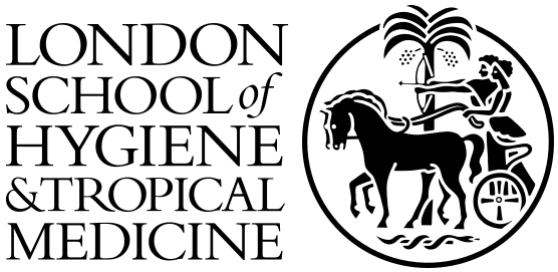

Breast cancer in women living with HIV: A first global estimate

V McCormack[1], O Febvey-Combes[1], O Ginsburg[2], I dos-Santos-Silva[3]

1 Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France
2 NYU Langone Medical Centre, New York, United States
3 London School of Hygiene and Tropical Medicine, London, United Kingdom

Corresponding author
Valerie McCormack, Section of Environment and Radiation, IARC, Lyon 69008, France. Tel + 33 4 72 73 85 66. Email: mccormackv@iarc.fr

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HIV, breast cancer, Africa

Abbreviations used

HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
WLWHA	Women living with HIV or AIDS

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Novelty and impact

Breast cancer is not a HIV-associated malignancy, but it occurs among women with as well as among women without HIV. Here we provide the first global and regional estimates of incident breast cancer in women with HIV. In 2012, more than 6000 women with HIV, most of them premenopausal women in sub-Saharan African, were diagnosed with breast cancer. Research into barriers to early diagnosis, care and outcomes is needed for this growing HIV-positive population.

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Abstract

There is a growing population of older women living with HIV/AIDS (WLWHA). Breast cancer is a common cancer in women worldwide, but the global number of breast cancers in WLWHA is not known. We estimated, for each UN sub-region, the number and age distribution of WLWHA who were diagnosed with breast cancer in 2012, by combining IARC-GLOBOCAN estimates of age-country specific breast cancer incidence with corresponding UNAIDS HIV prevalence. Primary analyses assumed no HIV-breast cancer association, and a breast cancer risk reduction scenario was also considered. Amongst 16.0 million WLWHA aged 15+ years, an estimated 6325 WLWHA were diagnosed with breast cancer in 2012, 74% of whom were in sub-Saharan Africa, equally distributed between Eastern, Southern and Western Africa. In most areas, 70% of HIV-positive breast cancers were diagnosed under age 50. Among all breast cancers (regardless of HIV status), HIV-positive women constituted <1% of the clinical burden, except in Eastern, Western and Middle Africa where they comprised 4 to 6% of under age 50 year old breast cancer patients, and in Southern Africa where this patient subgroup constituted 26% and 8% of breast cancers diagnosed under and over age 50 respectively. If a deficit of breast cancer occurs in WLWHA, the global estimate would reduce to 3600. In conclusion, worldwide, the number of HIV-positive women diagnosed with breast cancer was already substantial in 2012 and with an expected increase within the next decade, early detection and treatment research targeted to this population are needed.

Introduction

The evolution of the HIV epidemic, in particular with expansion of access to antiretroviral therapy, has resulted in an increase in the number of people living with HIV or AIDS (PLWHA) in middle and old age. Over age 50, this population has doubled since 1995 and, in 2013, UNAIDS estimated that it was between 4.0 and 4.5 of the 35 million PLWHA.[1] At these older ages, the risks and management of non-communicable diseases become increasingly relevant[2], including of cancers that are neither AIDS-defining nor HIV-associated. The latter cancers now constitute the majority of cancers in PLWHA in more developed settings,[2] which has spurred their epidemiologic and clinical research.[3]

A common malignancy worldwide, regardless of HIV prevalence, is breast cancer. Notably, this malignancy is the first or second most common cancer in women in all but 9 countries worldwide (Figure 1), including in the sub-regions of Southern, Eastern and Western Africa where 60% of women living with HIV or AIDS (WLWHA) aged over 50 years reside.

Several studies have documented breast cancer in WLWHA. These studies predominantly originated from North America and Europe,[4,5] especially since the widespread uptake of antiretroviral therapy (HAART). Notably, between 1991-95 and 2001-05, there was a ten-fold increase in the absolute number of breast cancers in the US AIDS population (men and women).[6] HIV-positive breast cancer patients have also been documented in South Africa,[7-9] including within a 2007-2011 breast cancer case series in Soweto's Chris Hani Baragwanath Academic Hospital which included 151 women co-affected by HIV and breast cancer.[7] The HIV-positive breast cancer patient population is expected to further increase in absolute size over the coming decades, assuming that access to HAART continues. It is thus timely to build the epidemiologic evidence base for breast cancer in WLWHA. Pertinent issues are diverse[10] and have begun to be addressed,[11,12] ranging from breast cancer awareness and early breast cancer detection in WLWHA, to clinical co-management of two diseases. The need for research on these issues will in part depend on the number of WLWHA affected by breast cancer. In the present study, amongst the 16 million WLWHA aged 15 years and over, we provide the first global estimates of the number of HIV-positive women who were newly diagnosed with breast cancer in 2012. We also examine their age and geographical distribution worldwide, and identify the settings where HIV-positive breast cancer patients constitute a substantial proportion of the breast cancer patient profile. Finally, a systematic literature review was conducted to assess the consistency of our estimates with published reports of HIV-positive breast cancer patients.

Methods

Breast cancers in WLWHA

We estimated the number of new breast cancers occurring in WLWHA aged 15 years and over in

2012, overall, by age, and UN sub-region. The basis of the primary estimation, which will be considered later, was to assume that there was no direct or indirect association between HIV and breast cancer risk, thus the number of HIV-positive breast cancers was calculated as the total number of breast cancers multiplied by the corresponding HIV prevalence in a given age-country stratum.

For each country, age-specific breast cancer incidence (number of new cases) in 2012 was sourced from IARC GLOBOCAN.[13] They were available for 184 countries or territories and in 5-year age bands: 15-19, 20-24, … , 70-74, and 75+ years. These estimates are of variable quality depending on the country, ranging from high quality cancer registries included in Cancer Incidence in Five Continents (CI5) with national, regional or low (<10%) coverage, to lower quality national rates, regional rates or frequency data. The methods for generating the GLOBOCAN estimates include either projections of most recently available incidence rates to the 2012 population, modelling of mortality, survival or mortality:incidence ratios, or weighted averages of local rates or of neighbouring countries' estimates.[13] For 158 of the 184 countries, corresponding age-specific HIV prevalence estimates for females were obtained from UNAIDS, which were estimated for a similar period, in 2013. For simplicity, from here on we refer to all derived combined estimates as for the year 2012. The estimates published by UNAIDS incorporate multiple sources of prevalence data (e.g. HIV prevalence surveys among the general population, prevalence among pregnant women, surveys among populations at increased risk of HIV), programmatic data as well as modelling assumptions. The latter depended on the type of HIV epidemic in a country, i.e. whether it was a generalized population epidemic (e.g. in most of sub-Saharan Africa), an epidemic concentrated in intravenous drug users (e.g. Eastern Europe and Central Asia) or if it was concentrated in other high risk populations (e.g. Asia or Latin America).[14] The modelled estimates of people living with HIV aged over 50 years were further validated against survey data. The 27 countries that did not have HIV prevalence data are listed in Supplementary Table 1; they are expected to have small HIV-positive populations, thus their omission here should be inconsequential.

To estimate HIV-positive breast cancers, the primary method assumed no association, either direct or indirect, between HIV and breast cancer risk for a given country and age stratum. This assumption was made because breast cancer is not a HIV-associated cancer; several studies in HIV-endemic areas have shown that the HIV prevalence among breast cancer patients is similar to that of the age-matched source population.[7-9] However, US investigations have shown a deficit of breast cancer in WLWAH, which could not be explained by potential differences in reproductive or other lifestyle factors. Most notably, incidence in the US HIV/AIDS Cancer Match study suggests a 42% breast cancer deficit in the US HIV-positive population.[15] Based on these latter observations, we also provide a lower worldwide estimate.

Literature review

To assess the degree of consistency of the present estimates with the previous literature, we systematically reviewed studies that have documented the occurrence of breast cancer in HIV-positive women either as part of breast cancer case series or breast cancers occurring in HIV cohorts. The review search identified articles containing the terms "cancer" and "HIV", through a literature search conducted with the US National Library of Medicine PubMed on 18th October 2017, and, so as to be relevant to the HAART era, it was restricted to articles published in English after 1st January 2000. This search yielded 760 results after excluding reviews and commentaries. These 760 publications were screened and deemed eligible if they reported on at least five HIV-positive women with breast cancer.

Statistical analysis

The GATHER checklist was followed for these global estimates (Supplementary Table 2). The primary estimates of breast cancers in WLWHA assume no association between HIV and breast cancer risk. In a given country i (i=1, . . ., 184 for all countries worldwide) and age group j (j=15-19,20-24, 25-29, … 70-74, 75+ years), we estimated the number of breast cancers in WLWHA (y_{ij}) as the number of incident breast cancers in women in that country-age stratum n_{ij} multiplied by the HIV prevalence proportion (p_{ij}) in that stratum: $y_{ij} = n_{ij}\, p_{ij}$. Breast cancers in WLWHA are presented by aggregating over age group j and UN world sub-regions[16] and based on these aggregate estimates, the proportion of all breast cancer patients who are HIV-positive was calculated as $y_{i.}/n_{i.}$ All analyses and graphics were performed in STATA version 14.0. In the presentation of results, sub-regional estimates are provided but not country-specific estimates, in line with conditions of use of the UNAIDS data.

We also considered the impact of uncertainties in the estimates of WLWHA and in the breast cancer - HIV association. For the former, uncertainty in the number of WLWHA at older ages is relatively small, of the order of ±5%[1], and for the latter, a 42% deficit of breast cancer found in the US HIV population[15]. We therefore also estimated a lower bound on the number of breast cancers in WLWHA, by multiplying estimates by (1-0.05)(1-0.42). An upper bound was not calculated because there is no suggestion of an excess of breast cancer in WLWHA.

Results

Global estimates of breast cancer in WLWHA

In 2012 worldwide, there were an estimated 16.0 million WLWHA worldwide (aged 15+ years). The highest HIV-prevalence proportions were in sub-Saharan Africa, which had 12.8 million (80%) of all WLWHA. At ages 15+ years, Southern Africa had the highest HIV prevalence (20.0%, 4.1 million

WLWHA). Despite much lower HIV prevalence of 5.4% in Eastern Africa (5.5 million WLWHA) and 2.5% in Western Africa (2.3 million WLWHA), these sub-regions also have large WLWHA populations. Other sub-regions had low (<1%) HIV prevalence, but WLWHA populations were still substantial in size in North America (0.28 million), South America (0.37), Eastern Europe (0.39), South Eastern Asia (0.62) and South Central Asia (0.8). Most WLWHA over age 15 in each sub-region were young, with only 5.0 million WLWHA (31%) aged 40+ years. Breast cancer ranked amongst the top three cancers in women in all sub-regions (Figure 1).

The age-structure of the WLWHA population and corresponding age-specific breast cancer incidence rates are shown in Figure 2, for eight sub-regions were there were at least 100,000 WLWHA over age 15 years, and all other sub-regions combined. The overall pattern is one of relatively low breast cancer incidence rates in regions with large populations of WLWHA. For example, in Eastern Africa, the sub-region with most WLWHA, breast cancer incidence rates were relatively low compared to world averages, giving an estimated 1563 breast cancers in HIV-positive women. Because breast cancer incidence rates were higher in Southern Africa and, at older ages, in Western Africa, those two sub-regions had nearly as many HIV-positive breast cancers as Eastern Africa despite fewer WLWHA (Figure 3, Supplementary Table 3). Outside of sub-Saharan Africa, breast cancer incidence rates were high at old ages (>60 years) in certain sub-regions, e.g. Northern America and Europe, but these population groups have small populations of WLWHA. Consequently, an estimated 6325 breast cancers occurred in WLWHA in 2012 worldwide (Supplementary Table 3), of which 75% were in sub-Saharan Africa, and outside this sub-region, Northern America, South Central Asia and South America also each had over 200 such women. Under the scenario of a breast cancer deficit, total number of breast cancers in WLWHA worldwide would reduce from 6325 to 3610 (not considered further).

The majority (70%) of HIV-positive breast cancers were diagnosed below age 50, most at 35-49 years, whilst in North America only 43% occurred at these ages (Figure 3), which reflects the younger age structure of the HIV-positive population. The proportion of breast cancer patients who were HIV-positive – a key indicator for health planning and resource allocation – is shown, by sub-region and age, in Figure 4. These proportions are very low (<1%) in every sub-region, except, under age 50 in the Caribbean (1%), in Middle, Western and Eastern Africa (4-6%), and Southern Africa (26%), and, over age 50, in Eastern (3.2%) and Southern Africa (7.6%).

Literature review

Table 1 lists published studies worldwide that have documented the occurrence of breast cancer in at least five HIV-positive women. Unsurprisingly, most studies originated from sub-Saharan Africa and

the US, i.e. locations with considerable patient populations and/or research infrastructure. In these publications, amongst breast cancer series the range of HIV-prevalence in Southern (11% to 32%), Eastern (11 to 14%) and Western Africa (≤5%) are in line with our estimates, whilst elsewhere the low HIV prevalence in unselected breast cancer patients required study designs other than breast cancer case series, i.e. mostly HIV cohorts. Mean/median age at breast cancer diagnosis amongst those who were HIV-positive ranged from 37 to 48 years in all studies with the exception of a US study of 43 women (median 53 years). HIV-positive breast cancer patients were diagnosed at younger ages than their HIV-negative counterparts, in line with our global estimates.

Discussion

Using country-level estimates of HIV prevalence and breast cancer incidence from UNAIDS and IARC-GLOBOCAN respectively, we estimated the worldwide burden of new breast cancers in WLWHA to be 6300 in 2012, 75% of which occurred in Southern, Eastern and Western Africa. Because the HIV-positive population has a young age structure, 75% of this patient population was diagnosed at ages 35-54 years. Although Southern Africa has a smaller population of WLWHA than Eastern Africa, the two sub-regions each had one-quarter of patients due to higher breast cancer incidence rates in the latter sub-region. Under the scenario that a deficit of breast cancer occurs in WLWHA, as has been observed in the US, the worldwide burden would be nearer 3600.

The size of this patient population is already appreciable in absolute terms. Ranking countries worldwide by the number of incident breast cancers in 2012, the WLWHA population would rank 38th out of 184 countries (i.e. 80th percentile), with a total breast cancer incidence similar to that of Sweden. In comparison with the AIDS defining malignancy, Kaposi Sarcoma (KS), for every 5 women with KS, there were an estimated 2 breast cancers in WLWHA.[17] Further, this absolute incidence burden is expected to increase in size over the next 1-2 decades, owing to ageing of the current HIV population and to an additional 1 million women newly diagnosed with HIV each year. However, we deliberately did not attempt to predict the future burden, because of the uncertainties around several parameters, including continued access to HAART and the breast cancer risk factor profile of the young HIV-positive population.

These global estimates of the HIV-positive breast cancer patient population are subject to an assumption of no HIV-breast cancer risk association. This assumption is supported by three sub-Saharan African studies, where the HIV prevalence among breast cancer patients was similar to that of the age-matched source population.[7-9] These studies were conducted in South Africa, and included patients diagnosed both in the pre-HAART[9] and post-HAART era[7,8]. Lending further plausibility to this assumption, for a given setting, our estimated HIV-prevalence among breast cancer patients was

consistent with the published studies from that sub-region, as reviewed. Together, these suggest that the deficit of breast cancer in HIV+ women in the US may not be a universal feature of WLWHA. However, further studies on the HIV-breast cancer risk link in HIV endemic areas are needed, as few have been able to examine how incidence is affected by HIV directly or through indirect pathways, e.g. due to altered distributions of breast cancer risk factors such as parity, age at first birth and breast feeding. The US results may also differ to African findings as the former are set within populations regularly screened for breast cancer, some of which are over-diagnoses, whereas in most HIV endemic sub-regions almost all breast cancer patients are diagnosed at symptomatic stages.

The estimates are also limited by uncertainties in HIV prevalence data and, especially, in breast cancer incidence data. GLOBOCAN estimates have larger uncertainties in some HIV-endemic countries in sub-Saharan Africa as the region has few population-based or other cancer registries. Notably, of 54 African countries/territories listed in GLOBOCAN, only seven had high-quality data (four in North Africa and three in countries with a high HIV prevalence). The large populations of Nigeria, South Africa and Ethiopia had lower quality national cancer incidence data, and in twenty, mostly smaller, countries data from neighbouring countries were used to generate national cancer incidence estimates. Nevertheless, the GLOBOCAN estimates are well-recognized as the most accurate data-driven estimates currently available.

An opportunity and need exists to improve outcomes for HIV-positive breast cancer patients facing two chronic diseases. Where the majority of this patient population lies, in sub-Saharan Africa, breast cancer is typified by an advanced stage distribution at diagnosis and poor survival.[18] Prolonged intervals to diagnosis are a major contributor to late stage,[19] but for WLWHA, their established contact with the health system for HAART medication offers an opportunity to educate about breast and other cancers, to encourage early presentation, and ensure referral, diagnosis and treatment not only of AIDS-associated malignancies, but also of other common cancers. Similar to the integration of cervical cancer screening into HIV clinics,[20] this contact provides a valuable opportunity for breast health awareness, education and early presentation in order to minimize delays to diagnosis, achieve early stage diagnosis and ultimately improve survival, should breast cancer arise. Examples of such programs include the Swaziland Breast and Cervix Cancer Network and the Tanzania Health Promotion Support group's program, which provide HIV testing, cervical inspection by visual inspection with acetic acid (VIA) and referrals for suspected breast cancer via a mobile clinic. However, in the context of the younger patient and the sub-Saharan African setting, benign breast disease, tuberculosis and, occasionally, Kaposi sarcoma of the breast add to diagnostic challenges. Turning to higher-income countries, attendance of breast cancer screening amongst WLWHA was higher than that of the general population in France,[21] but lower in Ontario, Canada,[22] thus a setting-

specific evaluation of early-diagnosis interventions needed in WLWHA is warranted.

In the sub-Saharan African region, where 75% of HIV-positive breast cancer patients live, breast cancer survival rates are generally some of the lowest worldwide. For HIV-positive and HIV-negative women combined, 5-year breast cancer survival estimates are 24% in Nigeria, 46% in Ethiopia, and 64%/80% in black/white South Africans,[23-26] which compare to over 85% in the US.[27] Moreover, HIV-positive breast cancer patients have lower survival than their setting-matched HIV-negative counterparts. A study in the US revealed excess all-cause mortality in HIV-positive breast cancer patients relative to women with only one of the two diseases.[28] Moving to sub-Saharan Africa, there are two relevant survival studies. In the Uganda Cancer Cohort, 24 HIV-positive women with breast cancer had 2-fold increased mortality rates (hazard ratio 2.04; 95% CI 0.76, 5.47) compared to HIV-negative breast cancer women,[29] whilst in 88 HIV-positive breast cancer patients in Soweto, a non-significant increased mortality rate was seen (hazard ratio 1.4) relative to their HIV-negative counterparts.[30] In addition to further survival studies, research needs to address side-effects and survivorship, with relevant studies currently underway[12,19]. Clinically, concerns have been raised related to delays in initiating primary or adjuvant chemotherapy in highly immuno-suppressed patients, HAART-chemotherapy interactions, and a higher incidence of intolerance to, and side-effects of, chemotherapy, including chemotherapy-induced neutropenia[31], which are often exacerbated in the HIV-positive cancer patient.[3] In palliative care patients in South Africa and Uganda, Selman et al. found lower quality of life in HIV-positive patients than in cancer patients, and lack of psychosocial support mechanisms for the small proportion of women with both diagnoses.[32] Some countries such as Uganda have prioritized palliative care for HIV and cancer patients.

In conclusion, the estimated 6300 new breast cancer patients diagnosed in 2012 amongst women living with HIV is substantial. Research that addresses the impact of these combined comorbidities along the entire patient journey for both diseases is warranted in the settings we identified here.

Contributions: VM conceived the idea for the study. OF and VM performed statistical analyses. VM, IdSS, OF and OG contributed to the interpretation and writing.

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Table 1: Reports published since 2000 of at least 5 HIV-positive women with breast cancer, in (A) studies of breast cancer or of all cancer types, and (B) HIV cohorts.

Continent, sub-region Country, location/study, First author (sorted by sub-region alphabetically and by decreasing no. of HIV-positive breast cancers)	Year of breast cancer diagnosis	No. of women in breast cancer series (A) or in cohort (B)	No. HIV-positive women with breast cancer (% of all breast cancers)	Median/mean age at breast cancer diagnosis in WLWHA; all
A. Cancer or breast cancer focused studies (case series/case-control studies)				
Africa, Eastern Africa				
Uganda, ABC-DO, McKenzie[19]	2014-17	439	49 (11)	45; 48
Zambia, ABC-DO, McKenzie[19]	2014-17	251	36 (14)	45; 50
Uganda, Coghill[29]	2003-10	220	24 (11)	-
Africa, Southern Africa				
S. Africa, Soweto, Cubasch[7]	2006-12	1092	151 (14)	44; 55
Namibia, Windhoek, McKenzie[19]	2014-17	503	56 (11)	47; 54
S. Africa, Johannesburg, Sitas[9]	1995-99	687	43 (6)	-
S. Africa, Pretoria, Phakathi[8]	2009-14	161	31 (19)	-
S. Africa, Cape Town, Langenhoven[33]	2010-11	586	31 (5 to 7)	42; 56
S. Africa, Durban, Ngidi[31]	2012-15	65	21 (32)	41; 49
Africa, Western Africa				
Guinea, Conakry[34]	2007-12	278	14 (5)	37; 49
Nigeria, Aba/Owerri, McKenzie[19]	2014-17	462	11 (3)	43; 46
Benin, Ivory Coast, Niger, Togo, Jaquet[35]	2009-12	294	17 (6)	-
America, Northern America				
US, New York, Parameswaran[36]	1996-2011	*	52 (*)	-
US, Miami Jackson Memorial Hosp. Gomez[4,37]	1989-2013	*	47 (*)	46; -
US, Baltimore-Washington, Presti[38]	2004-14	3012	43 (1)	53; 60
US, Harlem, Oluwole[39]	1995-2008	600	11 (2)	-
B. HIV-focused studies (predominantly cohorts)				
Africa, Eastern Africa				
Uganda, Kyadondo county, Mbulaiteye[40]	1989-2002	8423*	15	-
Africa, Western Africa				
Nigeria, Abuja, Akarolo-Anthony[41]	2009-12	10580 (8/8)	16	-
America, Northern America				
US, HIV Cancer Match Study, Shiels[6]	2001-05	419137 py	337	-
AIDS	2004-07	276702 py	203	-
AIDS	2004-07	284504 py	166	-
HIV	1996-2010	NA	108	-
US, Connecticut, Michigan, Texas, Suneja[42]	-	NA	23	46;-
US, WIHS, HERS HIV cohorts, Hessol[43]	2000-10	NA	17	48; 55
US, Maryland, Singh[44]	2002-10	699	5	46
US, New Orleans, Ruiz[45]	1996-2008	902	5	-
Canada, British Columbia, Chiu[46]				
America, South America				
Brazil, Rio de Janeiro, Andrade[47]	1996-2009	860	9	46
Europe				
France, ONCOVIH study, Spano,[5] Lanoy[48]	2006	~93100**	19	44
Italy, Brescia Calabresi[49]	1999-2009	5253**	9	42
Italy, MASTER cohort, Gotti[50]	1998-2012	13388**	30	42
Southern Asia				
India, Pune, Godbole[51]	1996-2008	-	68 (23 prevalent)	-
Eastern Asia				
China, Beijing, Yang[52]	2008-13	399	6	-

* Design factor: percentage not provided if this was a fixed factor by design; NA – not provided in the original publication or not relevant; **men and women; py=woman-years;

Figure Legends

Figure 1: Rank of breast cancer amongst new cancers in all women, by country, 2012. Source: IARC Globocan

Figure 2: Sub-region-specific age distribution of WLWHA and corresponding age-specific breast cancer incidence rates in 2012 (equivalent worldwide rates are also shown for comparison). Regions with over 100,000 WLWHA over age 15 are shown, and the remaining sub-regions are combined in 'other' (Western, Northern and Southern Europe, Northern Africa, Central America, Western Asia, Melanesia, Polynesia, Micronesia and Australia/New Zealand).

Figure 3: A. Total and age-specific number of women age 15+ years living with HIV/AIDS, by UN sub-region. B. Estimated number of breast cancers in women living with HIV/AIDS in 2012, by UN sub-region.

Figure 4: Age-specific percentage of newly diagnosed breast cancer patients who are HIV-positive, by UN sub-region.

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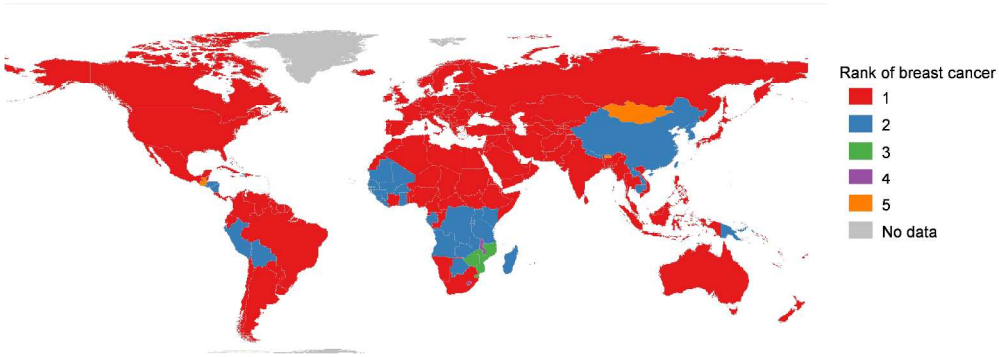

Figure 1: Rank of breast cancer amongst new cancers in all women, by country, 2012. Source: IARC Globocan

891x322mm (120 x 120 DPI)

Figure 2

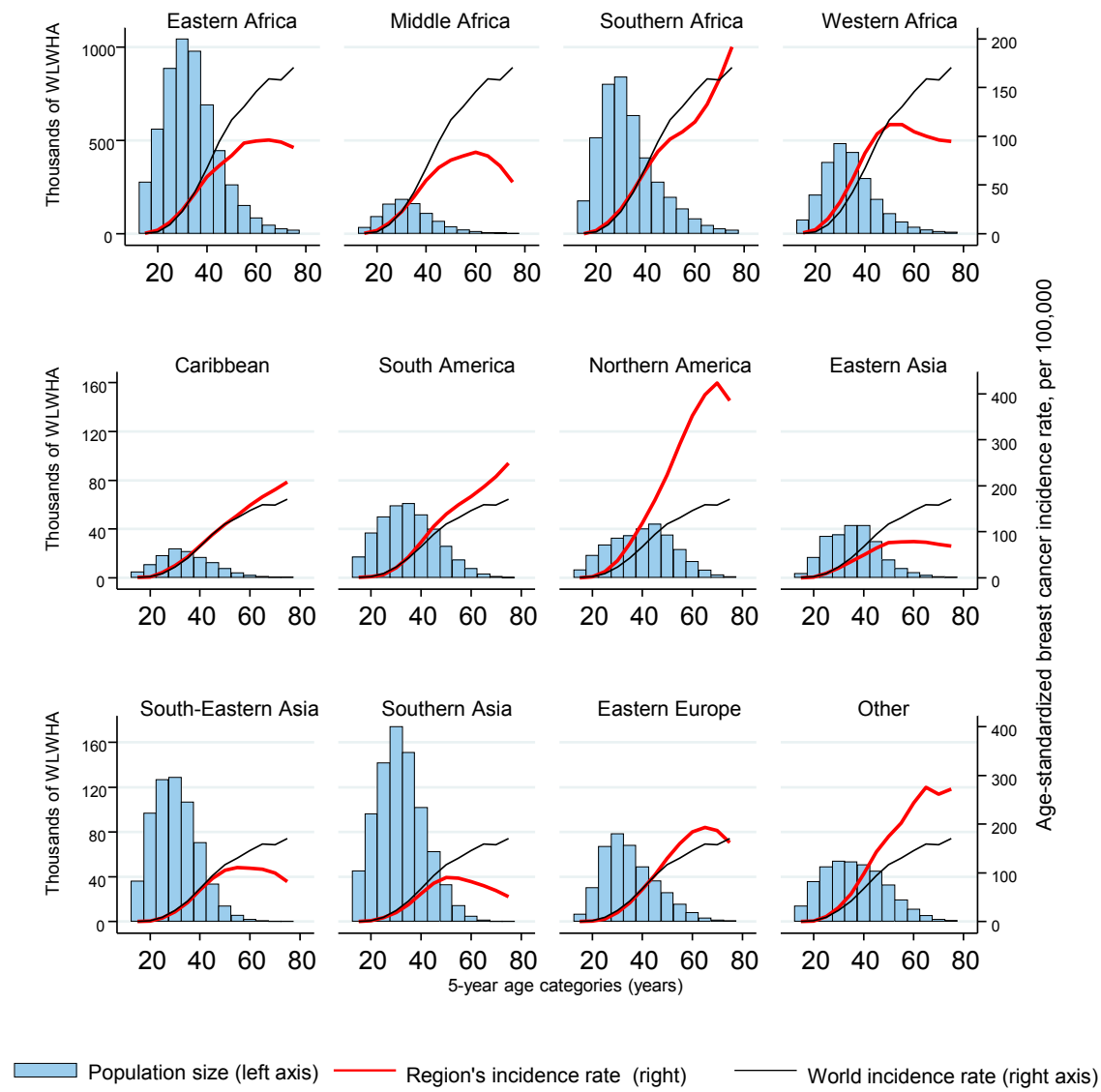

Figure 3

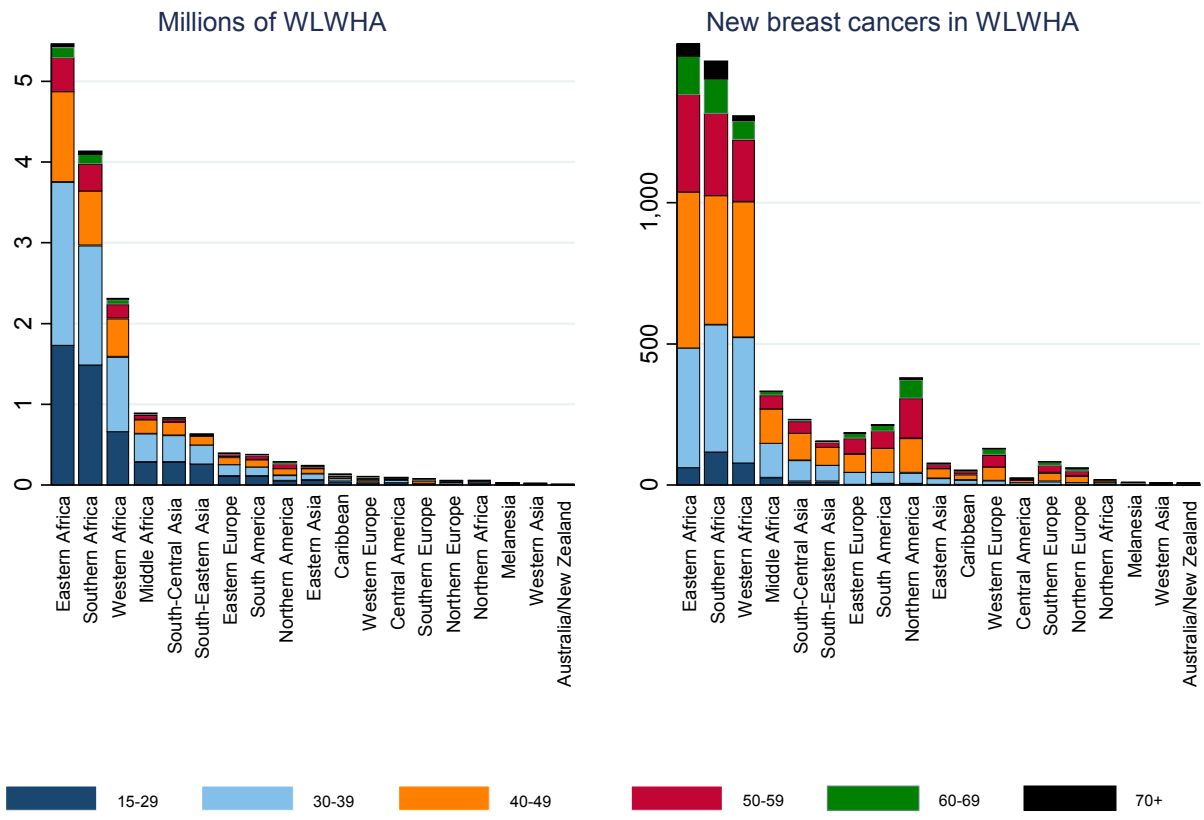

Figure 4