A Nationwide Cohort Study on the Incidence of Meningioma in Women Using Postmenopausal Hormone Therapy in Finland

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The authors conducted a nationwide cohort study to evaluate the association between postmenopausal hormone therapy and meningioma incidence in Finland. All women who had used hormone therapy at least for 6 months at the age of 50 years or older during 1994–2009 were included. Women who had used postmenopausal hormone therapy were identified from the medical reimbursement register of the Social Insurance Institution (131,480 estradiol users and 131,248 estradiol-progestin users), and meningioma cases were identified from the Finnish Cancer Registry. During the average 9 years of follow-up, 289 estradiol users and 196 estradiol-progestin users were diagnosed with meningioma. Ever use of estradiol-only therapy was associated with an increased risk of meningioma (standardized incidence ratio = 1.29, 95% confidence interval: 1.15, 1.44). Among women who had been using estradiol-only therapy for at least 3 years, the incidence of meningioma was 1.40-fold higher (95% confidence interval: 1.18, 1.64; \( P < 0.001 \)) than in the background population. In contrast, this risk was not increased in users of combination therapy (standardized incidence ratio = 0.93, 95% confidence interval: 0.80, 1.06). There was no difference in risk between continuous and sequential use of hormone therapy. Estradiol-only therapy was accompanied with a slightly increased risk of meningioma.

Abbreviations: CI, confidence interval; ET, estradiol-only therapy; EPT, estradiol-progestin combination therapy; HT, hormone therapy; NETA, norethisterone acetate; OR, odds ratio; SIR, standardized incidence ratio.

Meningioma is at least twice as common in women as in men. The difference is even more pronounced with spinal meningiomas, which have a female: male ratio of 4:1 (1). The majority of meningiomas are intracranial; spinal meningiomas represent about 10% of all meningiomas (2). Less than 10% of meningiomas are atypical or malignant (3). An increased incidence of breast cancer has been detected among meningioma patients and vice versa (4–6). This suggests that meningiomas and breast cancer share common risk factors. Because postmenopausal hormone therapy (HT) is associated with breast cancer risk, it might also be a determinant for meningioma incidence. Moreover, both of these tumor types express estrogen and progesterone receptors (6–10), and in both diseases the amounts of estrogen and progesterone receptors have effects on prognosis (8, 9, 11–13). The association between menopausal HT and meningioma risk has been assessed only in few studies. Thus far, the results have been inconclusive: Cohort studies (14–16) have shown uniformly positive associations between HT and meningioma risk, but results from case-control studies have been inconsistent (17–20).

In Finland, the use of postmenopausal HT can be traced reliably using the medical reimbursement register. Therefore, we evaluated the impact of different components and routes of administration of postmenopausal HT on the risk of intracranial and intraspinal meningiomas in a cohort of women who represented the entire postmenopausal Finnish female population.

MATERIALS AND METHODS

Data collection

With permission from the Finnish National Institute for Health and Welfare, we collected from the medical
reimbursement register data on all women (n = 1,082,442) who had bought estradiol-only hormone therapy (ET) or estradiol-progestin combination hormone therapy (EPT) in 1994–2009. This register covers all use of postmenopausal hormone therapy, as these regimens are available only with a doctor’s prescription. Only women who had purchased ET or EPT for at least 6 months by the age of 50 years or older were regarded as users and included in the final study cohort. In Finland, estradiol is the only systematically administered estrogen available. The average age of women at menopause in Finland is 51 years (21).

As postmenopausal therapy, systemic estradiol can be administered either orally or transdermally. The dosage of transdermal estradiol is 50 μg/day in fixed EPT preparations, and those of oral estradiol are 1 and 2 mg/day. The progestin component can be administered sequentially or continuously with estradiol. In our cohort, some women used nonstandard EPT regimens that combined oral estradiol (1.0–2.0 mg/day) or transdermal estradiol (25–100 μg/day from a patch or 0.5–1.5 mg/day from a gel) with oral progestin courses lasting 10–14 days in intervals of 1–3 months. The sequential regimen included progestin courses of 10–14 days’ duration that were added at 1–3-month intervals to a continuous estradiol regimen. A “continuous combined regimen” was defined as the use of progestin every day in addition to estradiol. “Oral EPT” was defined as a regimen in which both estradiol and progestin were taken orally, whereas the term “transdermal EPT regimen” referred to the use of transdermal progestin with oral or transdermal estradiol.

Because we did not have data on the use of HT before 1994, we assumed that we had the complete history of ET or EPT use only for those participants who started their first ET or EPT regimen in 1995 or later, and analyses related to short-term HT use (<5 years) were restricted to this subcohort. For the subcohort of patients who had used either ET or EPT for at least 5 years, the year 1994 was included in the analyses. The mode of estradiol-progestin intake was classified based on the first EPT used. Lyytinen et al. (22) showed that of Finnish women who started their HT regimens with oral EPT, 94% continued to use it for at least 5 years, whereas of the women who started their HT regimens with norethisterone acetate (NETA), only 74% still used it after 5 years.

The cohort was followed for incident meningioma cases until the end of 2009 through the nationwide population-based Finnish Cancer Registry. This registry receives notifications of cases of meningioma with histologic information from all hospitals and pathology laboratories in Finland, and its coverage is nearly comprehensive; however, the rate of reporting is slightly lower for benign tumors (23).

**Statistical analysis**

The expected number of meningioma cases was calculated by multiplying the number of person-years in each 5-year age group by the corresponding average meningioma incidence among all Finnish women during the same period of observation. The analyses were indirectly adjusted for age and calendar period. To calculate standardized incidence ratios (SIRs), the observed numbers of cases were divided by the expected numbers of cases. Exact 95% confidence intervals were defined under the assumption that the observed numbers followed a Poisson distribution. This was confirmed using a negative binomial regression model, which showed no departure from the assumption (likelihood ratio test, $P = 0.5$ and overdispersion parameter alpha very close to zero).

**RESULTS**

We followed 131,480 women who used ET from 1994 to 2009. In these women, a total of 289 meningiomas were diagnosed (Table 1). Among EPT users (n = 131,248), 194 meningiomas were observed. NETA was the most widely used progestin, followed by medroxyprogesterone acetate and then dydrogesterone. NETA was the only progestin available both in the oral and transdermal forms. Other progestins were combined together and analyzed as a single group. The average follow-up time was 9 years. The age distributions of ET and EPT users are shown in Table 1.

The use of ET for at least 6 months was associated with a significantly increased risk of meningioma (SIR = 1.29, 95% confidence interval (CI): 1.15, 1.44; $P < 0.001$). Among women who had been using ET for at least 3 years, the incidence rate was 1.40-fold higher than that in the general population (95% CI: 1.18, 1.64; $P < 0.001$). Among EPT users, the SIR of meningioma was not elevated (SIR = 0.93, 95% CI: 0.80, 1.06). Results of mutually exclusive exposure times are shown in Table 2.

Both continuous EPT use and sequential EPT use were associated with comparable risk estimates. Neither oral nor transdermal long-term use of EPT was associated with an increase in meningioma risk when all such users were analyzed as one group (Table 3). Comparison of the oral and transdermal forms was possible only with regimens that contained NETA. In women exposed to NETA, a slightly higher meningioma risk was associated with the transdermal mode of administration (for long-term use of oral NETA, SIR = 0.84, 95% CI: 0.62, 1.09, and for transdermal NETA, SIR = 1.10, 95% CI: 0.47, 2.16), but the number of cases was low (8 observed cases in transdermal-use group).

We also evaluated spinal meningiomas separately among women who had used ET or EPT for at least 5 years. Similar to what was seen with all meningiomas, the incidence of spinal meningioma was elevated among EPT users ($n = 12$, SIR = 1.59, 95% CI: 0.82, 2.78) and not elevated among EPT users ($n = 14$, SIR = 0.94, 95% CI: 0.51, 1.57).

**DISCUSSION**

We evaluated the incidence of meningioma in a nationwide cohort of more than 130,000 ET users and a comparable number of EPT users. We found a significantly elevated meningioma risk in women who used ET but no excess risk among users of EPT.

The strengths of our study include the large sample size and long follow-up period, with more than a quarter of a million women followed for an average of 9 years (maximum of >15 years). The validity of the results is greatly enhanced by the availability of HT data from a comprehensive registry.
which eliminated errors associated with self-reports and recall. In Finland, the national medical reimbursement register covers all women who have bought any systemic HT in Finland from 1994 onward. In previous studies, use of HT was self-reported, and except in the Million Women Study (15), the risk was not analyzed by type of HT. Our cohort was so large that we could analyze women using ET separately from those using EPT. Further, nationwide population-based cancer incidence data were utilized. The completeness of data on malignant tumors in the Finnish Cancer Registry is greater than 95% because of hospital notifications and routine linkages with hospital discharge records and death certificates. For benign tumors, the completeness of data is likely to be lower. Results of a survey within a single hospital suggested that more than one-third of the cases may be missed, particularly those in elderly patients who do not receive histologic confirmation of or surgical treatment for meningioma (24). Yet, the incidence rates of meningiomas in Finland are similar to those of other Nordic countries, which indicates a high level of data completeness (25). HT is unlikely to affect the likelihood of notification, and therefore any incompleteness would likely result in nondifferential misclassification, diluting any differences.

A weakness of the present study is that despite the large cohort size, we were unable to demonstrate or exclude small risks (SIR $\leq 1.5-2$) related to single preparations or to the mode of administration. Further, confounding by indication (or contraindication) is a concern, as in any nonexperimental pharmacoepidemiology study. However, confounding by indication would likely affect results for all HT regimens similarly, as the indications are largely similar for the various preparations. We could not adjust the models for parity, body mass index, or educational level, as this information was not available. Because the national medical reimbursement register does not cover the use of HT before 1994, the missing information (HT use before 1994) could have caused exposure misclassification. For this reason, the first year was excluded from the analyses of women with less than 5 years of HT exposure.

The first large study to investigate the association between meningioma risk and HT use was the Nurses’ Health Study (14). According to that study, current users of HT had an elevated risk of meningioma (odd ratio (OR) $= 1.86$, 95% CI: 1.07, 3.24) compared with never users. Since that study, several other study groups have attempted to determine the relation between HT use and meningioma incidence (15–20, 26). A large US clinic-based cross-sectional study that included 355,318 female patients had similar results (26). They found an elevated risk of meningioma (OR $= 2.2$, 95% CI: 1.9, 2.6) among women using HT. In the Million Women Study, Benson et al. (15) found that ever users of HT had a significantly higher risk of meningioma (OR $= 1.32$, 95% CI: 1.05, 1.66) than did never users. The risks were similar for current users and past users. Current use of ET carried a significantly increased risk of meningioma (OR $= 1.44$, 95% CI: 1.03, 2.02), unlike use of EPT (OR $= 1.10$, 95% CI: 0.77, 1.56). The Women’s Health Initiative trial of HT, which included 16,600 women randomized to various treatment regimens, was too small to contribute data on issue (no results on meningioma were published, but the expected

**Table 1.** Study Participants by Age and Type of Hormone Therapy Used for at Least for 6 Months in Finland, 1994–2009

<table>
<thead>
<tr>
<th>Hormone Therapy Type and Age Group</th>
<th>No. of Women</th>
<th>No. of Woman-Years</th>
<th>No. of Meningioma Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol only</td>
<td>131,480</td>
<td>1,189,236</td>
<td>289</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>31.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–59</td>
<td>23.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>27.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>14.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 80$</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol + any progestin</td>
<td>131,248</td>
<td>1,020,110</td>
<td>194</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>75.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–59</td>
<td>17.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 80$</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol + medroxyprogesterone acetate</td>
<td>35,859</td>
<td>318,537</td>
<td>68</td>
</tr>
<tr>
<td>Estradiol + norethisterone acetate</td>
<td>62,632</td>
<td>483,108</td>
<td>86</td>
</tr>
<tr>
<td>Estradiol + dydrogesterone</td>
<td>17,876</td>
<td>105,382</td>
<td>16</td>
</tr>
</tbody>
</table>

number of cases was below 20 for both arms combined). The multicenter European Prospective Investigation Into Cancer and Nutrition Study cohort included 276,000 women and 194 meningioma cases (16). Current use of HT was associated with an elevated risk of meningioma (OR = 1.79, 95% CI: 1.19, 2.71). In a recent population-based case-control study with 265 meningioma cases, Korhonen et al. (20) found no evidence of increased meningioma risk among HT users. The totality of evidence seems to indicate that there is a slightly increased risk of meningioma associated with current HT use. In these studies, estrogen-only and estrogen-progestin therapy were often combined in analyses. Also, the estrogen component was often conjugated equine estrogen, which contains a number of estrogen-like components. Conjugated equine estrogen is not used in Finland, and because of this, both ET and EPT users were exposed to estradiol in our study. In addition to our finding that the meningioma risk is limited to estrogen-only HT, the use of a different estrogen component might explain some of the discrepancy between the results from previous studies and those from ours.

The higher risk of meningioma among users of ET compared with that in users of EPT still needs to be explained. In Finland, clinical practice guidelines on the optimal use of HT recommend that only women who have undergone

<table>
<thead>
<tr>
<th>Duration of Use</th>
<th>6 Months</th>
<th>36 Months</th>
<th>60 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIR</td>
<td>95% CI</td>
<td>SIR</td>
</tr>
<tr>
<td>Mode of combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential</td>
<td>0.87</td>
<td>0.71, 1.05</td>
<td>0.85</td>
</tr>
<tr>
<td>Continuous</td>
<td>0.91</td>
<td>0.67, 1.20</td>
<td>0.94</td>
</tr>
<tr>
<td>Route of administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>0.92</td>
<td>0.79, 1.05</td>
<td>0.88</td>
</tr>
<tr>
<td>Transdermal</td>
<td>1.03</td>
<td>0.61, 1.63</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.
hysterectomies should use ET, and this policy has not changed during the last 2 decades. The most common reason for hysterectomy is uterine fibroids (27). Fibroids contain receptors for both estrogen and progestin, as do most meningiomas (28). Thus, a possibility exists that ET users represent women who are characterized with exaggerated estrogen sensitivity that becomes expressed both in fibroid and meningioma risk growth.

There is no association between estrogen and progesterone receptor expression in meningiomas, which suggests that progesterone receptors in meningiomas are estrogen-independent (29). However, the finding that ET is associated with a higher risk of meningioma than is EPT suggests that progesterone might inhibit estrogen function in meningiomas. This effect may be mediated through progesterone receptors, which are present in most meningiomas. Unfortunately, we did not have information on the receptor status of the meningiomas.

Also, different progestins seem to have different risks (e.g., with regard to breast cancer) (22). The finding of an association between meningioma risk and different progestins and regimens reported by Benson et al. (15) was based on fewer than 20 cases in each progestin category, and the study had a very low power to demonstrate a difference between them. Similar to what was seen in our study, both continuously and sequentially administered progestin removed the increased risk associated with estradiol-only therapy.

We found some evidence of an increased risk of meningioma associated with ET, but no elevated incidence among users of EPT. Neither the mode of combination nor the route of administration affected meningioma risk in EPT users.

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