The Epidemiology of Male Breast Cancer in Eight High-income European Countries.

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Background & Objectives:

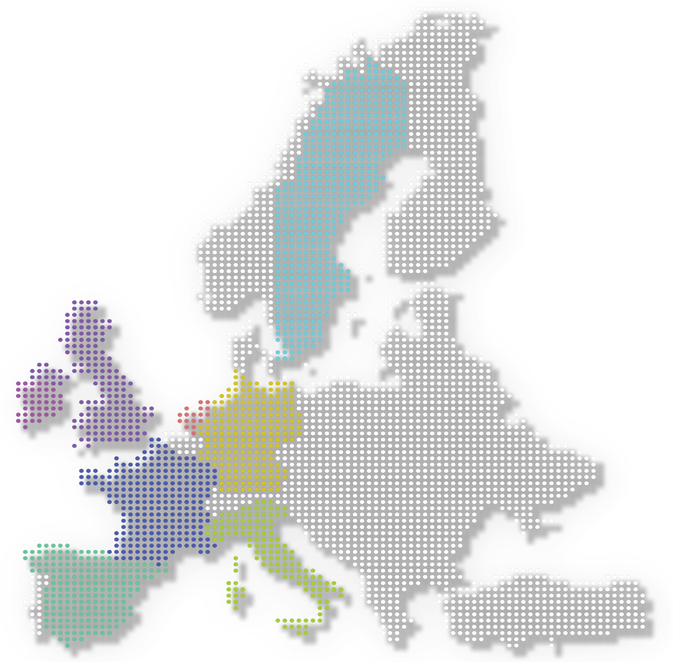
Worldwide, breast cancer has the greatest incidence and number of cases out of all malignancies[1]. Male breast cancer is considered as an extremely rare cancer, and as a result is often overlooked: many cancer registry reporting networks, such as the European Cancer Information System (ECIS), do not report male breast cancer incidence and prevalence.

The risk factors for male breast cancer are a family history of male breast cancer, the presence of mutated BRCA1 or 2, hyperoestrogenism as a result of obesity, Klinefelter's syndrome, treatments involving exogenous oestrogen, and androgen deficiency due to hypogonadism or as a result of treatment for prostate cancer[2].

Male breast cancer is diagnosed through ultrasound or mammography and biopsy, staged using the TNM staging, and treated very much in the same way as female breast cancer, with survival by corresponding subtype and stage in males being very similar to that in females[3].

This study aims to forecast the incident cases of male breast cancer in eight high-income European countries: France, Germany, Ireland, Italy, the Netherlands, Spain, Sweden, and the United Kingdom, over a 10-year period, and report the expected stage at diagnosis and molecular subtype in these countries.

Figure 1. Age-standardized Incidence (ASR) Per 100,000 of Male Breast Cancer in 2022



Methods:

The incidence of male breast cancer was ascertained from national cancer registries in Germany[4], Ireland[5], Netherlands[6], Sweden[7] and England[8], which all report newly diagnosed incident cases of breast cancer (ICD-10 C50) in males. For France, Spain and Italy, the crude incidence was derived from the corresponding regional registries included in IARC CIX[9], reporting newly diagnosed cases of breast cancer (ICD-10 C50) in males.

The crude incidence forecast over the next 10 years was derived using an average of the most recent three years of data, because country-specific historical data showed no change over time and overweight and obesity in adult males, the main quantifiable risk factor for male breast, has been relatively constant[11].

We estimated the age-standardized incidence (ASR) using the country- and age-specific incidence and the Revised European Standard Population[10].

We reviewed the literature and used peer-reviewed epidemiological studies on unselected male breast cancer patients from European countries to establish the TNM stage at diagnosis I-IV (AJCC 8th Edition) and molecular subtype proportion based on hormone receptor (HR), epidermal growth factor receptor 2 (HER-2) receptor and nuclear protein Ki67 combinations.

For our estimations of molecular subtype, only papers reporting HER-2 proportions using immunohistochemistry and confirmation of scores of 2+ using fluorescence in situ hybridization (FISH) were used. The molecular subtypes reported in this study are combinations based on HR positivity and HER2+ overexpression:

- Luminal A: HR+ and HER2- or Ki-67 >14%.
- Luminal B: HR+ and HER2+ or Ki-67 >14%.
- HER-2: HR-/HER2+
- Triple negative breast cancer (TNBC): HR-/HER2-.

Results: Incidence

Across the eight countries under study, the age-standardised incidence ranges from 1.3 per 100,000 in Spain and Sweden to 1.8 in France and Germany (Figure 1).

The age-specific incidence of male breast cancer is estimated to remain constant over the next 10 years as the prevalence of overweight and obesity in male adults, the key quantifiable risk factor for male breast cancer, has been relatively constant[11].

Male breast cancer risk increases with age and in conjunction with the aging population across all the countries, we estimate the incidence will increase over the next ten years, ranging from 1.2% per year increase in Germany to 2.9% per year in Ireland (Figure 2).

This equates to approximately 4,900 newly diagnosed cases of male breast cancer in 2022 and an expected 5,300 cases in 2032.

Figure 2. Crude Incidence per 100,000 of Male Breast Cancer, in 2022 and 2032.

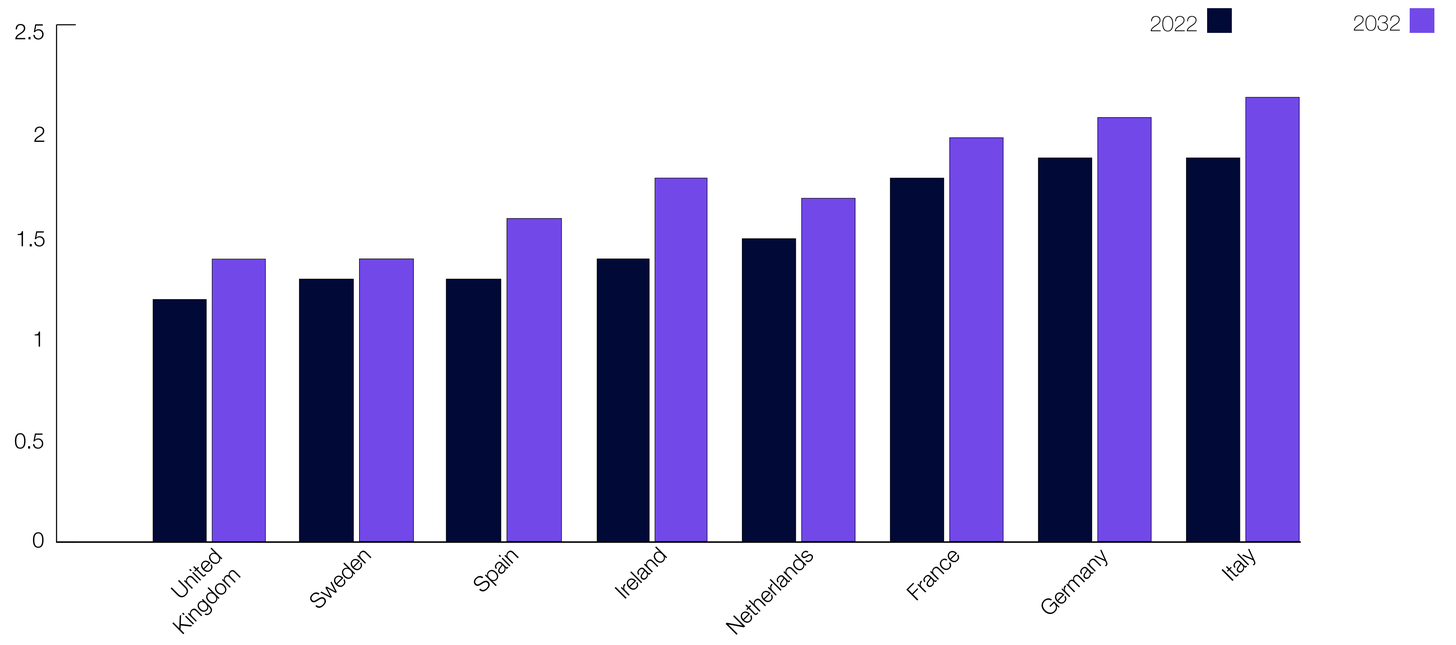


Figure 3. Distribution of Molecular Subtypes in Male Breast Cancer (left) and Female Breast Cancer (right).

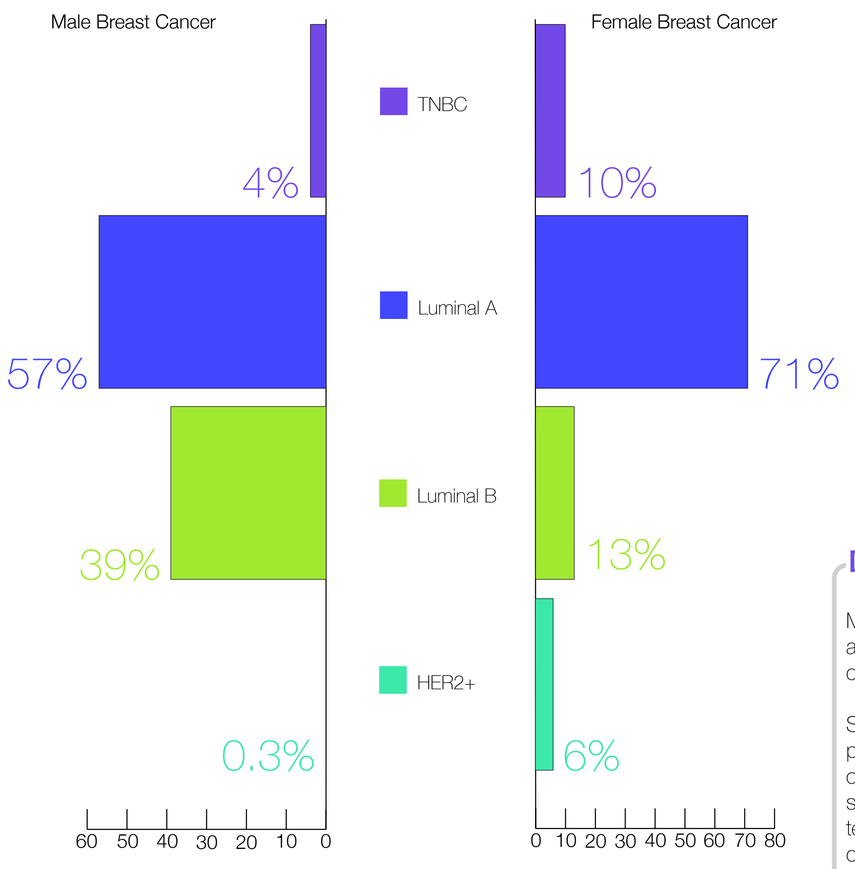


Figure 4. Stage at Diagnosis in Male Breast Cancer.

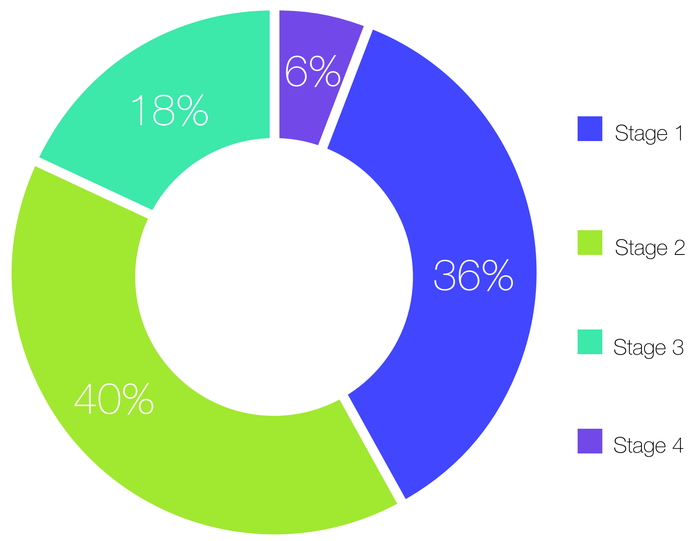
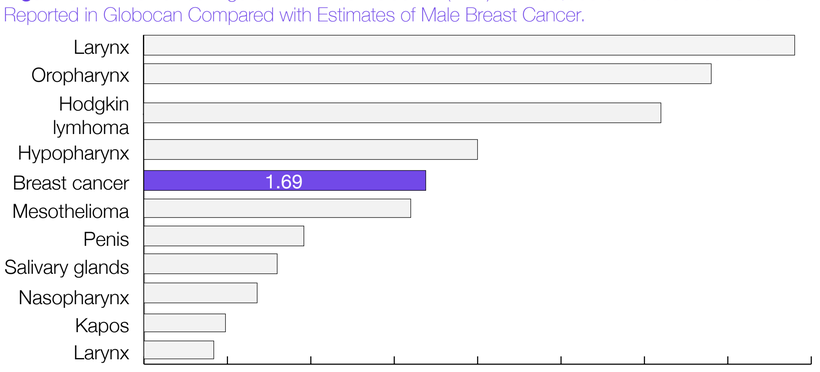


Figure 5. The 10 Lowest Age-standardized Incidence (ASR) Per 100,000 of Male Cancer Sites Reported in Globocan Compared with Estimates of Male Breast Cancer.



Results: Molecular Subtype

Our review of the literature for the molecular subtype in male breast cancer patients identified three papers for inclusion from Germany, the Netherlands, and Spain[12-14]. The majority of papers reported oestrogen receptor, progesterone receptor, and HER-2 receptor positivity independently which did not allow the derivation of the molecular subtype groupings under study. However, the ranges from these papers were used to validate the results from the selected papers which showed HR positivity to be approximately 93%.

Based on the results of the literature review, male breast cancer displays a very different molecular subtype distribution to female breast cancer (Figure 3)[15-18]:

- In male breast cancer, 96% of cases are HR+ compared with approximately 84% in female breast cancer.
- HER-2 overexpression in male breast cancer (40%) is two-fold greater than that of female breast cancer (19%).
- HER-2 overexpression with HR negativity is extremely rare at 0.4% in male breast cancer, compared with 6% in female breast cancer.
- The proportion of TNBC in male breast cancer patients (4%) is less than half that in female breast cancer patients (10%).

Results: Stage at Diagnosis

Our review of the literature for the stage at diagnosis for male breast cancer identified six papers for inclusion from France, Italy, Spain, and Portugal[2,19-23]. As male breast cancer is rare, the majority of papers either merged the findings with other global sources or focused on non-metastatic or metastatic male breast cancer.

Based on the results of the literature review, despite there being no screening for male breast cancer, the overwhelming majority of cases, 76%, are diagnosed with stage 1 or 2 disease and only 6% are diagnosed with metastatic disease (Figure 4).

Discussion:

Male breast cancer is not commonly reported in cancer registries. Our estimates of incidence and ASR across the eight European countries under study in comparison with other male cancers is shown in Figure 5.

Stage at diagnosis and molecular subtype are prognostic factors for survival and the prevalence of these at diagnosis in male breast cancer vary when compared to female breast cancer. Stage at diagnosis in male breast cancer would be expected to differ due to lack of screening; typically in solid tumours with no screening programmes, the stage distribution tends towards the more advanced stages 3 and 4. However, the location and physiology of the pectoral tissues in males may make identification of any masses or changes to the area around the nipple more noticeable by male patients, perhaps accounting for the large proportion of male breast cancer patients being diagnosed with stage 1 or 2 disease. We did not identify any European studies reporting the cross over of stage at diagnosis by molecular subtype. This would be interesting as it would guide understanding to whether the greater proportion of HR positive tumours, which tend to be less aggressive in female breast cancer, could be the driving factor behind the earlier stage at diagnosis distribution in breast cancer in males.

The molecular subtype distribution of male breast cancer has a positive impact in terms of treatment options: with over 95% of male breast cancer positive for HR and nearly 40% overexpressing HER-2 there are numerous combinations of targeted therapies available for early-stage adjuvant treatment as well as in the advanced stages of disease. Among the male breast cancer patients with tumours expressing HR, these patients are eligible for targeted therapies such as the HR+ targeted therapies abemaciclib (must also be HER2 negative) or neratinib (must also be HER2+). For the many patients overexpressing HER2, with or without the presence of HR, they are eligible for the HER2 targeting therapies such as trastuzumab or pertuzumab.

Although the characteristics of male breast cancer tumours by stage at diagnosis and molecular subtype vary when compared to female breast cancer, breast cancer prognosis is dependent on the combination of stage and molecular subtype. Studies have been carried out comparing male breast cancer and there have been varying results with some papers showing poorer disease-free survival but similar overall survival[24]. While rare cancers do not always have a large arsenal of treatment options, male breast cancer benefits from the considerable research that has gone into female breast cancer and the resulting treatment practices can be applied to male breast cancer. However, more research is needed to understand the outcomes and perhaps inform treatment guidelines for male breast cancer.

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