

HOW WILL TRASTUZUMAB AFFECT LIFE INSURANCE?

BY ANGUS S. MACDONALD AND EDWARD ROCHE

ABSTRACT

Trastuzumab (trade name Herceptin) is a new anti-cancer drug, effective in the 15–25% or so of cases in which the tumour shows over-expression of the HER2 gene. Recent epidemiology suggests that Trastuzumab may significantly improve survival after onset. We combine these results with an existing actuarial model of breast cancer diagnosis and mortality, to estimate the impact on life insurance premiums (term assurances expiring at age 65). We find that premiums are reduced by up to about 1%, although this is subject to very great uncertainty that can only be resolved by many more years of epidemiology. Nevertheless, since Trastuzumab is one of the first major examples of a radically new form of treatment — monoclonal antibodies — even an effect of this magnitude indicates that the possible overall impact could be large.

KEYWORDS

Breast Cancer; Critical Illness Insurance; HER2 Genotype; Herceptin; Trastuzumab

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1. INTRODUCTION

Medical advances are, or ought to be, of great interest to actuaries involved in long-term health and life insurance. It is quite conceivable that the diagnoses and treatments that will trigger insurance claims in ten years' time have not been envisaged yet. Recognition of this led the Faculty and Institute of Actuaries to set up the Actuaries' Panel on Medical Advances (APMA) in 2001. In reorganised form, since 2004 it has actively sponsored the construction of models that may be useful in understanding the risk factors and processes underlying disease; a necessary first step towards measuring the impact of new medical interventions that act on disease endpoints indirectly, by modifying the underlying risk factors and processes.

The main project undertaken by APMA to date, a model of ischaemic heart disease, is described elsewhere (Chatterjee, Macdonald & Waters, 2007a, 2007b, 2007c). In 2006, Dr Virginia Warren, a member of APMA, drew our attention to early studies of the impact of treatment with Trastuzumab (better known in the UK under its trade-name Herceptin) on survival after breast cancer. This topic was of interest for several reasons.

- (a) Trastuzumab is an early example of a genetically-targetted treatment, a major focus of much research in the pharmaceutical industry.

- (b) Breast cancer is one of the major causes of death among women, in particular of women at ages when insurance cover tends to be in force, therefore of obvious interest to APMA.
- (c) For the reason just stated, breast cancer had been studied intensively at the Genetics and Insurance Research Centre (GIRC) at Heriot-Watt University, which had published actuarial models of breast cancer in a series of papers (Macdonald, Waters & Wekete (2003), Gui *et al.* (2006), Lu, Macdonald & Waters (2007)). Thus the modelling tools were at hand relatively easily.
- (d) Trastuzumab exemplifies the kind of problems that APMA faces.
 - (1) It is a newly-emerging treatment.
 - (2) It treats a major disease with a measurable impact on overall mortality.
 - (3) Epidemiology is just now becoming available, inevitably based on short-term studies.

Moreover, Herceptin has gained a high media profile, and caused much controversy, in the UK, because of the approval process undergone by drugs before they may be prescribed uniformly throughout the National Health Service in England and Wales. The National Institute for Clinical Excellence (NICE) is charged with assessing ‘value for money’ of clinical treatments, a process that can take much time. Until NICE reaches a decision, prescribing practices are decided locally, often called the ‘postcode lottery’. Thus, women with HER2-positive early stage BC were not routinely prescribed Herceptin on the NHS prior to August 2006, as it had not been approved by NICE. This led to a highly politicised campaign for fast track approval, by bodies such as the ‘Fighting for Herceptin’ group, and most notably, ministerial intervention in the supposedly independent workings of NICE. Note that the NHS in Scotland has a separate approval procedure that performs broadly the same functions as NICE but, in this case at least, seems to reach decisions much faster.

The question is: what conclusions may APMA draw from this particular medical advance? Perhaps just as interesting, what lessons can be learned about the actuarial modelling of genuinely new medical advances?

In Section 2 we describe briefly the epidemiology of breast cancer and the recent, earliest, studies of Trastuzumab. In Sections 3 and 4 we formulate and parameterise a model of life history allowing for breast cancer and treatment. We use this to calculate sample term assurance premiums in Sections 5 and 6, and our conclusion are in Section 7.

2. THE EPIDEMIOLOGY OF BREAST CANCER AND TREATMENT WITH TRASTUZUMAB

2.1 *Staging of Breast Cancer*

Our study combines results from two other studies.

- (a) Smith *et al.* (2007) is a study of the survival of two cohorts of women, one treated with Trastuzumab and the other not. This is the source of epidemiology relating specifically to Trastuzumab, but does not by itself furnish the basis for modelling breast cancer in general.

- (b) Lu, Macdonald & Waters (2007) is a study of income protection insurance (IPI) and breast cancer genetics. It incorporates a model of breast cancer based on population data, and also (vital for this study) the progression of breast cancer through various stages.

The treatment available for breast cancer (BC) depends on how far advanced it is when diagnosed. Only patients with *invasive BC* were eligible for Trastuzumab treatment in Smith *et al.*'s study. This is defined as cancer that has spread from its origin in the ducts or lobules of the breast to the surrounding tissue. Depending on the extent of its spread, invasive BC is further categorised as follows:

- (a) *Early breast cancer (Early BC)*: Cancer cells are confined to the breast and armpit area.
- (b) *Locally advanced breast cancer (LABC)*: The tumour is larger than 4cm and may have spread into the lymph nodes or other tissues next to the breast.
- (c) *Metastatic breast cancer*: Cancer cells have spread past the breast and axillary lymph nodes to other locations.

These definitions, based on the SEER Summary Staging Guide (Young *et al.*, 2001) were used in the model of Lu, Macdonald & Waters (2007).

2.2 *The Epidemiology of Breast Cancer and the HER2/neu Oncogene*

'Oncogenes' are a class of genes that promote cell growth and multiplication. If these genes undergo mutations (because of internal or external factors) they can become abnormally activated which means that they will stimulate cell division and promote tumour formation. This abnormal activity can be aggravated if the mutated gene undergoes amplification, meaning that multiple copies of it are reproduced in a single chromosome, hence increasing the output of the affected gene product (see Roses (1999)).

The HER2/neu (HER2) oncogene behaves in this way. Under amplification, it produces too much of the HER2 protein, involved in a transmembrane growth factor receptor, which stimulates cell division. Approximately 15–25% (Smith *et al.*, 2007) of women with Early BC have amplification of the HER2 gene or overexpression of the associated receptor, which we will call 'HER2-positive status'. Breast tumours producing too much of this protein tend to be more aggressive, and HER2-positive status is associated with a particularly bad prognosis, in particular shorter disease-free survival times (meaning survival without recurrence of breast cancer, or death from any cause) and worse overall survival. The greater the gene copy number the worse the prognosis; see Slamon *et al.* (1997).

Note that HER2-positive status is a property of the tumour rather than of the woman who carries it. It is not a variant of the HER2 gene carried in the nuclear DNA and it is not inherited in the usual Mendelian fashion. Any woman is, in principle, capable of developing an HER2 positive tumour. In the absence of any known heritable qualities of HER2 status, we assume that it arises randomly in the population of BC sufferers.

Trastuzumab (better known under the trade name Herceptin) is particular type of drug — a monoclonal antibody — specifically targetted against the activity of the HER2 gene. It is an adjuvant treatment, meaning that it is offered in addition to the conventional

treatments of surgery, chemotherapy and radiotherapy. Early results reported in Smith *et al.* (2007) indicate that Trastuzumab with chemotherapy will have significant effects on the disease-free and overall survival rates of HER2-positive BC patients.

2.3 The Herceptin Adjuvant Trial

We draw epidemiology from an international study by Piccart-Gebhart *et al.* (2005) called the Herceptin Adjuvant (HERA) trial, and a follow-up study of the same patients reported in Smith *et al.* (2007). We give the briefest summary below, referring the reader to the foregoing papers for details.

- (a) The HERA trial involved 5,102 women with HER2-positive early stage invasive BC who have completed a defined course of treatment, including at least four courses of chemotherapy. Patients were randomised at the end of treatment to one of three groups: an observation group that did not receive Trastuzumab (1,698 women), a group that received Trastuzumab for 1 year (1,703 women) and a group that received Trastuzumab for 2 years (1,701 women). The median time from detection of BC to randomisation was 8.4 months (Piccart-Gebhart *et al.* (2005)). Smith *et al.* (2007) did not report results from the third group so we only consider the first two.
- (b) The primary endpoint of the trial was disease-free survival, but the secondary endpoint was overall survival (of more interest to us).
- (c) After 1 year's treatment a significant disease-free survival benefit emerged among the 1-year treatment group compared with the observation group. Women in the latter were then given the option of switching to one of the treatment groups. After 0–48 (median 23.5) months' follow-up from randomisation 90 deaths had occurred in the observation group and 59 in the 1-year treatment group. Smith *et al.* (1997) report Kaplan-Meier estimates for the survival probability 3 years after randomisation of 0.924 for people in the 1-year treatment group and 0.897 for people in the observation group.

The results indicated that Trastuzumab provided a significant overall survival benefit in early stage invasive BC. Such a large benefit is unusual in BC trials, with similar benefits in such a short period having been seen before only in trials for tamoxifen, according to Smith *et al.* (2007) “the most successful treatment ever developed for breast cancer”.

3. SPECIFICATION OF A LIFE HISTORY MODEL

Patients are classed as HER2-positive or HER2-negative depending on the expression or amplification of the HER2 oncogene after the onset of BC.

Macdonald (1999) proposed a Markov framework for incorporating the study of genetics into insurance. We use a similar approach and develop a semi-Markov model to model the effects of the drug Trastuzumab on life insurance. We do not divide the women into different subpopulations as in Macdonald (1999) and subsequent papers because there is no evidence that a woman will be predisposed to develop HER2-positive BC. Instead we model the life history of a woman in the general population who may develop BC. This drug will benefit people with HER2-positive status after onset of BC so the life history includes the events that a person who is diagnosed with BC is tested and has either HER2-positive status or HER2-negative status.

- The model in Figure 1 represents the life history of a woman who may develop BC.
- (a) Women are in the healthy state before the detection of BC. Entry into the various BC states represent diagnosis of BC, rather than the clinical progression of undetected tumours.
 - (b) The medical studies cited above admitted only women with early-stage invasive BC. In terms of the model of Lu, Macdonald & Waters (2007), this includes two of the three categories of invasive BC (see Section 2.1) namely Early BC and LABC. We distinguish these in the model. We do not include separate states to represent the third category of invasive BC, namely metastatic BC. Deaths following detection of BC in its metastatic stage should, ideally, be included in deaths from the healthy state. Thus we assume that Trastuzumab will not be part of the treatment protocol for metastatic BC.
 - (c) Lu, Macdonald & Waters (2007) estimated transition intensities from a healthy state to Early BC or LABC states.
 - (d) After onset of BC, women are classed as HER2-positive or HER2-negative, depending on the expression or amplification of the HER2 oncogene. Based on the occurrence rates of HER2-positive BC from Piccart-Gebhart *et al.* (2005), we assume that 25% of tumours diagnosed at the Early BC and that the LABC stages are HER2-positive.
 - (e) Note that HER2 status is only determined after tumour formation. Unlike earlier actuarial studies of genetics and insurance, which modelled heritable genetic variants, we do not subdivide the population by genotype from birth.

4. ESTIMATION OF INTENSITIES

4.1 Detection Rates of Breast Cancer

We assume aggregate detection rates (ignoring HER2 status) of Early BC and LABC to be those of the general population. Lu, Macdonald & Waters (2007) parameterised their BC detection model based on data from the ‘SEER 9, Regs Public use datasets’, adjusted to distribute unclassified diagnoses uniformly between LABC, Early BC and Metastatic categories. They obtained the detection rates for Early BC and LABC shown in Table 1. We fitted truncated gamma functions (of age x , denoted $^{PopEarlyBC}\mu_x$ and $^{PopLABC}\mu_x$ respectively) to these aggregate rates using least squares minimisation, as follows:

$$^{PopEarlyBC}\mu_x = \frac{0.1756}{\Gamma(9.711)} 0.1085^{9.711} e^{-0.1085x} x^{8.711}$$

$$^{PopLABC}\mu_x = \frac{0.08489}{\Gamma(8.04034)} 0.09430^{8.04034} e^{-0.09430x} x^{7.04034}.$$

We then assume that detection rates of HER2-positive and HER2-negative tumours in our model are 25% and 75%, respectively, of these aggregate rates (see Section 3).

Lu, Macdonald & Waters (2007) used US data, but they showed that UK data was comparable. We assume here that these rates will be relevant for people in the HERA trial.

4.2 Baseline Mortality

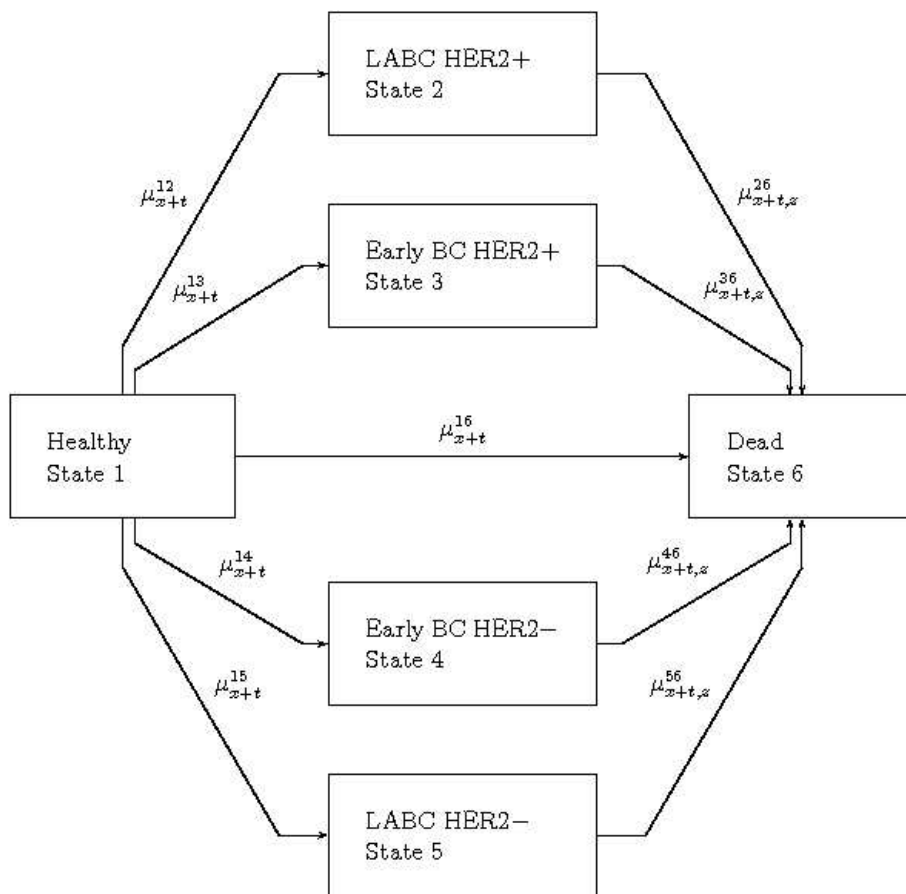


Figure 1: The life history model for a woman who may develop breast cancer.

Table 1: Detection rates of invasive Early BC and LABC, based on the SEER 9 Regs Public use database, from Lu, Macdonald & Waters (2007). Rates are per 100,000 woman-years.

Age	Early BC	LABC	Age	Early BC	LABC
20–24	0.6	0.5	55–59	150.4	95.2
25–29	3.9	3.6	60–64	183.5	105.8
30–34	12.8	11.2	65–69	220.6	109.8
35–39	31.4	25.9	70–74	247.1	114.8
40–44	63.9	45.7	75–79	266.9	117.7
45–49	101.8	70.1	80–84	262.1	115.5
50–54	124.8	81.8	85+	233.7	113.1

In our model, a woman diagnosed with BC cannot return to the normal healthy state. This means that mortality before and after onset of BC will be different.

There is no evidence that the HER2 gene affects the mortality of a person who does not develop BC. Therefore mortality from the healthy state will be that of the general population — which we take to be the ELT15 life table — adjusted to take into account deaths from the BC states represented in the model. We confined our attention to ages 20–65, bearing in mind the ages of the subjects of the HERA trial, and the ages of most financial relevance. For computational convenience we fitted the following piecewise-parametric model to the ELT15 Females table:

$$\begin{aligned}\mu_x^{ELTFemales} &= 0.0001957e^{0.0225135x} & 20 \leq x \leq 29 \\ \mu_x^{ELTFemales} &= 0.001230507 - 0.00002946724x & 29 < x < 30 \\ \mu_x^{ELTFemales} &= 0.0000153e^{0.104x} & 30 \leq x \leq 65.\end{aligned}$$

From these we must remove deaths of women diagnosed with Early BC or LABC. Lu, Macdonald & Waters (2007) fitted the following ratio (denoted $\phi(x)$ at age x) of the number of deaths from BC to the total number of deaths, based on UK population data from 1990–92:

$$\phi_x = \begin{cases} \frac{6.58}{\Gamma(15.37)} (0.32^{15.37} e^{-0.32x} x^{14.37}) & x \leq 54 \\ 0.681664 - 0.0141702x + 0.0000756614x^2 & x > 65 \end{cases}$$

(with linear interpolation between these formulae between ages 54 and 65). We use this although it is not strictly correct, since it includes the deaths of women whose BC was diagnosed at the metastatic stage. It seems reasonable to assume that the effect will be small, because recent improvements in cancer detection procedures have led to increased early detections of the disease (*i.e.* before metastasis). Hence in our model:

$$\mu_x^{16} = \mu_x^{ELTFemales}(1 - \phi_x).$$

4.3 Mortality After Onset of Breast Cancer

As mentioned earlier, HER2-positive status is associated with a worse prognosis after onset of BC, but we cannot find any quantitative expression of this. Therefore we first assume that, without treatment with Trastuzumab, mortality after onset of BC is the same for HER2-positive and HER2-negative women. Since we know this to be unrealistic, we test the sensitivity of the results to this assumption in Section 6.

Lu, Macdonald & Waters (2007) modelled mortality after onset of BC and proposed a ‘standard’ mortality term depending on age, denoted $\mu_x^{standard}$, plus a term, denoted μ_z^{stage} , depending on the stage at, and duration z since, diagnosis of BC. They took the standard age-dependent term to be $\mu_x^{standard} = \mu_x^{ELT15Females}$ and fitted the following functions μ_z^{stage} of duration z :

$$\begin{aligned}\mu_z^{EarlyBC} &= -3.722 \times 10^{-3} + 1.028 \times 10^{-2}z - 1.996 \times 10^{-3}z^2 \\ &\quad + 1.685 \times 10^{-4}z^3 - 6.507 \times 10^{-6}z^4 + 9.388 \times 10^{-8}z^5 \quad (\text{Early BC}) \\ \mu_z^{LABC} &= +2.652 \times 10^{-2} + 3.024 \times 10^{-2}z - 7.370 \times 10^{-3}z^2 \\ &\quad + 6.722 \times 10^{-4}z^3 - 2.752 \times 10^{-5}z^4 + 4.127 \times 10^{-7}z^5 \quad (\text{LABC}).\end{aligned}$$

Table 2: Level net premium, unit term assurance to age 65 (Trastuzumab not available).

Age	Premium	Age	Premium	Age	Premium	Age	Premium	Age	Premium
20	0.00132	30	0.00206	40	0.00335	50	0.00555	60	0.00931
21	0.00137	31	0.00216	41	0.00352	51	0.00585	61	0.00980
22	0.00143	32	0.00227	42	0.00370	52	0.00615	62	0.01033
23	0.00150	33	0.00238	43	0.00389	53	0.00648	63	0.01089
24	0.00156	34	0.00250	44	0.00409	54	0.00682	64	0.01149
25	0.00164	35	0.00262	45	0.00431	55	0.00718		
26	0.00171	36	0.00275	46	0.00453	56	0.00756		
27	0.00179	37	0.00289	47	0.00476	57	0.00797		
28	0.00187	38	0.00304	48	0.00501	58	0.00839		
29	0.00196	39	0.00319	49	0.00528	59	0.00884		

4.4 Mortality After Treatment With Trastuzumab

In Section 2.3 we mentioned that Smith *et al.* (2007) reported Kaplan-Meier estimates of overall survival rates 3 years after randomisation (0.924 for the treated group, 0.897 for the untreated group). Such limited information supports only the simplest model of the relationship between mortality with and without treatment. We assume:

- (a) proportional hazards; that is, the force of mortality with treatment is a constant multiple of that without treatment; and
- (b) treatment begins 8.4 months (the median time) after the tumour is detected (see Section 2.3).

The 3-year survival probabilities above correspond to a hazard ratio of 0.7271724.

As mentioned in Section 2.3 we have no data on the survival rate for those women who received Trastuzumab for 2 years. This group might, in due courae, yield important results, as a peak of relapses in the cancer occurs between 18 and 24 months (Piccart-Gebhart *et al.* (2005).

5. LIFE INSURANCE PREMIUMS

5.1 Numerical Methods

The model in Figure 1 is semi-Markov; the intensities from states 2, 3, 4 and 5 to state 6 are duration dependent. Numerical methods for handling models of this kind have been described elsewhere (see for example Guitierrez & Macdonald (2004)) and we refer the reader there. We need only state that we need to write down the integro-differential equations for occupancy probabilities and prospective policy values, and solve them numerically. We used a routine based on Simpson's Rule from Press *et al.* (1996). We considered only term assurance policies sold to healthy womn and expiring at age 65, and for all expected present values we used an interest rate of 5% *p.a.* effective.

5.2 Premiums Assuming HER2 Status Does Not Affect Mortality

In this Section we assume that the mortality of HER2-positive and HER2-negative women after onset of BC is the same. Table 2 shows samples of the continuous level

Table 3: Level net premium, unit term assurance to age 65 (Trastuzumab available).

Age	Premium	Age	Premium	Age	Premium	Age	Premium	Age	Premium
20	0.00131	30	0.00204	40	0.00333	50	0.00553	60	0.00929
21	0.00136	31	0.00215	41	0.00350	51	0.00582	61	0.00979
22	0.00142	32	0.00225	42	0.00368	52	0.00613	62	0.01033
23	0.00149	33	0.00236	43	0.00387	53	0.00646	63	0.01089
24	0.00155	34	0.00248	44	0.00407	54	0.00680	64	0.01149
25	0.00162	35	0.00261	45	0.00428	55	0.00716		
26	0.00170	36	0.00274	46	0.00450	56	0.00754		
27	0.00178	37	0.00287	47	0.00474	57	0.00795		
28	0.00186	38	0.00302	48	0.00499	58	0.00837		
29	0.00195	39	0.00317	49	0.00525	59	0.00882		

net premiums assuming Trastuzumab is not available. Table 3 shows the corresponding premiums after the introduction of Trastuzumab. The difference is shown in Figure 2, in terms of the percentage changes in the premiums. The greatest effect is for women age 28, for whom the premium reduces to 99.3% of its original amount.

6. PREMIUMS ALLOWING FOR DIFFERENTIAL MORTALITY

Slamon *et al.* (1997) found that tumours with DNA containing more than 5 copies of the HER2 gene were associated with shorter overall survival times than tumours with no amplification, a distinction we ignored in Section 5. More generally, they found a negative correlation between gene copy number and survival time. They did not quantify this in a way directly useable in our model, however. Here, we carry out a simple sensitivity analysis, by assuming that the mortality of women with HER2-positive BC is twice that of women with HER2-negative BC. So that aggregate mortality after BC onset remains unchanged we multiply $\mu_{x,z}^{26}$ and $\mu_{x,z}^{36}$ by 1.6, and $\mu_{x,z}^{36}$ and $\mu_{x,z}^{46}$ by 0.8.

The effect of this assumption is also shown in Figure 2, in terms of percentage of the original premium. The greatest change after the introduction of Trastuzumab is 99.102%, slightly greater than before, for women 30 years old, approximately the same as before. We conclude that only a very substantial difference of mortality based on HER2 status would materially alter our results.

7. CONCLUSIONS

Trastuzumab is of interest to APMA because it is a novel treatment for a major cause of disease and death. It is one of the first of a new class of treatments — monoclonal antibodies — that could have much wider impact. Early studies, based on at most three years of follow-up, suggest that its impact may equal that of the most significant ‘breakthrough’ drug of the past, tamoxifen. However, it is only suitable for use in about 15–25% of cases, because it targets the over-expression of a single gene.

Using a semi-Markov model, we estimated the impact of Trastuzumab on selected life insurance regular net premiums (term assurances expiring at age 65) to be a reduction of slightly less than 1%. We make the following observations.

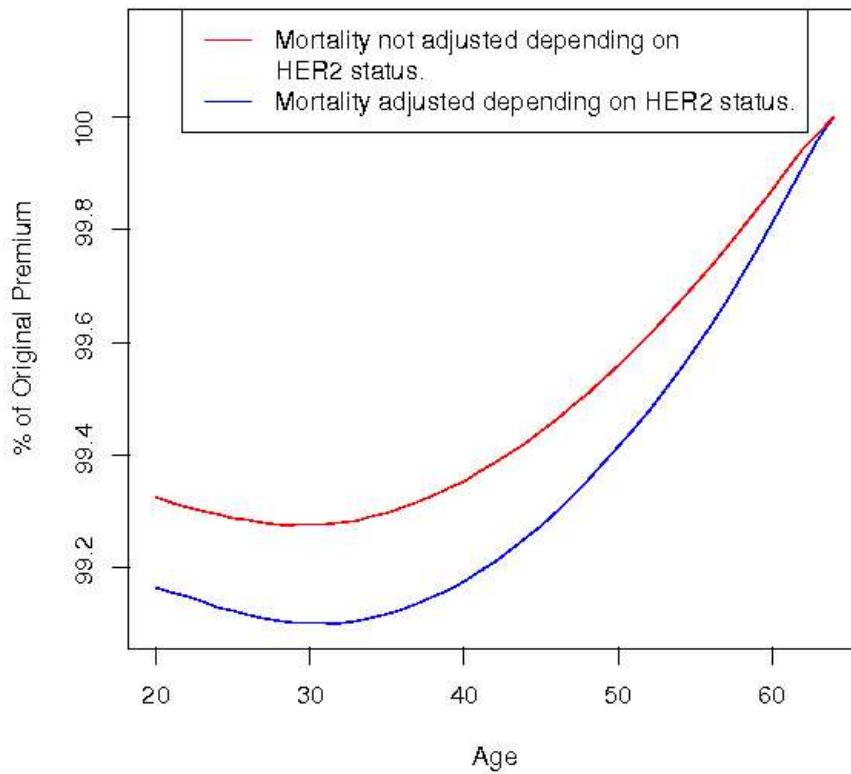


Figure 2: The effect of Trastuzumab on life insurance premiums: premiums for term insurance expiring at age 65, with Trastuzumab treatment, as a proportion of those without Trastuzumab treatment.

- (a) Some parameters of our model are very uncertain, in particular we have extrapolated the long-term effect of trastuzumab treatment from a short-term study, by assuming a constant hazard ratio. If the treatment effect diminishes over time, the difference in premiums will be smaller than we have found. At present, this is completely unknown.
- (b) While 1% is a rather small number, it results from the possible impact of *one* treatment on approximately 25% of cases of *one* type of cancer. This treatment is novel and may be the precursor of a whole class of new treatments for cancer. In that context, 1% may be a large number, even if it may be accepted only as an order of magnitude.
- (c) This study illustrates several fundamental problem faced by APMA.
 - (1) As research leads to specific, highly-targetted treatments, acting through intermediate risk factors such as HER2 status, more detailed models of disease processes are needed to assess their contribution to the overall burden of disease (and its financial consequences). The construction of even quite simple models is very demanding.
 - (2) The terms of long-term insurance contracts are such that the true financial effects of new medical treatments may always be beyond reach: soon after introduction because epidemiology takes time; and later because medical studies often focus on a few key measures of effectiveness, such as 5-year or 10-year survival rates.

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