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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Prescription of hormone replacement therapy prior to and after the diagnosis of gynecological cancers in German patients

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Abstract

Purpose Little is known about how a gynecological cancer diagnosis affects a gynecologist's decision to prescribe hormone replacement therapy (HRT). Therefore, the goal of this study was to analyze the prevalence of HRT prescription prior to and after the diagnosis of four gynecological cancers in women followed in gynecological practices in Germany.

Methods This study included women who were diagnosed with breast, uterine, ovarian, or vulvar cancer in 281 gynecological practices in Germany for the first time between January 2011 and December 2017. The first outcome of the study was the proportion of women with at least one HRT prescription in the year prior to and in the year after cancer diagnosis. The second outcome of the study was the proportion of gynecological practices that issued at least one HRT prescription in the year prior to and in the year after cancer diagnosis.

Results A total of 7189 women were included in this study. The proportion of women receiving at least one HRT prescription significantly decreased between the year prior to and the year after cancer diagnosis in the breast cancer (16.3% versus 2.3%) and the uterine cancer groups (13.4% versus 5.8%), but not in the ovarian cancer (17.6% versus 15.1%) and the vulvar cancer groups (10.8% versus 13.1%). Similar findings were obtained for the proportion of gynecological practices that issued at least one HRT prescription.

Conclusion HRT prescriptions significantly decreased after the diagnosis of breast and uterine cancers but not after the diagnosis of ovarian and vulvar cancers.

Keywords Hormone replacement therapy · Ovarian cancer · Gynecological cancers · Gynecological practices · Germany

Introduction

Hormone replacement therapy (HRT), a treatment consisting of sex hormones (e.g., estrogen or progesterone), is prescribed to relieve climacteric symptoms (e.g., fatigue, irritability, and palpitation) in women during the menopausal transition and in the first years following menopause (Fait 2019). The prescription of HRT has a beneficial impact on bone mineral density (Ghebre et al. 2011), fracture risk (Zhu et al. 2016) and mental health (Gleason et al. 2015), and is associated with increased quality of life (Zethraeus et al. 1997). In addition, there is a negative association between HRT use and mortality in early postmenopausal women (i.e. < 60 years) (Hodis and Mack 2014). At the economic level, previous research has found that the prescription of HRT in women with menopausal symptoms is cost-effective (Lekander et al. 2009a, b).

Although HRT is associated with numerous positive outcomes, recent data indicate that the prevalence of HRT use has decreased in Europe (Ameye et al. 2014) and the U.S. (Sprague et al. 2012) over the last decades. This trend may be explained by the fact that there has been some concern about the relationship between the prescription of HRT and the occurrence of gynecological cancers (Grady et al. 1995; Zhou et al. 2008; Wang et al. 2017; Liu et al. 2019). For

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example, a systematic review and meta-analysis of 35 prospective studies revealed that users of estrogen-only therapy and users of estrogen plus progestin therapy exhibited a 1.14- and a 1.76-fold increase in the risk of breast cancer compared with non-users, respectively (Wang et al. 2017). Another meta-analysis of 36 studies also revealed that there was a significant positive association between menopausal HRT and ovarian cancer (pooled risk ratio [RR] = 1.29) (Liu et al. 2019). The relationship between HRT and gynecological cancer may involve enhanced mitosis, induced expression of sex hormone receptors, and promoted vascularization (Gambacciani et al. 2003). For this reason, the International Menopause Society has recommended not to prescribe HRT and rather use non-hormonal treatments in women with a history of breast cancer (Baber et al. 2016; Deli et al. 2019). However, for other gynecological cancers such as ovarian cancer, there are no international guidelines outlining the prescription of HRT in cancer survivors (Deli et al. 2019). In the case of ovarian cancer, there are different types of tumors, and sex hormones may have differential effects on these tumors. Thus, the management of patients with a history of ovarian cancer is rather complex, and there is no consensus between countries. For example, HRT may be prescribed for women under 45 years of age after non-conservative treatment in France (Sénéchal et al. 2019), whereas the use of HRT is not recommended after the treatment of ovarian cancer in Germany (Wagner et al. 2013).

From this perspective, it is important to investigate the impact of different gynecological cancer diagnoses on HRT prescription patterns of gynecologists. Therefore, the goal of this study was to analyze the prevalence of HRT prescription prior to and after the diagnosis of four gynecological cancers (i.e. breast cancer, uterine cancer, ovarian cancer, and vulvar cancer) in women aged 50–70 years who were followed in gynecological practices in Germany.

Methods

Database

This retrospective study was based on the nationwide Disease Analyzer database (IQVIA). This database contains demographic, clinical, and pharmaceutical variables anonymously obtained by IQVIA from a nationwide sample of general and specialist practices (Rathmann et al. 2018). The quality of these data is assessed on a regular basis, and it has been previously shown that the Disease Analyzer database is representative of German practices.

Study population

This study included women who were diagnosed with breast (International Classification of Diseases, 10th revision [ICD-10]: C50), uterine (ICD-10: C54), ovarian (ICD-10: C56), or vulvar cancer (ICD-10: C51) in 281 gynecological practices in Germany for the first time between January 2011 and December 2017 (index date). As the number of patients with malignant neoplasm of cervix uteri (ICD-10: C53) and malignant neoplasm of unspecified part of the uterus (C55) were very small, uterine cancer included malignant neoplasm of corpus uteri (C54) only.

The inclusion criteria were the following: (i) no other cancer diagnosis prior to the index date; (ii) an observation time of at least 12 months prior to the index date; (iii) a follow-up of at least 12 months after the index date; and (iv) age between 50 and 70 years at the index date. After applying these criteria, the study population consisted of 7,189 women, including 6,184 women with breast cancer, 484 women with uterine cancer, 391 women with ovarian cancer, and 130 women with vulvar cancer (Fig. 1).

Study outcomes

The first outcome of the study was the proportion of women with at least one HRT prescription (ATC: G03) in the year prior to and in the year after cancer diagnosis. The second outcome of the study was the proportion of gynecological practices that issued at least one prescription for HRT in the year prior to and in the year after cancer diagnosis.

Statistical analyses

Mean (standard deviation [SD]) age and age distribution (i.e. 50–55, 56–60, 61–65, and 66–70 years) were studied in each of the four cancer groups (i.e. breast cancer, uterine cancer, ovarian cancer, and vulvar cancer). Differences in the proportion of women with at least one HRT prescription and the proportion of gynecological practices that issued at least one HRT prescription between the year prior to and the year after gynecological cancer diagnosis were analyzed using Chi-squared tests in the four cancer groups separately. p values were corrected using the Benjamini and Hochberg adjustment method, and p values lower than 0.05 were considered statistically significant. All analyses were carried out using SAS 9.4 (SAS Institute, Cary, USA).

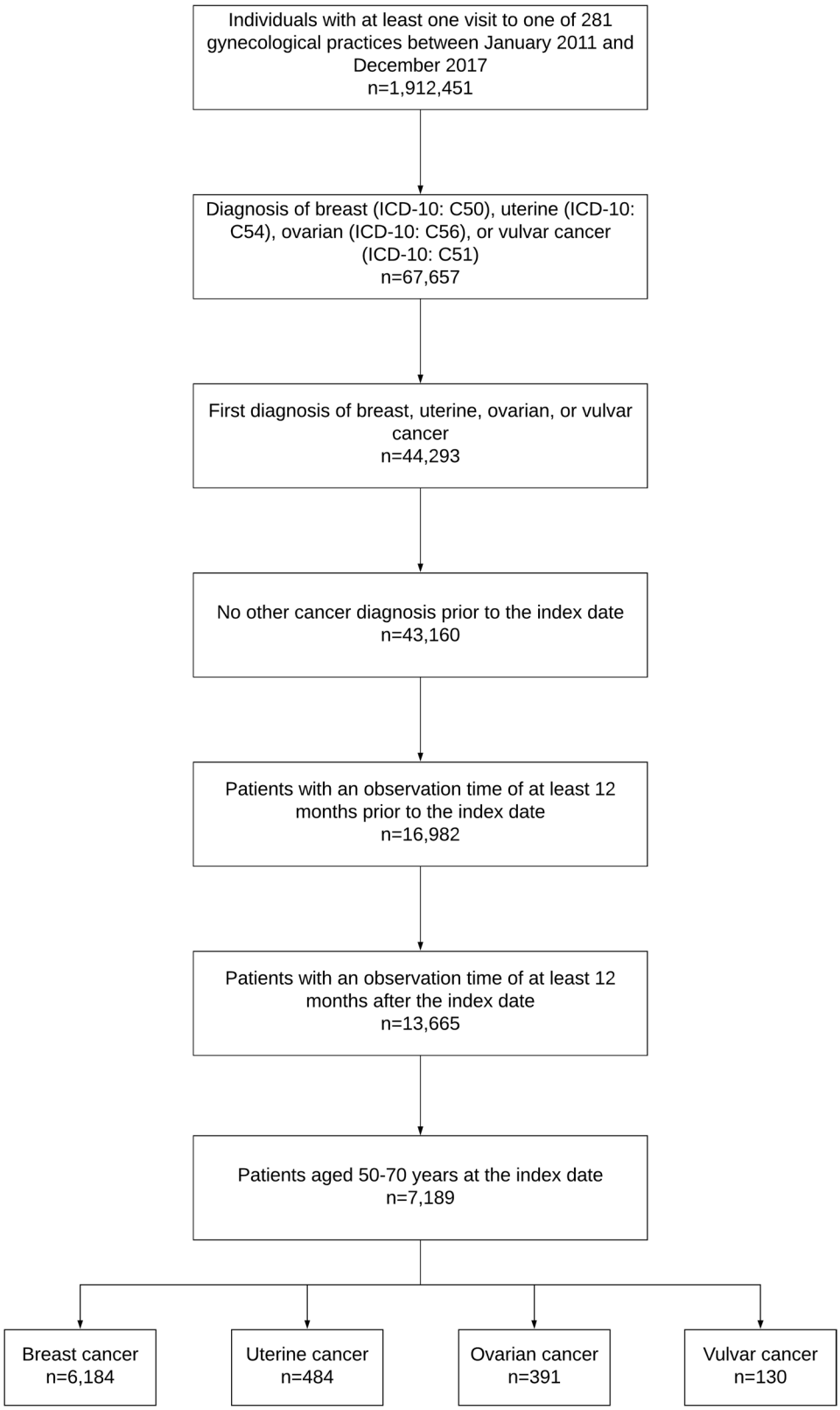

Fig. 1 Selection of study patients

Table 1 Mean (standard deviation) age and age distribution of the study patients

Age	Breast cancer ($n=6184$)	Uterine cancer ($n=484$)	Ovarian cancer ($n=391$)	Vulvar cancer ($n=130$)
Mean (standard deviation) in years	59.5 (6.1)	61.1 (5.8)	59.4 (5.9)	59.0 (5.9)
50–55 years (%)	31.9	21.1	30.2	29.2
56–60 years (%)	22.8	24.0	25.3	30.8
61–65 years (%)	23.6	26.5	24.3	23.8
66–70 years (%)	21.7	28.4	20.2	16.2

Results

A total of 7,189 women were included in this study. Mean (standard deviation) age ranged from 59.0 (5.9) years in women with vulvar cancer to 61.1 (5.8) years in those with uterine cancer (Table 1). The proportion of women receiving at least one HRT prescription significantly decreased between the year prior to and the year after cancer diagnosis in the breast cancer (16.3% versus 2.3%, p value = 0.002) and the uterine cancer groups (13.4% versus 5.8%, p value = 0.002), but not in the ovarian cancer (17.6% versus 15.1%, p value = 0.075) and the vulvar cancer groups (10.8% versus 13.1%, p value = 0.649; Fig. 2). There was also a decrease in the proportion of gynecological practices that issued at least one HRT prescription between the year prior to and the year after the diagnosis of cancer in women with breast cancer (86.5% versus 25.9%, p value = 0.002) and uterine cancer (26.4% versus 11.9%, p value = 0.002), but not in those with ovarian cancer (31.8% versus 22.3%, p value = 0.069) and vulvar cancer (19.4% versus 20.8%, p value = 0.835; Fig. 3).

Discussion

In this study including almost 7200 women followed in gynecological practices in Germany, we found that the prevalence of HRT use significantly decreased after the diagnosis of breast or uterine cancer. In contrast, there was no significant difference in terms of women or gynecological practices with at least one HRT prescription between the year prior to and the year after the diagnosis of ovarian or vulvar cancer. To the best of our knowledge, this is the first study investigating the differential impact of these four gynecological cancers on gynecologists' HRT prescription patterns.

One major finding of this study is that the prevalence of HRT use did not significantly change after the diagnosis of ovarian cancer. Although there are different types of ovarian cancer, a large body of research has consistently found that HRT does not have negative effects on survival in women with a history of ovarian cancer. For example, a prospective nationwide cohort study of 799 women diagnosed with ovarian cancer showed that HRT use after cancer diagnosis was associated with an increased survival rate (hazard ratio = 0.57) (Mascarenhas et al. 2006). In

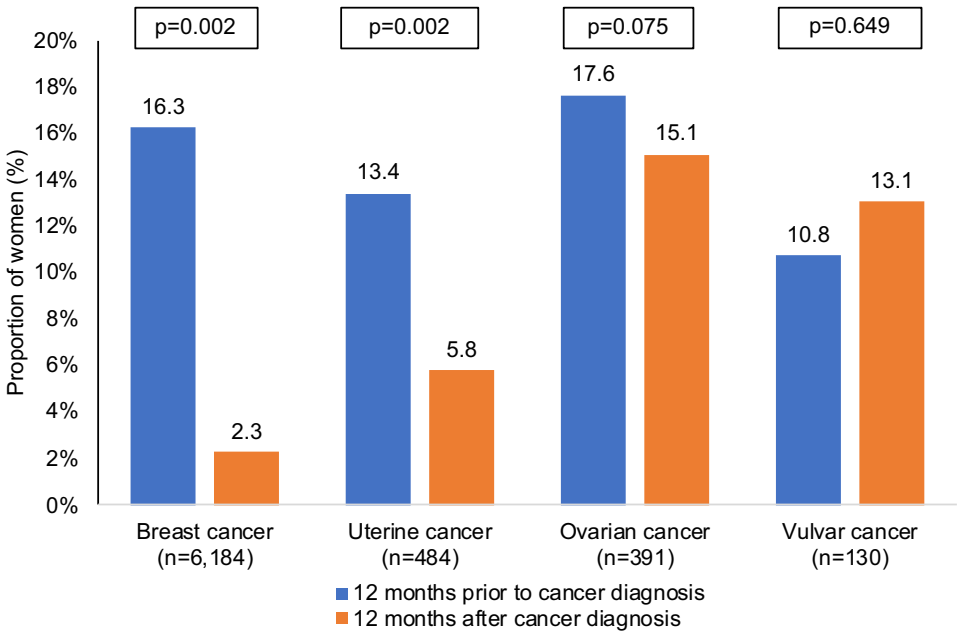

Fig. 2 Proportions of women with at least one hormone replacement therapy prescription by cancer type

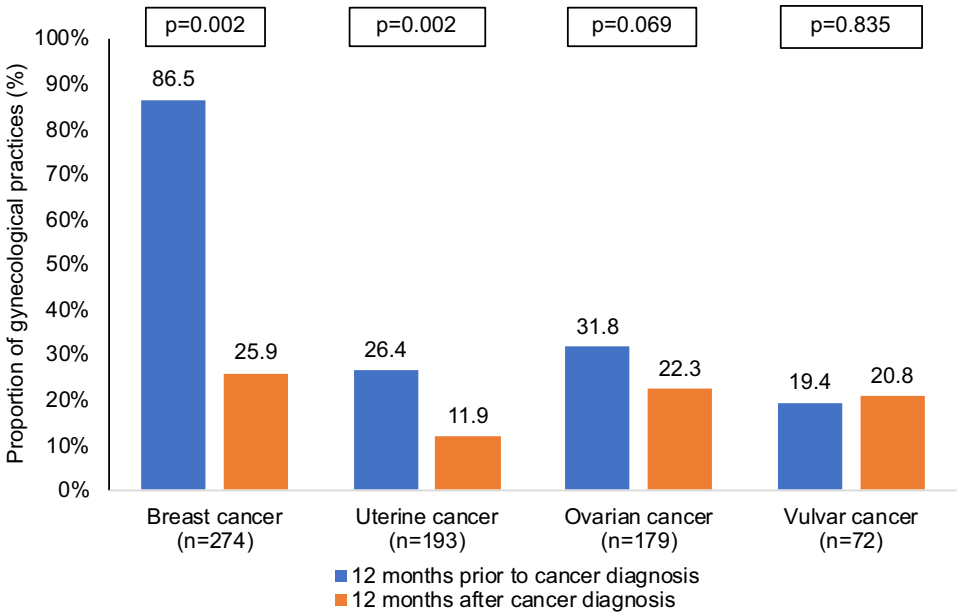

Fig. 3 Proportions of gynecological practices that issued at least one hormone replacement therapy prescription by cancer type

addition, a systematic review and meta-analysis of six studies revealed that there was a significant reduction in ovarian cancer-related deaths among women receiving HRT (odds ratio [OR] = 0.47), while there was no significant relationship between the prescription of HRT and disease recurrence (Pergialiotis et al. 2016). These findings suggest that HRT might safely be prescribed to alleviate climacteric symptoms in women with a history of ovarian cancer. The results of the present study conducted in Germany further indicate that gynecologists have a favorable attitude towards the prescription of HRT in ovarian cancer survivors. This is in line with a previous study using data from 286 physicians from Sweden, of which 100% of gynecologic oncologists and 66% of gynecologists knew that HRT is not contraindicated in women with a history of ovarian cancer (Halldorsdottir et al. 2018). Regarding vulvar cancer, we found that the prevalence of HRT use did not significantly change after diagnosis. As a matter of fact, the majority of vulvar cancers are squamous cell carcinomas and not estrogen dependent, and the prescription of HRT is not contraindicated after the diagnosis of this type of cancer.

Another important finding is the significant decrease in the prevalence of HRT prescription after uterine cancer diagnosis. Although approximately 90% of endometrial cancers are sensitive to sex hormones (e.g., estrogen), the literature has found no increase in the recurrence rate or decrease in free survival in endometrial cancer patients who were prescribed HRT compared to those who were not prescribed HRT. A U.S. matched case–control study of 150 participants estimated that the disease-free interval was significantly longer in women receiving than in those not receiving HRT (Suriano et al. 2001). Moreover, it was observed in a study including 102 patients with endometrial cancer that the immediate use of HRT was not significantly associated with disease recurrence or death rate (Ayhan et al. 2006). Despite these data, our study results indicate that, in Germany, gynecologists may have a negative attitude towards prescribing HRT in women with a history of uterine cancer. Interestingly, in a descriptive survey of physicians from Germany, 46% and 75% of respondents believed that estrogen replacement therapy was contraindicated in patients with low- and high-risk endometrial cancer, respectively (Hancke et al. 2010). In contrast, a survey of 363 gynecologists from Japan revealed that 65% of them would consider prescribing HRT to endometrial cancer patients with a low risk of recurrence, while the respective figure was 49% for patients with a high risk of recurrence (Yokoyama et al. 2015). Taken together, these findings underline the fact that the attitude of gynecologists likely differs between countries.

Finally, this study including 7189 individuals from Germany showed a sharp decrease in the HRT use after the diagnosis of breast cancer. International guidelines have advised against HRT prescription in breast cancer survivors (Baber et al. 2016; Deli et al. 2019). Menopausal symptoms are frequent in women with a history of breast cancer, and they can result from chemotherapy, radiotherapy, and antiestrogenic endocrine therapy (Deli et al. 2019). A population-based cohort of 5023 women aged 20–75 years from China found that the prevalence of at least one menopausal symptom (e.g., hot flashes, night sweats, or vaginal dryness) 6 months after breast cancer diagnosis was 67% and 46% in premenopausal women and postmenopausal women, respectively (Dorjgochoo et al. 2009). Therefore, the management of menopausal symptoms in breast cancer survivors

is important and should rely on non-hormonal strategies such as selective serotonin reuptake inhibitors, weight loss, and cognitive behavioral therapy (Biglia et al. 2019).

The two major strengths of this study are the number of women and gynecological practices available for analysis and the use of real-world data. However, the present findings should be interpreted in the light of several limitations. First, there was a lack of information about the characteristics of gynecologists (e.g., age, sex, and area of expertise), although these characteristics might have impacted the odds of prescribing HRT. Second, hospital data were not available, although a substantial proportion of women diagnosed with gynecological cancers might have been followed in this setting. This might have biased the findings of this study. Third, very few women were diagnosed with vaginal and cervical cancers, and these women were not included in the analysis. Thus, the present results cannot be extrapolated to these two types of cancer. Fourth, there was no information on TNM status, tumor stage and hormone receptor status, while data on menopausal status were not available in the database.

The number of HRT prescriptions significantly decreased after breast and uterine cancer diagnosis but not after ovarian and vulvar cancer diagnosis. Further research is needed to gain a better understanding of the characteristics of gynecologists (e.g., age, sex, and area of expertise) that may play an important role in HRT prescription patterns in women with a history of gynecological cancer.

Author contributions Louis Jacob managed the literature searches, wrote the first draft of the manuscript, and corrected the manuscript. Karel Kostev contributed to the design of the study, performed the statistical analyses, and corrected the manuscript. Matthias Kalder contributed to the design of the study, managed the literature searches, and corrected the manuscript. All authors contributed to and have approved the final manuscript.

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Availability of data The data analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Code availability The code used during the current study is not publicly available but is available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval The database includes only de-identified data in compliance with the provisions of German data protection laws. No ethics approval is needed for retrospective data analyses that use anonymous data in Germany.

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