

# Postmenopausal Hormone Therapy and the Risk of Ovarian Cancer: A Review of the Literature

**Editor's note:** This article presents a brief summary of the current data in a concise format with an emphasis on a tabular presentation.

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To date, the question of the use of postmenopausal hormone therapy (HT) and the risk of ovarian cancer has not been adequately answered. Even the canceled estrogen-progestin (EPT) arm of the Women's Health Initiative (WHI) failed to reach a conclusion. This article evaluates the data from recent studies and attempts to make sense of the results.

## A Look at the Research:

### Clinical Implications

The canceled EPT arm of the WHI reported an increase in ovarian cancer that was not statistically significant, prompting the authors to say: "The possibility of an increased risk of ovarian cancer incidence and mortality remains worrisome and needs confirmation"<sup>1</sup> (Table 1).

The Kaplan-Meier curves suggested an increasing effect over time, but this, too, was not statistically significant. There were no differences reported in histologic type, stage or grade (but the small numbers make it essentially impossible to assess subcategories). It is of importance to note that there were two endometrioid cancers in the treated group and none in the placebo group.

Although the lifetime risk of ovarian cancer is small, the prevalence of postmenopausal HT combined with an increase in the risk of ovarian cancer

**Table 1.**  
**Ovarian Cancer Cases and Mortalities in the EPT Arm of the WHI**

	EPT	Placebo	Hazard Ratio
Cases	20	12	1.58 (0.77-3.24)
Deaths	9	3	2.70 (0.73-10.0)

**Table 2.**  
**Factors That Influence the Risk of Ovarian Cancer**

#### Factors That Decrease the Risk of Ovarian Cancer

- Use of steroid hormone contraceptives
- Pregnancy and parity; a greater effect with a recent pregnancy and pregnancy at older age<sup>3</sup>
- Breastfeeding<sup>4</sup>
- Hysterectomy and tubal ligation<sup>5</sup>
- NSAIDs<sup>6</sup>

#### Factors That Increase the Risk of Ovarian Cancer

- Increasing BMI<sup>7</sup>
- Infertility<sup>8</sup>
- Caffeine intake<sup>9</sup>
- Two or more eggs per week<sup>10</sup>
- Family history of ovarian and breast cancer

#### Mixed Reports on Decreased Risk

- Alcohol intake<sup>11</sup>

#### Mixed Reports on Increased Risk

- Cigarette smoking<sup>12,13</sup>

could yield an increase that would be of public health significance. For this reason, it is useful to review the recent epi-

demologic data on this important issue. There have been 20 case-control studies

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and four cohort studies assessing the relationship between postmenopausal

hormone therapy and the risk of ovarian cancer.<sup>2</sup> The relative risks encompass a wide range, from below 1.0 to greater than 1.0. Two limitations are immediately apparent. The data reflect largely the use of estrogen without a progestin;

only a small number of cases exposed to estrogen-progestin are available. In addition, because this is a relatively infrequent cancer, all studies have been hampered by relatively small numbers.

The investigators have found it

**Table 3. Assessment of Ovarian Cancer Risk in Recent Studies**

**CASE-CONTROL STUDIES**

**Australian case-control study<sup>14</sup>**

Estrogen only	RR = 1.27 (0.86-1.88)
E-P	RR = 1.34 (0.83-2.17)

Summary: No significant overall effect.

Note: The only significant increase was in 18 cases with endometrioid cancer.

**Italian case-control study<sup>15</sup>**

	Cases	Controls	Relative Risk
Ever use, estrogen only	62	151	1.1 (0.8-1.5)
Use > 2 yrs	22	45	1.4 (0.8-2.5)

Summary: No significant effect.

**Swedish case-control study—borderline tumors<sup>16</sup>**

	Cases	Controls	Relative Risk
Estrogen only	19	259	1.63 (0.95-2.79)
Sequential E-P	19	348	1.15 (0.59-2.24)
Continuous E-P	13	280	0.59 (0.23-1.53)

Summary: No significant effect.

**Swedish case-control study—invasive tumors<sup>17</sup>**

	Cases	Controls	Relative Risk
Estrogen only	59	259	1.43 (1.02-2.00)
Sequential E-P	87	348	1.54 (1.15-2.05)
Continuous E-P	55	280	1.02 (0.73-1.43)

Summary: A significant small increase with estrogen-only and sequential E-P, but not with continuous E-P.

Note: 302 of 617 (49%) cases were endometrioid cancers.

**Pittsburgh case-control study<sup>18</sup>**

	Cases	Controls	Relative Risk
Ever use	484	926	0.94 (0.74-1.19)

Summary: No significant effect; no increase with duration; no differences with CEE compared to other estrogens; no increase with E-P.

**COHORT STUDIES**

**American Cancer Society prospective mortality study<sup>19</sup>**

	Deaths	(No.)	Rate Ratio
Ever use, estrogen only	255	1.51	(1.06-1.43)
< 10 yrs.	31	1.14	(0.79-1.65)
10+ yrs.	31	2.20	(1.53-3.17)

Summary: A significant increase with long duration of therapy.

Problems: No data on type of therapy; information from a single questionnaire in 1982; users not identical to nonusers (more use of oral

contraceptives (OCs), more smokers, more tubal ligations, more educated, fewer children, thinner).

**Breast Cancer Detection Demonstration Project cohort<sup>20</sup>**

	Cases	Relative Risk
Estrogen only	120	1.60 (1.20-2.00)
E-P	18	1.10 (0.64-1.70)

**Duration of use**

10-19 yrs.	21	1.80 (1.10-3.00)
20+ yrs.	16	3.20 (1.70-5.70)

Summary: A significant increase with estrogen-only, linked to duration of use.

Problems: Adjusted only for OC use; increase with duration only in hysterectomized women; product names and doses missing for two-thirds of users; 58% of cases came from women recommended to have surgery or had surgery for breast lumps. When analyzed according to histology, only endometrioid cancer was significantly increased (7 cases; RR = 5.5, CI = 1.9-16.2)

**POOLED CASE-CONTROL STUDIES**

**European collaborative analysis of 4 case-control studies<sup>21</sup>**

	Cases	Controls	Odds Ratio
Ever use, estrogen only	109	146	1.71 (1.30-2.25)

Summary: A significant increase.

**European collaborative analysis of 5 case-control studies<sup>22</sup>**

	Cases	Controls	Odds Ratio
Ever use, estrogen only	171	287	1.28 (1.05-1.56)

Summary: A small significant increase.

**META-ANALYSES**

**Meta-analysis of 12 case-control studies, 1992<sup>23</sup>**

Hospital-based:	RR = 0.90 (0.70-1.30)
Population-based:	RR = 1.10 (0.90-1.40)

**Meta-analysis of 9 studies on invasive cancer selected from 27, 1998<sup>24</sup>**

Ever use:	RR = 1.16 (1.03-1.29)
10+ yrs.	RR = 1.27 (1.00-1.61)

Test for trend for increasing risk with duration of use: not significant.

**Meta-analysis of 15 case-control studies, 2000<sup>25</sup>**

Overall RR = 1.10 (0.90-1.30)

4 US studies with community controls: RR = 1.30 (1.00-1.60)

Summary: A borderline, significant increase in one meta-analysis with long duration of use; problems with all meta-analyses: assumed that controlling for risk factors was uniform in all studies.

difficult to control for all the factors that influence the risk of ovarian cancer. This is because there are multiple factors, and information regarding each factor is not readily available (Table 2, page 23).<sup>3-13</sup>

Summaries of recent case-control, cohort, and pooled case-control studies, as well as summaries of meta-analyses are presented in Table 3 (page 27).<sup>14-25</sup> It should also be noted that in one randomized trial and two retrospective cohort analyses, no detrimental effect on prognosis after surgery for ovarian cancer could be detected in patients subsequently treated with hormones.<sup>26-28</sup>

## Conclusions

A major problem has been the impact of endometrioid cancers, an ovarian cancer that logically can be expected to be influenced by estrogen therapy. In many of the studies, the overall results are swayed by the increase in endometrioid cancers, which could originate in hormonally-stimulated endometriosis.<sup>29</sup> An accurate analysis requires a separate consideration of endometrioid cancers, but this is difficult because the small numbers do not allow effective subcategorization.

Another concern is the time line associated with the development of ovarian cancer. The study of ovarian cancer in the atomic bomb survivors documented that the disease increased 25 years later.<sup>30</sup> How could postmenopausal HT produce an effect rapidly (especially because so few women have maintained therapy for many years) unless there is an effect on pre-existing malignant cells?

It is not difficult to review these numbers and conclude that there is no uniform story, that there are studies with both positive and negative results, and that all of the studies struggle with limited power because of small numbers, and confounding factors because of the difficulties in assessing and controlling for risk factors. The case-control and cohort studies<sup>14-20</sup> irregularly controlled for level of education, parity, oral contraceptives use, body mass index, tubal ligation, and family history

of ovarian and breast cancer; not a single study controlled for all known risk factors! It is appropriate to emphasize the weak associations and the mixed story, but at the same time the seriousness of the specific relationship dictates that postmenopausal HT and the risk of ovarian cancer remains an unresolved issue. ■

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## References

1. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. The Women's Health Initiative randomized trial. *JAMA* 2003;290:1739-48.
2. Riman T. Hormone replacement therapy and epithelial ovarian cancer: Is there an association? *J Br Menopause Soc* 2003;9:61-8.
3. Whiteman DC, Siskind V, Purdie DM, et al. Timing of pregnancy and the risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2003;12:42-6.
4. Siskind V, Green A, Bain C, et al. Breastfeeding, menopause, and epithelial ovarian cancer. *Epidemiology* 1997;8:188-91.
5. Green A, Purdie D, Bain C, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer: Survey of Women's Health Study Group. *Int J Cancer* 1997;71:948-51.
6. Fairfield KM, Hunter DJ, Fuchs CS, et al. Aspirin, other NSAIDs, and ovarian cancer risk (United States). *Cancer Causes Control* 2002;13:535-42.
7. Purdie DM, Bain CJ, Webb PM, et al. Body size and ovarian cancer: Case-control study and systematic review (Australia). *Cancer Causes Control* 2001;12:855-63.
8. Ness RB, Cramer DW, Goodman MT, et al. Infertility, fertility drugs, and ovarian cancer: A pooled analysis of case-control studies. *Am J Epidemiol* 2002;155(3):217-24.
9. Goodman MT, Tung KH, McDuffie K, et al. Association of caffeine intake and CYP1A2 genotype with ovarian cancer. *Nutr Cancer* 2003;46:23-9.
10. Pirozzo S, Purdie D, Kuiper-Linley M, et al. Ovarian cancer, cholesterol, and eggs: A case-control analysis. *Cancer Epidemiol Biomarkers Prev* 2002;11:1112-14.
11. Goodman MT, Tung KH. Alcohol consumption and the risk of borderline and invasive ovarian cancer. *Obstet Gynecol* 2003;101:1221-8.
12. Green A, Purdie D, Bain C, et al. Cigarette smoking and risk of epithelial ovarian cancer (Australia). *Cancer Causes Control* 2001;12:713-19.
13. Goodman MT, Tung KH. Active and passive tobacco smoking and the risk of borderline and invasive ovarian cancer (United States). *Cancer Causes Control* 2003;14:569-77.
14. Purdie DW, Bain CJ, Siskind V, et al. Hormone replacement therapy and risk of epithelial ovarian cancer. *Br J Cancer* 1999;81:559-63.

15. Chiaffarino F, Pelucchi C, Parazzini F, et al. Reproductive and hormonal factors and ovarian cancer. *Ann Oncol* 2001;12:337-41.

16. Riman T, Dickman PW, Nilsson S, et al. Risk factors for epithelial borderline ovarian tumors: Results of a Swedish case-control study. *Gynecol Oncol* 2001;83:575-85.

17. Riman T, Dickman PW, Nilsson S, et al. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J Natl Cancer Inst* 2002;94:497-504.

18. Sit ASY, Modugno F, Weissfeld JL, et al. Hormone replacement therapy formulations and risk of epithelial ovarian carcinoma. *Gynecol Oncol* 2002;86:118-23.

19. Rodriguez C, Patel AV, Calle EE, et al. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001;285:1460-5.

20. Lacey JV Jr, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 2002;288:334-41.

21. Negri E, Tzonou A, Beral V, et al. Hormonal therapy for menopause and ovarian cancer in a collaborative re-analysis of European studies. *Int J Cancer* 1999;80:848-51.

22. Bosetti C, Franceschi S, Trichopoulos D, et al. Relationship between postmenopausal hormone replacement therapy and ovarian cancer. *JAMA* 2001;285:3089-90.

23. Whittemore AS, Harris R, Itnyre J, and the Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: Collaborative analysis of 12 US case-control studies. II: Invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992;136:1184-1203.

24. Garg PP, Kerlikowske K, Subak L, et al. Hormone replacement therapy and the risk of epithelial ovarian carcinoma: A meta-analysis. *Obstet Gynecol* 1998;92:472-9.

25. Coughlin SS, Giustozzi A, Smith SJ, et al. A meta-analysis of estrogen replacement therapy and risk of epithelial ovarian cancer. *J Clin Epidemiol* 2000;53:367-75.

26. Eeles RA, Tan S, Whitelaw E, et al. Hormone replacement therapy and survival after surgery for ovarian cancer. *Br Med J* 1991;302:259-62.

27. Ursic-Vrscaj M, Bebar S, Zakej MP. Hormone replacement therapy after invasive ovarian serous cystadenocarcinoma treatment: the effect on survival. *Menopause* 2001;8:70-5.

28. Hopkins ML, Fung Kee Fung K, Le T, et al. Ovarian cancer patients and hormone replacement therapy: A systematic review. *Gynecol Oncol* 2004;92:827-32.

29. Modesitt SC, Tortolero-Luna G, Robinson JB, et al. Ovarian and extraovarian endometriosis-associated cancer. *Obstet Gynecol* 2002;100:788-95.

30. Tokuoka S, Kawai K, Shimizu Y, et al. Malignant and benign ovarian neoplasms among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1980. *J Natl Cancer Inst* 1987;79:47-57.