

This Week's Citation Classic

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Ziel H K & Finkle W D. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N. Engl. J. Med.* 293:1167-70, 1975.
[Dept. Obstet. and Gynecol., Kaiser-Permanente Med. Ctr., Los Angeles, and Dept. Med. Econ., Kaiser Foundation Health Plan, Southern California Region, CA]

Using the case-control technique, patients with endometrial cancer were compared to a twofold age-matched control group of patients from the same population. Fifty-seven percent of the patients with endometrial cancer used conjugated estrogens, whereas 15 percent of the control patients used conjugated estrogens. The risk of endometrial cancer associated with estrogen use was 7.6 times greater than without estrogen use. Risk increased with duration of exposure: from 5.6 for less than five years' use to 13.9 for greater than seven years' use. These data strongly support the association of endometrial cancer and conjugated estrogens use. [The *SCI*[®] indicates that this paper has been cited over 320 times since 1975.]

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"I (Harry K. Ziel) am indeed fortunate to work with a group of gynecologic oncologists who constantly review pathologic materials from the membership of the Kaiser Foundation Health Plan of Southern California, a large prepaid health plan. In the early-1970s, we were struck with the increasing frequency with which endometrial cancer was developing. One unusual feature of this cancer epidemic was that these women did not have the usual obese habitus which one traditionally associates with endometrial cancer. Rather, these

cancer patients were of average stature. Furthermore and most interesting, these normally sized women with endometrial cancer had a common denominator; most had used an estrogen, usually a conjugated estrogen, for many years.

"I remember joking about the association of estrogen with endometrial cancer at our weekly micropathologic reviews. I would quip, 'Premarin effect!' with no knowledge of the hormonal history whenever a slide of endometrial cancer was projected. Most commonly, when the drug history was recited, I was correct. Arthur Saltz, my chief at that time, goaded me more than once, saying, 'Harry, nobody will believe you until you prove it.'

"As luck would have it, I met an MIT graduate, William D. Finkle, who collaborated with me to evaluate the hypothesis totally.

"Today, 24 studies have been reported worldwide which associate estrogen use with endometrial cancer.^{1,2} Cancer incidence correlates consistently with the amount of estrogen used and with duration of use in these studies. After our publication in December 1975, estrogen use abruptly fell. After estrogen use diminished, the incidence of endometrial cancer reached a plateau, then decreased.

"Our report has taken on the aura of a classic because it reversed scientific thinking on the safety of estrogen and because it established risk estimates for development of endometrial cancer following finite durations of estrogen exposure.

"No man stands alone. We owe everything to our associates. To develop a concept, we need the stimulation of both supporters and antagonists. The ingredients of a concept exist all the time. The people who receive credit for a concept are the ones who are just lucky enough to be exposed to the proper experiences and ideas, who are forced to react to them, and who then formalize a resultant concept into a report."

1. Schwarz B E. Does estrogen cause adenocarcinoma of the endometrium?
Clin. Obstet. Gynaecol. 24:243-51, 1981.
2. Mahboubi E, Eyer N & Wynder E L. Epidemiology of cancer of the endometrium.
Clin. Obstet. Gynaecol. 25:5-17, 1982.