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Breast cancer in Portugal: Temporal trends and age-specific incidence by geographic regions

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ABSTRACT

Background: Female breast cancer incidence rates have been increasing in Portugal for years. We, therefore, conducted the first nationwide breast cancer study to assess regional differences.
Methods: Cases were obtained from population-based cancer registries covering the country's Mainland (South, North, Centre), as well as the two Autonomous Regions (Azores and Madeira), for the time-period 1998 through 2011. Analyses were restricted to ages 30–84 years and stratified by region. We used the age-period-cohort (APC) framework to complement standard descriptive techniques and to forecast future trends. Estimable APC parameters included net drift, longitudinal age-specific incidence rate curves, and fitted age-specific incidence rate ratios.
Results: There were 71 545 breast cancer cases diagnosed in Portugal at ages 30–84 years from 1998 to 2011. The South presented the highest age-standardized rate (155.8/100 000), while the North presented the fastest rate of increase (3.6%/year). Age-specific statistical interactions were observed between regions. Younger women in the North revealed a decreased risk of developing breast cancer compared to women from the same age group in the South and Centre, while that risk was reversed in older women ($p < 0.05$). We estimate that from 2014 onwards, the North might rank first among all regions.
Conclusion: The variant patterns observed could be due to a combination of different screening practices and/or exposure to risk factors across regions. Disease heterogeneity among younger and older women may also explain part of the differences in age-specific rates. These results justify continued monitoring of breast cancer incidence by region.

1. Introduction

Breast cancer is the most frequent cancer and the leading cause of cancer mortality among Portuguese women, with an estimated 6088 new cases and 1570 deaths in 2012, accounting for 30% of all cancer cases and 16% of all cancer deaths [1]. Notwithstanding the recent declines in incidence rates observed in some western countries, attributed to reductions in the use of postmenopausal hormone replacement therapy and to plateaus in participation of mammography screening [2], cancer registries operating in Portugal have reported increases in breast cancer age-adjusted incidence rates [3–6]. These registries cover the Southern, Northern, and Central parts of the country's mainland, representing around 95% of the whole population, as well as the archipelagos of the Azores and Madeira, both located in the north Atlantic Ocean, and representing the remaining 5%.

Temporal increases in breast cancer incidence can be driven by factors related to 1) age at diagnosis, 2) events that impact all ages at a given point in time such as changes in screening or diagnostic practice patterns (period or secular effects), and/or 3) factors that vary from one generation to the next such as changes in reproductive patterns (birth-cohort) [7]. To account for the effects of these three interrelated variables, cancer surveillance researchers have used age-period-cohort

Abbreviations: APC, age-period-cohort; ICD-10, International Classification of Diseases Tenth Revision; ASR, age-standardized rate; EAPC, estimated annual percentage change; IRR, incidence rate ratio; ER, estrogen-receptor; WHO, World Health Organization

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(APC) models [8]. APC modeling is a mathematical approach that provides a unique set of estimable functions and parameters in order to better understand the impact of age, period, and cohort effects on disease trends [9].

In this study, we aim to describe breast cancer incidence temporal trends in Portugal by complementing standard descriptive methods with the APC framework. We will specifically analyze past and expected trends by South, North, Centre, Azores, and Madeira geographic regions to further hypothesize for differences across the country. To our knowledge, no studies describing these trends have ever been published, and certainly no head to head comparison between geographic regions have ever been performed.

2. Methods

Invasive breast cancer cases (ICD-10 code C50) by single age and district/region of residence were obtained for the 14-year time-period 1998 through 2011 from four population-based cancer registries that cover the entire country of Portugal. Only first primary breast tumors, as defined by international coding rules [10], have been included in the analyses. Female population estimates by single age and district/region of residence for the same period were obtained from Statistics Portugal. We restricted analyses to ages 30–84 years to avoid low counts at extreme ages. Results were stratified by geographic regions (South, North, Centre, Azores, and Madeira) and three age groups according to the likelihood of mammographic screening: age 30–44 years (unlikely to be screened and a surrogate to early onset breast cancers), age 45–69 years (likely to be screened), and age 70–84 years (unlikely to be screened and a surrogate to late onset breast cancers).

Age-standardized (ASR) incidence rates expressed per 100 000 woman-years were computed by the direct method by using the European standard population as the reference [11]. The estimated annual percentage change (EAPC) of the ASR was computed using weighted log-linear regression [12]. Cumulative risks measuring the risk which a woman would have of developing breast cancer during the age span 0–74 years, assuming no other causes of death were in operation, were assessed for each region [11].

We used the age-period-cohort (APC) framework to complement standard descriptive techniques as well as to forecast future incidence trends. APC models were fitted to one-year periods so there were 55 single-year age groups (30, 31, …, 84 years), 14 single-year calendar periods (1998, 1999, …, 2011), and 68 partially overlapping 2-year birth cohorts (1914, 1916, …, 1981) [13]. Estimable APC parameters included net drift, longitudinal and cross-sectional age-specific incidence rate curves, and fitted age-specific incidence rate ratios (IRR) [14].

In brief, net drift is the APC model analog of the EAPC and it measures the overall long-term secular trend that is attributable to both calendar time (period or secular effects) and the successive cohorts enrolled in the study (birth-cohort effects). The longitudinal and cross-sectional curves are two different ways of summarizing the age-associated natural history. However, contrary to the cross-sectional curve, the longitudinal curve, also named age-at-onset curve, is adjusted for period and cohort effects. It is constructed by extrapolating from observed age-specific rates of each birth cohort to estimate past, current, and future rates for a referent cohort, thus taking into account the experience of all cohorts in the study (see Supplementary Fig. 1). The choice of the referent cohort is arbitrary, but has been conventionally set to the mid-cohort because it corresponds to the birth cohort tracking the longest amount of time within the registry [15].

We used the Wald test to obtain *P* values to assess statistical interactions between a pairwise of age-specific longitudinal curves (e.g., North vs. South) and the Bonferroni test to correct for multiple comparisons [16]. Briefly, an “interaction” is said to occur when an unknown factor in some way alters the effect of an exposure–disease relationship [17]. The interaction could be quantitative or qualitative. A quantitative interaction occurs when the unknown factor modifies only the magnitude of the effect (e.g., higher or lower rates in one region compared to another). Graphically, no reversal or crossing of the IRR with aging is observed. By contrast, a qualitative interaction occurs when there is a change not only in magnitude but in the direction of the effect (e.g., compared to a different region, younger women would present a lower risk of developing breast cancer while that risk would be reversed in older women). Regions with no interaction would be parallel on the log scale or proportional on the absolute scale [18].

Finally, we also projected ASRs up to 2025, as described elsewhere [19]. Estimates are obtained by multiplying the estimated longitudinal age incidence rate curve in a referent birth cohort by the rate ratio between birth-specific cohorts and the referent cohort. Statistical analyses and graphical plotting were performed in Matlab, version R2016a (MathWorks Inc, Natick, MA, USA). Goodness of fit for each APC model was assessed by the square root of the usual over-dispersion parameter σ^2, and by similarity between observed and fitted rates [19]. All hypothesis tests were two-sided, and *P* values < 0.05 were considered statistically significant.

3. Results

During the time period 1998 through 2011, there were 71 545 breast cancer cases diagnosed in Portugal between the ages 30 through 84 years (Table 1). Almost half of these cases (47.5%) were among Southern women, 27.7% among Northern women, 20.6% among Centre women, and the remaining 4.2% among women living in the Portuguese Autonomous Regions (Azores and Madeira). APC models were successfully fitted to the observed incidence data, with the models presenting negligible over-dispersion values (data not shown) and fitted confidence bands (shaded areas) consistently following close to observed rates (dots) (Fig. 1). APC age effects are shown in Supplementary Fig. 1, and period and cohort effects in Supplementary Fig. 2.

The South presented the highest ASR (155.8 per 100 000 woman-years), followed by the North (132.4/100 000) and Centre (126.5/100 000) (Table 1). A similar ranking was observed by age group as well as for the cumulative risk of developing breast cancer before the age of 75. In the 14-year study, the ASR increased 1.6% (95% confidence interval, 0.9–2.3) per year among Southern women, 3.6%/year (3.1–4.1) among Northern women, and 2.3%/year (1.3–3.3) among Centre women. Statistically significantly different EAPCs were also observed in all age groups, with South and Centre presenting the fastest rate of increase in the age group 30–44 years. Net drifts, measuring the overall log-linear trend in the period and cohort effects, were almost equal to the EAPCs, but presented narrower confidence intervals.

Fig. 1 presents overall age-standardized and age-specific temporal trends in breast cancer incidence for each geographic region as well as for the whole country. Excluding the Azores and Madeira, which depicted unstable rates due to a low number of cases, breast cancer incidence rates increased throughout the 14-year study period in all age groups, with the steepest increases being observed in the North. Age groups 45–69 and 70–84 presented similar rates in the North, and in the Centre, rates in the middle age groups (45–69) even surpassed rates in older ages (70–84).

Fig. 2 shows the APC fitted age-at-onset curves on a pairwise comparison between two of the three main regions. After correcting for multiple comparisons through the Bonferroni test, the *P*-values for the null hypothesis of no interactions between regions were statistically significantly different for North vs. Centre (Fig. 2A) and North vs. South (Fig. 2C). In both pair of regions, qualitative age interactions were observed (Fig. 2D and Fig. 2F, respectively), with the IRR crossing the reference line for the older ages. These interactions were more pronounced in the North vs. South, where IRR values were always statistically significantly different before and after the crossover.

Fig. 3 shows the observed and projected incidence rates for each of the three main regions. The South always presented the highest ASR