Introduction

Breast cancer is the most common cancer worldwide. In 2020, 2,261,419 women were diagnosed with breast cancer, representing 25.8% of all cancers detected in women that year. Belgium showed the highest age-standardized rate (ASR, compared to the world population) of breast cancer incidence worldwide (113.2 per 100,000), high age-standardized mortality rates but also high 5-year survival chances. In 2021, 77.1% of breast cancers were diagnosed at stage I or II, and the 5-year relative survival was equal to 92.1% between 2017 and 2021 in Belgium.

There is ample evidence of a socioeconomic gradient in health and mortality. For cancer, the picture is more heterogeneous. International studies have illustrated a diversity in the social patterning of cancer. The association between markers of socioeconomic position (SEP) and cancer ranges from negative over non-existent to positive, depending on the site of cancer, the socioeconomic indicator and the epidemiological indicator – incidence, mortality, and survival – that is used. In a meta-analysis, Lundqvist et al. (2016) concluded that breast cancer mortality was higher for more affluent women. The only exception was observed in a Norwegian study showing lower breast cancer mortality for higher educated women. To understand these inconsistent results, it is important to underline that these associations vary over time. During the 1990s, Strand et al. (2007) found higher breast cancer mortality for higher educated women in Denmark, Norway, England and Wales, Belgium, Austria, Switzerland, Turin and Madrid, but not for women in Finland, France and Barcelona. A recent study showed that this positive association had become weaker or even disappeared in the 2000s in many of these countries. For Belgium specifically, differences by education were no longer significant in the 2000s.

Cancer mortality is the result of an interplay between cancer incidence and survival. Educational attainment can be linked to both these cancer parameters through different mediating variables. Being overweight, limited physical activity, using hormone replacement therapy, alcohol abuse and smoking for instance are associated with a higher risk of being diagnosed with breast cancer. Higher educated women have been shown to be more physically active, smoke less, and are less likely to be obese in higher income countries. Despite these risk-reducing behaviours, most studies report higher breast cancer incidence rates for higher educated women. To explain this, fertility patterns (number of children and age at first full-term childbirth) have been put forward in literature, although in some studies differences persist after taking fertility history variables into account. In their meta-analysis, Dong & Qin (2020) concluded that the association turned insignificant only when alcohol consumption, age at menopause or hormone replacement therapy were additionally included.

With respect to breast cancer survival, a large body of literature found poorer survival chances for the most deprived and lower educated women. Studies showed that higher body weight (measured through Body Mass Index (BMI), waist circumference and waist-to-hip ratio), unhealthy diet, and limited physical activity were associated with reduced breast cancer survival chances. Additionally, multiple studies reported that deprived or lower educated women were more likely to receive a breast cancer diagnosis in a more advanced stage of the disease. Rosskamp et al. (2021) found a positive relationship between educational level and breast cancer incidence, but a negative association between education and stage at diagnosis among women living in Belgium; lower-educated women being more likely to receive a diagnosis in an advanced (or unknown) stage. This was in line with a Swedish study showing higher incidence rates, but lower fatality rates for higher-educated women.

In this paper, we have three main objectives:

a) To map educational differences in breast cancer incidence, survival, and mortality in Belgium during the 2004-2013 period. We aim to assess the extent to which educational disparities in breast cancer mortality are influenced by differences in incidence and survival. This comprehensive approach considers multiple cancer indicators, which is relatively rare in the existing literature
b) Update earlier trends in breast cancer mortality in Belgium for the 2004-2013 period.
c) Investigate the role of reproductive factors (i.e. age at first childbirth and parity) as mediating factors in the relationship between education and breast cancer outcomes.

We will control for socioeconomic factors and menopausal status because risk factors tend to vary between pre- and postmenopausal women.

Data & Methods

Data

Data consisted of a linkage between the 2001 Belgian Census, the Belgian Cancer Registry (BCR) and register data on all-cause and cause-specific mortality. Our study population consisted of all women aged 30-69 at baseline (i.e. January 1st 2004). We excluded women under 30 as their socioeconomic and sociodemographic characteristics might still be undetermined. Additionally, we used an upper age limit of 69 to increase comparability with previous studies. Given the different risk factors for pre-and postmenopausal women, we stratified the analysis by menopausal status. As direct information on menopausal status was unavailable, we used age as a proxy and allocated women younger than 50 to the pre-menopausal group and women aged 50 or older to the postmenopausal group.

Socioeconomic and sociodemographic variables were derived from the 2001 census. Educational attainment was categorized using the International Standard Classification of Education (ISCED) distinguishing primary education or less (ISCED 0-1), lower secondary education (ISCED 2), higher secondary education (ISCED 3-4) and tertiary education (ISCED 5-8). Fertility variables consisted of the number of children (0, 1, 2, 3 or 4 or more children) and a women's age at first childbirth (< 20 years, 20-24 years, 25-29 years, 30-34 years, > 35 years). To include nulliparous women in the analysis, we constructed a variable combining both parity and age at first birth (e.g. no children; first child born before age 20 years and 1 child, … first child born before age 20 and 4 or more children; …, first child born after age 35 and 1 child, …, first child born after age 35 and 3 or more children). As the category 'first child born after age 35 and four or more children' contained very few respondents, we grouped all women with 3 or more children. Control variables included age at baseline, house ownership (owner/tenant), living arrangement (couple/single/other), country of birth (Belgium/other), all derived from the census data. For each of the socioeconomic variables, women with missing values were included in a separate category, since we hypothesised these women related to a potentially precarious group. For fertility indicators and country of birth, missing values were more difficult to interpret and therefore women with a missing value on either of these variables were excluded from the analysis (7.0% in total).

The BCR collects nationwide data on all new cancer diagnoses in Belgium since 2004. Our analysis included all first invasive breast cancer (ICD-10: C50) diagnoses during 2004 to 2013. In situ and secondary tumours were not included. Since treatment of the first cancer could influence the risk of a subsequent cancer (e.g. when a mastectomy is performed), we chose to include first breast cancer diagnoses only. Based on clinical and pathological information, a "combined TNM Stage" variable was constructed ranging from stage I to stage IV, prioritising pathological tumour stage except in case of clinical evidence of metastasis, in which case the clinical tumour stage prevailed.

Data on vital status (alive, emigrated or deceased) and cause of death (ICD-10) between January 1st 2004 and December 31st 2013 were obtained from the National Register and the Death Certificates.

Methods

Age-standardized rates (ASR's per 100,000 person-years) and 95% confidence intervals were computed for breast cancer mortality (ASMRs) and breast cancer incidence (ASIRs), using the age distribution of the Belgian population at baseline as standard. For overall and cause-specific survival we focused on the 5-year interval after diagnosis, based on the definition of Mariotto et al. (2014). This approach is similar to a previous study by Rosskamp et al. (2021). Survival chances were obtained through nonparametric estimates of the survival functions by educational level, using the Kaplan-Meier method. To account for competing risks in cause-specific survival, we also estimated survival chances based on the cumulative incidence function (CIF) to see if these differed substantially.

To control the association between educational attainment and breast cancer mortality and breast cancer incidence for other factors, Poisson regression models were used. The Poisson assumption that higher means have higher variances was not met in our survival data. Due to the smaller total population (i.e. counting individuals with a breast cancer diagnosis only) and the inclusion of stage at diagnosis, several categories had a high number of deaths and a rather low variance. Hence, we chose to use Cox proportional hazard models for the survival analysis. All our analyses were conducted with the SAS enterprise software.

In the Poisson models (i.e. mortality and incidence analysis) we used the log of the person-years lived (or at risk) as the offset in our analysis. For our incidence and mortality analysis the starting point is the 1st of January 2004. For mortality, time at risk is calculated as the time between this starting point and the last observation date (LOD), either due to the end of the observation period (December 31st, 2013), death or emigration. For incidence, the time between the starting point and incidence date or LOD (in case of no breast cancer incidence) is considered. Finally, for survival, we looked at the time elapsed between the date of diagnosis and all-cause mortality (overall survival) and breast cancer-specific mortality (cause-specific survival). Since we focused on the 5-year period after diagnosis, we set this time variable to 5.0 years for all women who survived past this point. Women who emigrated were censored for both survival outcomes and women who died from other causes than breast cancer were censored for the cause-specific survival analysis. As a form of sensitivity analysis, we used Fine and Gray's competing risk model for breast cancer specific survival. To fulfil the proportional hazard assumptions, interactions with time-points were included when significant at the 0.01-level.

For all cancer outcomes, we followed a stepwise approach and gradually introduced socio-economic and socio-demographic control variables. The initial model included age at baseline in 5-year intervals and educational level, whilst the final model also included fertility indicators, country of birth, property ownership and living arrangements. For overall and cause-specific survival the final model additionally includes stage at diagnosis.

Given the role of fertility indicators in the association between education and breast cancer incidence and mortality, we calculated the excess portion eliminated (EPE). This indicator was introduced by Vanderweele(2014) and further refined by Suzuki (2016). In this study, the EPE is calculated as the degree to which deviations from a 1.0 relative risks (i.e. no difference with tertiary educated women (ref)) are reduced when fertility indicators are added to the model. A positive EPE value indicates that the difference between an educational category and the reference category was reduced; a negative EPE showcases the opposite. To calculate relevant EPE values we used three additional models. All socio-economic and socio-demographic control variables were included in EPE model 1, but none of the fertility indicators are added in this model. Parity (ref: no children) was added in EPE model 2 and the cross-classification of parity and age at first childbirth (ref: no children) in EPE model 3. By comparing EPE model 2 and 3 to EPE model 1, it was possible to quantify the role that fertility characteristics play in the association between breast cancer and education when controlled for socioeconomic variables.

Finally, to allow for comparison over time and differently structured populations, we calculated the RII for breast cancer mortality. We followed the same approach as previous studies and calculated this indicator by using Poisson regression. Each educational category was given a rank, based on the proportion of the population having a lower educational level. The RII thus gives an indication of the difference in breast cancer mortality between the hypothetically highest and lowest education.

Results

In this extended abstract, we would like to highlight three of our main findings:

1) We found a noteworthy shift in the social gradient for breast cancer mortality during the 2004-2013 period. Unlike earlier studies, we no longer observed a 'reversed social gradient. For postmenopausal women there were minimal differences in breast cancer mortality across educational levels. As indicated by the relative index of inequality (RII) of 1.02. For premenopausal women however, we observed an opposite gradient. The RII for this group was 0.81 and significantly (95%) lower than 1.
2) We found that the almost non-existent differences in breast cancer mortality for postmenopausal women resulted from an interplay between breast cancer incidence and survival. Higher-educated women showed a significantly higher incidence risk, but also significantly higher survival chances. The same pattern was observed for premenopausal women, where the interplay resulted in lower breast cancer mortality for the higher-educated.
3) Compared to other studies, we found a rather limited impact of the fertility variables as mediating factors. What's even more surprising is that we observed the largest impact on breast cancer mortality, not breast cancer incidence, in the premenopausal age group. We argue that this could partially be explained by an interaction effect between age at first childbirth and parity. Specifically, we found that having one or more children was beneficial, compared to nulliparous women, when the first child was born before a women reached the age of 30. However, when a women was older than 30 at the time of her first child's birth, the results were more heterogeneous.

In our final paper, we also present policy recommendations, especially with regards to breast cancer survival (all-cause or cause-specific). Our findings indicate that controlling for variables relating to financial means (e.g. house ownership) and stage at diagnosis had the largest impact on all-cause and cause-specific survival 5-years after diagnosis. Previously, stage at diagnosis, has been interpreted as a proxy for timely access to healthcare and/or a screening programme. Other studies found that participation in said breast cancer screening programme substantially decreased breast cancer mortality. Hence, the barriers, financial or other, to this early access to healthcare/screening should be further reduced as much as possible.