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The impact on productivity costs of reducing unemployment in patients with advanced breast cancer: A model estimation based on a Portuguese nationwide observational study☆

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ABSTRACT

This study aimed to characterize the employment status and work-related conditions of patients with advanced breast cancer (ABC) in Portugal and quantify the productivity costs of premature abandonment of the work market while evaluating strategies to promote employment. The analysis was based on a cumulative incidence model for estimation of ABC prevalence and on a cross-sectional study characterizing the employment status of patients with ABC. This study was conducted in Portuguese hospitals, between Nov2021-Dec2022 and included patients diagnosed with ABC for at least 6 months, aged 66 or less and consenting for a self-answered questionnaire regarding work status. A total of 2151 working-aged women were estimated to have ABC in 2019 in Portugal, with productivity costs amounting to 28,676,754€ over 2019–2021. 112 patients from 9 hospitals were included in the study, average age was 52yr, 48 % had a postsecondary educational degree level and 87 % reported having a paid job at the time of diagnosis, mostly full-time. At the time of the study, only 38 % of the patients maintained the job status. The remaining were unemployed (51 %), on medical leave (25 %) or retired (24 %). Stop working was a personal choice for only 5 %. A subsidized part-time employment regimen, despite increased government costs, would allow a reduction in productivity costs, leading to a positive balance of

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2,431,329€ over the same period. This study suggests that the majority of patients with ABC abandon the labor market before the age of retirement. Flexible work arrangements would benefit the patient, the government and the society. ‘

1. Introduction

In 2019, breast cancer (BC) was the most common neoplasm diagnosed among women in Portugal, with an incidence rate of 156 per 100,000 women [1]. In total, 8482 cases of female BC were diagnosed in Portugal – an increase of 29,7 % vs 2010. No official data exist regarding the prevalence of BC in Portugal. According to the most recent national Portuguese data, 59 % of new female BC diagnoses occur in women between 20 and 64 years [1], representing the predominant working age period.

Advanced or metastatic breast cancer (ABC) is, at the moment, an incurable albeit treatable disease, responsible for almost all mortality associated with this cancer. It requires continuous treatment and surveillance, similar to a chronic disease, and has enormous impacts on all areas of patients' lives, including their professional lives. Breast cancer, and particularly ABC, is responsible for a loss of work productivity, due to associated symptoms as well as side effects of treatment and the added time that needs to be spared for treatments, exams and consultations [2–7]. Therefore, these patients have a higher risk of leaving the labor market, compared with the general population [8], leading to a loss of active population, with negative psychological, social and economic impacts [9].

With the advances in diagnosis and effective treatment approaches for ABC within the last few years, more patients are living longer with advanced disease. With more years to live, the attention dedicated to employment and working conditions for these women is paramount. The loss of employment may derive partly from the lack of willingness or policies to accommodate ABC patients' needs, such as flexible work arrangements. However, most of these patients may be able and willing to continue to work and to be productive members of society, if they are given the necessary conditions to do so, with expected substantial benefits not only for the patient and the family, but also for the society [10].

Regrettably, patients with BC have a higher risk of unemployment than the general population [8,12,13]. Most studies approaching employment after cancer refer to survivors and their return to work and scarce information exists regarding patients living with advanced incurable disease. Job abandonment by patients with ABC is a problem with significant social and economic impact, since it is directly linked to a loss of active population who do not feel that the conditions to continue working are met [14]. Greater integration between health and employment policies can play an essential role in reducing the negative impact of the disease in general, and BC in particular, on the patients' labor market situation, contributing to a better quality of life and more inclusive economies [15].

As part of an ABC Global Alliance initiative, the Centre for Evidence-Based Medicine (Centro de Estudos de Medicina Baseada na Evidência, CEMBE) of the Lisbon School of Medicine (Universidade de Lisboa) and Evigrade, Health Care Research and Consulting, Unipessoal, Lda. (Evigrade, an IQVIA company) developed a project to estimate the productivity costs of nonemployment due to female ABC. This work was based on (i) an observational cross-sectional study to characterize the employment status and working conditions of patients with ABC in Portugal and (ii) an original cumulative incidence model to estimate the prevalence of working-aged women with ABC. The results further allowed for appraisal of public policies' impact on this question.

2. Methods

Productivity losses associated with ABC constitute an indirect economic cost, which can be measured in the foregone earnings of women who transitioned to nonemployment due to the disease. To estimate the productivity costs of ABC, this study was restricted to the costs of nonemployment due to the disease and did not account for lost productivity arising from premature death or absenteeism. Besides generating productivity costs, nonemployment of working-aged women with ABC is also associated with government transfers, namely in the form of disability pensions and unemployment subsidies. While these government transfers do not constitute a productivity cost (i.e., they are an income redistribution mechanism), their quantification is relevant as they are part of the government budget balance. To quantify the amount allocated to disability pensions, the probability that women with ABC abandon the labor market due to early retirement on health grounds was estimated. These estimates are based on reported probabilities of employment cessation due to retirement on women's qualifications per age group and the percentage of employed population per age group.

A cumulative incidence model was developed to estimate costs. For this estimate, women's wages were also required. Additionally, to quantify the impact of ABC on women's productivity, evidence on the effects of ABC on women's labor market situation was required, which led to the design of a nationwide observational cross-sectional study.

The cost of transition to nonemployment due to ABC was estimated in two scenarios. The base case scenario corresponded to that observed with the current labor market policies. The alternative scenario evaluated the impact of a subsidized part-time employment regimen designed to foster ABC women's continued participation in the labor market. For the purposes of model building, we had to acknowledge that, while some patients would prefer to completely stop working, others would prefer to work half-time and still others work full time. For this reason, the model was built to allow to estimate costs for a mid-point scenario of 50 % part-time employment, that could be further adapted to fit other scenarios.

2.1. Cumulative incidence model

The costs associated with the transitions to nonemployment due to ABC were evaluated based on the disease prevalence during 2019. The year was decided in order to achieve a 3-year period of analysis, in view of the median overall survival (OS) of ABC being 3 years. As the legal retirement age in 2019 was 66 years and 5 months [16], this study was restricted to women who would be aged 66 or less in case of survival. For the purposes of this study, patients with stage IV disease were assumed not to work in the 6 months prior to death. A similar approach was followed when projecting future productivity costs for the 2019 cohort.

Prevalence estimates for 2019 were obtained considering a time horizon of up to 10 years from the moment of diagnosis. Hence, ABC patients included in the analysis correspond to women diagnosed in 2019 with stage IV BC, as well as women diagnosed between 2010 and 2018, those with earlier stage diagnosis between 2010 and 2018 that had distant recurrence until 2019 and from 2019 to 2021 for the 2019's cohort of working-aged ABC women.

2.2. Cross-sectional study design

The observational cross-sectional study was based on a two-part questionnaire applied to a convenience sample of ABC patients from a set of public and private hospitals in mainland Portugal. The first part of the questionnaire was about the ABC diagnosis and was answered by the assistant physician. The patients completed the second part of the questionnaire regarding the sociodemographic characteristics and the disease impact on the patients' professional lives.

Patients were included if they met the following inclusion criteria:

- Less than 66 years old; and
- Diagnostic of inoperable stage IIIB, IIIC or stage IV BC for at least 6 months.

Patient recruitment began in November 2021 and was initially expected to last 45 days; however, this period was extended to reach the sample size needed (at least 100 patients), taking approximately one year.

2.3. Statistical analysis

For the estimation of ABC's productivity costs, the human capital method [17] was applied, which assumes that earnings reflect the underlying productivity of workers. According to the human capital approach, the productivity cost of ABC corresponds to foregone earnings, which can be decomposed into foregone ABC patients' earnings and foregone employers' contributions to Social Security.

The Markov model was used to track patients diagnosed between 2010 and 2018 as well as in 2019 itself. In this model, the transition of patients between health states was considered at yearly cycles. Hence, health states were modeled as follows: at the time of diagnosis, the patient could have locoregional disease (stages I-III) or metastatic disease (stage IV). In each cycle, a patient initially diagnosed with stage I-III BC could transition to a disease-free state, remain in the same state, have a metastatic recurrence or die. Patients diagnosed with stage IV BC could remain in the ABC state, or die.

To estimate the prevalence of ABC patients in 2019, BC incidence data for the years 2010–2019 was needed. Based on existing data for 2010, 2018 and 2019, incidence per age group was estimated for 2011–2017, through linear regression.

Annual death probabilities, by disease stage at diagnosis were estimated based on the BC Kaplan-Meier survival curves reported by André et al. [18]. The survival curves were extrapolated based on exponential parametric models. The recurrence probability was estimated based in previous existing evidence [19,20].

A descriptive analysis of the collected data was carried out for the cross-sectional study. Discrete variables were described using absolute and relative frequencies, and continuous variables using trend and dispersion measures, namely mean and standard deviation. Missing data were not considered in the calculation of percentages. The analyses were performed using the R software, version 3.6.1 (R Core Team 2019. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria), and Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA).

3. Results

3.1. Observational cross-sectional study

The observational cross-sectional study recruited a total of 112 patients with ABC from 9 Portuguese hospitals (2 patients were excluded from the final sample due to non-completion of the provided questionnaire). The setting of the hospitals where the patients were being treated (and recruited) was evenly distributed (43 % from the private sector and 57 % from the Portuguese National Health Services) (Table S1 of Supplementary Appendix).

Patients' demographic characteristics are summarized in Table 1. All patients were women and the mean age was 52 years (SD 29–66). The majority of patients had stage IV disease (85 %). Regarding academic level, 50 % of the recruited women completed university education, 32 % were high school graduates, and 21 % completed primary education.

3.1.1. Characterization of the working situation

Regarding patients' work situation at the time of ABC diagnosis, 97 patients (87 %) reported having paid work at the time. Among those, a clear majority was working full-time (91 %) compared to part-time (9 %) and 60 % represented employees with permanent contracts (Table S2, Supplementary Appendix).

Table 1
Demographic patient characteristics.

Variables	n (%)
Female gender	112 (100)
Age, years, mean (SD) [min,max]	52 (8.26) [29,66]
Disease Staging	
IIIB	7 (6)
IIIC	10 (9)
IV	94 (85)
Academic Level	
Primary education	23 (21)
Secondary education	35 (32)
University education	53 (48)

At the time of questionnaire completion, 46 % of ABC patients did not have any paid job, 38 % did have a paid job and 15 % were on sick leave (patients who reported having a current paid job and who, at the same time, indicated a reason for having stopped working, were considered on sick leave) (Table S3, Supplementary Appendix). Most patients with current paid work reported having a full-time job (83 %). Even so, 32 % of the inquired had reduced their working hours after ABC diagnosis, and the reasons for this reduction were: own choice (5 %), physical disability (4,5 %), intellectual disability (1 %) and other reasons (1,8 %) (Table S4, Supplementary Appendix). The reduction in working hours was predominantly seen in patients with higher education compared to lower levels of education (21 % higher education, 3 % secondary education and 0 % basic education).

Of the patients who had paid work at the time of ABC diagnosis, 62 % stopped working (of these, 51 % are currently unemployed, 25 % are on sick leav[e] and 24 % are retired). The job dropout rate was higher among the patients with primary education (88 %), followed by those with secondary education (71 %). Patients with higher education had a lower proportion of job abandonment (46 %). The main reasons for stop working were physical disability (55 %) and intellectual disability (16 %), with 20 % of early retirement. Mean age of retirement was 49,7 years (SD 6.88).

3.2. Productivity cost of unemployment

The annual cost of a woman's nonemployment corresponds to the foregone fourteen monthly salaries (twelve months plus holidays and Christmas subsidies) and the foregone employer's yearly contribution to Social Security (23,75 % of gross monthly base wage). Weighting women employees' average gross monthly base wages (Table 2) with the proportion of women with paid work by education level and age group, average salaries per age group were calculated (Table 3).

Table 2
Women employees' average gross monthly base wage in 2019, by level of education.

	Gross monthly base wage[a] (€)
Primary education	681.15
Secondary education	802.99
Higher education	1384.98

Note: The average gross monthly base wage by level of education refers only to employees (i.e., it does not account for self-employed workers' remuneration).

[a] - The gross monthly base wage corresponds to the gross amount paid in cash and/or in kind to workers in the reference period and corresponds to the regular working hours, regardless of whether they were absent due to vacation, maternity leave, strike, professional training, sickness leave or workplace accident for one month or less. It does not include regular bonuses, allowances, or extra work remuneration.

Source: Comissão para a Cidadania e a Igualdade de Género (CIG), Igualdade de Género em Portugal 2021 Trabalho e Emprego.

Table 3
Women with paid work by education level and age group in Portugal.

Age group	Women with paid work				Weighted average gross monthly base wage (€)
	Total	Primary education	Secondary education	Higher education	
20–24	110,417	12 %	56 %	32 %	972.51
25–29	199,968	11 %	37 %	51 %	1088.69
30–34	220,966	17 %	34 %	49 %	1069.73
35–39	261,551	21 %	33 %	46 %	1046.13
40–44	311,420	26 %	32 %	43 %	1020.57
45–49	320,958	35 %	29 %	36 %	971.12
50–54	281,249	46 %	26 %	28 %	907.65
55–59	245,498	53 %	23 %	24 %	878.69
60–64	156,863	55 %	21 %	24 %	876.81
65+	52,847	64 %	13 %	23 %	856.68

Source: Instituto Nacional de Estatística, I.P.

Not all women with ABC will, however, be part of the labor force and employed at the moment of stage IV BC diagnosis or metastatic recurrence. Hence, the probabilities of transitioning to nonemployment reported by participants in the observational study (Table S3, Supplementary Appendix) were weighted by the labor force participation rate in each age group and by the employment rate by age and education level. This enabled the calculation of an age-dependent probability that a woman diagnosed with ABC will transition from paid work to nonemployment (Table S5, Supplementary Appendix).

Additionally, for productivity cost calculation, the prevalence of ABC in 2019 was determined, based on BC incidence, survival and recurrence probabilities. Data on BC incidence was calculated based on previous existing data [18] (Fig. S1, Supplementary Appendix). The estimated 10-year survival was 83,49 %, 71,74 %, 38,47 % and 2,45 % for women diagnosed at stages I, II, III and IV, respectively, already taking into consideration that women with metastatic disease do not work in the last 6 months of their lives (Fig. 1). Probabilities of locoregional and distant recurrence were also estimated, by disease stage at diagnosis and year since diagnosis (Tables S6 and S7, Supplementary Appendix). Based on the Markov model described before, the number of BC survivor patients in 2019, and their distribution by disease stage was estimated. Metastatic disease was estimated to have occurred in 4176 women of all ages and 2151 working-aged women.

The estimated number of working-aged women with ABC in 2019 coupled with weighted average gross monthly base wages and probabilities of transitioning from paid work to nonemployment enabled the quantification of the cost of nonemployment due to ABC in 2019. In 2019, from the 2151 working-aged women with ABC, approximately 830 (38.60 %) women were in a situation of nonemployment due of ABC. Their estimated foregone earnings amounted to 10,750,468€ in 2019. The nonemployment of these 830 ABC women also translated into a decrease of 2,553,236€ in employers' contributions to Social Security (23.75 % of estimated annual gross wages). Hence, in 2019, the estimated total cost of nonemployment of ABC working-aged women was 13,303,704€.

Nonemployment of working-aged women with ABC is also associated with government transfers, namely in the form of disability pensions and unemployment subsidies. Of 830 women who stopped working due to ABC, 283 (34.04 %) women were estimated to receive disability pension in 2019. Since the average annual disability pension per recipient was 5511€ in 2019 [21], implying government funds allocated to disability pensions in the population under study amounted to 1,557,568€ in 2019.

Based on participants in the observational study, the probability that women transition to nonemployment due to dismissal is limited. Indeed, from women diagnosed with stage IV BC, only 7 % of patients with secondary education reported having been dismissed. The estimated probability that women with ABC will be dismissed due to the disease accounts for the percentage of employed women in the Portuguese population and for women's qualifications per age group. The duration of unemployment subsidies is capped, depending on beneficiaries' age, and earning records. As women's mean age at BC diagnosis was 52 years, in 2019, the model assumes the duration of the unemployment subsidy corresponds to that defined for women aged 50 or more and who have earning records equal to or greater than 24 months. Under these conditions, and assuming women were employed in the 20 years prior to dismissal, women receive an unemployment subsidy for at most 780 days (2.14 years). Therefore, the estimation exercise assumed that the unemployment subsidy is limited to two years. According to estimates, 53,723€ of government funds were allocated to unemployment subsidies for working-aged women with ABC in 2019. Hence, in total, 1,611,291€ of government transfers related to disability pensions and unemployment subsidies were granted to ABC women aged between 20 and 66

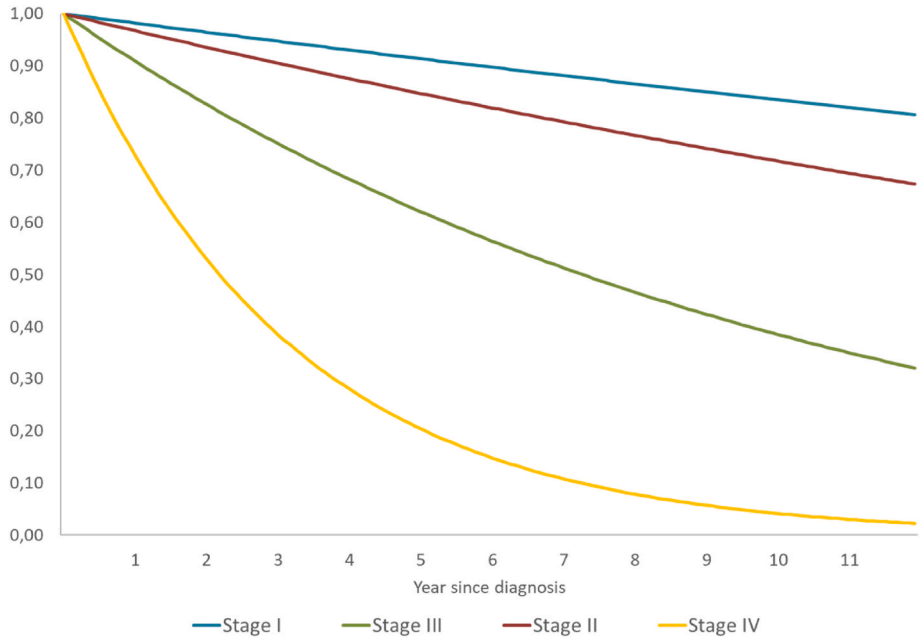

Fig. 1. Exponential parametric survival curves, by disease stage at diagnosis.

years, in 2019. Between 2019 and 2021, for the cohort of working-aged women with ABC in 2019, the total productivity cost due to ABC amounts to 28.676.754€. Government transfers, in the frm of disability pensions and unemployment subsidies, totaled 3.392.967€ and 75.899€, respectively, from 2019 to 2021 (Tables S8 and S9, Supplementary Appendix). Fig. 2 summarizes the quantification of the cost of nonemployment of working-age women due to ABC, in Portugal, according to the current legal employment framework.

An alternative scenario was evaluated after the base case scenario, corresponding to the current legal employment framework for women with ABC. In this alternative scenario, ABC patients who would otherwise transition to a situation of nonemployment due to the disease are granted the possibility to benefit from subsidized part-time employment. In such regime, those who would stop working in the base scenario are now allowed to work 20 h a week but earn the full-time equivalent wage, with 50 % of the wage paid by the employer and 50 % by the government. The employer and the government would evenly share the contributions to Social Security. Like in the base case scenario, it is assumed that women with ABC have not worked in the last 6 months of their lives. In the alternative scenario, the productivity costs due to ABC correspond to 50 % of the productivity costs registered in the base case (Table S10, Supplementary Appendix).

Since women who would transition to a situation of nonemployment due to the disease (38.60 %) still work part-time (20 h/week) in the alternative scenario, no unemployment subsidies nor disability pensions would be paid. Instead, government funds would finance 50 % of their gross wages and associated contributions to Social Security. Moreover, it was assumed that ABC women, who, in the base case, reported working part-time (2.9 %), would also benefit from the subsidized employment scheme. Over the three years 2019–2021, the estimated government transfers to ABC women would amount to 15,419,914€, an increase of 11,951,048€ relative to the base case scenario (Table S11 of Supplementary Appendix). The gain in government transfers would nonetheless be outweighed by the decrease in productivity costs (14,338,377€), leading to a positive balance of 2,431,329€ over the same period (Fig. 3).

4. Discussion

Breast cancer, the most common malignancy among women, is diagnosed mainly while patients are still of working age. Therefore, added to all the burden that the disease represents for patients, it also has a tremendous economic and social impact on society, due to the loss of productivity and early abandonment of the labor market. This study allowed us to describe the sociodemographic and labor characteristics of patients with ABC in Portugal and to estimate further productivity costs associated with this disease.

The designed observational cross-sectional study provided some significant findings. While most patients were either unemployed on sick leave or retired after ABC diagnosis, this was essentially not due to the patient's initiative, with physical and/or intellectual disabilities being prevalent motifs. Moreover, the results revealed an inequity related to the patient's educational level. Of patients with ABC and with a university education, 21 % could reduce their working hours, contrary to those with secondary or basic education. Also, these patients were less likely to abandon work than the ABC patients with less education. These results are in line with previously published data from the Portuguese population. Monteiro et al. (2019) studied the employment status of women recently diagnosed with BC and treated at the Portuguese Institute of Oncology of Oporto. The patients were interviewed at diagnosis and 5 years after diagnosis. Of the 242 women employed at the time of diagnosis, only 66,9 % (n = 162) were still employed 5 years later. About a third of the women suffered a change in their employment

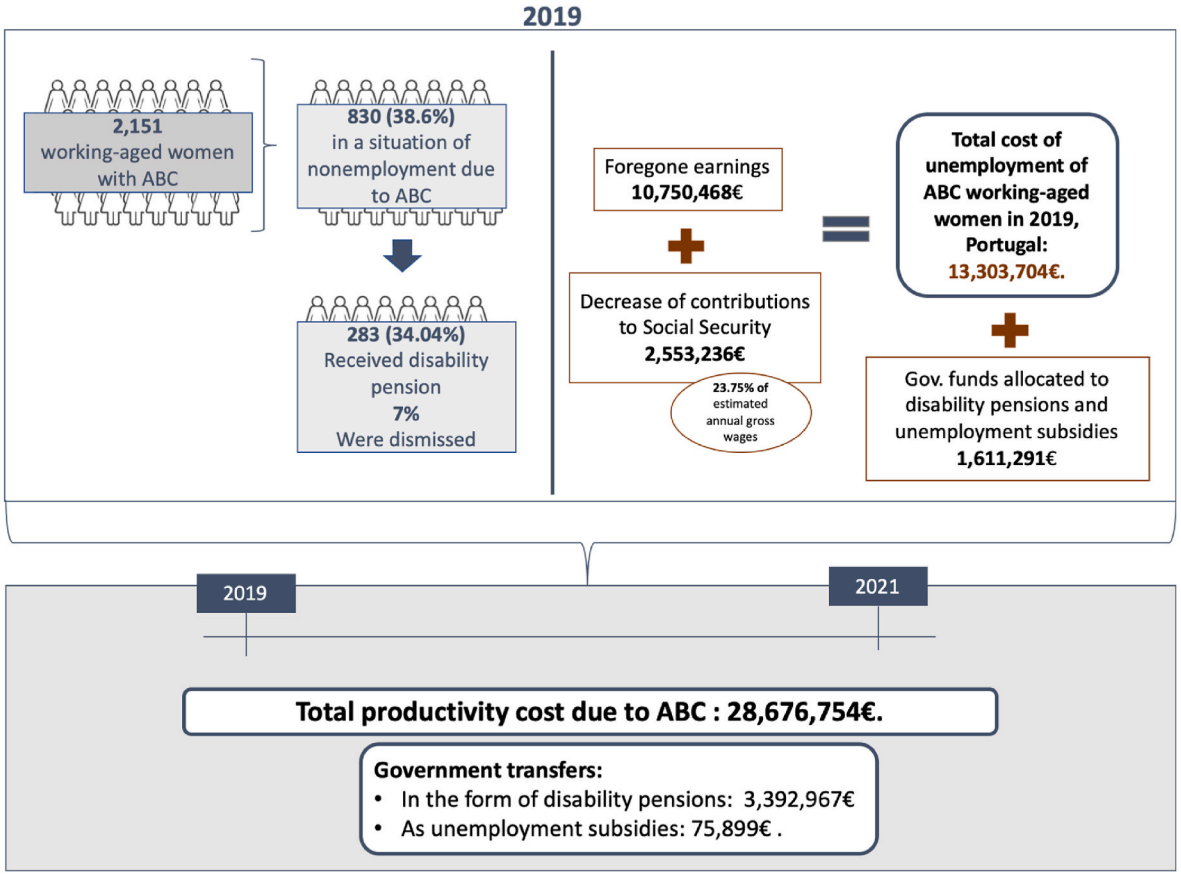

Fig. 2. Productivity cost of unemployment for working age-women with ABC, according to the current legal employment framework.

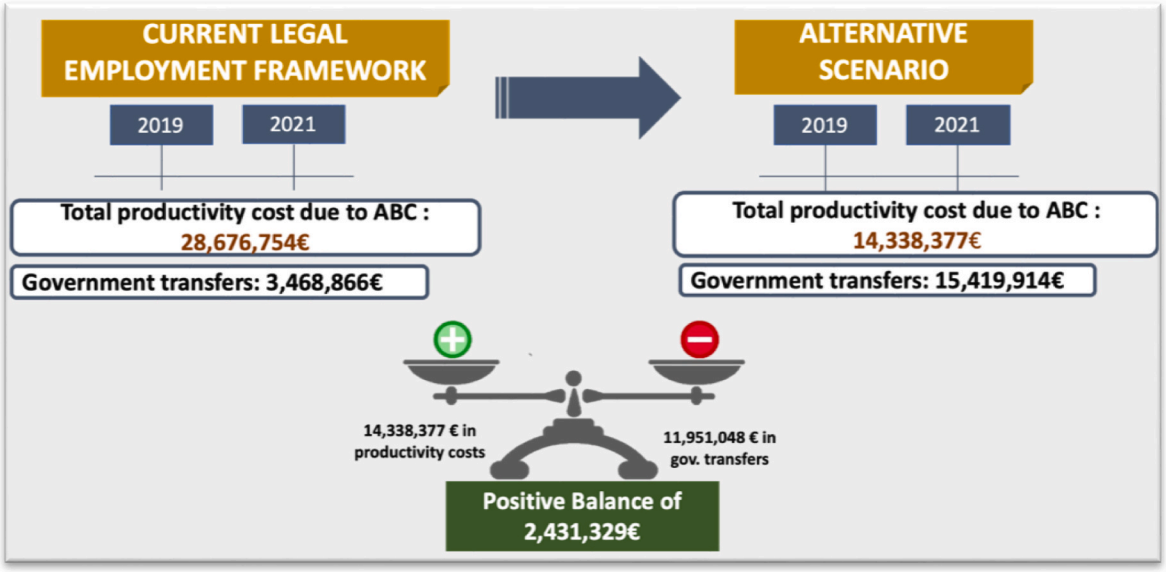

Fig. 3. Current employment framework and alternative scenario for women with ABC.

status and mostly becoming unemployed (10,7 %), or taking early retirement (11,2 %) [22]. Our results thus add to existing evidence and further suggest that many patients with ABC would want to continue working if they were given the conditions to adapt their work/schedule to their new capacities.

Hence, the estimation of productivity costs of nonemployment due to ABC allowed us to evaluate possible labor market policies designed to promote ABC women's employment. Resorting to a cumulative incidence model with a time horizon of 10 years, 2151 women aged between 20 and 66 were estimated to have stage ABC in 2019, among which 38.60 % were estimated to be in a situation of nonemployment due to the disease. An alternative labor scenario was designed with productivity costs during a 3-year period estimated at 28,676,754€ and government transfers valued at 3,468,866€. In this scenario, in which ABC patients would benefit from subsidized part-time employment, productivity costs due to the disease would be halved and government funds allocated to working-aged ABC women would increase by 11,951,048€. A 14,338,377€ decrease in productivity costs would outweigh the increase in government transfers. It is worth mentioning that, in the alternative scenario, it was assumed that only ABC women who in the base case scenario transitioned to a situation of nonemployment due to the disease or who claimed to work part-time would be eligible for the subsidized part-time regime. However, it is plausible such a welfare program would create incentives for working-aged ABC women to work part-time instead of full-time, which could translate into both higher productivity costs and more government funds allocated to these women. Furthermore, the inability to maintain an active professional life and respective salary, contributes substantial for the huge financial toxicity suffered by patients living with ABC, and their families and the employment status is often related to insurance coverage.

Several efforts have already been made to change the labor landscape for cancer patients. The European Society of Medical Oncology in collaboration with the International Psycho-Oncology Society, published a guide with supporting guidelines on returning to work [23]. The European Cancer Patient Coalition (ECPC), with the European Parliament and other organizations launched a joint initiative focused on protecting the employment rights of patients with advanced cancer, the "Dying to Work" [24]. This effort intends to develop legislation to protect the employment and social rights of people with cancer, similar to the work achieved with the European Union Pregnant Workers Directive, ascribing advanced incurable cancer to the same protected status. The "Transforming Breast Cancer Together" initiative raises awareness on multiple issues related to living with BC in Europe, promoting advocacy groups, publications and events [25]. The "Working with Cancer" pledge launched by the Publicis Foundation aims at erasing the stigma of cancer in the workplace [26]. Australia stands exemplary in the creation of flexible working arrangements. The Fair Work Act 2009, the core piece of Australian labor law legislation, regulates flexible ways of working, allowing employers and employees to agree on changes to working arrangements that suit them both, which are allowed to be requested by people with a disability such as cancer, under the National Employment Standards [27].

5. Conclusion

The right to work is a fundamental right and essential for every individual's well-being and dignity. The ability to work provides financial stability, social inclusion, and a sense of purpose. Any individual affected with advanced cancer should have the right to choose if continuing to work is their desire. Employers have a critical role to play in ensuring that people with cancer are not discriminated against in the workplace and need to provide the appropriate setting to help individuals with cancer fulfill their job responsibilities.

However, this can only be fully achieved with appropriate government support to provide alternatively adjusted and flexible working options for patients. Our study provides breakthrough data on an extremely relevant subject, advocating for the need to reflect on existing laws and bringing to the stage the discussion of policies that can be improved, with significant impact on the social economy, but ultimately ensuring that patients with ABC in Portugal and worldwide can remain active in the labor market.

CRediT authorship contribution statement

Leonor Vasconcelos de Matos: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration. **Margarida Borges:** Formal analysis, Data curation, Conceptualization. **Ana Teresa Oliveira:** Formal analysis, Data curation, Conceptualization. **Carolina Bulhosa:** Methodology, Investigation, Formal analysis. **Luís Silva Miguel:** Methodology, Formal analysis. **Tiago Fidalgo de Freitas:** Writing – review & editing, Resources. **Renato Cunha:** Writing – review & editing, Resources, Project administration. **Ana Duarte Mendes:** Writing – review & editing, Resources. **Ana Júlia Arede:** Writing – review & editing, Resources. **Cristiana**

Marques: Writing – review & editing, Resources. **Diogo Alpuim Costa:** Writing – review & editing, Investigation. **Jorge Alves Correia:** Validation, Software, Resources. **Margarida Brito:** Writing – review & editing, Resources. **Mário Fontes e Sousa:** Writing – review & editing, Resources. **Teresa Guimarães:** Writing – review & editing, Resources. **Fatima Cardoso:** Project administration, Data curation, Conceptualization.

Ethics

This study was approved by the Ethical Committee for Health and by the Executive Board of all involved centers and is in accordance with all national and international guidelines for good research and publication practices. It was conducted in accordance with the Declaration of Helsinki and good clinical practice.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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