**Modelling of other\_adult\_cancers 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.

**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.

**Other adult cancers**

We individually model the occurrence of certain adult cancers (cervical, oesophageal, breast, bladder, prostate) and Kapasi’s sarcoma on non-Hodgkins lymphoma occurring in people with HIV and included within the overall AIDS designation. This module covers other adult cancers apart from these (Melanoma of skin, Ovary, Stomach, Kidney, Lip, oral cavity, Colon, Lung, Rectum, Hodgkin lymphoma, Penis, Salivary glands, Vulva, Thyroid, Leukaemia, Vagina, Anus, Brain, nervous system, Larynx Nasopharynx, Corpus uteri, Pancreas, Multiple myeloma, Testis, Oropharynx, Gallbladder, Mesothelioma, Hypopharynx). Together these other cancers comprise approximately one third of all cancers occurring in Malawi (<http://gco.iarc.fr/today/data/factsheets/populations/454-malawi-fact-sheets.pdf>), although none individually represents more than 1.5% of all incident cancers in Malawi.

**Model structure**

**Variables modelled**

The model updates information on each individual with regard to other\_adult\_cancers status every 3 months. The model structure is described in Figure 1. Variables that we create for each man aged over 35 in relation to other\_adult\_cancers (Table 1) are as follows: other\_adult\_cancers status (oac\_status; none, site\_confined, local\_ln, metastatic), date of any diagnosis of other\_adult\_cancers (oac\_date\_diagnosis), date of any attempted curative treatment (oac\_date\_treatment) and at what stage (oac\_stage\_at\_which\_treatment\_given; no, yes site\_confined, yes local\_ln).

**Incidence of site\_confined other\_adult\_cancers**

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 other\_adult\_cancers from Malawi cancer registry and other studies (Chasimpha et al, 2017), incidence of other\_adult\_cancers is assumed to be dependent on age. Other causes are unknown. HIV infection increases the risk of all non-AIDS incident cancers (Shiels et al, 2009) and is applied as a risk ratio to the incidence of site\_confined cancer. This is assumed to be equal for all other\_adult\_cancers and is independent of infection stage. People with HIV on treatment and virally suppressed are assumed to have no additional risk.

**Progression between cancer states**

Informed by data on progression of other\_adult\_cancers in the absence of treatment (Popiolek et al; 2013) we assume an annual rate of progression from site\_confined other\_adult\_cancers to local\_ln of 0.5 per year, and from local\_ln to metastatic cancer of 0.5 per year. The rate of progression from untreated metastatic cancer to death is 0.7 per year.

**Incidence of early other adult cancer symptoms**

Presentation at late stages of cancer is common in the region (Kingham et al; 2013). 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 a generic notional symptom of “early other adult cancer symptoms”. The rate of appearance of the symptom is assumed to be 0.05 per 3 months at site\_confined stage, and this rate increases by 1.5 times at higher stages, similarly for pelvic pain.

**Treatment for other\_adult\_cancers**

We consider potential medical treatment aimed at cure amongst people who are diagnosed. Depending on stage this might include surgery,chemotherapy and adjuvant treatments. We recognise that availability of 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). There is generally low access to treatments (Kingham et al; 2013).

**Effect of treatment**

The rate ratio for local\_ln cancer for people treated with site\_confined cancer is estimated as 0.1, while the rate ratio for metastatic cancer in people treated at local\_ln stage is 0.2. Clearly these effects will differ by cancer type and site and this represents a attempt to convey the average.

**Rate of death from other\_adult\_cancers**

The death rate from bladder cancer in people with metastatic cancer is assumed to be 0.70 per 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 other\_adult\_cancers: 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 other\_adult\_cancers, 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 other\_adult\_cancers: 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 other\_adult\_cancers: 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*

Early other adult cancer symptoms 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 (generic) diagnostic test is undertaken. If that investigation confirms Other\_adult\_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 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 other\_adult\_cancers 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. Other\_adult\_cancers status**



**Table 1. Properties modelled.**

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

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| --- |
| **Table 2. Description of parameters and proposed values**  |
| **Parameter** | **Proposed value** | **Description** |
| r\_site\_confined\_none | 0.00005 | annual rate of incident other cancer for 15-29 year old men |
| rr\_site\_confined\_age3049 | 5 |  |
| rr\_site\_confined\_age5069 | 7 | rate ratio for incident other cancer for people age 50-69 |
| rr\_site\_confined\_agege70 | 12 | rate ratio for incident other cancer for people age 70+ |
| rr\_site\_confined\_hiv | 4.13 | Rate ratio for incident other cancer for people with unsuppressed HIV infection |
| r\_local\_ln\_site\_confined\_other\_adult\_ca | 0.15 | rate of progression to t2+ bladder cancer from tis\_t1 |
| rr\_local\_ln\_other\_adult\_ca\_undergone\_curative\_treatment | 0.1 | rate ratio for progression to local\_ln other cancer if had attempted curative treatment at site\_confined |
| r\_metastatic\_local\_ln | 0.15 | annual rate of progression to metastatic other cancer if local\_ln |
| rr\_metastatic\_undergone\_curative\_treatment | 0.2 | rate ratio for progression to metastatic other cancer if had attempted curative treatment at local\_ln |
| r\_death\_other\_adult\_cancer | 0.2 | annual rate of death in people with metastatic other cancer |
| r\_early\_other\_adult\_ca\_symptom\_site\_confined\_other\_adult\_ca | 0.02 | annual rate of attempted curative treatment for diagnosed other-confined cancer |
| rr\_early\_other\_adult\_ca\_symptom\_local\_ln\_other\_adult\_ca | 3 | rate ratio for attempted curative treatment for local\_ln other cancer (relative to rate for other\_confied) |
| rr\_early\_other\_adult\_ca\_symptom\_metastatic\_other\_adult\_ca | 10 | annual rate of diagnosis of site\_confined cancer |
| rp\_other\_adult\_cancer\_age3049 | 1.5 | rate ratio for diagnosis of other cancer if local\_ln compared with site\_confined |
| rp\_other\_adult\_cancer\_age5069 | 2 | rate ratio for diagnosis of other cancer if metastatic compared with site\_confined |
| rp\_other\_adult\_cancer\_agege70 | 4 | rate of starting palliative care if have metastatic cancer |
| sensitivity\_of\_diagnostic\_device\_for\_other\_adult\_cancer\_with\_other\_adult\_ca\_site\_confined | 0.8 |  |

**Table 3. Model outputs and observed data from Malawi – total non-AIDS cancers (ie all cancers except cervical, NHL, KS)**

(needs to be completed when health system constraints included)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Model Output** | **Observed Data** | **Notes** |
| Number of incident diagnoses of cancers per year  | ~6500 | 6,355(10,295 if including breast, prostate, oesoph, bladder) | Globocan 2018\* |
| Rate of diagnosed cancer cases(/100,000 aged > 15 per year)  | 73.7(in 2020) |  | During 2008 – 2010, Blantyre. Chasimpha et al. 2017. |
| Number of people living with cancer (any stage) in 2020, whether diagnosed or not | 45,500 | Not available by definition |  |
| Number of people living with **diagnosed** cancer (any stage) in 2020, whether diagnosed or not | ~15,000 |  | 16,626 (5 year prevalence) Globocan\* |
| Percentage of site-confined cancer cases diagnosed  | 44%  | No data identified data so far to inform. |  |
| Number of people given attempted curative treatment for cancers per year | ~6600 (will be much lower when health system constraints included) | Low but have not identified data so far. | 5 Malawian Oncologists in full time care; Masamba et al 2015 |
| % of people living with diagnosed cancer who are aged < 30, 30-49, 50-69, 70+  | 16%, 52%, 32% | --- |  |
| Number of deaths from cancer per year (modelled output includes people never diagnosed) | 2850 | 4145(7369 if including breast, prostate, oesoph, bladder) | Globocan 2018\* (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

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