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Breast cancer: a neglected disease for the majority of affected women worldwide

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Abstract

Recent progress with declines in mortality in some high income countries has obscured the fact that for the majority of women worldwide who are newly diagnosed, breast cancer is a neglected disease in the context of other numerically more frequent health problems. For this growing majority, it is also an orphan disease, in that detailed knowledge about tumor characteristics and relevant host biology necessary to provide even basic care are absent. With the possible exception of nutritional recommendations, current international cancer policy and planning initiatives are irrelevant to breast cancer. The progress that has occurred in high income countries has come at extraordinary fiscal expense and patient toxicity, which of themselves suggest non-relevance to women and health care practitioners in middle and low income countries. The implications of these circumstances seem clear: if the promise of the now 60 year-old Declaration of Human Rights, that the fruits of medical science accrue to all mankind, is to be realized with respect to breast cancer, a basic and translational global research initiative should be launched.

"Orphan-adjective: Not authorized, supported, or funded; not a part of a system; isolated, abandoned; lacking a commercial sponsor". [1]

I. INTRODUCTION: The Global Burden of Breast Cancer

It is anticipated that by 2010 breast cancer will be newly diagnosed in over 1.5 million women each year, and that 500 000 women worldwide will die of this disease [2,3]. While the incidence of new cases in some high income countries is stabilizing, and death rates are falling, both appear to be increasing in developing counties [4–8]. The majority of new cases now occur in women from low and middle income countries, in which the incidence is increasing by as much as 5% per year and three fourths of global breast cancer deaths occur [9,10]. In addition to aging of the now relatively young populations in low income countries, these trends are likely to continue, as breast cancer risk factors associated with general economic development become more prevalent. Delayed childbearing, lower parity and decreased breast feeding, along with greater body mass index and dietary fat consumption associated with the "westernization" of diet are likely to contribute to increasing risk [11–15]. To date, the only major public health intervention to address breast cancer risk concerns dietary/nutritional management.

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In sum, the global breast cancer burden will be increasingly in low and middle income countries. Barring some unlikely major public health breakthrough, the annual global mortality from this disease can only be expected to increase.

How should we frame a constructive response to this challenge? Significant media attention and high-profile fund-raising initiatives for breast cancer research in western countries have had a negligible impact on most women struggling with the disease in the rest of the world. Mammographic and MRI screening, advanced generation combination chemotherapy regimens, and targeted therapies are beyond the economic reach of most patients living where the increasing majority of the world's breast cancers occur. More importantly, the data upon which such advances are reflected in rigorous clinical practice guidelines are based almost entirely on studies in Caucasian women of European genetic backgrounds in high-resource countries. From economic resource, public health and data perspectives, in low and middle income countries breast cancer is a neglected and, indeed, an orphan disease.

In this communication we briefly summarize some of the evidence for population differences in breast cancer epidemiology, tumour characteristics and host biology, and argue against a "one size fits all" approach to global breast cancer control. We propose that a significant scaling up of clinical and translational research efforts in collaboration with local research teams, and with direct involvement of participants from low and middle income countries, is urgently needed.

II Breast Cancer Epidemiology: Differences among Populations

There are striking differences among populations in the age-specific incidence of breast cancer. Ethnicity and national origin are two of the stronger predictors of this variation, which represents a 5-fold difference among countries worldwide [16] Age-standardized incidence rates for breast cancer 1998–2002 were 110 (non-Hispanic Caucasians, California), 82.3 (Ontario, Canada), 41.3 (Hong Kong) and 14.7 (Jiashan, China) [3]. Reasons for these differences are not well understood. There are key inter-individual and inter-group differences in the distribution of reproductive risk factors, the highly penetrant but rare susceptibility genes BRCA1 and BRCA2 [17] as well as more prevalent, but lower-penetrance genes such as CHEK2 and FGFR [18] but these risk factor differences provide an incomplete explanation for the marked variation in population-attributable risks for the disease. Migration studies reveal that the incidence of breast cancer changes significantly over one to two generations to more closely reflect the breast cancer risk in the adopted country [19,20]. While it is difficult to tease out the causal factors to explain this observation, it seems to occur in parallel with changes in diet and other indicators of acculturation [15]. Indeed, dramatic increases in breast cancer incidence have been observed in countries which have undergone massive economic development over the past 50 years, including Japan, Singapore, and urban areas of China [21–25].

According to the AICR/WCRF report on "Food, Nutrition, Physical Activity and the Prevention of Cancer: a global perspective" [14] 38, 28, and 20% of all breast cancer cases might be prevented via a healthy diet, regular activity and maintaining a health body weight in the US, Brazil and China, respectively.

Perhaps the single most important resource in cancer epidemiology is high quality registration data, which require both accuracy and completeness of incidence and mortality reporting. More widespread cancer registration efforts are essential to evaluate differences in risk factors and natural history of all tumor types, and would allow for comparisons based on geographical regions, socioeconomic status and levels of industrialization. Comprehensive data collection and administration is a necessary component of developing

and planning cancer control initiatives, appropriate allocation of resources, and prioritization of cancer health policies [26]. The lack of reliable and complete census data often presents a particular challenge in low and middle-income countries.

III Biology – the tumour

In the first decade of the 21st century the model of breast cancer has been redefined from that of one disease to a heterogeneous group of related diseases which vary in risk factors, natural history, growth patterns and response to treatment [27]. Careful tissue specimen management and testing for hormone receptors is of pivotal importance in determining the broad parameters of appropriate treatment for patients with breast cancer –hormonal or non-hormonal, and at present should frame any discussion of breast tumour biology in different populations.

Earlier reports suggested that the majority of breast tumours from Asian women are estrogen receptor (ER) negative [28,29]. However, in the past ten years improvements in standardization and quality control of specimen handling and laboratory techniques have been implemented in many Asian centers. More recent data indicate that both pre-and postmenopausal Asian women with breast cancer, are just as likely to have ER positive tumors as Caucasians [30,31]. Tran and Lawson studied ER positivity among premenopausal breast cancer cases and found a *greater* proportion of ER+ tumors in a Vietnamese cohort, compared with the comparison group of Caucasian women in Australia [31]. Reliable, accurate hormone receptor testing and reporting has immediate and direct clinical implications, as misclassification of tumors as ER negative can result in the underutilization of likely highly efficacious endocrine treatments. Specifically, Tamoxifen, which is widely available in its generic form, is an important breast cancer treatment in the neo-adjuvant, adjuvant and metastatic settings, and is affordable in most countries.

Gene expression studies using DNA microarrays have identified breast cancer subtypes which reflect biologically distinct disease entities [32–35]. Perhaps not surprisingly, there is emerging evidence of considerable variation in the gene profiles of tumors from populations of different genetic/ethnic backgrounds. Most BRCA1-related breast cancer, but only 15% of sporadic breast cancer in Caucasian women appears to have the basal phenotype. However, several studies suggest that breast cancer in women of African ancestry may have a higher proportion of this subclass [36–38 and reviewed in 39]. A high frequency of basal-like tumors was observed in a Nigerian study, where 87 of 148 (59%) breast cancer cases were both ER- and HER2- [36].

To summarize, recent data suggests that targeting the hormonal pathway may be very relevant in managing breast cancer in many populations across the spectrum of resource levels. However, beyond this, we are relatively ignorant of population differences in other tumor characteristics which may impact on therapeutic efficacies and outcomes.

IV Biology – the host

Pharmacogenomics

Decades ago, certain anti-neoplastic agents were recognized to have disproportionate levels of toxicity in certain ethnic groups, and further research has since revealed ethnic variations in the frequency of gene polymorphisms for key enzymes in drug influx, metabolism and efflux, which can affect efficacy and toxicity. In their pharmacogenetics review, Deeken and colleagues show the interrelatedness of key factors involved in drug pharmacodynamics, pharmacokinetics and pharmacogenetics [40]. This is particularly relevant in medical oncology, where many drugs have a narrow therapeutic index with great potential for

serious toxicity, while at the other end of the continuum, sub-optimal dosing can mean the difference between cure and death from cancer. A recent issue of the journal Clinical Cancer Research (Dec 2008) dedicated five articles and an editorial to 'personalized medicine", including a review of breast cancer pharmacogenetics [41].

Specifically, data are accumulating on the impact of genetic polymorphisms in the cytochrome p450 gene and associated enzyme CYP2D6, which are involved in a key step in the metabolism of the selective estrogen receptor modulator, Tamoxifen. As reviewed by Sing-Huang Tan and colleagues [41 and Table 1], there are individual and group differences in the genetically determined ability to metabolize Tamoxifen to its more active metabolites, 4-hydroxy-tamoxifen and 4-hydroxy-N-desmethyltamoxifen (endoxifen) which are 50 to 100 times more potent than the parent compound. Goetz and colleagues reported a clinical correlation between individuals homozygous for the CYP2D6*4 allele and poorer disease-free and relapse-free survival as compared with heterozygotes or non-carriers of a single *4 allele [42]. A second study confirmed this finding [43]; however, subsequent studies have yielded conflicting results [44–46]. Of particular significance, there are at least 101 known variants of CYP2D6, of which 26% of these are partially or non-functional in Caucasians, but 50% are reportedly partially or non-functional in Asians [47,48]. The CYP2D6*10 allele is a major polymorphism which results in the intermediate metabolizer phenotype, common among Asian populations, including Chinese (37–70%) [49,50], Koreans (50%) [51,52] and Japanese (40%) [52,53].

The mechanistic hypothesis which now needs to be rigorously tested is that clinical outcomes are directly related to endoxifen blood concentrations [54].

Of key relevance to the treatment of hormone receptor negative and resistant breast cancer, several classes of chemotherapeutic agents have been shown to vary markedly in metabolic genotype and phenotype. A prospective study of women treated with anthracyclines and cyclophosphamide revealed a significantly higher rate of profound neutropenia among Chinese women compared with Caucasians [55]. More recently, common variants in the carbonyl reductase enzyme have been identified and have been associated with ethnic differences in the conversion of doxorubicin to its metabolite doxorubicinol, tumour response, and hematological toxicity [56].

The examples highlight the critical importance of understanding population differences in efficacy and toxicities of major cancer therapies.

V IMPLICATIONS FOR TREATMENT AND RESEARCH

This paper is not the first to draw attention to the looming crisis of breast cancer as a global public health issue. The mandate of Breast Health Global Initiative [57] is focused primarily on the planning side of cancer control, and includes the development of tailored recommendations for diagnosis, screening and treatment options for each of four economic tiers. These guidelines are evidenced-based, but almost exclusively derive from studies of Caucasian women from high-income countries.

Promising new targeted agents, such as small molecule tyrosine kinase inhibitors and monocolonal antibodies such as trastuzumab which targets breast cancer cells overexpressing her2neu are rapidly making their way into general oncology practice in high resource countries. These "smart bombs" of the oncology world will no doubt have increasing utility either as stand-alone or adjunct drugs in the armamentarium of anti-neoplastics. However given the experience to date with cost of these agents, and the likelihood that any of these drugs will be off-patent and 'genericized' in the coming decade, it is presently entirely beyond the reach of low and middle-resource countries to even

consider their use. According to the WHO a drug may be considered cost-effective if the annual cost per quality-adjusted life year saved, or QALY, is no greater than a country's per capita GDP (gross domestic product) [58]. China, a country undergoing tremendous economic growth, nonetheless had an estimated per capital GDP of $5300 in 2007. India's per capita GDP was $2700 [59]. Data on cost per quality-adjusted life year gained for trastuzumab ranges from $~ 20 0000 to $50 000, illustrating the point that costs for targeted agents will be excessive for at least half of the world's breast cancer patients who might benefit from this drug [60].

As the lion's share of drug development budgets are focused on targeted agents, we are concerned that the developing world will be increasingly left behind. The "treatment gap" that already exists between high, middle and low-resource populations will widen, unless new approaches to affordable, effective and tolerable therapies are properly evaluated in the relevant populations.

We submit that our current understanding of breast cancer causation and biology in low and middle resource, non-Western and non-Caucasian populations is significantly limited. We are only beginning to investigate factors which influence breast cancer incidence and mortality, distribution of tumor sub-types, host metabolic and pharmacogenomic factors. We must resist the urge to extrapolate what is known from one population to another. Emerging data presented here should give us pause in considering how we approach breast cancer control in populations where we have minimal or no data.

In order to address the issue of global cancer control in a more rational fashion, we propose that clinical trials, along with translational correlative science should be supported in low and middle-resource countries. It is our contention that the scientific knowledge gained from truly international, collaborative research partnerships are best suited to improve breast cancer care in resource-poor populations, and at the same time aid in the development of better-tailored, cost-effective cancer prevention and management approaches for women in the developed world.

In this paper we have not addressed the broad political and health system challenges relevant in bringing to bear evidenced-based medicine to global breast cancer control. It is essential that we consider at every step the social and ethnocultural milieu in which women live. Our colleagues in the social sciences should be engaged early and often to provide much needed context.

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Table 1

Summary of selected genetic polymorphisms that show differences in interethnic frequency distribution that may have influence on breast cancer therapeutics. Reprinted with permission from Tan et al, Clinical Cancer Research 2008; Vol 14:8021–9041

Table 3. Summary of selected genetic polymorphisms that show differences in interethnic frequency distribution that may have influence on breast cancer therapeutics

Genetic polymorphisms	Drug	Interethnic genetic variation	Clinical relevance to interethnic differences in drug disposition
CYP2D6	Tamoxifen		Poor metabolizer phenotype more common in Caucasians than Asians or Black Africans. Lower levels of enzyme activity in Asians and Black Africans compared with Caucasians in the extensive metabolizer phenotype group (119). Clinical relevance of this interethnic variation is unclear.
*CYP2D6*4*		Common in Caucasians. Rare in Asians and Black Africans.	
*CYP2D6*10*		Most common in Asians. Rare in Caucasians.	
*CYP2D6*17*		More common in Black Africans. Rare in Asians and Caucasians.	
*CYP2D6*2xn*		More common in Ethiopians and Saudi Arabians. Rare in Caucasians, Asians, and Blank Africans.	
*CTP3A4*1B*	Tamoxifen, taxanes	Commonest in Black Africans. Rare in Asians.	Has been associated with increased transcriptional activity but clinical association unclear.
*CYP3A5*3C*	Tamoxifen	Commonest in Black Africans followed by Asians. Rare in Caucasians.	Association unclear
CYP19A1	AIs		Association unclear
Arg^{39} variant		Present in 6.7% Han Chinese Americans (42). Rare in African-Americans, Caucasian Americans, and Mexican Americans (42).	
Cys^{264} variant		More common in African-Americans (22.5%) and Han-Chinese (11.7%) compared with Mexican Americans (5%) or Caucasian Americans (2.5%; ref. 42)	
CBR3 11G>A	Doxorubicin	Frequency of the A allele is 36% in Europeans, 47.5–57% in Chinese, and 27.3% in African-Americans (48, 120).	Associated with lower conversion of doxorubicin to doxorubicinol (48). Greater doxorubicin-induced myelosuppression has been observed in Chinese compared with Caucasians (47), although direct evidence of link with this polymorphism is still lacking.
CDA 208G>A ($Ala^{70}Thr$)	Gemcitabine	More common in Africans (13%) compared with Japanese (4.3%) or Europeans (0%; refs. 62, 83).	Association unclear
SLC28A1 1561G>A	Gemcitabine	More common in Caucasians (73%) compared with Chinese (12%), Malays (30%), or Indians (35%; ref. 84).	Association unclear
DCK	Gemcitabine	Asians have a higher allele frequency (15.6%) of this linked promoter polymorphism compared with Caucasians (2%; ref. 85).	Might predispose Asians to gemcitabine-associated toxicity but clinical association currently lacking.
-C360G/-C201T			