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Supplementary appendix

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MODELING BREAST CANCER EARLY DETECTION AND TREATMENT STRATEGIES FOR IMPROVING BREAST CANCER CONTROL IN LOW AND MIDDLE INCOME COUNTRIES: SUPPLEMENTARY APPENDIX

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TABLE OF CONTENTS

OVERVIEW

Data providing model inputs were obtained from a literature review of articles published in English or Spanish between 2005-2017 via PubMed, or using a standard internet search engine. Search criteria utilized Boolean operators and included the terms breast cancer, age specific incidence, screening, tumor stage at diagnosis, breast-cancer specific survival, treatment, estrogen receptor positive tumors, treatment specific survival, and country of interest. We used aggregate data from a number of East African countries, since an entire set of model inputs was unavailable for a single country in this region. Similarly, our inputs for Colombia come from multiple sub-regions, primarily Bogota and Cali. All inputs, sources, and assumptions are summarized in the Appendix Table.

BREAST CANCER INCIDENCE, STAGE AT DIAGNOSIS AND ESTROGEN RECEPTOR STATUS

We obtained registry data from the CI5 database[1] to model age-specific incidence rates, using Uganda for East Africa and the sub-region of Cali for Colombia (both 2003-2007). For stage at diagnosis, in East Africa, 70-80% of tumors are diagnosed in advanced stage;[2] we specified 78%, based on a meta-analysis of East African countries.[3] Estimates of ER positivity are heterogeneous[4], so we again used a meta-analysis that found that 41% of cases of African descent are ER+.[5] In Colombia, across 16 Bogota institutions, advanced stage cases were 45% and the ER+ were 72%.[6] Another Colombian study found 69% ER+;[7] we summarize this as 70%.

TREATMENT DISTRIBUTIONS

Very little information is available on treatment practices in East Africa and these vary considerably across facilities and regions. A recent review of breast cancer in East Africa[4] cited a study of 1226 newly diagnosed breast cancer patients in Nigeria[8] of whom only 35.2% underwent mastectomy due to the majority being advanced at diagnosis. In contrast, a study of breast cancer survival in a relatively large Ethiopian cohort (n=1226) reported that 97% of patients received surgery within 6 months while 79% and 77% received chemotherapy within 6 months and/or hormone therapy within 12 months respectively. In our model the baseline treatment strategy consists of mastectomy for localized cases but no systemic or radiation therapy, and palliative care for advanced-stage cases.

A Colombia study reported that 40.9% of patients received endocrine therapy.[9] In this study the ER+ distribution was not reported but assuming that 70% were ER+ (as noted above for Colombia) suggests that approximately 58% (40.9/70) ER+ patients did receive endocrine therapy. We were not able to ascertain the fraction of patients receiving radiation or systemic chemotherapy in this study or in Colombia in general. As specified in the main manuscript, we use treatment distributions from the US in 2000 to approximate contemporary treatment in Colombia (main text, Table 1). We note that the estimate above of 58% of ER+ patients receiving endocrine therapy matches the US 2000 estimate for early-stage ER+ cases (main text, Table 1).

TREATMENT EFFICACIES

Efficacy estimates for the treatment interventions were based on meta-analyses of randomized trials conducted around the world.[10,11] For endocrine therapy, we used a constant hazard ratio for breast cancer death of 0.7 for both stages; for chemotherapy a hazard ratio of 0.775 for both stages. Only ER+ women

could benefit endocrine therapy, whereas all could benefit from chemotherapy. The efficacy of the combination was taken to be the product of the two hazard ratios.

BASELINE STAGE-SPECIFIC SURVIVAL AND OTHER-CAUSE MORTALITY

This parameter reflects net, disease-specific survival, the survival from breast cancer in the absence of other causes of death. In several cases it was necessary to transform our survival inputs since stage-specific net survival $S_{obs}(t)$ was only available for a setting in which some patients had received the treatment we wished to model (e.g., endocrine therapy). We estimated $S_0(t)$ by assuming that for each stage, survival is the weighted sum of survival under each treatment (e.g., endocrine therapy versus none), where the weights reflect the proportion receiving treatment. For treatment j, survival is $S_0(t)^{h_j}$ where $h_j$is the hazard ratio (generating survival benefit) of treatment j. Accounting for the possibility the treatment distributions may differ for ER+ and ER- patients, we write the weights as the product of p_i, the proportion in the ER subgroup (ER+ or ER-), and p_{ij}, the proportion of each ER status group receiving treatment j. Then we can write $S_{obs}(t)$ as follows:

$$S_{obs}(t) = \sum_i p_i \left(\sum_j p_{ij} S_0(t)^{h_j} \right)$$

This equation is a fractional polynomial solvable using uniroot() in R. Note that it assumes that the two ER subgroups have comparable survival in the absence of the treatment.

In the East Africa setting, stage-specific survival estimates are available only on a cohort- or facility-specific basis and these likely do not represent population survival. Still, we use these results as a first approximation to the experience of East African cancer cases. Galukande et al[12] presented survival estimates for breast cancer cases treated at Mulango Hospital in Uganda. In this cohort there were no stage I /II deaths observed. We use the 5-year, net disease-specific survival for advanced-stage cases of approximately 35% in the model. An Ethiopian cohort[13] similarly found 33% 5-year metastasis-free survival among advanced cases, as well as 72% among early-stage cases. However, all ER+ patients in this cohort received endocrine therapy. Using expression (1), 5-year survival among early-stage cases in the absence of endocrine therapy is calculated to be approximately 69% (see Examples below for details). We use this estimate for baseline survival among early-stage cases in East Africa but note that this may reflect an optimistic estimate in this setting, as the patients in this cohort clearly had access to care and also received regular follow-up.

For Colombia, we extracted the 5-year relative survival for stages I-IV from a retrospective study of breast cancer mortality Cali from 1995-2004.[14] We weighted these estimates by their respective stage distributions from Pineros et al[15] to yield 5-year survival estimates of 55% for advanced-stage cases and 87% for early-stage cases. As noted above, however, we assume that these figures include systemic therapy for some cases; using expression (1) and assuming treatment distributions as in the US in 2000 (main text, Table 1), we calculate 5-year survivals of 41% for advanced-stage and 84% for early-stage cases in the absence of endocrine therapy (see Examples below for details). It is likely that these estimates also include other systemic therapies among a non-trivial fraction of the population. Therefore, for Colombia, our baseline setting treatment setting assumes that some patients received systemic chemotherapy; this is also reflected in baseline stage-specific survival inputs. In this setting, the treatment strategies evaluated by the models change only the fraction receiving endocrine therapy.

EXAMPLES: BASELINE SURVIVAL CALCULATION WITH EQUATION (1)

The following tables review notation and specify parameter values for East Africa and Colombia:

Table A1. NOTATION AND VALUES FOR BASELINE SURVIVAL CALCULATIONS: p_i AND $S_{obs}(t = 5)$

Description	**Notation**	**East Africa**	**Colombia**
Proportion of all cases that are ER positive	$p_{i=ER+}$	0.41	0.70
Proportion of all cases that are ER negative	$1 - p_{i=ER+}$	0.59	0.30
Within stage and ER group i, proportion treated with treatment j	p_{ij}	See table A2	See table A2
Hazard ratio for treatment j	h_j	See table A2	See table A2
Observed 5-year survival, all ER	$S_{obs}(t = 5)$	0.72 (early)	0.55 (advanced) or 0.87 (early)
Baseline 5-year survival, all ER	$S_0(t = 5)$	Estimate for early stage	Estimate for both stages

Table A2. NOTATION AND INPUTS h_j AND p_{ij} FOR BASELINE SURVIVAL CALCULATIONS. THE p_{ij} ARE IN %.

Stage	**ER Status *i***	**Treatment *j***	**Hazard ratio h_j**	**East Africa p_{ij}**	**Colombia p_{ij}**
Advanced	ER+	Endocrine	0.7	0	10
		Chemo	0.775	0	38
		Both	0.5425	0	50
		None	1	100	2
	ER-	Endocrine	1	0	3
		Chemo	0.775	0	85
		Both	0.775	0	10
		None	1	100	2
Early	ER+	Endocrine	0.7	100	58
		Chemo	0.775	0	8
		Both	0.5425	0	10
		None	1	0	24
	ER-	Endocrine	1	0	20
		Chemo	0.775	0	50
		Both	0.775	0	5
		None	1	100	25

Early stage, East Africa

In this setting there is only endocrine therapy and no chemotherapy. Therefore:

$$S_{obs}(t) = \sum_i p_i \left(\sum_j p_{ij} S_0(t)^{h_j} \right)$$

$$0.72 = 0.41 * (1 * {S_0}^{0.7}) + 0.59 * (1 * {S_0}^{1})$$

Advanced stage, Colombia

$$S_{obs}(t) = \sum_i p_i \left(\sum_j p_{ij} S_0(t)^{h_j} \right)$$

$$0.55 = 0.70 * \left(0.10{S_0}^{0.7} + 0.38{S_0}^{0.775} + 0.50{S_0}^{0.5425} + 0.02{S_0}^{1}\right) +$$
$$0.30 * (0.03{S_0}^{1} + 0.85{S_0}^{0.775} + 0.10{S_0}^{0.775} + 0.02{S_0}^{1})$$

For the ER negative, no treatment and endocrine have the same hazard ratios, as do chemo and both. Those terms can thus be combined, which simplifies the equation to:

$$0.55 = 0.70 * \left(0.10{S_0}^{0.7} + 0.38{S_0}^{0.775} + 0.50{S_0}^{0.5425} + 0.02{S_0}^{1}\right) +$$
$$0.30 * (0.05{S_0}^{1} + 0.95{S_0}^{0.775})$$

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