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ORIGINAL RESEARCH

Estimating Public Economic Gains from Early Breast Cancer and Curative Treatment: A Case Study in Human Epidermal Growth Factor Receptor (HER-2) Positive Targeted Therapies

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ABSTRACT

Introduction: Cancer diagnosis influences the choices that patients make regarding current and future labor market activity. These choices have implications for governments based on resulting changes in taxes paid and benefits received. In this analysis we explore how human growth receptor 2 (HER2)-positive residual invasive breast cancer and different treatments influence government accounts excluding health costs.

Methods: HER2-positive early breast cancer (eBC) health states from a published disease model were used to establish likelihood of working and wage impact at different stages of disease. The indirect productivity losses for an average woman aged 49 years were translated into fiscal consequences to government by applying an established government perspective-modeling framework. The fiscal projections (discounted) include gross tax revenue by disease stage, government transfer costs related to time off work and early retirement ,and net fiscal balance (e.g., gross taxes—transfers) in three countries Canada, Portugal, and Brazil.

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Results: The net fiscal balance in Canada for a healthy woman was C$109,551 compared with a HER2-positive eBC woman treated with trastuzumab emtansine (C$69,767) or trastuzumab (C$62,971). A similar pattern was observed in the three countries but reflecting the overall tax burden in each country, labor force activity, and available public benefits. Age at diagnosis was an important determinant of the likely net fiscal balance, as this influences the remaining working years.
Discussion: Women diagnosed with HER2-positive eBC were estimated to pay less lifetime gross taxes and receive more in sickness benefits compared with healthy women. Treatments that improve outcomes are likely to offer fiscal gains for government from improved work force participation.

Keywords: Fiscal analysis; Cost–benefit analysis; HER2-positive breast cancer; Life course modeling; Cancer survival

Key Summary Points

Following breast cancer diagnosis women face many personal changes that can influence their current and future employment activity.

These labor market choices can have broader economic consequences for government attributed to lost tax revenue and increased spending on public support programs.

Early diagnosis and effective interventions for women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer can improve health outcomes but can also positively influence fiscal metrics for government in terms of tax revenue and reduced spending on public support programs.

INTRODUCTION

Cancer and its treatments can have wide-reaching consequences that not only impact diagnosed patients but also extend to the entire household [1]. While the physical and quality of life impact of cancer on patients has been extensively studied [2], less is known about the impact of cancer diagnosis on the quality of life, mental health, and economics of household members [3]. Research has shown that cancer diagnosis can negatively influence household finances where it is common for patients to experience reduced labor force participation and income losses following diagnosis and treatment [4, 5]. Specifically for women diagnosed with breast cancer, it is not uncommon to experience wage losses and be out of the workforce for extended periods of time after diagnosis [6–9]. The financial effects can also extend to partners, caregivers, and family members of women with breast cancer where income loss and time off work are known to occur at a time when families are experiencing increased out-of-pocket expenses [10–12]. Although many cancer survivors will return to work following successful treatment, they frequently experience wage losses and employment discrimination for years to follow [7, 13].

Chronic health conditions and acute health events, such as cancer, can negatively impact both at the household and at the public economic level, as they can cause fiscal strain for governments owing to demands that arise from reduced numbers of tax-payers available to pay for public programs [14–16]. Conversely, healthy populations and the prevention of future health events can have positive fiscal effects for governments, as a healthy population helps to sustain tax revenue and reduce demand for public benefits [15, 17, 18]. The current labor shortages experienced around the world have brought to light the importance of maintaining a healthy workforce that helps drive economic growth. In the near future, as the population ages, maintaining a healthy workforce will become even more crucial to support the rising costs of public funding [19]. While many cancers primarily impact patients who have already

left the workforce, some can impact patients in the peak of their productive years.

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer-related deaths in women worldwide [20]. Approximately 15–20% of BCs overexpress or have the gene amplification for human epidermal growth factor receptor 2 (HER2-positive) [21]. The prognosis for HER2-positive early BC (eBC) was significantly improved following the introduction of the HER2-targeted agents. Since metastatic disease is currently incurable, improving the results of eBC therapy when the disease is still localized to the breast and regional lymph nodes but without distant metastases offers the best chance of cure and possible return to the workforce. Given the curative intent of HER2-positive eBC, and that it often afflicts relatively younger women, this would suggest the need for applying a broader economic perspective to illustrate some of the important costs and benefits faced by governments that can inform screening practices and interventions to optimize outcomes [20].

To illustrate the range of costs that fall on governments as a result of women diagnosed with HER2-positive eBC, we apply an established fiscal modeling framework integrated with previously published disease modeling [15]. The fiscal modeling described here shares many similarities with cost-effectiveness analysis in terms of the underlying natural history of disease and survival outcomes; however, it is enriched by translating how changes in outcomes influence work force participation and returning to work, an important metric for indicating a return to normalcy following treatment for patients previously diagnosed with cancer [23]. Importantly, our analysis excludes healthcare costs associated with breast cancer, which are well documented [22]. Instead, our focus is on other costs that impact government in relation to breast cancer, including changes in tax revenue from reduced work activity and public support benefits provided when women are unable to work due to their condition, i.e., transfer costs. We report findings from the analysis in three countries with unique health systems and social benefits protection: Canada, Portugal, and Brazil. It is envisaged that the work reported here can highlight the advantages of applying a broader government perspective to evaluate new policies and interventions for establishing treatment priorities.

METHODS

The fiscal analysis described here applies human capital theory, which translates changes in eBC morbidity and mortality into changes in expected tax revenues and transfer costs, i.e., social benefits payments, based on the impact of the condition on current and future employment activity per person. The fiscal analytic framework is based on accepted modeling practices used by central governments for evaluating the financial effects of different government policies [24, 25]. In the context of health, the fiscal analytic framework described here can demonstrate how resource allocation decisions and access to medical treatments for eBC can influence cross-sectorial governmental fiscal accounts [15]. At the core of the fiscal analysis is disease modeling, which determines how patients transition through health states analogously to a traditional cost-effectiveness model. The main difference from conventional healthcare economic evaluations is that the present framework accounts for how breast cancer influences short- and long-term labor force activity rates and resulting taxes paid, disability costs, transitions to retirement, and death. It should be noted that, in this fiscal approach, death has both positive and negative fiscal consequences, which are quantified within the framework.

Fiscal projections were based on comparing the general population (the general population is used as a proxy of the healthy population, i.e., the population that is breast-cancer-free) from each country, which was deemed as a population unaffected by BC, with patients diagnosed with HER2-positive eBC with residual invasive disease, treated with HER2-targeted agents that can be used in the adjuvant setting, i.e., trastuzumab, or trastuzumab emtansine (T-DM1). This population was selected for the fiscal analyses as patients with presence of residual

invasive disease (RD) after neoadjuvant therapy (i.e., non-pCR) are at an increased risk of disease recurrence [26]. Preventing recurrences may result in fiscal gains, as it may maintain patients' productivity levels. The starting age in the model was 49 years based on the population recruited into the clinical trial on which this analysis was based.

The HER2-positive eBC disease modeling included six health states: residual invasive disease-free survival (iDFS) on treatment; iDFS off treatment; non-metastatic recurrence; remission; metastatic setting; and death (Fig. S2). A lifetime horizon was applied and transitions between health states were defined on the basis of a previously reported clinical trial [26]. All patients entered the model in the "iDFS on treatment" health state. To model the the number of patients with disease recurrence, iDFS survival curves from the pivotal KATHERINE clinical trial were extrapolated over a lifetime horizon, and adjusted for cure proportion, duration of treatment effect, and background risk of death [26]. Further details of the disease modeling have been previously described in the literature and applied in our analysis, however health costs and other traditional economic evaluation outcomes, e.g., life years; quality-adjusted life years (QALYs), were excluded from our analysis, as the focus here is on non-healthcare governmental costs [27]. Therefore, the disease model reported here is instead used to calculate the time point of transitions between health states and survival [28]. This would then inform what fiscal states the patient would reside in under the various adjuvant treatment options. In the Supplementary Material, Fig. S3 presents how the proportion of patients in various health states changes over the model time horizon for the following health states: iDFS (on treatment and off treatment), recurrence (non-metastatic, remission, and metastatic setting), and death. For additional details on the disease modeling and a summary of key model assumptions and inputs, see Supplemental Material Section 3.

The linkage between eBC health states in the disease model and fiscal states (employed, inactive, disabled, retired, on sick leave) was established by conducting a targeted literature review for three countries, Canada, Portugal, and Brazil, to understand how patients change their employment activity following diagnosis, recurrence, and treatments for eBC. For each country we report findings in local currency, as the results are not comparable between countries. We account for death as a fiscal state in which there is no employment and no taxes paid, and no transfer benefits received. A targeted search strategy was developed to identify how eBC cancer diagnosis and successfully treated eBC survivors influences their labor force activity. Additionally, we sought to identify studies that report how metastatic disease might influence the ability or willingness to remain in the workforce. The details of the targeted literature search for informing employment transitions are provided in the Supplementary Materials. The core linkage studies that define labor force transitions within the disease model relative to the healthy population are described in Table 1 below.

Moreover, the fiscal model was populated with a range of macroeconomic data and age-specific population data that can be linked to earnings and taxes. The macroeconomic parameters consisted of inflation, wage growth, and discount rate. The model accounted for both direct and indirect taxes. Direct taxes were estimated from the tax wedge applied to age-specific earnings and indirect taxes estimated from the percentage of disposable income applied to the prevailing value-added tax (VAT) rate in each country. A list of the parameters from each country is provided in the Supplementary Tables S4–S10.

Fiscal Analysis Description

The fiscal analysis was built on the basis of the natural history of disease of a previously published cost-effectiveness model [27]. The latter simulated the disease on the basis of seven health states including death. Based on the proportions of patients in each health state of the disease model, patients were further distributed to five mutually exclusive fiscal stages. The description of health states and the link with fiscal stages is illustrated in Table 2. The

Table 1 Identified studies reporting impact of eBC outcomes on labor outcomes for estimating fiscal impact and used as model inputs

Fiscal metric	Rate applied in model to health state
Probability of short-term absence post-diagnosis	0.85 [29]
Risk ratio for exiting employment during BC recovery	1.35 [8]
Risk ratio for retirement of BC survivors	1.43 [8]
Probability of short-term absence BC recurrence	0.83 [29]
Risk ratio for exiting employment after achieving remission in recurrence	2.24 [8]
Risk ratio for retirement after achieving remission in recurrence	1.51 [8]
Proportion of women working in metastatic disease	0.35 [30]
Wage loss in spouses following BC diagnosis	2.4% [11]

symbols used are for illustrative purposes only, to demonstrate how people are likely distributed in different working states on the basis of their condition. Based on an average age of the cohort, gross annual income from wages was calculated for each combination of fiscal stages and health states. Subsequently, age-specific workforce participation rates were applied to income by age to estimate productivity losses for those with eBC compared with the healthy population. Direct and indirect tax revenue was then calculated by applying the tax wedge and the proportion of income that goes to indirect tax to gross annual earnings. Transfers costs incurred by governments consisted of long-term sick leave costs, caregiver benefit costs, disability, and retirement pensions. Sick leave costs were modeled only for patients in the health states "iDFS on treatment" and "non-metastatic recurrence." Sick leave costs were estimated as a proportion of earnings from employment. Moreover, caregiver costs were estimated for patients entering and during the health state of "metastasis." The details of the methods used are presented in the supplement. The net fiscal balance was then calculated by deducting all transfers received from the government from the lifetime gross taxes. Two scenarios were reflected in the net fiscal analysis: (1) excluding longevity costs attributed to pensions after the age of 65 years and (2) a scenario that includes the longevity costs attributed to survival, i.e., pension payments.

To explore the consequences of eBC on work activities and resulting net fiscal balance, we performed a sensitivity analysis of the parameters reported in Table 1 by varying each ±25% in a sensitivity analysis. This is particularly important, as we applied the same work-disrupting consequences identified in the literature in the three countries in our modeling, which are likely to vary in real life.

The analysis described here is based on a modeling study developed from previously published sources. No subjects were enrolled in this evaluation, and no individual patient data has been used in this analysis. Ethics approval was not required for conducting this study. The disease modeling and fiscal analyses were performed using Microsoft Excel.

RESULTS

The projected fiscal costs from the baseline age in the model, for the three scope countries are described in Table 3, based on respective currencies, from age 49 years over the remaining lifetime. Fiscal outcomes are presented in 2021 prices. Compared with the healthy population, the projected productivity and future gross tax revenue was lower among patients with eBC receiving treatment with either T-DM1 or trastuzumab in all countries. For patients with eBC, there was also an increase in sick leave costs observed in all countries. In general, the fiscal parameters move in a similar fashion for all three countries, although the overall values differ. The net fiscal balance has been presented

Table 2 Illustration of the link between health states and fiscal stages

Health states (j = 1-7) >>	General10 healthy population	iDFS on treatment	iDFS off treatment	Non-metastatic recurrence	Remission	Metastatic recurrence	Death
Fiscal states (I =1-5)>>							
Employed						-	Not applicable
Inactive				-		-	
Disabled				-			
Retired							
On-Sick leave			-				

Employed: Patients participating in the workforce based on local age-specific workforce participation rates. Inactive: Patients who do not participate in the workforce, are not retired or on long-term sick leave and are not recipients of disability allowances. Disabled: Receiving disability pension until the age of retirement. Post-retirement disability is added to state pension. Retired: Patients who are retired due to old age or retired prematurely, receiving retirement state pension. On sick leave: Economically active patients on long-term sick leave due to their disease, receiving long-term sick leave benefits.

Employed: patients participating in the workforce based on local age-specific workforce participation rates. *Inactive*: patients who do not participate in the workforce, are not retired, or on long-term sick leave and are not recipients of disability allowances. *Disabled*: receiving disability pension until the age of retirement. Post-retirement disability is added to state pension. *Retired*: patients who are retired owing to old age or retired prematurely, receiving retirement state pension. *On sick leave*: economically active patients on long-term sick leave owing to their disease, receiving long-term sick leave benefits

on the basis of deducting future government costs prior to the age of 65 years and those attributed to beyond the age of 65 years (longevity). The net fiscal balance was reduced in people with eBC compared with the healthy population in all three countries when longevity costs were excluded (Table 3, column g). When the costs of longevity were included in the analysis, the costs were further reduced for Canada and Portugal, and became negative in Brazil, which is explained by the difference in tax revenue in relation to transfers (Table 3, column f).

The time in each fiscal state is summarized in Table 4. The time spent in each fiscal state was expressed in terms of undiscounted life years (LYs) lived in each stage. Overall, the total number of LYs lived and productive LYs lived was considerably lower in the eBC populations compared with healthy individuals. Additionally, for all three countries, eBC treatment with trastuzumab overall led to lower productive life years lived (PLYL), life years lived in disability (DLYL), retirement life years lived (ReLYL), and life years lived in economic inactivity (InLYL) compared with patients with eBC treated with

Table 3 Lifetime discounted fiscal impact of HER2-positive eBC and comparative differences per person in three countries comparing healthy population with those treated with T-DM1 or trastuzumab shown in local currency (2021 prices) and discounted

			Fiscal perspective							Societal
			Gross tax revenue (a)	Sick leave costs (b)	Caregiver costs (c)	Early retirement costs—age < 65 years (d)	Pension costs* (e)	Net fiscal balance† (f)	Net fiscal balance excluding longevity‡ (f)	Productivity (h)
Canada (values in C$)	Populations	Healthy	254,847	0	0	24,551	145,296	109,551	230,296	667,139
		T-DM1	171,569	4777	2621	25,147	94,405	69,767	139,024	449,134
		T	155,728	5068	4015	24,524	83,673	62,971	122,121	407,664
	Incremental analysis	T-DM1 versus healthy	(83,278)	4777	2621	596	(50,891)	(39,785)	(91,272)	(218,005)
		T versus healthy	(99,120)	5068	4015	(28)	(61,623)	(46,580)	(108,175)	(259,475)
Portugal (values in €)	Populations	Healthy	176,676	0	0	19,019	135,285	41,391	157,656	321,813
		T-DM1	91,825	3833	5113	17,866	62,912	19,967	65,013	167,258
		T	83,431	4069	7642	17,604	56,158	15,561	54,115	151,969
	Incremental analysis	T-DM1 versus healthy	(84,851)	3833	5113	(1,153)	(72,373)	(21,423)	(92,644)	(154,555)
		T versus healthy	(93,245)	4069	7642	(1415)	(79,127)	(25,829)	(103,541)	(169,845)

Table 3 continued

			Fiscal perspective							Societal
			Gross tax revenue (a)	Sick leave costs (b)	Caregiver costs (c)	Early retirement costs—age < 65 years (d)	Pension costs* (e)	Net fiscal balance† (f)	Net fiscal balance excluding longevity‡ (f)	Productivity (h)
Brazil (values in R$)	Populations	Healthy	371,378	0	0	6921	297,678	73,700	364,457	603,866
		T-DM1	138,540	16,822	293	15,866	341,628	(220,203)	105,559	225,268
		T	126,265	17,268	430	19,588	299,749	(191,182)	88,979	205,309
	Incremental analysis	T-DM1 versus healthy	(232,838)	16,822	293	8945	43,950	(293,903)	(258,898)	(378,598)
		T versus healthy	(245,113)	17,268	430	12,667	2071	(264,882)	(275,478)	(398,558)

Negative numbers appear in brackets

T-DM1 trastuzumab emtansine, *T* trastuzumab

*Includes early retirement costs

†Net fiscal balance are based on pension costs over lifetime: $f = a - (b + c + e)$

‡Net fiscal balance excluding longevity costs up to age 65 years: $g = a - (b + c)$

Table 4 Time spent in each fiscal state (undiscounted life years)

	LYL	PLYL	DLYL	ReLYL	SiLYL	InLYL
Canada						
Healthy population	35.15	11.91	5.21	16.40	–	1.63
T-DM1	29.25	7.15	4.83	14.83	0.59	1.85
Trastuzumab	26.19	2.66	3.77	12.72	0.63	1.64
Portugal						
Healthy population	35.15	12.10	2.02	19.01	–	2.01
T-DM1	29.25	7.24	2.25	16.88	0.60	2.28
Trastuzumab	26.19	2.69	1.43	14.50	0.64	2.03
Brazil						
Healthy population	35.15	9.86	2.79	–	–	4.20
T-DM1	29.25	3.64	2.89	17.25	0.66	4.82
Trastuzumab	26.19	1.84	1.97	14.84	0.68	4.32

Differences in time in fiscal states is adjusted for female labor force participation rate
LYL life years lived, *PLYL* productive life years lived, *DLYL* life years lived in disability, *ReLYL* retirement life years lived, *SiLYL* life years lived with sick leave, *InLYL* life years lived in economic inactivity

T-DM1. Comparing the three countries, the overall trend appears to be in a similar direction, although the total number of InLYL was considerably higher in Brazil compared with Canada and Portugal.

We hereby present data on how age at diagnosis and treatment influences gross tax revenue. Figure 1 below illustrates gross taxes for the healthy population compared with patients with eBC treated with T-DM1 or trastuzumab in Canada. As there are similarities between countries, we highlight only the data for a single country; however, the corresponding results for Portugal and Brazil can be found in Figs. S1 and S2. The residual gross tax value declines for all individuals in the healthy population over their remaining working life. Those treated for residual invasive eBC start from a lower base net tax and decline steadily over the projected time horizon. The country with the largest differences among the baseline ages assessed was Canada.

Sensitivity Analysis

Figure 2 presents the percentage change to the incremental analyses' results when compared with the base case values reported in Table 3. The sensitivity analysis indicated that net fiscal balance results were most sensitive for short-term absences post-diagnosis and for the likelihood of retiring during recovery period. Across the inputs tested, the net fiscal balanced results did not vary by more than 10% in any case.

DISCUSSION

The fiscal projections presented across three countries demonstrate that patients with HER2-positive eBC with residual invasive disease experience more work losses compared with the healthy population, resulting in projected lower taxes paid over remaining working years. The fiscal results presented here are also compared with more traditional outcomes of societal perspectives using productivity losses. Overall, the patients with HER2+ eBC are projected to have

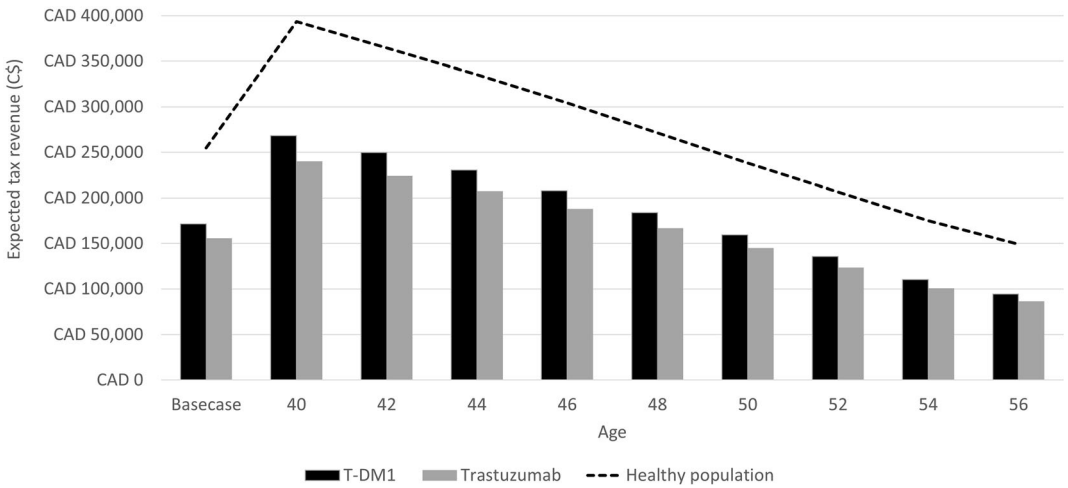

Fig. 1 Present value of expected gross tax revenue by age of diagnosis and treatment of patients with eBC Canada (local currency, 2021)

			Percentage change compared to base case value for the Net Fiscal Balance					
			Canada		Portugal		Brazil	
Parameter	Value range		T-DM1 vs. healthy	T vs. healthy	T-DM1 vs. healthy	T vs. healthy	T-DM1 vs. healthy	T vs. healthy
Short-term absence post diagnosis	Low	0.64	8%	7%	8%	7%	1%	2%
	High	1.00	-6%	-5%	-6%	-5%	-1%	-1%
Short-term absence post recurrence	Low	0.62	0%	1%	0%	1%	0%	0%
	High	1.00	0%	-1%	0%	-1%	0%	0%
RR inactive in recovery	Low	1.26	4%	3%	5%	3%	1%	1%
	High	1.44	-4%	-3%	-5%	-3%	-1%	-1%
RR retired in recovery	Low	1.32	8%	5%	7%	5%	0%	0%
	High	1.54	-6%	-4%	-7%	-5%	0%	0%
RR inactive in recurrence	Low	1.93	0%	1%	0%	1%	0%	0%
	High	2.55	0%	-1%	0%	-1%	0%	0%
RR retired in recurrence	Low	1.38	0%	0%	0%	0%	0%	0%
	High	1.64	0%	0%	0%	0%	0%	0%
Proportion women working in mBC	Low	0.26	-3%	-3%	-3%	-3%	0%	-1%
	High	0.44	3%	3%	3%	3%	0%	1%
Spouse wage loss following BC diagnosis	Low	0.02	0%	0%	0%	0%	0%	0%
	High	0.03	0%	0%	0%	0%	0%	0%

Fig. 2 Sensitivity analysis applied to employment metrics varying by ±25% for lifetime net fiscal balance

a considerable negative impact on the governmental net fiscal balance as well as considerable productivity losses to society when compared with a healthy population. To the government, only part of the societal productivity losses will be directly attributable to the government's fiscal accounts (e.g., income tax). Unlike the societal perspective, the fiscal perspective presented here captures those costs that typically fall directly on governments. The model indicates that reducing the proportion of women who develop recurrences and metastasis will have positive impact on the fiscal balance, as it will increase the number of LYs lived and the number of productive life years lived.

The results are presented in the original currency, as it is not feasible to compare costs across countries. This is because employment activity rates and social benefit programs, which influence fiscal costs, are different across countries. Consequently, there are likely to be variations in tax losses and transfer costs observed across different countries, which is evident in our work. Furthermore, the underlying disease modeling considers no differences in treatment efficacy across countries, which could, in theory, influence fiscal projections in each country. The sick leave costs reported here are caused by patients with residual invasive eBC discontinuing work while receiving treatment, although

the fiscal losses are a small proportion of lifetime taxes paid over their remaining lifetime. The reality is that many survivors return to work, which has been reported at around 43–93%, although there is considerable variation across countries that is further impacted by sociodemographic and clinical factors [31]. In addition, the amount of taxes paid by partners as caregivers is also reduced, although there is notable variation across countries. Comparing rows (b) and (c) in Table3 indicates that reduced taxes for patient and caregiver are comparable in Canada and Portugal; however, caregiver tax losses equate to a smaller proportion in Brazil. While we believe our approach is generalizable to other countries, it is important to recognize that the magnitude of effect will vary depending on cultural and policy factors rather than clinical outcomes.

Previous studies have documented the indirect societal losses attributable to breast cancer owing to reduced work activity [32]. The analysis described here has applied a different perspective by estimating how breast cancer imposes fiscal gains and losses for government applying a "government perspective" framework. A previous study in Europe has used top-down prevalence-based modeling approach to estimate public revenue losses in a single year attributed to breast cancer in Poland. The authors report tax losses of €211 million in a single year in which social insurance contributions and value added taxes (VAT) were the main revenue losses from breast cancer [33]. These results are not directly comparable to our findings, which use a bottom-up cohort modeling approach and projects costs over subsequent years. Nonetheless, the results described by Łyszczarz and Nojszewska illustrate the magnitude of the aggregate effects felt by government in relation to breast cancer in a single year.

The analysis described here helps to illustrate how cancer recurrence, such as eBC, can impact government tax revenue and social benefit costs. Despite advances achieved with the addition of 1 year of trastuzumab to standard (neo and adjuvant) chemotherapy in the treatment of patients with HER2-positive eBC, it is estimated that up to one in four patients will experience recurrence within 10–11 years of diagnosis [34, 35]. Since metastatic disease is currently incurable, improving the results of initial therapy, when the disease is still without distant metastases, offers the best chance of cure. For patients who are not cured, improved initial therapy may also lead to meaningful delays in disease recurrence and death. The results described in our analysis illustrate the likely fiscal gains from preventing disease recurrence in patients with residual invasive disease after neoadjuvant therapy. By comparing gross tax revenue for T-DM1 and trastuzumab in Table 3, we can see the likely fiscal benefits for governments from reducing the proportion of women with recurrences. The analysis here was informed by a study illustrating that 83% of women in Canada with recurrence will experience work loss during the treatment period [29]. For women in the metastatic health state, we apply the observation that only 35% of women continue to work during the metastatic period [30]. Both of these elements were used to adjust the work activity rate by age for women on which the fiscal projections are based. These findings suggest that new treatment options that reduce the risk of recurrence are still required for patients with HER2-positive eBC, and particularly those with high risk of recurrence that are likely to generate fiscal returns.

Women experiencing BC face a wide range of choices that can influence their household finances. While many will discontinue labor force activity during the treatment period, a considerable proportion of them will return to full-time work, while others will elect not to return to work and may consider part-time employment or permanently retire. A wide range of factors can influence these choices depending on their labor market skills, stage at diagnosis, intervention type, and a range of sociodemographic variables [36]. These employment choices not only impact households but, in turn, have consequences for governments owing to reduced tax revenue and likely increased expenditure on public benefits. While these patients have a perfectly legitimate claim for these benefits, society is better off when every person is able to work and

contribute. This is most evident in BC, which impacts women in the prime of their working careers, where earnings are highest. We believe the work described here helps to illustrate the importance of "return to work" as an important outcome in cancer care, as this often signals defeat of one's health condition and a return to normalcy. Importantly, the fiscal value applied to returning to work described here is likely to be undervalued when taking into consideration the role that work status can have on mental health in cancer survivors [37].

Advancing age with fewer workers represents a fiscal challenge for governments. As the remaining number of working years declines, ageing patients start to draw more from public programs, which are, in turn, funded by the less populous body of workers. The challenge of intergenerational fiscal transfers between citizens in different age groups has been widely researched in the literature of public economics [38]. However, as shown here, the consequences are even more dramatic when patients experience chronic and acute events, such as residual invasive eBC, which prevents them from reaching the employment levels of the healthy population norm (Table 1). To a large extent this is also influenced by age at diagnosis. This study highlights that patients diagnosed in earlier years represent a greater fiscal loss for governments; however, curative treatments that improve survival may lead to fiscal benefits for governments.

Age at diagnosis and treatment are important components that have fiscal consequences for governments. From a policy perspective, early detection and treatment without recurrence offers the greatest fiscal gain for governments, as this enables workers to be productive over the normal life course. Diagnosis at later age has less impact, as patients have fewer working years remaining and the option for early retirement might exist. The analysis described here focused on women with HER2-positive eBC with residual invasive disease, where a rich body of evidence has explored the relationship between treatment, recovery, and wages in this population. In practice, the fiscal framework could be applied to any cancer or health condition that influences choices patients are likely to make regarding labor market activity. Applying this approach to HER2+ residual invasive eBC is a good example to investigate, as it can afflict relatively young women for whom the prognosis is good, hence who are more likely to return to work. The methodology and results described in this study may also help inform some of the fiscal benefits that can be expected among other cancer treatments; however, applying this approach to cancers that are diagnosed, on average in older ages, would likely yield different results.

Improved cancer survival creates future expenditure for governments in relation to numbers of pension payment recipients. Here we report both pension costs likely to occur prior to normal retirement age and all pension costs for projected remaining life years. Pension costs that arise pre-retirement age represent those patients opting for early retirement or some form of permanent transition out of work and the associated costs paid by government. These costs were small in relation to all other pension costs for the three countries explored. These cost comparisons are presented in Table 3 columns (I) and (e). However, these fiscal projects are likely conservative because remaining working years and increased economic activity generate additional economic gains for society that are not accounted for here.

Fiscal projections are often produced and used by governments and central banks to assess the cross-sectorial impact on public accounts of policy changes and the introduction of new programs. When evaluating health programs, the most common perspective is that of the health service applying a welfarist approach for assessing value in an effort to achieve technical efficiency using cost-effectiveness analysis. From a public economic viewpoint, the health service perspective can be viewed as shortsighted, especially in tax-financed health systems, as it does not take a broader systems approach to understand how spending in health and outcomes achieved influences other government sectors, e.g., tax revenue and transfers. At the margin, every health event avoided, case cured, and death averted or delayed has both positive and negative fiscal consequences for governments. This

is most evident in patients with remaining working years, as they will continue to work and pay taxes and help to sustain the system for someone who is more in need than they might be. Every working-aged person out of the work force must be paid for by those remaining workers. The fiscal approach applied here is essentially a fiscal cost–benefit analysis that is already used by governments for informing resource allocation decisions [39]. For cancer survivors, the costs of curative treatment apply over a short period of time; however, the fiscal consequences of labor market choices that follow have sustained effects over long time horizons. We are advocating that the fiscal framework explained here should be adopted to evaluate some technologies alongside more traditional approaches to health technology assessments to inform decision-makers about fiscal sustainability.

Model Limitations

There are several limitations to the modeling work described here that are worth taking into consideration. Firstly, a limited number of studies were identified that describe the relative measure of effect associated with eBC recurrence and especially how invasive disease impacts employment in each country. Whilst our search identified several useful studies for Canada, we were unable to find comparable data on employment transitions for eBC health states in Portugal and Brazil. In the absence of local data, we applied the risk ratios for Canada on employment to these markets, which may over or underestimate the likely impact on employment and consequently the fiscal impact. We have explored how changes to these parameters may influence the net fiscal balance in each country and observed that no change influenced the findings by more than 10%. The choice made by women whether they return to work following treatment is governed by financial and cultural factors and the availability to access income support programs in each country. While this may be less of an issue in Portugal with a universal welfare system as found in Canada, these job transitions and the need to return to work may be less applicable in Brazil. A second limitation is that our analysis does not include healthcare costs for treating eBC with residual invasive disease and for future non-related health costs. This suggests that what we are showing here is only a segment of the costs that fall on governments. Another limitation in our analysis is the extrapolation of employment data over long periods of time. This limitation is common to all fiscal projections owing to lack of visibility over future work environments and likelihood for retirement policy changes. This does not make our analysis incomplete; rather, it suggests our work highlights a different range of costs. This work is not designed as a cost-effectiveness analysis, although it does use the engine from a previously described economic model that has been compared with the healthy population in each country [27]. It is also important to recognize that our analysis is limited to its consequences on governments. We do not consider the impact on household savings rates, which provide wealth in later years and associated taxes derived from investments or impact of additional private healthcare coverage. Similarly, our approach fails to take into consideration the interaction between different economic domains, which can give rise to growth attributed to economic multipliers [40]. As our approach is simply an accounting framework, there are likely to be broader economic gains from changes in health status that are not reflected here. Furthermore, our analysis does not capture many non-labor related activities that add value to society, such as caring for grandchildren or volunteering.

CONCLUSIONS

Early detection of HER2-positive breast cancer and curative treatment offers benefits that extend beyond the health service and benefits for families. The central policy implication of our work is that early detection and treatment and prevention can generate increased tax revenue from preventing metastatic breast cancer and mortality and associated sick leave costs. The fiscal framework described here can be used

in priority-setting and allocation decisions used alongside traditional cost-effectiveness analysis for informing decision-making.

Author Contribution. Svenn Kommandantvold performed model design, model development, analysis of results, review of results, data identification, manuscript development, and critical review of manuscript. Nikos Kotsopoulos performed model design, model development, analysis of results, review of results, data identification, manuscript development, and critical review of manuscript. Isabel Monteiro performed model design, review of results, data identification, manuscript development, and critical review of manuscript. Ana Ladeiras performed model design, review of results, data identification, manuscript development, and critical review of manuscript. Andrew Hogan performed model design, review of results, data identification, manuscript development, and critical review of manuscript. Felipe Araujo performed model design, review of results, data identification, manuscript development, and critical review of manuscript. Mark Connolly performed model design, model development, analysis of results, review of results, data identification, manuscript development, and critical review of manuscript

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Data Availability. The data on which the analysis is based was derived from published materials. All material used has been referenced appropriately to enable readers to identify sources of information.

Declarations

Conflict of Interest. Mark Connolly and Nikos Kotsopoulos received funding from Roche in relation to this work. Mark Connolly and Nikos Kotsopoulos hold no financial interests in the sponsoring company or competing interests in relation to this work. Svenn Kommandantvold, Isabel Monteiro, Ana Ladeiras, Andrew Hogan, and Felipe Araujo are employees of Roche, and own stocks/shares in, F. Hoffmann-La Roche Ltd.

Ethical Approval. This is a modeling study conducted using previously published reports, i.e., secondary data. No subjects were enrolled in this evaluation, and no individual patient data have been used in this analysis. Ethics approval was not required to conduct this study.

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