**Modelling of breast cancer within the Thanzi La Onse Model**

**Background: The Thanzi La Onse Model**

As part of the Thanzi La Onse program a model is being developed which aims to capture the health experiences of the population of Malawi and the consequent interactions with the health care system. The intent is that this model will help to inform future delivery of health care in Malawi. The model is an individual based model – which means we explcitly simulate the individual life and health experiences of a representative proportion of the population of Malawi. The simulation initiates on 1 Jan 2010 and we attempt to simulate the attributes of the population at that point. We can run the model forward to any specified future time point. Each potential intervention and its associated diseases are being modelled. This is being divided into separate disease/intervention modules. This document describes the module on breast cancer.

**Background: General approach to decisions on modelling causal influences and effects of interventions**

This module was designed in the context of an overall approach to modelling causal effects in general and causal effects of interventions in particular. The overal intent is to adopt as simple a structure as can be conceived, whilst still capturing the essential elements of a disease and the interventions used to prevent or treatment. We include a causal link between a “variable” (by which we mean a characteristic or property of an individual, whether that be demographic, social or biologic), and risk of disease or another variable if there is strong evidence from an overall body of studies that such a causal link exists and is at least moderately strong. In informing such decisions we place particular value on RCTs or studies with a quasi-experimental design such as analyses based on an instrumental variable There is no expectation that such studies will be from Malawi or even from Africa. If there are such local studies and in the unlikely event that they provide strong evidence to suggest that the causal link is substantively different in Malawi then the intent is that this is taken into account and the Malawi-specific link included.

In the special case of a potential causal variable which relates to whether an individual has experienced or is experiencing an intervention the intent is to only include interventions if there is substantial RCT evidence of their beneficial effect, based on trials with objectively ascertained clinical endpoints with low risk of serious bias. Whilst DCP-3 (and to some extent the Malawi EHP) provides an initial list of such interventions and the evidence to support them, where possible our intent has been to form our own opinion on intervention efficacy based on the source trials.

Unless there is evidence to the contrary, the intent is to summarize and incorporate intervention effects into the model as relative risks or rates rather than absolute differences due to the fact that such measures are less likely to differ substantively by context. Interactions between characterstics (on the multiplicative scale) are only to be be incorporated if there is strong evidence. Again, we have not intended to rely on data from Malawi or Africa for such evidence but if local evidence exists which strongly suggests a different effect than elsewhere then the intent is that this modified effect is incorporated in the model.

**Background: Demographic and social characteristics modelled**

Based on data on the distribution of the population in Malawi according to geographic location we assign individuals a geographic location, which maps onto whether they are classified as living in a rural or urban area. Informed largely by data from the Malawi DHS, variables are also created indicating the person’s wealth level (based on 5 quintiles), whether the person has access to improved sanitation, clean drinking water, hand washing facilities, and whether they experience indoor air pollution (wood burning stove). We assign individuals a current education status (none, primary, secondary) which is updated 3 monthly from age 5 to 20. From age 15 we assign BMI in 5 categories, tobacco use status, drinking excess alcohol, having low exercise, high sugar intake, high salt intake, and marital status (never, currently, widowed/divorced). The status with regard to such variables for individuals can change over time. The influences between these variables are described in detail in a separate document.

**Model structure**

**Variables modelled**

The model updates information on each individual with regard to breast cancer status every 3 months. The model structure is described in Figure 1. Variables that we create for each woman aged over 15 in relation to breast cancer (Table 1) are as follows: breast cancer status (brc\_status; none, stage 1, stage 2, stage3, stage 4), date of any diagnosis of breast cancer (brc\_date\_diagnosis), date of any attempted curative treatment (brc\_date\_treatment) and at what stage (brc\_stage\_at\_which\_treatment\_given; no, stage 1 – stage4).

**Incidence of (grade 1) breast cancer**

Table 2 describes the parameters and their values. Jointly, the chosen parameter values produce the model outputs shown in Table 3. Informed by incidence rates of breast cancer from Malawi cancer registry (Chasimpha et al, 2017), incidence of breast cancer is assumed to occur in women from age 20 years onwards and to be dependent on age only. We do not explitly model breast cancer in men, only as part of an “other male cancer” module. The annual rate in women aged 15-29 is assumed to be 0.00003 with a 20-fold higher rate in women 30-49 and women 50+ (Chasimpha et al).

**Progression between cancer stages**

Informed by data on progression of breast cancer in the absence of treatment (Johnstone et al 2000; Riffenburgh et al. 2001) showing a median survival of around 2-3 years we assume an annual rate of progression from stage 1 to stage 2 breast cancer of 0.5 per person year, similarly from stage 2 to stage 3 and from stage 3 to stage 4. The death rate in women at stage 4 is assumed to be 0.35 per woman year.

**Incidence of** **having a discernible breast lump**

Presentation at late stages of cancer is common in the region (Jedy-Agba et al 2017). In the initial report from the registry for very few cancer cases was their a cancer stage at diagnosis recorded (Msyamboza et al, 2012). We model the main symptom that leads to the possibility of presentation: having a discernible breast lump. The rate of appearance of having a discernible breast lump is assumed to be 0.20 per 3 months at stage 1, and this rate is assumed to be increased by 1.5, 2 and 2.5 at stages 2-4 respectively.

**Treatment for breast cancer**

At all stages of cancer except stage 4 cancer we consider potential medical treatment aimed at cure amongst people who are diagnosed. Depending on stage this might include surgery, radiotherapy, chemotherapy and adjuvant treatments. We recognise that availability if treatment is currently extremely limited in Malawi. There were reported in 2015 to be five Malawian oncologists and haematologists involved in full-time cancer care in the whole country (Masamba et al, 2015). The annual rate of receiving attempted curative treatment for a woman with diagnosed stage 1 breat cancer is assumed to be 0.05, similarly for women in stages 2 and 3.

**Effect of treatment**

The rate ratio for stage 2 cancer for women with stage 1 cancer if they received attempted curative treatment is estimated as 0.01, reflecting the high survival in high income settings for women diagnosed in stage 1 (of the order of 80% survival to 10 years), compared with the relatively rapid time to progression and death with no treatment (Johnstone et al 2000; Riffenburgh et al. 2001). The rate ratio for progression to the next stage for attempted curative treatment is assumed 0.05 at stage 2 and 0.5 at stage 3, reflecting the lower chance of achieving cure with later stage treatment.

**Rate of death from breast cancer**

The death rate from breast cancer in women at stage 4 is assumed to be 0.35 per woman year.

**Disability weights**

* For persons with any stage of cancer prior to metastatic stage and have never had any treatment, a disability-weight of 0.288 is applied, corresponding to "Diagnosis and primary therapy phase of breast cancer: Cancer, diagnosis and primary therapy, has pain, nausea, fatigue, weight loss and high anxiety”.
* For persons with any stage of cancer prior to metastatic stage and have ever had any treatment, a disability-weight of 0.049 is applied, corresponding to "Controlled phase of breast cancer, Generic uncomplicated disease: worry and daily medication, has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities”
* For persons with a cancer in metastatic stage and with no palliative care, a disability-weight of 0.451 is applied, corresponding to “Metastatic phase of breast cancer: Cancer, metastatic: has severe pain, extreme fatigue, weight loss and high anxiety."
* For persons with a cancer in metastatic stage and with no palliative care, a disability-weight of 0.451 is applied, corresponding to “Metastatic phase of breast cancer: Cancer, metastatic: has severe pain, extreme fatigue, weight loss and high anxiety."
* For persons with a cancer in metastatic stage and with palliative care, a disability-weight that is applied that is equal to those with earlier stage cancers without treatment.

**Health System Interactions**

*Care Seeking & Diagnosis*

Urinary symptoms or pelvic pain are assumed to trigger healthcare seeking to a Non-Emergency Generic Appointment at Facility Level 1, whereupon referral to further health system interaction is indicated. In that appointment, a biopsy test is undertaken. If that investigation confirms Breast Cancer and if the stage of cancer is not stage 4 then the patient is referred to initiate treatment. If the cancer is confirmed and is in stage 4, the patient is referred to Palliative Care.

We aim for these rates to eventually be informed by data on stage of oesophageal cancer at diagnosis from the cancer registry, although in the initial report from the registry for very few cancer cases was there a cancer stage at diagnosis recorded (Msyamboza et al, 2012).

*Treatment Initiation & Monitoring*

Treatment is implemented for the patient in a separate single appointment, following diagnosis of any form of stage prior to stage 4 (low/high grade dysplasia and stages 1-3). The patient is monitored every year thereafter, and if the patients has progressed to stage 4, the patient is initiated on Palliative Care.

*Palliative Care*

Patients initiated on palliative care remain on palliative care and received a monitoring appointment each month. No benefit for the patient is in effect.

**Main Limitations**

The main limitations are the relative lack of data to directly inform many of the parameter values. Underlying progression of the condition is assumed to follow a similar course as in studies in other parts of the world. For incidence of breast cancer and rates of diagnosis and availability of curative treatment it is necessary to consider data from Malawi itself given that these are likely to depend on the setting. As it becomes possible to perform more analyses in collaboration with the cancer registry we expect to be able to further inform our parameter values. In future iterations we will consider breaking down attempted curative treatment into surgery, chemotherapy, radiotherapy, and endocrine therapy etc. There is also uncertainty over disability weights.

**Figure 1. Breast cancer status**



**Table 1. Properties modelled.**

|  |  |
| --- | --- |
| **Variable** | **Description** |
| brc\_status | none, breast\_confined, metastatic |
| brc\_date\_diagnosis | date diagnosis |
| brc\_stage\_at\_which\_treatment\_given | received attempted curative treatment (never, yes breast\_confined, yes local\_ln) |
| brc\_date\_treatment | date attempted curative treatment for breast cancer |
| brc\_date\_palliative\_care | date start palliative care (note this is not breast cancer-specific) |

|  |
| --- |
| **Table 2. Description of parameters and proposed values**  |
| **Parameter** | **Proposed value** | **Description** | **Notes**  |
| r\_stage\_1\_breast\_ca\_age1529 | **0.000005** | monthly rate of incident stage 1 breast cancer for women age 15-29 | Chasimpha et al 2017 |
| rr\_stage\_1\_breast\_ca\_age3049  | **20** | rate ratio for stage 1 breast cancer for women age 30-49 | Chasimpha et al 2017 |
| rr\_stage\_1\_breast\_ca\_age50+  | **20** | rate ratio for stage 1 breast cancer for women age 50+ | Chasimpha et al 2017 |
| r\_stage2\_breast\_ca\_stage1 | **0.15** | monthly rate of progression to stage 2 breast cancer from stage 1 | 2001 - riffenburgh - cancer survival and progression rates by stage untreated2000 – johnstone |
| rr\_stage2\_breast\_ca\_curative treatment\_stage1 | **0.05** | rate ratio for progression to stage 2 breast cancer if had attempted curative treatment at stage 1 | https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival#heading-Three |
| r\_stage3\_breast\_ca\_stage2 | **0.15** | monthly rate of progression to stage 3 breast cancer from stage 2 | 2001 - riffenburgh - cancer survival and progression rates by stage untreated2000 - johnstone |
| rr\_stage3\_breast\_ca\_curative treatment\_stage2 | **0.05** | rate ratio for progression to stage 3 breast cancer if had attempted curative treatment at stage 2 | https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival#heading-Three |
| r\_stage4\_breast\_ca\_stage3 | **0.5** | monthly rate of progression to stage 4 breast cancer from stage 3 | 2001 - riffenburgh - cancer survival and progression rates by stage untreated2000 - johnstone |
| rr\_stage4\_breast\_ca\_curative treatment\_stage3 | **0.5** | rate ratio for progression to stage 4 breast cancer if had attempted curative treatment at stage 3 | https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival#heading-Three |
| r\_breast\_lump\_discernible\_stage1r\_breast\_lump\_discernible\_stage2r\_breast\_lump\_discernible\_stage3r\_breast\_lump\_discernible\_stage4 | **0.05****2****4****10** |  |  |
| r\_death\_breast\_ca | **0.1** | monthly rate of death in women in stage 4 breast cancer | https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival#heading-Three |

**Table 3. Model outputs and observed data from Malawi calibration to be updated**

(note this is with treatment given in 100% of diagnosed people stage1-stage3)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Model Output** | **Observed Data** | **Notes** |
| Number of incident diagnoses of breast cancer in women per year  | ~1200 | 1216 (2018) | Globocan\* |
| Rate of diagnosed breast cancer cases(/100,000 women aged > 15 per year) in 2020 | 26.2 (women aged 15+) | 9.6 (women of any age)  | During 2008 – 2010, Blantyre. Chasimpha et al. 2017. |
| Number of women living with breast cancer (any stages 1 - 4) in 2019, whether diagnosed or not | ~3100 | Not available by definition |  |
| Number of women living with diagnosed breast cancer (any stages 1 - 4) in 2019 | ~2300 | No data identified data so far to inform. | 2181 (5 year prevalence) Globocan\* |
| Percentage of incident breast cancer cases diagnosed at stage 3 or 4 |  70%  | 75% (sub Saharan Africa range 30-100) | Jedy-Agba et al 2016Youngblood et al 2020 |
| Number of women given attempted curative treatment for breast cancer per year | 1040 | Low but have not identified data so far. |  |
| % of women living with diagnosed breast cancer who are aged < 30, 30-49, 50+  | 5%, 63%, 32% | --- |  |
| 1 year survival from diagnosis in context of chemotherapy and surgery treatment availability |  | 74%Stage 2 93%Stage 3 85% Stage 4 43%  | Youngblood et al 2020 |
| Number of deaths from breast cancer per year in women (includes women never diagnosed)  | 480  | 601  | Globocan\* (Method: Estimated from national incidence estimates by modelling, using incidence:mortality ratios derived from cancer registry data in neighbouring countries) |

\* Globocan Methods: Incidence Country-specific data source: National Cancer Registry of Malawi Method: Most recent rates from a single registry applied to 2018 population Mortality Country-specific data source: No data Method: Estimated from national incidence estimates by modelling, using incidence:mortality ratios derived from cancer registry data in neighbouring countries Prevalence Computed using sex-; site- and age-specific incidence to 1-;3- and 5-year prevalence ratios from Nordic countries for the period (2000-2009), and scaled using Human Development Index (HDI) ratios

\*\* In Sudan, trained volunteers screened 70% of a target population of 15 000 women. They found 138 breast masses with 4 early-stage and 5 advanced breast cancers, compared with 1 early-stage and 3 advanced cases self-reported by women in the control villages (Abuidris et al., 2013). In the United Republic of Tanzania, a similar intervention led to an increase in the number of earlystage breast cancers, over a 3-year period, from 9% to 67% (Ngoma et al., 2015).

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