAN (http://globocan.iarc.fr/). Historical trend data for specific countries are age-adjusted (to the world population) rates extracted from CI5plus (http://ci5.iarc.fr/CI5plus/ci5plus.htm).

The analysis for Mexico uses official mortality data published by the Ministry of Health. We use the sub-national series that spans 1979 to 2010 at the state level.[30] The state-level data aggregates over a wide range of municipalities, including both larger urban centres where access to health and other services tends to be better and levels of poverty less severe, and smaller, poorer municipalities with much less access.

These data are aggregated according to the index of deprivation (marginalization) developed and maintained by the National Population Council.[31] Mexico's five-category deprivation index differentiates the 32 states (federal entities) and municipalities according to the proportion of the population with low levels of education, residence in inadequate dwellings (without drainage, electricity or water, or characterized by overcrowding or earth flooring), low household monetary income and rural residence. The index,

which is derived from classifying the Mexico's approximately 2,500 municipalities that vary greatly in population and socioeconomic conditions, is closely aligned with the level of poverty. The most recent index was calculated in 2010, using census data, and the data presented below apply this categorization retrospectively to the entire time series of mortality data. Additional analysis was undertaken applying earlier indices by period with little change in the overall results.

Basic sensitivity analysis was also undertaken to take account of possible bias from misclassification of uterine cancer deaths. The trends over time are little affected by sensitivity analysis that reclassifies a proportion of deaths listed as cervix.[i]

Equity aspects of the women´s cancers transition

Both incidence and death from cervical cancer, a disease that can be prevented,[33] is increasingly concentrated among poor women. At the same time, the burden of breast cancer is rising in these same populations.

A recent analysis of the global burden of cancer in relation to the Human Development Index (HDI), showed that breast cancer incidence rates have been increasing in almost all regions in the world, irrespective of the level of economic development.[25,34] By contrast, the incidence of cervical cancer has been declining in most regions, including countries of both higher and lower income, with the exception of only the very poorest countries.[6,25] As a result of these diverging trends, breast cancer has now surpassed cervical cancer to become the most common female cancer in the majority of countries with the exception of some of the poorest countries where cervical cancer is still the most common cancer among women. Consequently, regions made up predominantly of low- and middle-income countries are facing a dual female cancer burden – their historically high and persisting incidence burden from cervical cancer as well as an emerging high incidence burden from breast cancer. As survival from both breast and cervical cancer are positively associated with level of socioeconomic development, a greater proportion of the mortality burden is also seen in less developed regions.

Long-run trend data on cancer incidence are sparse,[35] but existing information clearly demonstrates a cervical-breast cancer transition, which began in high income countries (i.e. in North America, Europe, Australia, New Zealand and Japan) and is now evident in low- and middle-income countries (i.e. all other regions). For instance, in Denmark, the age-adjusted incidence of breast cancer surpassed that of cervical cancer prior to the 1950s, with the differential growing due to the marked increase in breast cancer over the next five decades (Figure 1a). The cross-over in the age-adjusted incidence rates of these two cancers occurred much later in Asian and Latin American populations – e.g., only in the mid-1970s in Osaka, Japan (Figure 1b), during the 1980s in Costa Rica (Figure 1c), and in the early 1990s in urban India (Figure 1d).

The cervical-breast cancer transition, and its consequences, can now be clearly observed in Africa, where breast cancer has recently surpassed cervical cancer to become the most common female cancer in the continent.[36] Certain regions in Africa now have the added challenge of not only the highest incidence and the highest mortality rates from cervical cancer worldwide, but also the growing challenge of breast cancer. Though breast cancer incidence rates are lower than in wealthier countries, mortality rates are much higher due to late detection and lack of access to treatment (Figure 2).

In the case of Mexico, the women´s cancers transition for women from the mortality data that span the period 1955 to 2010[5,37] shows mortality from cervical cancer peaked at almost 17 per 100,000 women in the late 1980s and subsequently fell continuously, reaching a low of just close to 7.5 per 100,000 women in 2010. By contrast, breast cancer mortality rose steadily until the mid-1990s and has since remained stable at a rate of approximately 9.5 per 100,000 women. These rates converged between 2005 and 2006 and, since that point in time, breast cancer has been the leading cause of cancer death in women.

The equity aspects of the women's cancers transition in Mexico is most clearly seen by analyzing within-country trends. The 32 states are classified into five categories according to their level of marginality (a composite index of poverty and access to basic services where high marginality is associated with the greatest poverty). In the 1980s, the range in marginalization-specific absolute differences in cervical versus breast cancer rates was relatively small. This is largely because cervical cancer mortality rates had not yet peaked in the poorer states and because the middle-income states had not passed far into the transition. By the late 1980s, the overall pattern is quite clear: the absolute differences in the

[i] *There is some evidence of imprecise coding of uterine cancer deaths due to difficulties in identifying the origin of the cancer as cervix or corpus uteri.[32] This could bias our results by underestimating the number of deaths attributable to cancer of the cervix. This bias could be associated with poverty, as miscoding may be more likely where training and human resources for health are lower. Thus, basic sensitivity analysis was also undertaken by reclassifying uterine cancer deaths in women below age 50 as cervical cancer, the rationale being that cancer originating in the uterus is very uncommon in younger women. The trends over time are little affected by this reclassification.*

mortality rates between cervical and breast cancer increase steadily with marginalization. The states in the highest marginalization category had the greatest difference in C-V rates.

The challenge of the transition in women's cancers is further illustrated by analysing trends in mortality rates separately for cervical and breast cancers within Mexico at the sub-regional level. There is a clear progression in the cervical-breast cancer transition by category of state marginalization. In poorer states, cervical cancer continues to be the primary cause of cancer-related mortality for women, although the gap has narrowed significantly. In wealthier parts of the country, breast cancer is the dominant cause of death from cancer in women. In some states, this has been the case since the late 1980s (Figure 3). In states with the highest levels of marginalization (represented by Oaxaca), cervical cancer mortality rates continue to be almost double those of breast cancer, although the gap has closed substantially from the fourfold difference of the early 1990s. Indeed, in Oaxaca in the early 1990s, the difference between the cervical and breast cancer mortality rate reached up to fivefold with a high of close to 20 deaths per 100,000 women from cervical cancer compared to rates of breast cancer mortality of less than 5.

The smallest C-V (cervical-breast or C-V) differences occurred in the wealthiest states where the rates were close to inverting. In these states, the twofold gap that was evident in the early 1980s had closed by the early to mid-1990s. By 2008, the inverse was true: breast cancer mortality was approximately double that of cervical cancer with rates of over 13 per 100,000 for breast cancer compared to below 7 per 100,000 for cervical cancer. In the case of Nuevo León, one of the wealthiest states of Mexico, the crossover in mortality rates occurred prior to 1985.

In the two decades spanning 1990 to 2010, the relative levels of mortality for women's cancers in Mexico were driven by persistently higher levels of cervical cancer mortality in the poorer states. The women living in these states, the poorest in the country, continue to face a double cancer burden. Yet, deaths from cervical cancer are beginning to decline even in the poorer regions and the gap between rich and poor states for cervical and breast cancer mortality in Mexico will likely narrow further in the future. Over time, and especially with the recent introduction of national coverage of HPV vaccination to prevent cervical cancer, breast cancer will dominate both in incidence and mortality.[38]

The challenge of the transition in women's cancers is further illustrated by analysing trends in mortality rates separately for cervical and breast cancers within Mexico at the sub-regional level

Health systems must offer prevention, treatment and palliation responses that are appropriate to each disease. In the absence of efforts in vaccination, screening and treatment of precancer lesions, cervical cancer mortality will become a persistent burden restricted increasingly to the poorest countries and the poorest women

Conclusions and policy recommendations

The global cross-sections, historical data and within-country trends clearly illustrate the transition in women´s cancers. Low- and middle-income countries, and especially poorer women, face a double burden of cervical and breast cancer and strategies are required to meet the challenge of both diseases in the context of programmes that promote the health of women.

Health systems must offer prevention, treatment and palliation responses that are appropriate to each disease. In the absence of efforts in vaccination, screening and treatment of precancer lesions, cervical cancer mortality will become a persistent burden restricted increasingly to the poorest countries and the poorest women. It is a moral and equity imperative to prevent cervical cancer through HPV vaccination and screening for precancerous lesions, while offering treatment to those women affected by cervical cancer.

There is reason to hope that with increased community health measures for detecting and managing precancerous lesions of the cervix, and expanded coverage of the HPV vaccine, that cervical cancer mortality will continue to decline globally.[39] The remaining challenge is one of equity, and the imperative will be to ensure that cervical cancer does not become another neglected "tropical" disease of the poor.

At the same time, breast cancer is likely to increase and

Figure 3: **Trends in the mortality rate from cervical and breast cancer in Mexico by category of state marginality, 1979–2010**

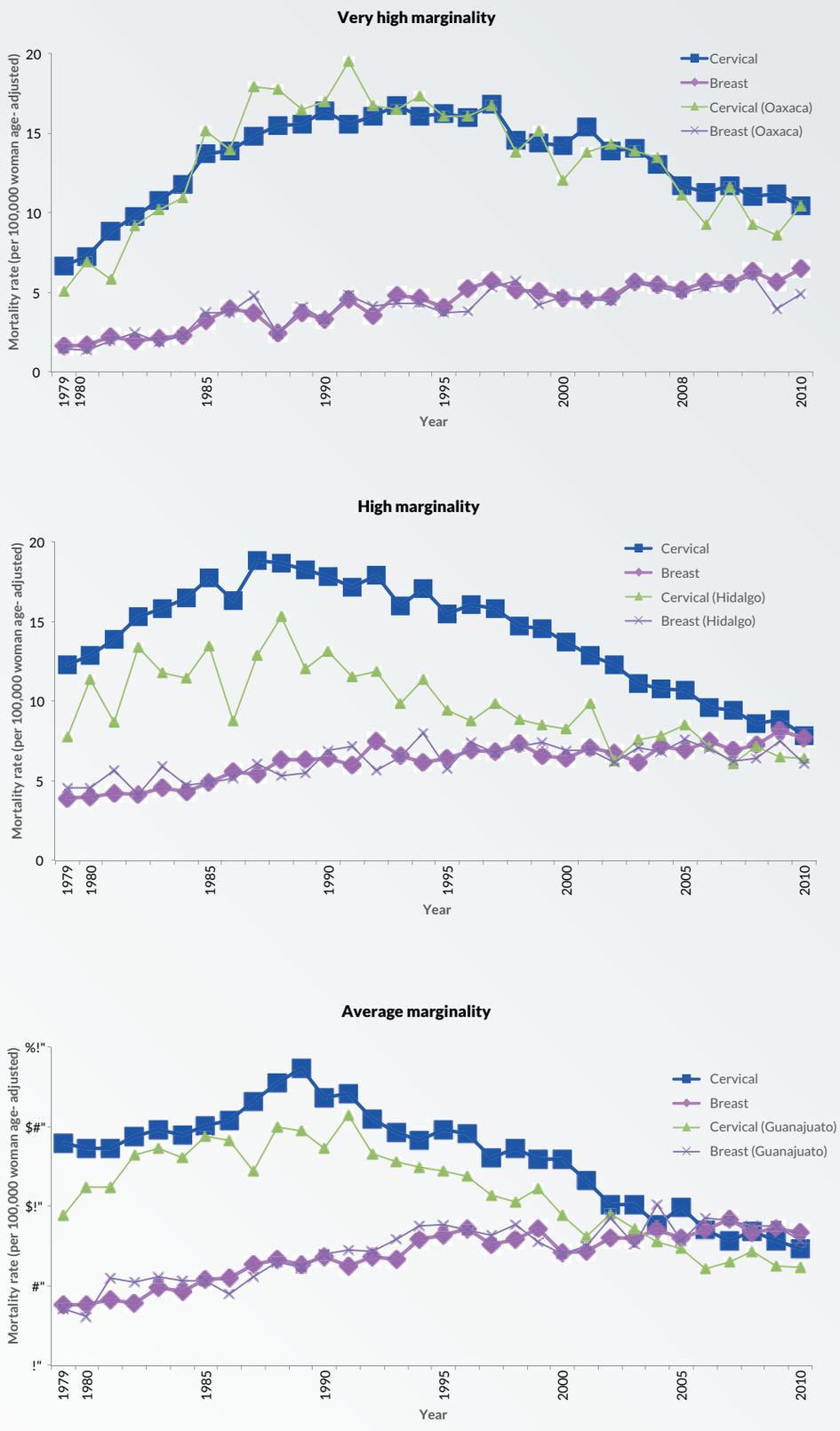
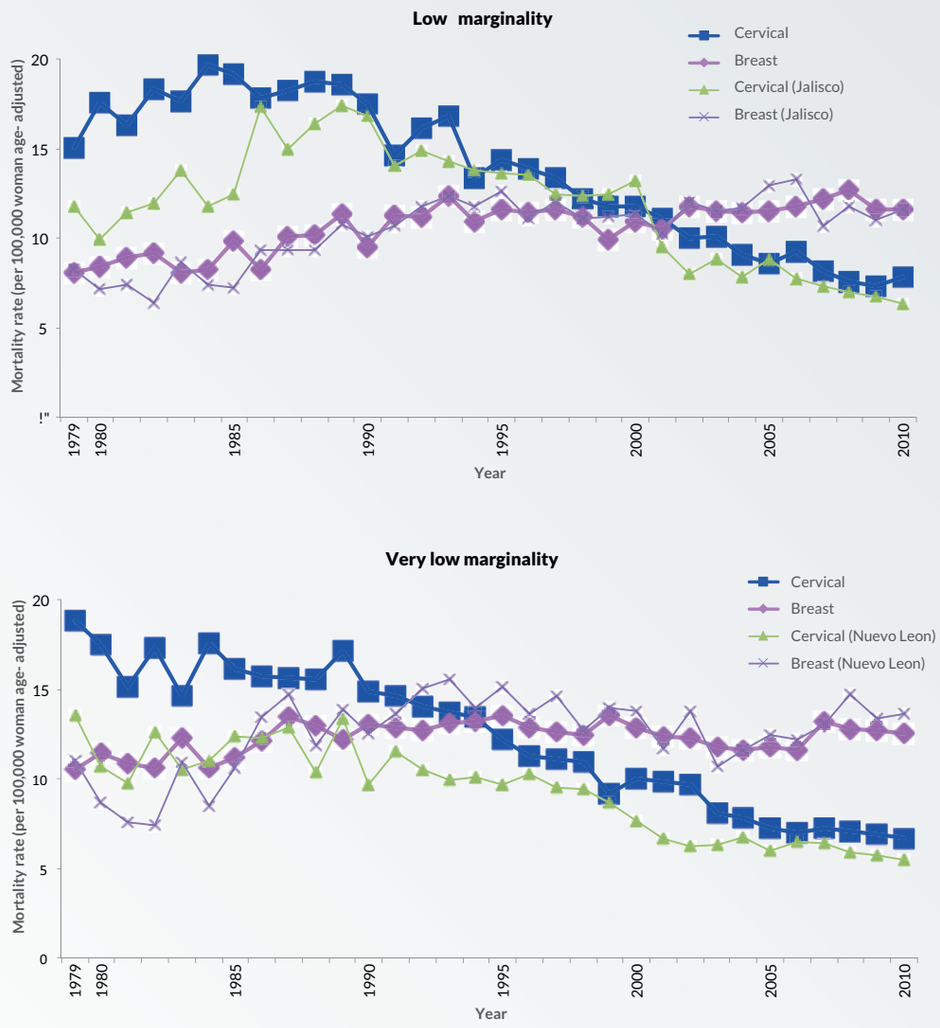


Figure 3: **Trends in the mortality rate from cervical and breast cancer in Mexico by category of state marginality, 1979–2010** continued



Notes: These data are aggregated according to the index of deprivation (marginality) developed and maintained by the National Population Council. Mexico's five-category deprivation index differentiates the 32 states (federal entities) and municipalities according to the proportion of the population with low levels of education, residence in inadequate dwellings (without drainage, electricity or water, or characterized by overcrowding or earth flooring), low household monetary income, and rural residence.

Source: Statistics based on data from Directorate General of Health Information (DGIS). Database of general deaths 1979-2010. [on line]: National System of Health Information (SINAIS). [Mexico]: Ministry of Health. < http://www.sinais.salud.gob.mx > and National Population Council (CONAPO). Deprivation index by State and Municipality 2010. [on line]: <http://www.conapo.gob.mx/es/CONAPO/Indices_de_Marginacion_2010_por_entidad_federativa_y_municipio>.

emerge as a major cause of mortality within these same populations. Future increases in life expectancy, as well as in the prevalence of risk factors related to the adoption of western lifestyles, will affect the incidence of women's cancers in low- and middle-income countries.[40] Even modest changes in reproductive behaviour, patterns in childbearing (reductions in the number of children, reduced age at menarche and increases in age at first birth and nutrition (obesity) – factors that are associated with increased economic and social development and improvements in the situation of women and are hence not easily reversible – can translate into substantial increases in the breast cancer burden in these countries.[41] Moreover, breast cancer is also associated with risk factors related to postmenopausal weight gain and alcohol consumption. Attempts to minimize risk factors and to maximize protective factors such as good breast-feeding practices[42] are important for reducing population-level breast cancer risk and these should be further studied and evaluated. These interventions will at the same time, support women's health across the life cycle.

While primary prevention can help to curb the rise in breast cancer incidence,[43] the effects will not be felt for several decades. In the case of breast cancer, the few known, population-based, preventive interventions must be

combined with early detection and treatment to mount an effective response to a cancer that is rapidly becoming a leading cause of death in low- and middle-income countries.

Resource stratified guidelines have been developed for breast cancer that offer alternatives for countries to make evidence-based decisions in setting priorities and these need to be applied and integrated into programmes for women´s health.[44] Indeed, if countries ignore the emerging challenge of breast cancer because it is not associated with a quick, preventive fix, we are likely to see the emergence of a gaping cancer divide. If early detection and access to effective treatment are denied to poor women, mortality will decline only among the rich countries and the wealthy, while continuing to increase among poor women.

For both cervical and breast cancer, there are important opportunities to apply a diagonal approach that will strengthen health systems and improve women's health and cancer care and control simultaneously.[5,18,41] This involves integrating key interventions on women´s cancers such as education and early detection, into maternal health, sexual and reproductive health and anti-poverty programmes that focus on women. It also requires promoting policy dialogue, research and international action that cut across false boundaries and silos such as those that have separated women on women's health with that on NCDs.[45]

Integrated approaches will help to meet the many facets of women's cancers that are related to motherhood, sexuality, menopause, and to face the barriers associated broader issues of discrimination against women. These actions can and should be effectively catalyzed through national and global strategies to curb not only the tide but also the swell of women's cancers as part of the larger, emerging challenge of chronic and non-communicable disease. •

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