COMMENTARY

Epidemiology and Clinicopathology of Breast Cancer in Metro Manila and Rizal Province, Philippines

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Abstract

The breast cancer incidence in the Philippines is among the highest in Asia. Age-standardized incidence rates (ASR) in Metro Manila and Rizal Province derived from the Philippine Cancer Society-Manila Cancer Registry and the Department of Health-Rizal Cancer Registry showed increase from 1980 to 2002, and were significantly higher in 7 cities in Metro Manila and significantly lower in 14 cities/municipalities mostly in Rizal Province. The AJCC Clinical Stage did not change from 1993 to 2002 among incident cases, the average distribution being: I=5%, IIA=20%, IIB= 18%, IIIA=9%, IIIB=10%, IV=11%, Unknown=28%. The International Agency for Research on Cancer attempted to run a randomized screening trial in 1995-1997 in the Philippines based on clinical breast examination by trained nurses and midwives. Unfortunately, even after home visits by a team equipped to perform needle biopsy, only 35% of screen-positive cases eventually had a diagnostic test. The estimated prevalence of BRCA mutations among unselected patients in the Philippine General Hospital (PGH) in 1998 was 5.1%, with a prevalence of 4.1% for BRCA2 mutations alone. There is a continuing effort at improving IHC hormone receptor testing at PGH, particularly on early fixation in buffered formalin. It was observed that hormone receptor-positive proportions tended to be higher in core needle biopsy specimens (72%) compared to mastectomy specimens (65%). During the years 1991, 1994 and 1997, 97% of incident cases of early breast cancer underwent modified radical mastectomy, 18% had postoperative radiotherapy, 51% had adjuvant hormone treatment and 47% received adjuvant chemotherapy. Survival of incident cases in 1993 to 2002 was compared to that of Filipino-Americans and Caucasians in the SEER 13 database. The age-adjusted 5-year relative survival, using period analysis, of Metro Manila residents, Filipino-Americans and Caucasians were 58.6%, 89.6% and 88.3% respectively.

Key Words: Breast cancer - incidence trends - treatment - epidemiology - Philippines

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Introduction

International agencies are in agreement that the global cancer burden will continue to increase, and that the greater proportion of the increase will occur in developing countries. Breast cancer has been for decades the most common cancer among women in developed countries and is now also the leading female cancer in most developing countries (Curado et al., 2007). The incidence is expected to increase, mainly due to decreasing fertility and "westernization" of lifestyles.

An increase in breast cancer survival had been observed in some developed nations, and was mainly attributed to earlier detection and appropriate adjuvant treatment of early breast cancer. This is unfortunately not the case in many developing countries. This review was conducted to assess the available epidemiologic and clinicopathologic information on breast cancer in a developing country, the Philippines.

Incidence and Incidence Trends

Two population-based cancer registries, the Department of Health – Rizal Cancer Registry (DOH-RCR) and the Philippine Cancer Society – Manila Cancer Registry (PCS-MCR), have been generating incidence data since the 1980s, and had contributed to the Cancer Incidence in Five Continents (CIFC) of the International Agency for Research on Cancer starting with Volume V (CANCERMondial http://www-dep.iarc.fr/). The

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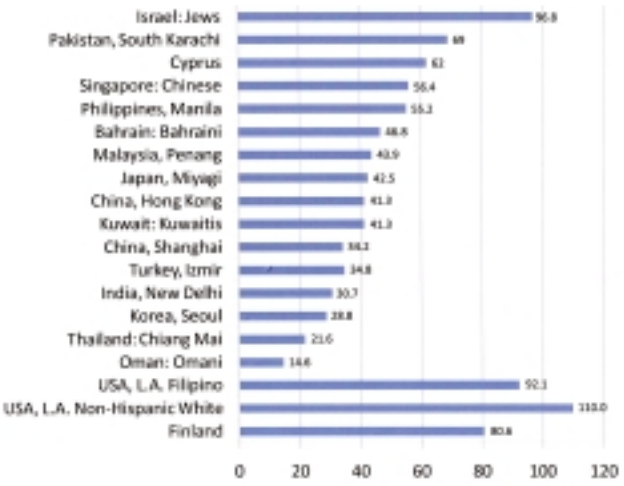

Figure 1. Age-adjusted (World) Incidence Rates of Female Breast Cancer per 100,000 in Asian Cancer Registries, U.S.A. Filipino and Non-Hispanic White Women in Los Angeles, and in Finland (Curado et al, 2007).

registries cover an area of 1,978 square kilometers with a population of 11.2 million (2000 Census). The area includes the city of Manila, the historic and current capital city, and surrounding highly urbanized and rapidly urbanizing cities and municipalities which are now collectively known as Metro Manila, also called the National Capital Region (NCR). To the east are the rural municipalities of Rizal Province. During the period 1998-2002, the overall age-standardized rate (ASR) was 52.2 (PCS-MCR 56.1, DOH-RCR 48.8) (Redaniel et al., 2008). Figure 1 shows that the Philippine ASR was lower than the chosen American, Finnish and Israeli populations, but higher than many other Asian populations. The ASR of Filipino-American residents in Los Angeles, U.S.A. was much higher than that of Filipinos residing in the Philippines (Curado et al.,2007).

Figure 2 shows that temporal-spatial maps reveal that the 1980-1984 ASRs had increased to those of 1998-2002, with the greatest increases seen in the city of Manila and some adjoining cities (Laudico et al., 2008). Figure 3 illustrates the wide variance in 1998-2002 ASRs, with the cities of Manila, Quezon, San Juan, Mandaluyong, Makati, Pasig and Parañaque having significantly higher ASRs. The rates decrease eastward, with significantly lower rates seen in the rural areas of Rizal province (Redaniel et al., 2008).

Table 1. Numbers of Breast Cancer Cases and Controls, Odds Ratios and 95% Confidence Limits by Numbers of Full-term Pregnancies. From the nested case-control study of the IARC trial on clinical breast examination screening in Metro Manila and Rizal Province, Philippines, 2000-2001, OR estimates by uncontrolled logistic regression (Parkin et al., 2002)

Pregnancies	No. Cases	No. Controls	OR	95% CI
Nulliparous	25	115	3.3	1.6-6.7
1-2	30	161	2.7	1.4-5.4
3	16	161	1.3	0.7-3.1
4-5	23	244	1.3	0.6-2.6
≥6	14	193	1.0	
Unknown	15	104	2.2	0.9-5.0

Two factors may partially explain the variance – parity and internal migration. Many reports had consistently demonstrated that decreasing parity increases breast cancer risk, and vice versa. Table 1 shows that the nested case-control study in the International Agency for Research on Cancer (IARC) trial on clinical breast examination screening in Metro Manila and Rizal Province (2000-2001) revealed an Odds Ratio (OR) of 3.3 (95% CI 1.6-6.7) among nulliparous women compared to an OR of 1 among women with 6 or more full-term pregnancies (Parkin et al., 2002). The city of Manila had been home to the country's elite and middle class since the Spanish Colonial era. Manila was devastated during World War II, and the 1950s saw the beginning of massive real estate developments in the "suburbs", in the form of gated subdivisions and other forms of housing for the wealthy and middle class families. This started in Makati and Quezon City, followed by those in Mandaluyong, San Juan, Pasig and Parañaque. This massive housing

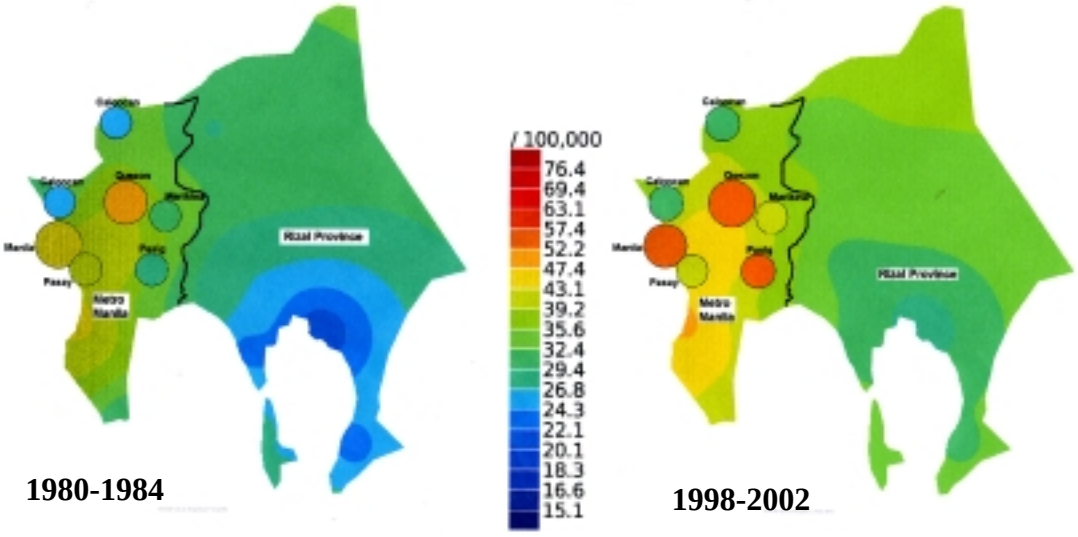

Figure 2. Age-adjusted (World) Incidence of Female Breast Cancer per 100,000 Person- years in Metro Manila and Rizal Province, by Period (Laudico et al, 2008)

Table 2. Distribution of 1,615 Incident Breast Cancer Patients by the American Joint Commission on Cancer (AJCC) Stage and Diagnosis Year, Metro Manila, Philippines, N (%)

Stage (AJCC)	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	Total
I	6 (4.1)	9 (5.7)	7 (4.2)	8 (4.8)	8 (5.4)	6 (3.3)	13 (9.9)	11 (6.1)	6 (3.4)	8 (5.0)	82
IIA	19 (13.0)	26 (16.6)	23 (13.9)	35 (21.1)	30 (20.1)	36 (19.7)	29 (22.1)	45 (24.9)	46 (25.8)	29 (18.2)	318
IIB	29 (19.9)	23 (14.7)	25 (15.2)	23 (13.9)	21 (14.1)	36 (19.7)	22 (16.8)	27 (14.9)	33 (18.5)	44 (27.7)	283
IIIA	11 (7.5)	13 (8.3)	13 (7.9)	14 (8.4)	9 (6.0)	17 (9.3)	18 (13.7)	12 (6.6)	23 (12.9)	13 (8.2)	143
IIIB	16 (11.0)	15 (9.6)	13 (7.9)	20 (12.1)	16 (10.8)	20 (10.9)	9 (6.9)	14 (7.7)	23 (12.9)	10 (6.3)	156
IV	14 (9.6)	17 (10.8)	17 (10.3)	21 (12.7)	17 (11.4)	26 (14.2)	14 (10.7)	22 (12.2)	23 (12.9)	13 (8.2)	184
Unknown	51 (34.9)	54 (34.4)	67 (40.6)	45 (27.1)	48 (32.2)	42 (23.0)	26 (19.9)	50 (27.6)	24 (13.5)	42 (26.4)	449
Total	146	157	165	166	149	183	131	181	178	159	1,615

development did not occur in Caloocan, Malabon, Navotas, Pasay, Las Piñas and Pateros. Although income-city-specific fertility rates over time may not be available, it is surmised that fertility rates in the high incidence areas had decreased with increasing prosperity, relative to the lower incidence areas. Lifestyle changes are also usually more substantial and rapid among the more affluent. This housing boom and resulting migration of wealthy and middles class families has continued, and now involves the cities of Marikina, Cainta, Taguig, Las Piñas amd Muntinlupa, and an increase in breast cancer incidence can be expected in the future.

Screening and Clinical Stage

The IARC attempted a population-based randomized screening trial (1995-1997), using Clinical Breast Examination (CBE) by trained nurses and midwives, involving 12 municipalities (202 health centers), and randomized by municipalities. Out of 151,168 women interviewed and offered CBE, 3,479 were found to have lumps (screen positive) and were referred to identified outpatient clinics. Only 21% spontaneously complied. Home-visit teams, composed of a doctor and nurse equipped to perform needle biopsies, were formed, but 42% of visited screen positive women actively refused needle biopsy. Only 1,220 women (35%) eventually had a diagnostic test.

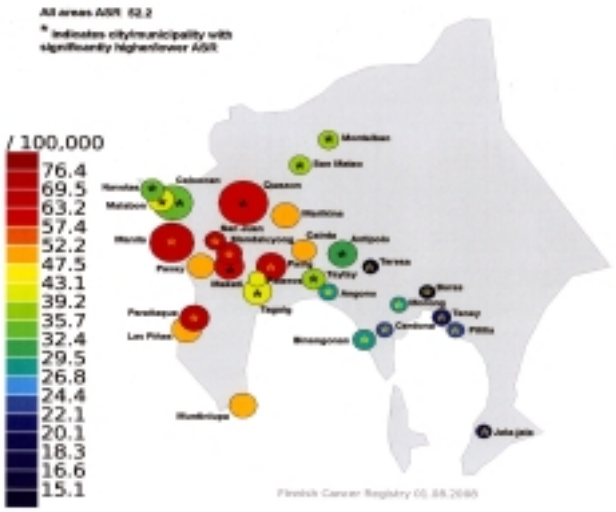

Figure 3. Age-adjusted (World) Incidence of Female Breast Cancer per 100,000 Person- years in Metro Manila and Rizal Province for 1998-2002 (Laudico et al, 2008)

The unexpected result that jeopardized the whole intervention was the unforeseen reticence of women found to have abnormalities and informed of the implications to their life, to pursue diagnosis and treatment. The authors also suggested that lack of trust in the health system and in one's chances to be cured may discourage action. (Pisani et al., 2006). It is thus not unexpected that the stage distributions of breast cancer have not changed significantly during 1993-2002 (Table 2). The proportion of Stage I cases in 1993 was 4.11%, and 5.03% in 2002. As a comparison, among Filipino residents in the United States in 1992-1997, 36.3% and 47.8% were diagnosed in Stage I and Stage II respectively (Chu et al., 2002)

BRCA1 and *BRCA2* Mutations

The estimated prevalence of BRCA mutations among unselected cases in the Philippine General Hospital in 1998 was 5.1% (95% CI: 2.6-7.6%), with a prevalence of 4.1% (95% CI: 1.8-6.4%) for BRCA2 mutations alone. Compared with non-carrier cases, the cumulative risk of breast cancer for first-degree relatives of mutation carriers was 24.3% to age 50, compared with <4% for first-degree relatives of non-carriers (RR = 6.6; 95% CI: 2.6-17.2). (Matsuda et al., 2002)

Hormone Receptor Assay

Some current evidence-based clinical practice guidelines suggest that hormonal receptor status (estrogen/progesterone) should be the starting point for the systemic treatment of breast cancer, be it in an adjuvant or metastatic setting (NCCN 2008, Laudico et al., 2006). The consequences of mislabeling a patient as hormone receptor negative (HR-) could be dire, as this would deprive the patient of appropriate treatment and could also lead to treatment that may not be as effective as hormonal therapy.

Some reports notwithstanding, the authors believe that there ought to be no major differences in the proportions of hormone receptor positive cases (HR+) between most ethnic groups, if standardization of procedures and scoring methods were followed. A EUROCARE-based

publication reported that 83% of cases in European countries were HR+ (Allemani et al., 2004). A SEER-based report showed that during 1992-1998, HR+ rates among women 50 years of age and older ranged from 64% among Koreans to 84% among Non-Hispanic whites, and was 79% among Filipinos (Li et al., 2002). Another SEER-based report showed that in 1992-1997 and among all women with breast cancer, the HR+ rate among Filipinos was 77% (Chu et al., 2001).

At the Philippine General Hospital, HR+ cases increased from 59% to 69% (p=0.003) after key breast tissue specimen fixation procedures were implemented, including prompt fixation in buffered formalin and optimal (10-36 hours) fixation (Uy et al, 2007). It was also noticed that the HR+ rates tended (p=0.5) to be higher in core needle biopsy (CNB) specimens (71.9%) compared to mastectomy specimens (64.5%). Factors that could explain these differences could be related to the highly labile nature of the receptor proteins and the ability to promptly fix them in buffered formalin which could be inherently different between CNB and mastectomy.

Currently, we are unaware of any other publications or reports from other Philippine hospitals regarding their experience on hormone receptor assay. Initiatives by individual physicians in the past to try to improve the quality of assays have been unsuccessful. The Philippine College of Surgeons had just initiated a national effort at improving and standardizing immunohistochemical (IHC) testing of hormone receptors.

Adjuvant Treatment

In spite of, or perhaps because of, the persistent anecdotal complaints of Philippine surgeons nationwide that in their setting most hormone receptor assay results were "negative", adjuvant hormone therapy (HT) was given to 51% of cases. Out of 738 incident cases of early breast cancer in 1991, 1994 and 1997, 97% underwent modified radical mastectomy, only 18% had postoperative radiotherapy, and 47% received chemotherapy (CT). The use of adjuvant HT significantly increased over time in all age-groups. Among the 524 patients who received systemic adjuvant treatment, 38.0% had a combination of HT and CT. The proportions of women receiving combined CT and HT also increased over time. Majority of the prescribing physicians were either surgeons (68.9%) or medical oncologists (29.2%), and the proportions did not change with time (Laudico et al., 2004).

Survival

A random sample of 1,615 incident cases in 1993 to 2002 was compared to 4,203 Filipino-Americans and 202,928 Caucasians from the SEER 13 database. The mean ages were 51.4, 53.0 and 62.4 years for NCR residents, Filipino-Americans and Caucasians respectively. The cumulative age-adjusted 5-year relative survival (%), using period analysis, were, 59% (s.e. 4.1), 90% (s.e. 1.2), and 88% (s.e. 0.1) respectively (Redaniel et al., 2009). The differences in survival were mainly attributed to the larger proportion of patients diagnosed in earlier stages among the SEER populations, as compared to Metro Manila residents. This further highlights the difficulties in breast cancer screening and early detection in the Philippines.

Future Considerations

It could be that the Philippine Department of Health (DoH) may now be interested in providing more support to population-based cancer registration through additional manpower to the two registries, Department Orders that would facilitate active cancer registration, and the promotion of a coordinated and standardized system. Two existing registries are of interest, one in Cebu City in the Central Philippines and the other in Davao City in Southern Philippines. These two cities are the second and third largest urban areas.

From the data gathered for this review it seems obvious that the strategy and methods of the Philippine Cancer Control Program have not resulted in improvement in early detection, and it would be appropriate to rethink and refocus the Program. A modern and sustained campaign to promote the message that breast cancer is curable ought to be a priority, while simultaneously improving the availability of and accessibility to basic diagnostic and treatment facilities in public hospitals. The number of medically needy patients is expected to increase and it would be futile to launch a new and correct public information campaign if a large segment of the population cannot afford the expense.

There is already enough indirect evidence that clinical breast examination and breast self-examination can increase survival, and future intervention studies should see if a combination of an appropriate message that is adequately delivered, in combination with sufficient public funding of necessary services for the needy, could work.

The Philippine College of Surgeons (PCS) needs to step up efforts at improving compliance with its Clinical Practice Guidelines, which are truly evidence-based and community-oriented. This it could do through its chapter members, relating with like-minded health organizations, and insurance companies and HMOs. The PCS can start by sustaining the effort at educating surgeons to properly fix CNB specimens, and identifying and promoting regional laboratories that can accurately perform hormone receptor assays.

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