This is an Accepted Manuscript of an article published in Gynecologic Oncology, available at: https://doi.org/10.1016/j.ygyno.2021.09.013

Parity, menopausal hormone therapy, and risk of ovarian granulosa cell tumor – a population-based case-control study

Saara Bryk[1], Sushmita Katuwal[2], Ulla-Maija Haltia[1], Johanna Tapper[1], Juha S. Tapanainen[1,3], Eero Pukkala[2,4]

[1] Department of Obstetrics and Gynecology, Helsinki University Hospital and University of Helsinki

[2] Faculty of Social Sciences, Tampere University, Tampere, Finland

[3] Department of Obstetrics and Gynecology, University of Oulu, Oulu University Hospital and Medical Research Centre PEDEGO Research Unit

[4] Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

Corresponding author

Saara Bryk, M.D., Ph.D.

Obstetrics and Gynecology, Helsinki University Hospital, PO Box 140, 00290 Helsinki, Finland

e-mail: saara.bryk@hus.fi

Tel. +358504271190

Abstract

Objective Adult-type ovarian granulosa cell tumors **(**AGCTs) are hormonally active neoplasms with limited epidemiological data available. We evaluated the effect of parity and postmenopausal hormone therapy (HT) use on the risk of AGCT in a population-based case-control setting.

Methods We identified all women diagnosed with AGCT during 1994-2015 (n=505) from the Finnish Cancer Registry. For each case, five controls matched for age were selected from the National Population Registry, which also provided data on parity and ages at deliveries. Information on postmenopausal HT by different regimens (estradiol-only, sequential estrogen-progestin and continuous estrogen-progestin) was obtained from nationwide Prescription Register. The association between parity, ages at deliveries, HT use, and AGCT incidence was evaluated by odds ratios (ORs) using a conditional logistic regression model and stratified by age at index date (<55 years or ≥ 55 years).

Results Parity and age at first or last delivery had no significant effect on AGCT risk. Systemic postmenopausal HT had been used by 20.4% of women who were later diagnosed with AGCT. The risk for subsequent AGCT was significantly decreased among users of estradiol-only therapy for at least five years (OR 0.28; 95% confidence interval 0.08-0.94) and continuous estradiol-progestin therapy for 6 months to 5 years (0.23; 0.08-0.71).

Conclusions Unlike in epithelial ovarian cancer, AGCT development is not clearly associated with parity, and users of postmenopausal HT do not seem to carry an excess risk for AGCT formation.

Introduction

Ovarian granulosa cell tumors (GCTs) constitute the majority of sex cord-stromal tumors, and approximately 3-5% of ovarian malignancies [1]. These neoplasms are further classified in juvenile (JGCT) and adult-type ovarian granulosa cell tumors (AGCTs), AGCTs forming the vast majority (95%) of GCTs [1]. AGCTs are characterized by the transcription factor *FOXL2* (402C-G) mutation, but the etiological factors in the carcinogenesis are widely unknown [1]. Epidemiological data on these rare tumors are scarce and limited by small number of cases [2].

AGCTs are hormonally active neoplasms with a high expression of follicle-stimulating hormone (FSH) and estrogen beta (ERß)-receptors, and they typically secrete estradiol, anti-Müllerian hormone (AMH) and inhibins [1,3]. As granulosa cells are biologically responsive to gonadotropins, it has been suggested that hormonal factors such as alterations in FSH levels may contribute to AGCT pathogenesis [4]. AGCT most often presents in perimenopause or early postmenopause, a period characterized by fluctuations and eventual increase in gonadotropin levels [1,5]. After menopause, FSH levels rise due to natural decline in ovarian estrogen and inhibin secretion and subsequent loss of negative feedback regulation in the pituitary–gonadal axis. FSH has been shown to increase AGCT cell viability in a recent report, supporting the role of hormonal changes in tumor formation [3]. FSH levels remain low during pregnancy and during use of oral contraceptives, which both have been reported to protect against AGCT, similarly to epithelial ovarian cancer [2,6]. Although it is suggested that repeated ovulation contributes to ovarian carcinogenesis, substantial uncertainty remains about the mechanism of these protective factors [7].

Postmenopausal hormone therapy (HT) is commonly used to treat climacteric symptoms and to prevent osteoporosis in peri- and postmenopause, causing subsequent decline in serum FSH levels. However, long-term HT use, particularly combined estrogen-progestin therapy (EPT) has been shown to increase the risk for breast cancer, and an increased risk for

epithelial ovarian cancer has also been observed [8,9,10]. On the other hand, several studies report contradictory effects of HT depending on the histological subtype of ovarian cancer, and often there is considerable heterogeneity among different HT regimens studied [8,10]. In Finland, it is uniformly advocated that HT is only used in symptomatic women, and EPT is the treatment of choice for all non-hysterectomized women.

To our knowledge, there are no prior reports evaluating the role of antecedent menopausal hormone therapy use and the development on AGCT, and the potential protective effect of reproductive factors such as parity require further investigation. Utilizing the unique nationwide, population-based cancer and prescription registers, our aim was to evaluate the effect of parity and HT use by different treatment regimens on the risk of AGCT in a population-based case-control setting.

Materials and Methods

We identified all women newly diagnosed with AGCT (ICD-O-3 topography C56.0-C56.9, morphology 8620-8622) between 1st January 1994 until 31st December 2015 (n=505) from the Finnish Cancer Registry (FCR). The cancers recorded at the Finnish Cancer Registry have been notified by hospitals, pathological and hematological laboratories, physicians and dentists, and from death certificates [11].

For each case of AGCT, five control women were randomly selected from the National Population Registry (NPR) who were at the risk of AGCT with follow-up data available, i.e. had not emigrated and were alive at the time of cancer onset of the cases (index date), and were matched for age. The NPR also provided information on the dates of birth of children. The NPR includes accurate information on a high proportion of childbirths of women born after the mid-1930s and the Finnish Cancer Registry is virtually complete as regard to cancer incidence since 1953 [12,13]. Out of the women fulfilling the inclusion criteria, no one was excluded.

Postmenopausal hormone therapy

Information on postmenopausal HT was obtained from nationwide Prescription Register of the Social Insurance Institution of Finland. The register includes data on systemic HT purchases in Finland since 1994, and we had access to data up to 31 December 2013. Systemic HTs are available in Finland only with doctor's prescription and automatically registered. In our study, the purchase of HT after the age of 50 years was counted as postmenopausal HT.

Systemic HT in our study was categorized as estradiol only-therapy and EPT, and vaginal estradiol was not counted as an exposure in the analyses. EPT was defined as continuous when oral or transdermal estradiol was combined daily with progestin, and sequential when progestin was combined with oral or transdermal estradiol for 10–14 days every 1 to 3 months.

Statistical analysis

A conditional logistic regression model for matched cases and controls was used for both univariate and multivariate analyses. Odds ratio (OR) with 95% confidence intervals (CI) was used to evaluate the association between study variables and AGCT. Reproductive variables included in our study were parity (nulliparous, parous), number of children (1, 2, 3+), age at first birth (<25 years, 25–29, 30+ years), and age at last birth (< 30, 30–34, 35+ years). Duration of use of each type of HT was categorized into <6 months, 6 months to 5 years, and >5 years. For case-control sets with index date before 2015, for which we had data on recent HT purchases, we also studied the effect of the recency of the use of HT. This variable was categorized as current use (within 12 months before index date), use between 12 months up to 5 years, and use of >5 years before index date.

The analyses were stratified according to age at index date. The younger age stratum included women aged <55 years, assuming that HT use started at menopause has no marked effect on cancer risk before the age of 55. The second case-control sets included women with index age ≥55 years. All analyses were performed using R statistical software, version 1.2.1335.

Results

Over half (53.9%) of the 505 women diagnosed with AGCT were at least 55 years of age (Table 1). Nearly half of the women (48.7%) had their cancer diagnosis between ages 50 to 69, i.e. in perimenopausal or postmenopausal period. Only 2.6% of the AGCT cases were diagnosed in young women aged less than 20 years.

Parity

Parity and age at first and last childbirth as predictors of AGCT by age at the time of diagnosis are presented in Table 2. In women diagnosed with AGCT at less than 55 years of age, the majority (71.2%) were parous with at least one childbirth, and the risk for AGCT did not differ significantly between nulliparous and parous women (OR 1.05, 95% CI 0.73-1.49). The odds ratio of AGCT decreased slightly along with increasing parity, but not significantly. Age at first childbirth was not clearly associated with AGCT, whereas increasing age at last birth showed a tendency for a higher OR.

Of women who had their cancer diagnosed at age 55 or older, over 80% were parous (OR 1.43, 95% CI 0.62-3.28). Number of children was not significantly associated with AGCT, but increasing age at first childbirth showed a gradually increasing OR of 1.31 (95% CI 0.64-2.66) and 2.47 (0.75-8.16) for age groups 25-29 years and 30 years or more when compared to women who had their first child at less than 25 years of age. Women older than 30 years at last

birth had lower OR for AGCT than women having their last child at less than 30 years of age (OR 0.53-0.59). However, no statistically significant differences emerged.

Hormone therapy

Systemic postmenopausal HT had been used by 69 women (aged ≥50 years) who were later diagnosed with AGCT (20.4%), compared to 451 women in the control population (26.6%) (Table 1). Sequential EPT was the most common regimen used, with 30 (43.5%) users among cases and 181 (40.1%) users in the control group. In both groups, approximately one-third of women using HT had a continuous estradiol-progestin regimen (31.9% and 32.4%, respectively), and estradiol-only therapy was used by 17 cases (24.6%) and 124 controls (27.5%).

For AGCT in ages 55+, the use of estradiol-only therapy for use duration up to 5 years showed decreased ORs for AGCT, while significant protective effect against AGCT was observed among women who used estradiol-only therapy for more than 5 years (OR 0.28, 95% CI 0.08-0.94) and among women who used continuous EPT for 6 months to 5 years (OR 0.23, 95% CI 0.08-0.71) (Table 3). In both sequential and continuous EPT group, a large proportion of women had used the regimen for only 6 months or less (36.7% and 54.5%, respectively). This short-period use of continuous EPT showed an increased OR of 1.76, which was not statistically significant (95% CI 0.75-4.14). In both EPT groups, HT exposures of more than 5 years showed decreased ORs for AGCT.

Compared to never-users, the risk of AGCT was significantly lower for women who had used estradiol-only therapy for 1-5 years prior to cancer diagnosis (OR 0.31, 95% CI 0.11-0.88) (Table 4). Among both sequential and continuous EPT users, there was no increase in AGCT risk either among current users (within 12 months of cancer diagnosis) nor among

recent users (12 months to five years). In all time interval categories, the ORs for AGCT were below unity (0.30-0.80).

Discussion

This nationwide case-control study on parity and postmenopausal hormone therapy and ovarian AGCTs showed that parity and age at first or last delivery had no significant effect on cancer risk. Both estradiol-only therapy for at least five years and continuous EPT for 6 months to 5 years decreased the risk for subsequent AGCT significantly.

It is well established that hormonal and reproductive factors such as infertility, nulliparity, and late age of menopause predispose to ovarian cancer, whereas high parity, and use of oral contraceptives (OCs) reduce this risk [14-16]. The data on the effect of age at first or last delivery are inconsistent; it has been suggested that ovarian cancer risk is reduced by both first and last pregnancy at older age [14-17]. The protective effect of OCs and parity have also been suggested to play a role in the development of AGCT [2, 14]. Our study revealed no significant effect of parity, increasing number of children or increasing age at first or last delivery on the risk of AGCT, although in younger women, a slightly increased OR was observed along with increasing age at last birth, and in women aged 55 or more at the time on cancer diagnosis, the OR increased with increasing age at first birth.

The effect of postmenopausal HT on ovarian cancer has been studied extensively, and current evidence supports that the long-term use of HT, especially EPT but also systemic estradiol-only therapy, increases the risk for epithelial ovarian cancer, particularly serous type [8, 10, 18]. The risk is not associated with progestin type, mode, or route of administration of EPT [8, 18]. This risk seems to differ according to the histological subtype, so that the risk for mucinous cancer is not similarly increased [8, 18]. The effect of HT use on pure AGCT incidence has, to our knowledge, not been addressed in any previous study, and considering

the distinctive nature of AGCT compared to epithelial ovarian carcinoma, findings regarding epithelial tumors cannot be readily applied to AGCT.

Numerous recent reports along with a Cochrane Review have concluded that postoperative HT does not have a negative effect on prognosis after epithelial ovarian cancer, although evidence remains limited [19-22]. However, it is recommended that topical or systemic HT should not be advocated to AGCT patients, and non-hormonal options should be used as first-line therapy to treat menopausal symptoms [23-25]. A rather recent French guideline suggested that HT could be considered after early stage AGCT [26]. In our previous analysis, nearly half of AGCT patients used HT postoperatively, and no increased risk for tumor recurrence was observed [27]. Based on the current results, the risk for primary AGCT is not increased in women having used HT prior to cancer diagnosis. Although post-treatment HT is not addressed in this study, it can be hypothesized that there would be no definite need to limit the use of HT among AGCT survivors with disturbing climacteric symptoms. This is of particular significance, as these women may undergo premature menopause as a result from surgical treatment for AGCT. Importantly, risk assessment and patient information regarding postoperative HT use should be performed individually.

This is the first known report on the association of HT on the occurrence of AGCT. Considering the rarity of the tumor, the strengths of our study are the large sample size of more than 500 women with AGCT. Moreover, we use standardized national data sources with virtually complete information of childbirths and detailed information on HT purchases. The national character of the study has both its advantages and limitations: socioeconomic differences in Finland are relatively low with women sharing similar lifestyles, which minimizes potential confounding factors. The Finnish population is ethnically rather homogenous, which may be a limitation to wider generalization of our findings. The number of cases in HT categories were partly small, and statistical significance was only reached in

few analyses. Furthermore, we made assumptions regarding menopausal age and the potential cancer risk involved with HT use, using 55 years as cut-point in our analyses. This is based on the average menopausal age of 51 years in Finnish women, as well as previous findings by Koskela-Niska et al, that use of any HT regimen for less than five years had no significant effect on ovarian cancer risk [8, 28-29]. We could not exclude from the control population women who had had an oophorectomy, the estimated proportion of such women in the Finnish population from a similar period is so low (4%), that this exclusion would not have affected the conclusions of our analyses [29]. Finally, prescription registry data does not necessarily reveal the actual use of HT, but it is likely that women who had bought the HT product also used it, since a large part of the product price is paid by themselves.

Our study offers evidence that unlike in epithelial ovarian cancer, AGCT development is not clearly associated with parity, and users of postmenopausal HT do not carry an excess risk for AGCT formation. However, more data on the effect of reproductive hormones in AGCT tumorigenesis are still needed, and the safety of postmenopausal hormone therapy in AGCT survivors calls for further evaluation.

Acknowledgements

This study received funding from the Sigrid Juselius Foundation, the Academy of Finland (295760), and Helsinki University Hospital Funds.

The authors declare no conflict of interest.

Author contribution

Design of the project was carried out by SB, EP, JT and U-MH, and collection and statistical analysis of data by SK and EP. SB has drafted the initial manuscript. All six authors have participated in the final preparation of the manuscript.

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Table legends

Table 1. Characteristics of cases and controls

Table 2. Multivariate conditional logistic regression analysis for parity, age at first birth, and age at last birth as predictors of granulosa cell tumor diagnosed among women, by age at index date

Table 3. Multivariate conditional logistic regression analysis by the type of postmenopausal hormone therapy and duration of exposure as predictors of granulosa cell tumor diagnosed among women aged 55+ years, adjusted for parity.

Table 4. Multivariate conditional logistic regression analysis by timing of postmenopausal hormone therapy use as predictor of granulosa cell tumor diagnosed before the year 2014 among women aged 55+ years.