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Do the dose or route of administration of norethisterone acetate as a part of hormone therapy play a role in risk of breast cancer: national-wide case-control study from Finland

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We examined the associations between various doses and routes of administration of norethisterone acetate (NETA) in estrogen–progestagen therapy (EPT) and the risk of breast cancer in Finland. All Finnish women with first invasive breast cancer diagnosed between the ages of 50–62 during 1995–2007 (n = 9,956) were identified from the Finnish Cancer Registry. For each case, 3 controls of the same age were retrieved from the Finnish Population Register. The use of estradiol+NETA-therapy by the cases and controls was traced from the national Medical Reimbursement Registry. The data were analyzed with multivariate conditional logistic regression, adjusting for parity, age at the first birth, and health care district. The continuous mode of NETA use tended to be associated with a higher rate ratio for breast cancer than the sequential use. The use of continuous "low" dose (NETA 0.5 mg + estradiol 1.0 mg) was associated with an increased rate ratio of breast cancer already in less than 3 years of use (odds ratio 1.94; 95% confidence interval 1.39–2.70) while a risk elevation for "high" dose (NETA 1.0 mg + estradiol 2.0 mg) was seen after 3 years use (1.71; 1.51–2.54). Oral and transdermal use of NETA were accompanied with comparable risks for breast cancer. In conclusion, the dose or route of administration of NETA in EPT do not modify the risks for breast cancer.

It is established that the use of postmenopausal estrogen–progestagen therapy (EPT) is associated with a higher risk elevation for breast cancer than is the sole use of estrogen.[1–3] This may imply that progestagen, alone or in combination with estrogen, is more crucial for the possible initiation and/or growth of breast cancer than is estrogen. Modern recommendations advocate the use of the lowest effective doses, and then the main focus has been placed on the dose of estrogen.[4–9] Indeed, no data exist on the daily dose-dependence between progestagen and the risk for breast cancer, although the higher risks associated with continuous EPT rather than sequential EPT use may hint at such a dependence.[1,10]

In Finland, the most common progestagen as a part of EPT is norethisterone acetate (NETA), which can be given both orally and transdermally.[3] Notable concomitant reductions both in the NETA and estradiol content have taken place in the commercial EPT preparations during recent decade, and after Women's Health Initiative study, the use of postmenopausal hormone therapy (HT) declined by ~25% in Finland.[11] All this stimulated us to study if the dose or route of NETA administration in combination with estradiol is a determinant for the risk of breast cancer.

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Materials and Methods

Cases and controls

The source population of the study was the entire female population in Finland. The cases of this study consist of all women in the source population with their first invasive breast cancer diagnosed between January 1, 1995 and December 31, 2007 in 50–62 years of age, were identified from the Finnish Cancer Registry (n = 9,956). The coverage of the Cancer Registry is almost 100%.[12]

For each cancer case, 3 control women born at the same time (±1 month) and alive and free of breast cancer at the date of breast cancer diagnosis of the case were randomly selected from the Finnish National Population Register (n = 29,868). The same registry also contributed data on dates of birth of the children and place of residence of the cases and controls (northern, eastern, western, southern and central Finland).

Exposure of norethisterone acetate and estradiol

The use of hormone therapy by the cases and controls was traced from the national Medical Reimbursement Registry, which contains data on the purchases of systemic hormone

Table 1. Types and doses of norethisterone acetate (neta) and estradiol in fixed commercial products analyzed in the present study

Regimen	Dose of NETA (mg)	Dose of estradiol (mg)	Days of NETA and estradiol	Commercial name
Sequential NETA + estradiol				
Oral				
Norethisterone acetate	1	1	12/28	Mericomb mite®
	1	1	12/28	Novofem®
	1	2	10/28	Trisekvens®
	1	2	12/28	Mericomb®
Transdermal				
Norethisterone acetate	0.17	0.05	14/28	Evorel sequi®
	0.25	0.05		Sequidot®
	0.25	0.05		Estalis sekvens®
	0.25	0.05		Estracomb®
Continuous NETA + estradiol				
Oral				
Norethisterone acetate	0.5	1	28/28	Activelle®
	1	2		Kliogest®
	0.7	2		Merigest®
Transdermal				
Norethisterone acetate	0.17	0.05	28/28	Evorel conti®
	0.25	0.05		Estalis®

therapy since 1994 in the whole of Finland. Its coverage is practically 100%, because systemic hormone therapy, available only with a doctor's prescription, is partly reimbursed. Women who had bought HT for at least 6 months were considered as users, never users served as a reference category. All the cases and controls were included in the analysis and were divided into the different exposure categories (estrogen-only therapy, progestagen therapy, tibolone, estrogen-progestagen therapy, various progestagens, and mode of regimens) and the exposure in each category of HT was at least 50% of the total exposure except in the NETA category in which NETA must be given for at least 70% of the total HT-exposure time. If a woman had switched between the different NETA regimens, the route of NETA administration, or the NETA doses, she was included into the group with the mixed use of NETA, because the dose or route of administration could not be determined; these mixed use data were used only for analyzing the impact of the duration of NETA exposure on the breast cancer risk. All exposure categories were divided to similar duration categories. However, for the present substudy only the exposure to systemic NETA + estradiol with different doses and mode of administrations are presented; other associations have been published before.[13]

NETA-containing EPT regimens were classified according to the NETA dose as oral and transdermal preparations (Table 1). An oral sequential "high" dose NETA regimen contained 1.0 mg/day NETA for 10–14 days (+estradiol 1.0 or 2.0 mg/day). Oral continuous "high" dose NETA contained 0.7 mg or 1.0 mg/day NETA every day concomitantly with estradiol (2.0 mg/day), while a continuous "low" dose regimen contained NETA 0.5 mg/day (+ estradiol 1 mg/day). Transdermal NETA + estradiol-regimens were classified as sequential (0.17 mg or 0.25 mg of NETA for 14 days) as a complement to estradiol 0.05 mg/day or as continuous (0.17 mg or 0.25 mg of NETA/d) concomitantly with estradiol 0.05 mg/day.

Statistical methods

A multivariate conditional logistic regression model was used to estimate, by means of the odds ratio (OR), the rate ratio for breast cancer associated with the use of various NETA + estradiol regimens. The age at first birth, parity and the health care district of residence were added to the model as confounders. Possible interactions between the variables were tested with likelihood ratio statistics. Estimates of the model parameters and 95% confidence intervals were computed by the maximum likelihood technique. All statistical analyses were performed with STATA software, release 9.2.

Results

Altogether, 885 breast cancer cases had used NETA + estradiol. The majority (85%) of 329 cases using a " high" NETA dose sequentially had taken it as a complement to 2.0 mg of

Table 2. Risk for breast cancer among postmenopausal women using various oral norethisterone acetate (NETA) + estradiol-regimens

Regimen	Cases	Controls	OR[2]	95% CI[3]	*p*-value
Sequential NETA (1 mg day^{-1} for 10–14 days) + estradiol[1]					
<3 years	164	441	1.21	1.01–1.46	0.04
3 < 5 years	87	199	1.48	1.14–1.90	0.003
≥5 years	78	146	1.89	1.43–2.50	0.001
					p for trend 0.009
"Low" dose continuous NETA (0.5 mg/day + estradiol 1.0 mg/day)					
<3 years	57	98	1.94	1.39–2.70	0.001
3 < 5 years	27	39	2.45	1.49–4.02	0.001
≥5 years	6	7	3.08	1.02–9.23	0.05
					p for trend 0.30
"High" dose continuous NETA (1.0 mg/day + estradiol 2.0 mg/day)					
<3 years	48	131	1.21	0.87–1.70	0.26
3 < 5 years	38	74	1.71	1.15–2.54	0.007
≥5 years	37	64	2.03	1.34–3.06	0.001
					p for trend 0.05

[1]2.0 mg in 85% of cases. [2]Odds ratio, adjusted with age, parity, age at first birth and health care district, no user as reference category.
[3]Confidence interval.

Table 3. Risk for breast cancer among postmenopausal women using transdermal norethisterone acetate (NETA) + estradiol by duration and mode of regimen

Regimen	Cases	Controls	OR[1]	95% CI[2]	*p*-value
Sequential NETA + estradiol +					
<3 years	43	104	1.45	1.01–2.08	0.05
3 < 5 years	13	38	1.20	0.64–2.27	0.57
≥5 years	17	25	2.11	1.14–3.93	0.02
					p for trend 0.43
Continuous NETA + estradiol					
<3 years	25	45	1.78	1.08–2.92	0.02
3 < 5 years	13	13	3.55	1.64–7.71	0.001
≥5 years	3	6	1.54	0.38–6.25	0.54
					p for trend 0.54

[1]Adjusted for age, parity, age at first birth and health care district, no user as reference category. [2]Confidence interval.

estradiol, and only 15% had used 1.0 mg of estradiol, and therefore this group was analyzed on its own regardless of the dose of estradiol.

The use of a sequential oral "high" dose of NETA (with estradiol) was accompanied by duration-dependent elevations in the risk for breast cancer; the rate ratio was 1.48 (95% CI 1.14–1.90) after 3 years of exposure (Table 2).

Two hundred thirteen patients had used continuous oral NETA (with estradiol) regimens; the dose of NETA was "low" in 90 patients (42%) and "high" in 123 patients (58%) (Table 2). The use of a "low" dose NETA-regimen was associated with an increased risk for breast cancer already in 3 years of use (1.94; 1.39–2.70), however no statistically significant difference emerged between the rate ratios of "low" and "high" dose continuous regimens regardless of the duration of exposure.

Transdermal NETA (all doses combined), given sequentially or continuously (together with estradiol 0.05 mg) was also accompanied with an elevated rate ratio for breast cancer in less than 3 years of exposure, and this rate ratio appeared higher for continuous than for sequential regimens, although not significantly (Table 3); by large, the rate ratios associated with the transdermal use of EPT were comparable to those of oral regimens. For mixed NETA use, rate ratios were of the same magnitude as those for pure NETA + estradiol use (Table 4).

We did also an analysis stratified by years (1995–2002 and 2003–2007) and breast cancer cases; this analysis did not modify our data and conclusions (data not shown).

Table 4. Risk for breast cancer in postmenopausal women using mixed norethisterone acetate + estradiol containing regimens[1] by duration

	Cases	Controls	OR[2]	95% CI[3]	*p*-value
<3 years	87	251	1.17	0.91–1.50	0.22
3 < 5 years	60	155	1.33	0.98–1.80	0.07
≥5 years	82	151	1.85	1.41–2.43	0.001
					p for trend 0.02

[1]Norethisterone acetate given orally or transdermally; sequentially or continuously. At least 50% of the total hormone therapy exposure is NETA containing products. [2]Adjusted for age, parity, age at first birth and health care district, no user as reference category. [3]Confidence interval.

Discussion

In line with previous data, the continuous use of EPT in our data was related with higher risk elevations for breast cancer than was the sequential EPT use.[1,2,10] However, we can present novel results that EPT-associated risks in breast cancer are not relative to the daily doses of NETA or to the route of NETA administration.

The strength of our study is the exact information of the EPT purchases. Because EPT is only partly reimbursed and the women pay the rest from their own funds, most probably they also use the EPT regimens they purchase. Furthermore, the large number of women using NETA-EPT products enabled us to analyze the impact of oral dose in statistically big enough populations. In practice, the "high" dose of oral NETA regimen (1.0 mg/day), refers to Kliogest® (NovoNordisk, Copenhagen, Denmark), which has been on the market since 1991, while the "low" dose of NETA regimen (0.5 mg/day) refers to Activelle® (NovoNordisk, Copenhagen, Denmark) which became available in 2001. The potential exposure times for both regimens exceeded 5 years, which is often used as a critical cut-off level for breast cancer risk, but the users of the "high" dose NETA regimen accumulated more follow-up years. Yet, due to the small numbers of cases, the conclusions on the impact of NETA + estradiol use for more than 5 years cannot be very strong.

We were able to adjust our results for some important confounders, such as the age at the first birth, parity, but we had no means to adjust our results for some other confounders (age at menarche or menopause, body size, family history of breast cancer). However, we feel that this should not cause any major bias, because HT users and nonusers seem to represent quite similar population subgroups in Finland.[14] Moreover, we could not analyze whether the cases and controls had undergone a mammography equally often. In Finland organized mammography screenings have been provided free of charge every second year from 50 years onward since the late 1980s, with a coverage of 95% among 50–59 years old women.[15] This should reduce the chance of diagnosis bias in our study. Because we could accurately assess the true durations of exposure for HT, it was quite expected that the decline in the use of HT in Finland[11] did not modify our results, as confirmed by our subgroup comparisons between breast cancer cases stratified by years.

It is established that NETA regulates endometrial function in a dose-dependent way.[16] In theory, such a relation may also exist in breast tissue. We compared the modern "low" and older "high" doses of oral NETA + estradiol regimens in regard to the risk for breast cancer; the former contains 50% less NETA than the latter. However, no significant difference in breast cancer risk emerged between these 2 regimens. This may indicate that there is no dose-dependence between NETA (as a part of EPT) and the risk for breast cancer. The estradiol dose also varied between 1.0 and 2.0 mg, but in view of the lacking or minimal evidence of the impact of estrogen doses of this magnitude for breast cancer risk[4–8] we are rather confident that our comparison between "low " and "high" NETA doses are reliable. It may be possible that the progestagen level inside the breast cells needs to exceed a "certain" threshold level to initiate or (more likely) to promote the growth of cancer; the higher levels do not potentiate this effect. This speculation may also be supported by our data on the significant breast cancer risk elevation even in women using the estradiol + intrauterine levonorgestrel (0.02 mg/day) releasing system which results in truly low levels of progestagen in circulating blood.[13]

A significant elevation for breast cancer was seen earlier for "low" dose rather than for "high" dose (Table 2). We feel it unlikely that a smaller dose would have triggered cancerous changes and/or promoted pre-existing tumors more strongly than did a higher dose, although of course our data cannot exclude such a possibility. We offer 2 other explanations. First, in Finland it is not customary to discontinue the use of hormone therapy before a mammography. Therefore, EPT-induced breast density which could have been more enhanced in women using "high" dose NETA-EPT,[17–19] may have masked small size-breast cancers in the "high" dose group but not in the "low" dose group.[20] Second, it is possible that the use of the "low" dose continuous NETA regimen could have started already before 50 years of age in some of our subjects. It was also conspicuous that the oral and transdermal administration of NETA was accompanied with comparable risks for breast cancer; these results are novel. Transdermal and oral NETA, apart from a big difference in the doses, result in comparable circulating levels of NETA[21,22] and they affect breasts similarly, as seen in our study.

In conclusion, the dose and route of administration of NETA as a part of the EPT do not appear to be significant determinants for the risk of breast cancer.

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References

1. Collins JA, Blake JM, Crosignani PG. Breast cancer risk with postmenopausal hormone treatment. *Hum Reprod* 2005;111: 545–60.
2. Flesch-Janys D, Slanger T, Mutschelknauss E, Kropp S, Obi N, Vettorazzi E, Braendle W, Bastert G, Hentschel S, Berger J, Chang-Claude J. Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. *Int J Cancer* 2008;123: 933–41.
3. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol-progestagen therapy. *Obstet Gynecol* 2009;113:65–73.
4. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol* 2000;152: 950–64.
5. Porch JV, Lee IM, Cook NR, Rexrode KM, Burin JE. Estrogen-progestin replacement therapy and breast cancer risk: the Women's Health Study (United States). *Cancer Causes Control* 2002;13:847–54.
6. Beral V, Million Women Study C. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362:419–27.
7. Chen WY, Manson JE, Hankinson SE, Rosner B, Holmes MD, Willett WC, Colditz GA. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Int Med* 2006;166:1027–32.
8. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol* 2006;108:1354–60.
9. Ettinger B. Rationale for use of lower estrogen doses for postmenopausal hormone therapy. *Maturitas* 2007;57:81–4.
10. Lee SA, Ross RK, Pike MC. An overview of menopausal estrogen-progestin hormone therapy and breast cancer risk. *Br J Cancer* 2005;92:2049–58.
11. Hemminki E, Kyyronen P, Pukkala E. Postmenopausal drugs and breast and colon cancer: Nordic countries 1995–2005. *Maturitas* 2008;61:299–304.
12. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. *Acta Oncol* 1994;33:365–69.
13. Lyytinen H, Dyba T, Ylikorkala O, Pukkala E. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intrauterine system carries a risk as well. *Int J Cancer* 2010;126:483–9.
14. Topo P, Luoto R, Hemminki E, Uutela A. Declining socioeconomic differences in the use of menopausal and postmenopausal hormone therapy in Finland. *Maturitas* 1999;32:141–45.
15. Sarkeala T, Heinävaara S, Anttila A. Organised mammography screening reduces breast cancer mortality: a cohort study from Finland. *Int J Cancer* 2008;122: 614–19.
16. Stanczyk FZ. All progestins are not created equal. *Steroids* 2003;68:879–90.
17. Lundstrom E, Wilczek B, von Palffy Z, Soderqvist G, von Schoultz B. Mammographic breast density during hormone replacement therapy: differences according to treatment. *Am J Obstet Gynecol* 1999;181:348–52.
18. Christodoulakos GE, Lambrinoudaki IV, Vourtsi AD, Vlachou S, Creatsa M, Panoulis KP, Botsis D. The effect of low dose hormone therapy on mammographic breast density. *Maturitas* 2006; 54:78–85.
19. Bremnes Y, Ursin G, Bjurstam N, Lund E, Gram IT. Different types of postmenopausal hormone therapy and mammographic density in Norwegian women. *Int J Cancer* 2007;120:880–4.
20. Kavanagh AM, Mitchell H, Giles GG. Hormone replacement therapy and accuracy of mammographic screening. *Lancet* 2000;355:270–4.
21. Brosnan JF, Sheppard BL, Norris LA. Haemostatic activation among post-menopausal women taking low-dose hormone therapy. Less effect with transdermal activation?*Thromb Haemost* 2007;97:558–65.
22. Cacciatore B, Paakkari I, Hasselblatt R, Nieminen MS, Viinikka L, Toivonen J, Tikkanen MJ, Ylikorkala O. Randomized comparison between orally and transdermally administered hormone replacement therapy regimens of long-term effects on 24-hour ambulatory blood pressure in postmenopausal women. *Am J Obstet Gynecol* 2001;184:904–09.