Maturitas 73 (2012) 152–157

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Population-based hormone receptor-specific incidence trends of breast cancer in Germany

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ARTICLE INFO

Article history:
Received 30 January 2012
Received in revised form 7 June 2012
Accepted 13 June 2012

Keywords:
Breast cancer
Estrogen receptors
Progesterone receptors
Incidence
Hormone replacement therapy
Cancer registry

ABSTRACT

Objectives: Several countries reported a drop in prescription of hormone replacement therapy (HRT) in the 2000s, followed by decreases in breast cancer incidence among postmenopausal women aged 50–69 years. The aim of this study was to provide hormone receptor specific incidence rates of breast cancer in Germany.
Methods: Breast cancer data were extracted from the cancer registries of the Federal States of Brandenburg and Saarland and the area of Munich for the period from 1998 to 2007. We obtained nationwide data on HRT prescription in 1998–2007 from health insurances. Multiple imputation was used on missing values for the receptor status. Age-standardized (European standard population) and age-specific rates were calculated.
Results: The age-standardized incidence rates in breast cancer were virtually constant over the entire period in all regions. In particular, no substantial changes over time occurred within the age- and receptor-specific analyses. In the same period we observed a drop in HRT use, starting in 1999 and leveling off in 2004. The incidence trends of carcinoma in situ of the female breast increased during the study period.
Conclusions: In our data, we did not observe an association between the decline in HRT prescription and breast cancer incidence among women aged from 50 to 69 years. The lack of temporal changes in breast cancer incidence may be explained by introduction of opportunistic and organized mammography screening and low absolute levels of HRT prescription in Germany.

1. Introduction

The Women's Health Initiative (WHI) showed under hormone replacement therapy (HRT) harmful effects in coronary heart disease, stroke, pulmonary embolism and increases in incident breast cancers [1]. The Million Women Study (MWS) offered similar results for breast cancer [2]. These reports affected prescription policy and contributed to a substantial decline in HRT prescriptions worldwide.

Analyses of data from the Surveillance, Epidemiology, and End Results (SEER) database showed that breast cancer incidence dropped by 7% from 2002 to 2003 in the U.S. Within the subgroup of women aged 50–69 years, the incidence drop was 12% for estrogen receptor-positive breast cancer [3]. The decline began in mid-2002 and coincided with the drop in postmenopausal hormone prescriptions that occurred after the early termination of the Women's Health Initiative (WHI) trial in June 2002 [4]. The observation that estrogen receptor-positive breast cancer showed the strongest incidence decline in the U.S. supports the hypothesis that the incidence decline is causally related to the decrease of the prescription prevalence of HRT.

Abbreviations: HRT, hormone replacement therapy; WHI, Women's Health Initiative; MWS, Million Women Study; SEER, Surveillance, Epidemiology, and End Results; HR, hormone receptor; BB, The Cancer Registry of the Federal State of Brandenburg; DCO, death certificate only; MCR, The Munich Cancer Registry; SL, The Saarland Cancer Registry; ICD-10, 10th edition of the International Classification of Diseases; IARC, International Agency for Research on Cancer; ER, estrogen receptor; PR, progesterone receptor; DDD, defined daily doses; ESP, European standard population; APC, annual percentage incidence change; 95%CI, 95% confidence interval; HERS, Heart and Estrogen/progestin Study; NHANES, U.S. National Health and Nutrition Examination Surveys.

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http://dx.doi.org/10.1016/j.maturitas.2012.06.008

The downturn in breast cancer incidence and fall in HRT have been reported by several registries including Australia, Canada and Western Europe [5–10]. The results underlined a striking association between HRT and breast cancer incidence.

To our knowledge, only a few countries have been able to provide breast cancer incidence according to hormone receptor status information including the U.S., France and Scotland [5,11–13]. The aim of this study was to provide hormone receptor (HR)-specific incidence rates of breast cancer from Germany using data from population-based cancer registries and study these rates in relation to HRT prescription rates.

2. Materials and methods

We extracted breast cancer data from the population-based cancer registries of the Federal States of Saarland and Brandenburg and from the Munich Cancer Registry for the period 1998–2007.

The cancer registry of the Federal State of Brandenburg (BB) was established in 1993 and comprises five hospital based cancer registries. Death certificate only (DCO) cases of the Federal State of Brandenburg were provided by the Common Cancer Registry of the New Federal States including Berlin. The Munich Cancer Registry (MCR) was established in 1978 and routinely records data for all cancer patients treated in Munich and the surrounding area. It receives clinical data from 73 hospitals and several hundred doctors in private practice. The Saarland Cancer Registry (SL) is a population-based cancer registry and covers the entire territory of the Federal State of Saarland. The registry was established in 1967. SL and MCR have been involved in several regional, national, and international research collaborations [14].

Population data were provided for Brandenburg and Saarland by the statistical offices of the federal states and for Munich by the registry itself by calendar year, gender and age groups (0–4, 5–9, . . ., 80–84, 85+ years). These regions included a population of about 6.9 million people.

Incident cases were defined as invasive breast cancers and carcinomas in situ coded as C50 or D05 (10th edition of the International Classification of Diseases, ICD-10) according to the rules for multiple primary cancers from International Agency for Research on Cancer (IARC) [15,16]. Table 1 presents an overview of the analyzed registry data. The proportion of histological verification was generally high with a range of 92.8–96.9%.

For cases with missing hormone receptor status information (estrogen receptor (ER) and progesterone receptor (PR)) in the electronic files, available pathology reports in all three registries were checked for this information. For the remaining cases with missing information on hormone receptor status, we tried to recontact the reporting pathologists. The final proportion of missing receptor status remained between 6.9% and 15.1%. We defined the following categories of receptor status: positive (ER+PR+), negative (ER−PR−) and mixed (ER+PR− or ER−PR+).

As simulation studies previously showed that multiple imputation tends to provide less biased analyses than complete case analyses we imputed to account for missing data of hormone receptor status information [17,18]. We assumed missing at random and included date of diagnosis, date of birth, duration of follow-up, region code and diagnosis confirmation for the imputation. We imputed 20 times applying PROC MI of SAS® (SAS Inc., Cary, NC, USA). The results from these 20 imputed data sets were summarized using Rubin's method [19].

Aggregated HRT prescription data for Germany were obtained from the WIdO-Institute [20]. Related hormone prescriptions were classified by the ATC system (Anatomical Therapeutic Chemical Classification System) as G03CA (estrogen), G03CX (tibolone) and G03FA/B (estrogen plus progestin), and were measured in defined daily doses (DDD). Ten DDDs per 1000 women per day indicates that 1% of the population on average got HRT prescription on a daily basis. Accordingly, DDDs were presented as prevalence estimates and were considered as a proxy for the use of HRT. Prescription data for Germany as a whole were provided from 1998 to 2007, aggregated in 5-year age groups. On the federal state level annual numbers of HRT prescriptions from 2001 through 2007 could not be stratified by age.

We estimated crude and age-standardized incidence rates using the European standard population (ESP) [21]. In addition, we calculated age-specific (0–49, 50–69, 70+ years) age-standardized incidence rates using the ESP. To obtain most precise incidence rate estimates of male breast cancer, we pooled the case files and corresponding person years at risk of the registries.

For the estimation of the annual percentage change (APC) in breast cancer incidence and HRT prescriptions, we fitted regression lines to the natural logarithm of the age-standardized incidence rates using calendar year as a regressor variable, i.e. $y = a + bx$, where $y = \ln(\text{rate})$ and $x =$ calendar year. The APC is then estimated as $100 \times (e^b - 1)$. These models assumed that the logarithm of the rates changed at a constant rate over the periods. All analyses were run in SAS® version 9.2 (SAS Inc., Cary, NC, USA).

Table 1
Baseline characteristics of breast cancer and carcinoma in situ of analyzed cancer registries in Germany, 1998–2007.

	Brandenburg	Munich	Saarland
Female			
Cases of invasive breast cancer (*n*)	15,716	26,358	8274
Histological verification (%)	94.7	92.5	96.8
Death certificates only (%)	4.8	5.8	2.0
Receptor status information (%)			
Estrogen positive	72.0	72.6	69.1
negative	21.1	13.6	16.0
missing	6.9	13.9	14.9
Progesterone positive	66.5	68.7	61.1
negative	26.3	17.1	23.9
missing	7.2	14.2	15.0
Cases of breast carcinoma in situ (*n*)	1022	2100	555
Histological verification (%)	99.2	99.9	99.1
Death certificates only (%)	0.8	0	0
Receptor status information (%)			
Estrogen positive	48.3	55.5	38.2
negative	32.3	14.3	13.3
missing	19.4	30.2	48.5
Progesterone positive	44.8	51.9	33.2
negative	35.6	17.6	18.4
missing	19.6	30.6	48.5
Male			
Cases of invasive breast cancer (*n*)	104	204	57
Histological verification (%)	100.0	90.2	91.2
Death certificates only (%)	0	6.9	7.0
Receptor status information (%)			
Estrogen positive	81.7	72.1	63.2
negative	13.5	4.4	3.5
missing	4.8	23.5	33.3
Progesterone positive	76.0	68.1	61.4
negative	19.2	8.3	5.3
missing	4.8	23.5	33.3
Cases of breast carcinoma in situ (*n*)	5	11	4
Histological verification (%)	100.0	100.0	100.0
Death certificates only (%)	0	0	0

3. Results

A total of 50,378 female breast cancer patients (ICD-10: C50) were registered in the three populations from 1998 through 2007. Age-standardized incidence rates were virtually constant in all the three registries for the whole period (120 in MCR, 110 in SL and 85 in BB per 100,000 person years) (results not shown).