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# Breast cancer by migrant background in Belgium: Lower risk, but worse survival in women of non-European origin

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Cancer Epidemiology

**Foreign and native populations differ in terms of breast cancer outcomes. Studies rarely distinguish between premenopausal and postmenopausal breast cancer, although the risk profile is different; nor between migrants of the first and second generation (FG and SG), which is crucial to examine genetic and environmental influences on breast cancer. This research fills these gaps by investigating patterns in breast cancer incidence and survival in different migrant groups by menopausal and migrant generational status, taking various risk factors into account. To this end, individually linked data from the 2001 census, the Belgian Cancer Registry and the Crossroads Bank for Social Security are used. Age-standardised incidence rates and incidence rate ratios are calculated by migrant background group, stratified according to ages 30–50 (premenopausal) and 50–70 (postmenopausal). Incidence rate ratios are examined with and without taking reproductive factors and socioeconomic position (SEP) into account. Relative survival percentages and relative excess risks of dying among premenopausal and postmenopausal patients are computed with and without controlling for the stage at diagnosis and SEP. Premenopausal breast cancer is further examined by migrant generational status. Breast cancer incidence is lower among non-European migrants compared to Belgians. Keeping SEP and known risk factors constant reduces much, but not all of the observed discrepancies. A risk convergence between SG migrants and Belgians for the development of premenopausal breast cancer is observed. Premenopausal breast cancer survival is worse among Moroccan patients due to a higher stage at diagnosis. This disadvantage is concentrated in the FG.**

## Introduction

Belgium is the highest risk setting for breast cancer in Europe with over 10,000 new diagnoses in 2015 and 2016, corresponding to a World Standardised Rate (WSR) of *circa* 105 per 100,000 person years.[1–5] As a country with more than 20% of the population of foreign origin (i.e., those born abroad or migrant offspring),[6] Belgium constitutes an interesting study setting for migrant differences in breast cancer.

Breast cancer is caused by multiple risk factors.[4,7–9] It is mostly postmenopausal disease and is usually hormone dependent, with increasing risks due to oral contraceptive use, nulliparity (i.e., not having children), late age at first childbearing, hormone-replacement therapy (HRT) and obesity. Inherited risk is, however, larger for early breast cancer.[10] Many risk factors for breast cancer are inversely related to an individuals' socioeconomic position (SEP), usually measured by educational level. The associations are especially strong for postmenopausal cancer due to the links between delays in reproduction and higher educational levels.[11]

Research finds lower breast cancer incidence among non-European migrants compared to host-country natives in West-European countries.[12–16] This is thought to be attributable to protective reproductive behaviours such as lower age at childbirth, higher parity levels and more frequent and longer duration of breastfeeding.[12,14,15,17] Other risk factors that may be unevenly distributed are the use of HRT, younger age at menarche and older age at menopause.[12,14,15] Immigrant daughters' (i.e., second-generation migrants [SG]) risk levels

**Additional Supporting Information** may be found in the online version of this article.

**Key words:** migrants, breast cancer, socioeconomic position, incidence, survival

**Abbreviations:** ASR: age standardised rate; BCR: Belgian Cancer Registry; CBSS: Crossroads Bank for Social Security; CI: confidence interval; EU: European Union; FG: first generation; HRT: hormone-replacement therapy; ICD: International Classification of Diseases; IRR: incidence rate ratio; NHW: non-Hispanic White; RER: relative excess risk; RS: relative survival; SEP: socioeconomic position; SG: second generation; SSA: sub-Saharan African; WSR: World Standardised Rate

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**What's new?**

**Foreign and native populations differ in terms of breast cancer outcomes. However, studies rarely distinguish between migrants of the first and second generation, which could shed light on the genetic and environmental factors influencing breast cancer. This research fills the gap by investigating patterns in breast cancer incidence and survival in different groups by migrant generational and menopausal status. Breast cancer incidence was lower among non-European migrants compared to Belgians. Accounting for socioeconomic position and known risk factors partly reduced the observed discrepancies. A risk convergence between second-generation migrants and Belgians for the development of premenopausal breast cancer was observed.**

are known to lie between those of first-generation (FG) migrants and host-country native levels as a consequence of shifts to lower numbers of children and later ages at childbearing among SG migrants.[14,18]

The chance of surviving breast cancer is generally high when it is detected at an early stage of the disease: over 90% of patients are still alive 5 years after diagnosis.[7] This has led to the implementation of early detection programmes in many industrialised countries. Breast cancer survival is also affected by tumour biology, the presence of comorbidities and treatment quality,[19] and has improved in most European countries since the mid-1990s, irrespective of screening.[4,20] In contrast to breast cancer risk, survival is higher with increasing SEP due to the availability of educational, economic and social resources that can be deployed to tackle this disease.[14]

Generally, ethnic minorities in the United States (US) and New Zealand are at a survival disadvantage compared to the non-Hispanic white (NHW) or Caucasian majority populations.[19,21–26] In Europe, detrimental outcomes have only been identified for black African women in South East England,[27] Surinamese women in the Netherlands[12] and non-European origin groups found to be at low risk of breast cancer in Sweden (i.e., Indians, East Asians, Latin Americans and Africans).[16] Authors point to differences in (the accessibility of) treatment[16,24–27] and genetic predisposition to more aggressive tumours as likely causes for the survival disadvantage.[14,23] Additionally, various scholars find later stages at diagnosis among some of the origin groups with lower breast cancer survival rates, and interpret these as a consequence of lower screening attendance due to limited accessibility of mammographic units and cultural differences in health behaviour.[12,14,16,25,27] Such detrimental stage distribution is not invariably observed among origin groups with lower survival, however.[12,14,17]

Importantly, accessing and navigating a foreign healthcare system can improve with longer spans of life spent in the country, as suggested by Swedish research identifying higher breast-cancer-specific survival among migrants with younger age at migration and longer duration of stay.[14] Although research considering differences between FG and SG migrants is rare, it is crucial to identify effects of growing up in the host country, as well as genetic and environmental contributions to differences in breast cancer survival by migrant background.[28]

Notably, research has established that risk and prognosis for breast cancer strongly differ by age at diagnosis,[7,10,29] raising the possibility that early- and late-age at onset of breast cancer result in different diseases.[10] Researchers should, therefore, design breast cancer studies that allow an assessment of age-specific outcomes.[30] Nevertheless, this approach is rare in migrant research on breast cancer and was mainly adopted in the US. The resulting evidence demonstrates a 'black-white crossover' in breast cancer risk[10,31–33]: African American women are at a higher risk of early-onset (before age 40), but lower risk of late-onset breast cancer than NHW women.[34,35] European studies point to earlier ages at diagnosis (younger than 50) for several migrant background groups,[36,37] with younger population structures among migrant groups,[37] or a higher prevalence of premenopausal breast cancer than among native populations as possible explanations.[36] A 'migrant-native crossover' in risk by age at onset of breast cancer has, however, not been observed to date. There are also no clear patterns by migrant background in survival outcomes across EU (European Union) countries. Examining premenopausal and postmenopausal breast cancer outcomes separately would allow researchers to identify discrepancies and help to find possible sites for intervention.

Although research from Belgium has identified a breast-cancer mortality advantage among all large migrant background groups with convergence to native rates by generational status, up until now, it was impossible to examine whether lower risk or better survival for breast cancer underlies those lower mortality levels.[38,39] A recent linkage of census data with the Belgian Cancer Registry (BCR) combines population with diagnostic information, thus allowing researchers to study incidence and survival simultaneously, and providing an opportunity to delve into the mechanisms underlying previously observed mortality differences. Using these linked data, our study aims to fill many gaps in migrant research on breast cancer: first, by simultaneously studying incidence and survival by migrant background. Second, by taking the association of reproductive factors with incidence, and stage at diagnosis with survival into account while controlling for the contributions of SEP to these relationships. Third, by studying incidence and survival separately by menopausal status at diagnosis. Finally, by splitting up the analyses by migrant generational status to explore within-group differences in outcomes between migrants and migrant offspring.

## Materials and Methods

### Study design and cohort

Data from the 2001 population census, containing socioeconomic and demographic information, were individually linked to the Crossroads Bank for Social Security (CBSS) and the standard cancer registration database for incidence years 2004 to 2013 from the BCR. CBSS data pertained to vital status for

cancer patients until July 1, 2017 at the latest. The BCR has been collecting nationwide data on cancer diagnosis since 2004, relying on information from the oncological care programmes (clinical pathway) and laboratories for pathological anatomy (pathological pathway).[40] All breast cancer diagnoses [International Classification of Diseases (ICD)10 code C50] were considered for the incidence analyses and a woman's first diagnosis for invasive breast cancer (i.e., Stages I–IV) for the survival analyses.

We selected women from the three largest EU and non-EU migrant groups in Belgium: French, Italian, Dutch, Moroccan, Turkish and sub-Saharan African (SSA) women. The country of origin was identified using four variables from the census in the following order: (*i*) nationality at birth of the father, (*ii*) nationality at birth of the mother, (*iii*) nationality at birth of the woman under study; or (*iv*) the current nationality of the woman under investigation.[41] The first variable with a value other than Belgian yielded the woman's origin country. The country of birth of women with foreign origin denoted generational status, with those Belgian-born or moving to Belgium before the age of one defined as SG migrants, and those born outside of Belgium or migrating from the age of one onwards considered to be FG migrants. Information on the birth country could not be used to determine the country of origin for a large part of the SG migrants because the parents' birth country was only known for those still living in the parental household at the time of the census. We, therefore, used a combination of the available nationality variables and birth country to maximise the available information in defining the country origin and generational status.

We considered women that were 30 or older at the start of the observation period (2004) until they reached the age of 70 during follow-up (2004–2013) to be at risk for breast cancer, and breast cancer diagnoses in this age range between 2004 and 2013 were examined in survival analyses (mortality follow-up until mid-July 2017). Premenopausal (ages 30–under 50) and postmenopausal cancer (ages 50–under 70) were studied separately. We chose the 50 years cut-off based on the eligibility for the organised breast cancer-screening program in Belgium, which invites women as of the age of 50 and until the age of 70 to get a screening mammography for early detection of postmenopausal breast cancer.

Analyses for premenopausal breast cancer were repeated with the migrant background split up by migrant generational status. We do not report results for postmenopausal breast cancer and the SSA premenopausal group by generation due to small cell counts. The age distributions of migrant groups, in particular, from outside the EU, are younger than the Belgian, decreasing the number of older SG migrants at risk for or diagnosed with postmenopausal breast cancer and limiting opportunities for robust analyses (Supporting Information Figs. S1a–f and S2a–f).

All statistical analyses were generated using SAS 9.4 (SAS Institute, Cary, NC).

### Incidence

Truncated age-standardised incidence rates (ASRs) and 95% confidence intervals (CI) were calculated for Belgians and each migrant background group. The ASRs were computed as the sum of weighted age-specific crude incidence rates per 5-year age group. The crude rates are the number of new breast tumours diagnosed between 2004 and 2013 in a group (numerator), divided by the person-time at risk for that group (denominator). The person-time was calculated as the time spent in follow-up between the age of 30 and 50 for premenopausal, 50 and 70 for postmenopausal breast cancer. Follow-up for an individual stopped at the following events occurred: breast cancer diagnosis, emigration, death, reaching the age of 50 (premenopausal) or 70 (postmenopausal) or December 31, 2013 (the end of the observation period). The complete population in Belgium at the start of observation was used as the reference population for the age standardisation. The weights in the premenopausal age range equal the age-specific reference population numbers divided by the total reference population between the ages of 30 and 49. For the postmenopausal age group, the same method was applied for the reference population between 50 and 69 years old.

We used Poisson regression models with the log of the person-time as the offset variable to compare incidence rates by estimating incidence rate ratios (IRRs) and adjusting them for known breast cancer risk factors such as SEP and reproductive behaviour extracted from the census. To measure SEP, we used the highest educational level obtained and home ownership. Education was divided in primary or less, lower secondary, upper secondary and tertiary education. Home ownership was categorised into tenants and owners and is used as a proxy for accumulated wealth.[42] Reproductive behaviour was operationalised using the number of children born alive (parity), and age at first childbirth. Parity is made up of women with no children, one child, two children, three children, four children or five or more children. Age at first childbirth contains women without children, and those aged [13–25], [25–30], [30–35], [35–40] and 40 and over. For each variable, a category for missing information was retained.

We examined a series of models testing the contribution of educational level, home ownership, parity and age at first childbirth to IRRs adjusted for age at the start of observation (categorised in 5-year groups). We first ran models adding education and home ownership separately, and combined to adjust for SEP. We consequently added parity and age of first childbirth to each of those models. Home ownership was a borderline significant variable in models that also included educational level and was thus not presented in the incidence results for this paper. The models shown are hence: adjusted for age at baseline (Model 1); age at baseline with adjustment for educational level (Model 2); and age at baseline, educational level, parity and age at first childbirth (Model 3).

### Survival

Survival analyses were performed for patients diagnosed between 2004 and 2013, with vital status provided by the CBSS until July 1, 2017. We computed 5-year relative survival (RS) as a proxy for breast cancer net survival, eliminating the influence of a different

**Table 1.** Description of the population at risk in Belgium on January 1, 2004 by migrant background (in percentages unless indicated otherwise)

| Characteristic | Belgian | Italian | French | Dutch | Moroccan | Turkish | SSA |
|---|---|---|---|---|---|---|---|
| **Premenopausal (30–49 years)** | | | | | | | |
| *n* | 1,363,035 | 51,037 | 29,275 | 19,128 | 37,184 | 22,556 | 14,788 |
| *Educational level* | | | | | | | |
| (Pre)primary | 4.7 | 7.8 | 7.0 | 4.5 | 10.9 | 25.1 | 8.4 |
| Lower secondary | 19.0 | 29.0 | 22.7 | 23.0 | 20.3 | 21.1 | 16.3 |
| Upper secondary | 34.3 | 32.3 | 25.2 | 32.6 | 22.9 | 19.6 | 26.5 |
| Tertiary | 36.5 | 19.7 | 27.8 | 31.4 | 11.6 | 5.5 | 27.5 |
| Missing | 5.5 | 11.3 | 17.2 | 8.6 | 34.4 | 28.8 | 21.4 |
| *Home ownership* | | | | | | | |
| Tenant | 23.7 | 25.4 | 38.6 | 27.4 | 47.5 | 28.4 | 55.7 |
| Owner | 72.1 | 67.7 | 49.1 | 66.0 | 41.5 | 62.0 | 27.7 |
| Missing | 4.2 | 6.9 | 12.4 | 6.6 | 11.0 | 9.7 | 16.6 |
| *Parity* | | | | | | | |
| No children | 22.0 | 18.4 | 16.0 | 22.5 | 12.3 | 6.3 | 13.0 |
| 1 child | 23.6 | 23.8 | 22.3 | 19.2 | 14.8 | 12.1 | 19.9 |
| 2 children | 32.3 | 31.4 | 26.6 | 29.4 | 16.6 | 24.2 | 19.5 |
| 3 children | 12.1 | 12.2 | 11.9 | 11.8 | 14.1 | 23.4 | 12.3 |
| 4 children | 3.3 | 2.9 | 4.2 | 3.1 | 9.9 | 14.0 | 6.4 |
| 5 or more children | 1.1 | 0.9 | 2.0 | 1.1 | 16.8 | 10.4 | 5.4 |
| Missing | 5.7 | 10.4 | 17.0 | 12.9 | 15.6 | 9.7 | 23.6 |
| *Age at first child* | | | | | | | |
| No children | 22.0 | 18.4 | 16.0 | 22.5 | 12.3 | 6.3 | 13.0 |
| [13–25] | 31.7 | 36.9 | 34.1 | 20.7 | 44.1 | 68.6 | 29.4 |
| [25–30] | 30.7 | 24.7 | 22.5 | 26.2 | 18.8 | 11.9 | 21.3 |
| [30–35] | 8.4 | 7.6 | 8.3 | 14.1 | 6.6 | 2.6 | 9.8 |
| [35–40] | 1.4 | 1.8 | 1.8 | 3.3 | 2.0 | 0.7 | 2.5 |
| [40 and over] | 0.1 | 0.2 | 0.2 | 0.3 | 0.4 | 0.1 | 0.4 |
| Missing | 5.7 | 10.4 | 17.0 | 12.9 | 15.8 | 9.9 | 23.7 |
| **Postmenopausal (50–69 years)** | | | | | | | |
| *n* | 1,645,904 | 56,174 | 30,974 | 24,414 | 23,384 | 13,141 | 8,017 |
| *Educational level* | | | | | | | |
| (Pre)primary | 16.8 | 23.2 | 19.9 | 14.3 | 12.7 | 28.5 | 12.9 |
| Lower secondary | 27.8 | 29.1 | 25.6 | 30.6 | 11.7 | 10.2 | 19.7 |
| Upper secondary | 24.3 | 17.9 | 19.4 | 24.7 | 7.0 | 6.2 | 21.3 |
| Tertiary | 21.9 | 7.8 | 15.8 | 19.8 | 3.0 | 1.9 | 23.8 |
| Missing | 9.3 | 22.0 | 19.3 | 10.7 | 65.7 | 53.2 | 22.3 |
| *Home ownership* | | | | | | | |
| Tenant | 18.1 | 19.1 | 31.7 | 24.1 | 39.1 | 24.7 | 47.5 |
| Owner | 78.1 | 75.8 | 60.2 | 71.0 | 51.7 | 66.4 | 39.4 |
| Missing | 3.8 | 5.0 | 8.1 | 4.9 | 9.3 | 8.9 | 13.1 |
| *Parity* | | | | | | | |
| No children | 10.8 | 6.9 | 8.2 | 12.3 | 4.8 | 2.0 | 7.6 |
| 1 child | 23.6 | 19.4 | 21.0 | 16.5 | 6.5 | 3.8 | 14.2 |
| 2 children | 35.7 | 35.7 | 30.8 | 35.5 | 8.5 | 10.5 | 20.0 |
| 3 children | 16.9 | 19.0 | 16.9 | 17.2 | 10.4 | 19.4 | 16.1 |
| 4 children | 6.1 | 8.0 | 7.7 | 6.0 | 11.5 | 20.8 | 10.4 |
| 5 or more children | 3.2 | 5.7 | 5.8 | 3.0 | 48.5 | 35.7 | 14.2 |
| Missing | 3.8 | 5.4 | 9.6 | 9.5 | 9.9 | 7.8 | 17.5 |

*(Continues)*

Table 1. Description of the population at risk in Belgium on January 1, 2004 by migrant background (in percentages unless indicated otherwise) (Continued)

| Characteristic | Belgian | Italian | French | Dutch | Moroccan | Turkish | SSA |
|---|---|---|---|---|---|---|---|
| *Age at first child* | | | | | | | |
| No children | 10.8 | 6.9 | 8.2 | 12.3 | 4.8 | 2.0 | 7.6 |
| [13–25] | 47.3 | 57.2 | 50.7 | 36.9 | 61.1 | 74.0 | 38.7 |
| [25–30] | 28.4 | 21.2 | 20.3 | 27.1 | 12.8 | 10.4 | 19.7 |
| [30–35] | 7.4 | 6.6 | 7.7 | 10.2 | 6.2 | 3.1 | 10.4 |
| [35–40] | 1.8 | 2.1 | 2.6 | 3.2 | 3.3 | 1.5 | 4.8 |
| [40 and over] | 0.3 | 0.4 | 0.6 | 0.5 | 1.1 | 0.4 | 1.0 |
| Missing | 4.0 | 5.6 | 9.9 | 9.7 | 10.8 | 8.6 | 17.9 |

Abbreviations: *n*, absolute number of women at risk; SSA, sub-Saharan African.



mortality background between population subgroups, calculated as the ratio of the observed survival in a patient group and the expected survival in a comparable group from the general population.[43] The expected survival was estimated from region-, sex-, age- and calendar-year-specific national life tables from Statistics Belgium[44] using the Ederer II method.[45]

Table 2. Description of the breast cancer patients diagnosed between 2004 and 2013 in Belgium by migrant background (in percentages unless indicated otherwise)

| Characteristic | Belgian | Italian | French | Dutch | Moroccan | Turkish | SSA |
|---|---|---|---|---|---|---|---|
| **All** | | | | | | | |
| *n* | 54,572 | 1,731 | 912 | 703 | 600 | 255 | 196 |
| *Age at diagnosis, m ± sd* | 55.5 ± 8.8 | 54.4 ± 8.8 | 55.7 ± 8.8 | 56.4 ± 8.9 | 48.8 ± 8.8 | 49.5 ± 9.3 | 50.2 ± 8.1 |
| **Premenopausal** | | | | | | | |
| *n* | 15,518 | 577 | 242 | 181 | 342 | 133 | 96 |
| *Combined TNM-stage* | | | | | | | |
| I/II | 83.2 | 85.8 | 84.7 | 85.1 | 76.9 | 80.5 | 79.2 |
| III/IV | 16.8 | 14.2 | 15.3 | 14.9 | 23.1 | 19.5 | 20.8 |
| *Educational level* | | | | | | | |
| Missing/(Pre)primary | 8.7 | 17.2 | 19.8 | 11.6 | 34.2 | 47.4 | 12.5 |
| Lower secondary | 17.3 | 28.4 | 26.0 | 14.9 | 26.3 | 24.1 | 16.7 |
| Upper secondary/Tertiary | 73.9 | 54.4 | 54.1 | 73.5 | 39.5 | 28.6 | 70.8 |
| *Home ownership* | | | | | | | |
| Missing/Tenant | 24.5 | 26.7 | 49.2 | 29.8 | 61.4 | 36.1 | 59.4 |
| Owner | 75.5 | 73.3 | 50.8 | 70.2 | 38.6 | 63.9 | 40.6 |
| *Age mother at first child, m ± sd* | 26.0 ± 4.1 | 25.4 ± 4.6 | 25.8 ± 4.9 | 27.5 ± 4.8 | 24.8 ± 5.0 | 21.7 ± 3.7 | 25.9 ± 5.2 |
| **Postmenopausal** | | | | | | | |
| *n* | 39,054 | 1,154 | 670 | 522 | 258 | 122 | 100 |
| *Combined TNM-stage* | | | | | | | |
| I/II | 84.1 | 87.6 | 83.3 | 83.5 | 82.6 | 80.3 | 80.0 |
| III/IV | 15.9 | 12.4 | 16.7 | 16.5 | 17.4 | 19.7 | 20.0 |
| *Educational level* | | | | | | | |
| Missing/(Pre)primary | 23.4 | 40.4 | 32.7 | 23.2 | 74.8 | 77.9 | 26.0 |
| Lower secondary | 27.9 | 30.8 | 28.8 | 27.4 | 13.6 | 12.3 | 11.0 |
| Upper secondary/Tertiary | 48.7 | 28.9 | 38.5 | 49.4 | 11.6 | 9.8 | 63.0 |
| *Home ownership* | | | | | | | |
| Missing/Tenant | 20.7 | 18.6 | 34.5 | 29.7 | 50.0 | 29.5 | 52.0 |
| Owner | 79.3 | 81.4 | 65.5 | 70.3 | 50.0 | 70.5 | 48.0 |
| *Age mother at first child, m ± sd* | 24.6 ± 4.2 | 23.9 ± 4.6 | 24.3 ± 4.7 | 25.4 ± 4.6 | 22.3 ± 5.3 | 22.0 ± 5.0 | 25.7 ± 5.1 |

Abbreviations: *n*, absolute number of patients; SSA, sub-Saharan African; m, mean; sd, standard deviation.
Variables for educational level and home ownership are re-categorized to avoid small cells.

**Table 3.** Truncated age-standardised incidence rates (ASR) for breast cancer and 5-year relative survival (RS) for breast cancer patients with 95% confidence intervals (CI)

| | Premenopausal | | | Postmenopausal | | |
|---|---|---|---|---|---|---|
| **Migrant background** | ***n*** | **ASR** | **95% CI** | ***n*** | **ASR** | **95% CI** |
| *Incidence*[1] | | | | | | |
| Belgian | 16,594 | 144.2 | 142.0–146.4 | 41,672 | 392.2 | 388.4–396.0 |
| Italian | 640 | 152.4 | 140.4–164.4 | 1,280 | 353.1 | 333.7–372.6 |
| French | 266 | 120.6 | 105.9–135.3 | 757 | 377.6 | 350.5–404.6 |
| Dutch | 197 | 126.9 | 108.6–145.3 | 545 | 344.9 | 315.7–374.1 |
| Moroccan | 364 | 122.3 | 109.7–135.0 | 276 | 186.0 | 163.5–208.5 |
| Turkish | 146 | 81.6 | 68.3–95.0 | 131 | 163.4 | 134.6–192.2 |
| SSA | 107 | 89.1 | 72.1–106.1 | 102 | 208.0 | 162.9–253.0 |
| *Relative survival*[2] | | | | | | |
| Belgian | 15,518 | 93.3 | 92.8–93.7 | 39,054 | 92.5 | 92.2–92.8 |
| Italian | 577 | 96.6 | 94.5–98.0 | 1,154 | 96.3 | 94.5–97.7 |
| French | 242 | 92.0 | 87.4–95.0 | 670 | 91.7 | 88.8–94.1 |
| Dutch | 181 | 95.2 | 90.6–97.8 | 522 | 92.6 | 89.5–95.1 |
| Moroccan | 342 | 88.3 | 84.2–91.5 | 258 | 90.0 | 85.0–93.7 |
| Turkish | 133 | 92.4 | 86.1–96.1 | 122 | 90.7 | 82.9–95.6 |
| SSA | 96 | 88.2 | 79.6–93.5 | 100 | 89.5 | 80.8–95.0 |

[1]*n*, absolute number of diagnoses; ASR, truncated age-standardised rate as the number of breast cancer diagnoses per 100,000 person years for the period 2004–2013.
[2]*n*, absolute number of deaths among patients; RS, relative survival 5 years after diagnosis; diagnoses between 2004 and 2013 with follow-up until July 1, 2017.
Abbreviations: CI, confidence interval; SSA, sub-Saharan African.

To compare RS between Belgian breast cancer patients and those with a migrant background, we modelled the relative excess risk (RER) of dying up to 5 years after diagnosis through regression models with a Poisson error structure.[46] The RER represents the ratio of the excess hazard due to breast cancer *vs.* the Belgian population.[12,46] An RER above one indicates a higher excess risk of dying due to breast cancer of a particular migrant background group as compared to the Belgian reference group during the first 5 years after diagnosis.

Information on the disease stage at diagnosis was used to adjust the survival models. Information on clinical and pathological stage at diagnosis is provided to the BCR and merged into a 'combined TNM stage' (tumour, nodes and metastasis). The pathological stage prevails over the clinical, except for cases diagnosed with clinical stage IV.[43] The stage at diagnosis has been used as a marker of timely access to care in research[26] and will be used as such in this paper as well. Patients diagnosed at Stage I or II and those with Stage III or IV were grouped. Patients with a missing stage at diagnosis were excluded from the survival analysis (6.2% of all patients). The SEP variables used for the incidence analyses were added but re-categorized into larger groups to avoid small strata (educational level in missing/(pre)primary, lower secondary, higher secondary/tertiary; home ownership in missing/tenant and owner).

**Table 4.** Adjusted incidence rate ratios (IRRs) for breast cancer diagnosed between 2004 and 2013 with 95% confidence intervals (CI)

| | **Model 1** | **Model 2** | **Model 3** |
|---|---|---|---|
| *Premenopausal* | | | |
| Belgian | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| Italian | 1.06 (0.98–1.14) | **1.10 (1.02–1.19)** | **1.10 (1.01–1.19)** |
| French | **0.82 (0.72–0.92)** | **0.85 (0.75–0.96)** | **0.85 (0.75–0.96)** |
| Dutch | 0.87 (0.76–1.00) | 0.88 (0.77–1.01) | **0.86 (0.75–0.99)** |
| Moroccan | **0.86 (0.78–0.96)** | 0.95 (0.86–1.06) | 0.99 (0.89–1.11) |
| Turkish | **0.57 (0.48–0.67)** | **0.64 (0.54–0.75)** | **0.69 (0.58–0.81)** |
| SSA | **0.62 (0.51–0.75)** | **0.65 (0.53–0.78)** | **0.65 (0.54–0.79)** |
| *Postmenopausal* | | | |
| Belgian | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| Italian | **0.90 (0.85–0.95)** | 0.95 (0.90–1.00) | 0.96 (0.91–1.02) |
| French | 0.96 (0.89–1.03) | 0.99 (0.92–1.06) | 0.99 (0.92–1.06) |
| Dutch | **0.88 (0.81–0.96)** | **0.88 (0.81–0.96)** | **0.87 (0.80–0.94)** |
| Moroccan | **0.50 (0.45–0.57)** | **0.57 (0.50–0.64)** | **0.63 (0.56–0.72)** |
| Turkish | **0.43 (0.36–0.51)** | **0.49 (0.41–0.58)** | **0.55 (0.46–0.65)** |
| SSA | **0.57 (0.47–0.69)** | **0.58 (0.48–0.71)** | **0.59 (0.49–0.72)** |

Model 1: Adjusted for age at baseline (categorical); Model 2: Model 1 + educational level; Model 3: Age at baseline + Parity (categorical) + Age at first childbirth (categorical) + educational level.
Abbreviations: Ref., reference group; SSA, sub-Saharan African.

Table 5. Five-year relative excess mortality risk ratios (RERs) for breast cancer diagnosed between 2004 and 2013 according to migrant background with 95% confidence intervals (CI)

| Migrant background | Model 1 | Model 2 | Model 3 | Model 4 |
|---|---|---|---|---|
| *Premenopausal* | | | | |
| Belgian | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Italian | **0.50 (0.30–0.83)** | **0.51 (0.31–0.85)** | **0.49 (0.30–0.81)** | **0.52 (0.32–0.86)** |
| French | 1.15 (0.71–1.86) | 1.14 (0.70–1.87) | 1.08 (0.66–1.76) | 1.06 (0.64–1.74) |
| Dutch | 0.69 (0.32–1.49) | 0.64 (0.28–1.45) | 0.71 (0.33–1.55) | 0.66 (0.30–1.45) |
| Moroccan | **1.57 (1.12–2.19)** | 1.23 (0.87–1.74) | 1.07 (0.75–1.52) | 1.12 (0.79–1.59) |
| Turkish | 1.01 (0.52–1.96) | 0.86 (0.44–1.70) | 0.72 (0.37–1.40) | 0.86 (0.44–1.68) |
| SSA | 1.69 (0.91–3.13) | 1.65 (0.91–2.98) | 1.63 (0.90–2.96) | 1.48 (0.81–2.71) |
| *Postmenopausal* | | | | |
| Belgian | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| Italian | **0.48 (0.31–0.75)** | **0.55 (0.37–0.80)** | **0.52 (0.36–0.75)** | **0.53 (0.31–0.90)** |
| French | 1.16 (0.84–1.60) | 1.18 (0.87–1.61) | 1.12 (0.83–1.51) | 1.00 (0.65–1.54) |
| Dutch | 0.99 (0.67–1.47) | 0.96 (0.66–1.41) | 1.04 (0.73–1.48) | 0.78 (0.43–1.42) |
| Moroccan | 1.45 (0.93–2.24) | 1.33 (0.86–2.06) | 0.98 (0.63–1.55) | 1.36 (0.84–2.21) |
| Turkish | 1.26 (0.63–2.54) | 1.27 (0.68–2.38) | 0.92 (0.49–1.74) | 1.35 (0.62–2.92) |
| SSA | 1.55 (0.78–3.06) | 1.29 (0.62–2.68) | 1.29 (0.64–2.58) | 1.07 (0.48–2.40) |

Model 1: age at diagnosis (categorical); Model 2: M1 + stage at diagnosis; Model 3: M2 + educational level; Model 4: M2 + home ownership.
Abbreviations: Ref., reference group; SSA, sub-Saharan African.

At the modelling stage, we first adjusted the RER for age at diagnosis, added stage at diagnosis and subsequently SEP. We evaluated goodness-of-fit by testing the ratio of the model deviance and degrees of freedom with a chi-square significance test ($p$-value <0.05). As a result, we chose to present the following models: adjustment for age at diagnosis (Model 1), age and stage at diagnosis (Model 2) and the age and the stage association corrected for educational level (Model 3) and home ownership (Model 4) separately.

For both incidence and survival, we verified the Poisson structure models for possible overdispersion by using the method of Lindsey[47] and detected no issues.

## Ethics

Authorisation for linkage between the census and Belgian Cancer Registry was granted by the Belgian InformatieVeiligheidsComité, previously called Privacy Commission. Ethical approval for our

Table 6. Truncated age-standardised incidence rates (ASR) for premenopausal breast cancer and relative survival (RS) for premenopausal breast cancer patients with 95% confidence intervals (CI)

| | Incidence[1] | | | Relative survival[2] | | |
|---|---|---|---|---|---|---|
| Migrant background | *n* | ASR | 95% CI | *n* | RS (%) | 95% CI |
| Belgian | 16,594 | 144.2 | 142.0–146.4 | 15,518 | 93.3 | 92.8–93.7 |
| FG Italian | 191 | 146.3 | 124.7–167.8 | 174 | 99.4 | 95.7–100.6 |
| SG Italian | 449 | 153.7 | 139.4–168.0 | 403 | 95.3 | 92.5–97.3 |
| FG French | 206 | 119.7 | 103.0–136.3 | 185 | 92.0 | 86.7–95.4 |
| SG French | 60 | 121.0 | 89.9–152.0 | 57 | 91.8 | 80.3–97.1 |
| FG Dutch | 141 | 118.6 | 98.2–138.9 | 129 | 94.5 | 88.6–97.7 |
| SG Dutch | 56 | 155.1 | 113.9–196.4 | 52 | 97.0 | 86.1–100.0 |
| FG Moroccan | 280 | 118.2 | 104.1–132.2 | 262 | 87.8 | 83.0–91.4 |
| SG Moroccan | 84 | 181.5 | 111.9–251.0 | 80 | 90.0 | 80.5–95.2 |
| FG Turkish | 120 | 76.3 | 62.5–90.1 | 110 | 92.5 | 85.4–96.5 |
| SG Turkish | 26 | 119.5 | 33.4–205.5 | 23 | 91.6 | 69.4–98.2 |

[1]N: Absolute number of diagnoses; ASR: truncated age-standardised rate as the number of breast cancer diagnoses between ages 30 and 50 per 100,000 person years for the period 2004–2013.
[2]*n*, absolute number of deaths among patients; RS, relative survival 5 years after diagnosis for patients aged 30–50 at diagnosis for patients diagnosed between 2004 and 2013 with follow-up until July 1, 2017.
Abbreviations: CI, confidence interval; FG, first generation; SG, second generation.

study was obtained from the Commission for Medical Ethics at Vrije Universiteit Brussel (Ref. No. BUN 143201734363).

### Data availability

The data that support the findings of our study are available in a secured workspace at the Belgian Cancer Registry after permission for use has been obtained from the InformatieVeiligheidsComité.

## Results

Tables 1 and 2 summarise the main characteristics of the population at risk (1) and breast cancer patients (2). Tables 3–5 list breast cancer risk and RS by migrant background and menopausal status. Premenopausal breast cancer outcomes by migrant generational status are given in Tables 6 and 7.

The descriptive table for the population at risk (Table 1) shows young ages at first childbearing for Moroccan and Turkish women as opposed to most other groups. Those at risk of premenopausal breast cancer have higher educational levels, older ages at first childbearing and higher percentages of nulliparous women compared to the group at risk of postmenopausal breast cancer. Among patients (Table 2), the mean age at diagnosis was lower for non-European than other women. Supporting Information Table S1 provides descriptive information for the population at risk or diagnosed with premenopausal breast cancer by generational status.

### Incidence

Table 3 demonstrates lower premenopausal than postmenopausal breast cancer incidence rates for each group. Non-European women (Turkish, Moroccan and SSA) were at lower risk than European women (Belgian, Italian, French and Dutch) for both age groups.

The relative differences in crude incidence risk obtained through Poisson regression are presented in Table 4. In general, migrant background groups were at lower risk of being diagnosed with invasive breast cancer compared to Belgian women, with substantial differences between Turkish and SSA women compared to Belgian ones for premenopausal,



**Table 7.** Premenopausal breast cancer incidence rate ratios (IRRs) and relative excess rates (RERs) with 95% confidence intervals (CI) by migrant background split up by generational status

| ***Incidence*** | **Model 1** | **Model 2** | **Model 3** |
|---|---|---|---|
| Belgian | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| FG Italian | 1.04 (0.90–1.20) | 1.11 (0.96–1.28) | 1.11 (0.96–1.28) |
| FG French | **0.81 (0.71–0.93)** | **0.84 (0.74–0.97)** | **0.85 (0.74–0.97)** |
| FG Dutch | **0.81 (0.68–0.95)** | **0.82 (0.69–0.97)** | **0.80 (0.68–0.94)** |
| FG Moroccan | **0.80 (0.71–0.90)** | 0.89 (0.79–1.00) | 0.93 (0.82–1.05) |
| FG Turkish | **0.53 (0.44–0.63)** | **0.59 (0.49–0.70)** | **0.64 (0.53–0.76)** |
| SG Italian | 1.06 (0.97–1.17) | **1.10 (1.00–1.21)** | 1.09 (0.99–1.20) |
| SG French | 0.83 (0.65–1.07) | 0.86 (0.66–1.10) | 0.86 (0.67–1.11) |
| SG Dutch | 1.08 (0.83–1.40) | 1.09 (0.84–1.42) | 1.08 (0.83–1.41) |
| SG Moroccan | 1.17 (0.95–1.46) | 1.24 (1.00–1.53) | **1.26 (1.01–1.56)** |
| SG Turkish | 0.92 (0.63–1.35) | 0.98 (0.67–1.45) | 1.02 (0.69–1.50) |

| ***Survival*** | **Model 1** | **Model 2** | | **Model 3** | **Model 4** |
|---|---|---|---|---|---|
| Belgian | 1.00 (Ref.) | 1.00 (Ref.) | Belgian | 1.00 (Ref.) | 1.00 (Ref.) |
| FG Italian | 0.09 (0.00–3.00) | **0.25 (0.07–0.95)** | FG EU | 0.67 (0.42–1.06) | 0.67 (0.43–1.07) |
| FG French | 1.18 (0.68–2.05) | 1.07 (0.61–1.87) | FG non-EU | 0.98 (0.69–1.40) | 1.10 (0.77–1.55) |
| FG Dutch | 0.81 (0.35–1.86) | 0.84 (0.36–1.96) | SG EU | 0.67 (0.43–1.06) | 0.69 (0.44–1.08) |
| FG Moroccan | **1.74 (1.20–2.51)** | 1.36 (0.93–1.99) | SG non-EU | 1.93 (0.48–1.80) | 0.91 (0.47–1.76) |
| FG Turkish | 1.03 (0.49–2.18) | 0.84 (0.39–1.79) | | | |
| SG Italian | 0.66 (0.39–1.10) | 0.65 (0.38–1.09) | | | |
| SG French | 1.08 (0.41–2.83) | 1.57 (0.58–4.25) | | | |
| SG Dutch | 0.41 (0.06–2.88) | 0.38 (0.06–2.48) | | | |
| SG Moroccan | 1.13 (0.54–2.36) | 0.97 (0.47–2.02) | | | |
| SG Turkish | 0.93 (0.22–3.88) | 1.14 (0.27–4.80) | | | |

*Incidence*: Model 1: adjusted for age at baseline (categorical); Model 2: M1 + educational level (categorical); Model 3: M2 + reproductive factors (parity and age at first childbearing; categorical).
*Relative survival*: Model 1: age at diagnosis (categorical); Model 2: M1 + stage at diagnosis; Model 3: M2 + educational level, regrouped migrant background by European Union and non-European Union origin; Model 4: M2 + home ownership, regrouped migrant background by European Union and non-European Union origin.
Abbreviations: FG, first generation; Ref., reference group; SG, second generation.

and all non-European groups (incl. Moroccan) for postmenopausal breast cancer.

Incidence among Turkish women was 43% (IRR 0.57, 95% CI 0.48–0.67) lower for premenopausal (Table 4, premenopausal, Model 1), and 57% (IRR 0.43, 95% CI 0.36–0.51) lower for postmenopausal breast cancer than among Belgians (Table 4, postmenopausal, Model 1). Adjustment for educational level and reproductive variables attenuated large parts of the risk advantages for Turkish (premenopausal and postmenopausal) and Moroccan women (postmenopausal) and even diminished the slightly lower risk of premenopausal breast cancer for Moroccan compared to Belgian women (Models 2 and 3). Upon keeping educational levels constant, the Italian IRR increased to a significantly higher premenopausal breast cancer risk and diminished the risk advantage for postmenopausal breast cancer compared to Belgian women (Model 2). Parity generally played a more prominent protective role against breast cancer for both age groups than the age at first childbearing (Supporting Information Table S2).

Examining premenopausal breast cancer by generational status revealed within-group differences, with a significantly lower risk compared to Belgians among FG migrants only (except for the Italian FG) (Table 7, incidence, Models 1–3).

### Survival

Relative survival 5 years after diagnosis was generally high for both age groups at breast cancer diagnosis and in each origin group. RER of dying among those diagnosed, as represented by RER in Table 5, followed a less distinct pattern by migrant background than the IRRs for incidence. Only the premenopausal Moroccan group had a survival disadvantage: excess risk of dying was 57% higher *vs.* Belgian premenopausal breast cancer patients (RER 1.57, 95% CI 1.12–2.19; premenopausal, Model 1). Adjusting for the stage at diagnosis reduces this disadvantage (RER 1.23, 95% CI 0.87–1.74; Model 2); further adjustment for education or home ownership further narrows the discrepancy. Italian premenopausal and postmenopausal patients are characterised by higher chances of surviving their diagnosis, with RERs of 0.50 (95% CI 0.30–0.83) and 0.48 (95% CI 0.31–0.75), respectively. This advantage hardly changed upon adjusting for the stage at diagnosis or SEP (Models 2–4), and even increased for postmenopausal patients upon adding SEP (Models 3 and 4 *vs.* Model 2).

The higher excess risk of dying among premenopausal Moroccan breast cancer patients is only observable for the FG (RER 1.74, 95% CI 1.20–2.51, survival, Model 1), again diminishing upon adjusting for the stage at diagnosis (Model 2). The Italian survival advantage was identified for the FG after adjustment for the stage at diagnosis, but RER for the FG had a wide CI. The survival models that take into account educational level or home ownership were presented for larger groupings of European and non-European women, as model fit by separate origin countries could not be guaranteed.

## Discussion

In our study, we examined breast cancer incidence and survival by the migrant background in Belgium simultaneously. We aimed to fill essential gaps in migrant research on breast cancer by considering incidence and survival for premenopausal and postmenopausal breast cancer separately and analysing these outcomes for FG and SG migrants.

Our study results attribute the lower breast cancer mortality level in most migrant background groups in Belgium[38,39] to a lower underlying risk of premenopausal and postmenopausal breast cancer, which was particularly pronounced for non-European origin groups (i.e., Moroccan, Turkish and SSA women). This lower breast cancer risk was, in turn, associated with lower educational levels and differences in the reproductive behaviour of groups of non-European origin compared to the European origin groups under study (Belgian, Italian, French and Dutch women). For women with non-EU backgrounds, percentages of nulliparous women are lower, and the number of children born per woman is generally higher. The observed breast cancer risk pattern corresponds to results for migrant groups in the Netherlands, England and Sweden.[12–17,36] The remaining breast cancer risk advantage we observed while keeping SEP and reproductive behaviour constant is likely to result from risk factors that are unaccounted for in our incidence analyses, such as differing breastfeeding customs, age at menarche, screening attendance, physical activity, tobacco use, obesity, hormone-replacement therapy, hormonal contraceptive use and genetic exposures.[8,36]

The survival analyses revealed an important disadvantage among premenopausal Moroccan breast cancer patients that appeared attributable to later stages at diagnosis compared to the native population. This finding is in line with prior studies conducted in New Zealand.[24–26] Differential tumour biology may underlie later stages at diagnosis and lower survival among premenopausal Moroccan women. Patients of Arab descent in Belgium have been shown to present with earlier ages at diagnosis and more luminal B breast cancer subtypes than European women.[48] The protective role of reproductive behaviour is thought to be smaller for this luminal B subtype, and its tumours grow slightly faster and have worse prognoses.[49] Information about histopathological (luminal A/B) and molecular (hormone-receptor status) subtypes is not part of standardised cancer registration in Belgium and could thus not be taken into account in our study but could provide a valuable addition to further research looking to uncover the survival disadvantage among premenopausal Moroccan breast cancer patients.

In contrast to the premenopausal Moroccan group, both premenopausal and postmenopausal Italian patients have a lower excess risk of mortality *vs.* Belgian patients. Considering stage at diagnosis and SEP did not explain this Italian advantage. Other valuable resources for those diagnosed with breast cancer such as healthcare navigation skills and strong

support from the social network may play a role. Studies delving into this high survival might consider Italian breast cancer patients' social contexts and health(care) behaviour.

Our study was one of the first to examine premenopausal and postmenopausal breast cancer by migrant background separately, this being crucial since aetiology and prognosis are known to differ between the two. Our findings demonstrate that migrant patterning in breast cancer outcomes is different according to menopausal status at diagnosis. First, we observed larger disparities in postmenopausal than premenopausal breast cancer incidence, in line with observations in South East England.[27] No incidence crossover pattern such as that identified in US-based research (i.e., higher premenopausal, but lower postmenopausal breast cancer incidence among African American women compared to Caucasians)[31,34] was found for any migrant background group in Belgium. Second, survival analyses by menopausal status pointed to premenopausal Moroccan patients as vulnerable due to later stage distributions than Belgians, whereas postmenopausal Moroccan patients' survival did not significantly differ from that of their Belgian counterparts. Analysing all breast cancer diagnosis combined would not have allowed us to identify this group as being at a particular disadvantage.

By further examining premenopausal breast cancer by generational status, two observations stand out: firstly, risk advantages were only visible for premenopausal FG migrants; second, the premenopausal Moroccan survival disadvantage did not persist into the SG. The incidence finding highlights an early breast cancer risk convergence of SG migrant to Belgian levels, in line with results from Swedish research.[14] Although the number of patients among SG Moroccan women is rather low, the premenopausal survival analysis by generational status offers several new insights into the Moroccan patients' excess risk of mortality. It indicates that this group's survival disadvantage is unlikely to be caused by genetic susceptibility to more aggressive breast cancer subtypes among Moroccan women, an often hypothesised explanation for survival disadvantages among groups of foreign origin in international research.[14,23] Alternatively, the lack of a disadvantage among SG Moroccan patients may be linked to the differences in reproductive behaviour between the FG and SG, namely increasing percentages of nulliparous women and decreasing number of children among SG Moroccan women, reducing the likelihood of being diagnosed with the more aggressive luminal B breast cancer subtype for the SG.[48] Another possibility is an improvement in knowledge and navigation of the Belgian health (care) system among migrants' offspring, putting them at an advantage compared to those migrating themselves.[50]

To the best of our knowledge, this is the first article to demonstrate inequalities in breast cancer outcomes by menopausal as well as generational status. The convergence in premenopausal breast cancer risk between SG migrants and Belgians emphasises the importance of risk awareness and prevention among natives and SG migrants alike. Worse survival among premenopausal Moroccan patients furthermore implies that appropriate risk awareness in women, risk assessment in primary care and the provision of timely and high-quality care are crucial.[24,51]

Despite its contributions, our study was subject to some limitations. First, we used 50 years of age as a surrogate marker for menopausal status. Information on actual menopausal status could yield more precise patterns. Additionally, research shows that a younger age within the premenopausal group still acts as an adverse prognostic factor,[29] which we accounted for by adjusting our RERs for age at diagnosis. Second, the BCR has a high coverage rate of Belgian breast cancer diagnoses,[52] but does not have information on the completeness of (breast) cancer registration by migrant background. Importantly, cancer outcome estimates were not thought to be substantially affected by such a phenomenon in other research,[36] nor do we think it impacted ours. Third, the cross-sectional character of the census limited the information on reproductive behaviour and SEP to 'one-shot' measurements even though parity and home ownership were subject to change during follow-up, particularly among premenopausal women.

A multidisciplinary research agenda that considers clinical, social and biological factors and interactions with the environment will allow a better understanding of how differences in breast cancer outcomes arise and how they can be alleviated.[53] Especially the observed premenopausal survival disadvantage among FG Moroccan women represents an interesting subject for further inquiry, for example, by assessing the underlying differences in tumour biology (e.g., hormone-receptor status), and by exploring how these women move from help-seeking toward diagnosis and treatment in Belgium.



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