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Postmenopausal Hormone Therapy and the Risk of Breast Cancer

ABSTRACT & COMMENTARY

CHEN AND COLLEAGUES FROM THE UNIVERSITY OF WASHINGTON in Seattle conducted a case-control study of primary invasive breast cancer and postmenopausal hormone therapy. In this study, 705 cases were matched with 692 randomly selected age-matched controls. Hormone use was ascertained largely through a pharmacy database, but also by the means of a questionnaire. Current use was defined as at least 2 prescriptions during the 6 months prior to the diagnosis of breast cancer. Specific hormone products were not identified. (*The table on page 91 highlights the main findings that were statistically significant.*)

Chen et al concluded that "recent" long-term use of postmenopausal hormone therapy is associated with an increased risk of breast cancer, with a greater effect on lobular cancer. The risk of lobular breast cancer was greater with the current use of combination estrogen-progestin therapy (OR, 3.91; CI, 2.05-7.44). The difference between a sequential regimen and a continuous regimen was not statistically significant (Chen CL et al. *JAMA.* 2002;287:734-741).

■ COMMENT BY LEON SPEROFF, MD

This case-control study was performed about as well as can be done and must be added to the list of positive reports on this subject in the last 2 years. Let's first address some criticisms of the study, and then decide how this report should influence clinical practice.

The cases in this study were not identical when compared with the controls. They differed in a greater prevalence of a positive family history of breast cancer, a greater use of mammography, and more of the cases were nulliparous. Chen et al report that they adjusted for family history and mammography, as well as parity. However, there was no adjustment for the number of pregnancies (remember that the younger a woman is with a full-term pregnancy and the more pregnancies she has, the more protected she is against breast cancer). There was also no adjustment for alcohol intake and level of education (the information was not available)—known risk factors for

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INSIDE

breast cancer. Confounding variables such as these can influence results when the differences observed are not great. The strength of the associations reported in this study is consistently weak (odds ratios less than 2.0) except for the increased odds ratios for lobular cancer. But here the conclusions are based on small numbers. The 3- to 4-fold increased risks associated with recent long-term use of estrogen only were based on 8 cases, and that with long-term use of estrogen and progestin, 17 cases.

There were several observations that deserve special attention. There was no significant increase in the risk of breast cancer in past users of hormone therapy. The significant increase in risk was observed in estrogen receptor-positive tumors, not in receptor-negative tumors. The associations observed were greater with lobular breast cancer, known to be a more hormonally sensitive cancer. And the increased risk was significant only with localized cancers, not with metastatic cancers. These observations are consistent with the possibility that those studies finding an increased risk of breast cancer associated with postmenopausal hormone therapy are detecting effects of hormone exposure on pre-existing tumors. This is also consistent with the recent uniform reports that breast cancers detected in women who are using postmenopausal hormone therapy are better differentiated, lower grade, lower stage diseases; hence, they are associated with better outcomes, and surveillance/detection bias is not the only explanation for better survival.[1-6] Lower grade tumors are present even when there is no difference in the prevalence of mammography comparing hormone users and nonusers, or when the data are adjusted for the method of detection.[5-8] These biologic differences imply that hormone treatment promotes the growth of a malignant locus already in place, and it presents clinically with a more favorable biology. This conclusion is consistent with the fact that virtually all the positive studies find that any increase in risk disappears within 5 years of discontinuing hormone therapy, and tumors occur at an earlier stage and a younger age in women using hormone therapy.

Chen et al translate their numbers into estimates of attributable risks. They state that the increased risk of lobular cancer would increase the incidence from 23 per 100,000 women per year to 70, and because most breast cancer is ductal cancer (85% of the cases) the increase would be from 230 per 100,000 women per year to 349. Sometimes it is clinically helpful to present statistical ratios into actual numbers, but I am concerned about it here. This is an estimate based upon selected odds ratios in this study that might reflect confounding influences or the earlier detection of pre-existing tumors. To share these numbers with patients would inappropriately grant them a firmness they don't deserve, and it would unnecessarily frighten patients.

Chen et al are guilty of a practice that I call "selective reporting." They point out that their results are consistent with previous studies and the collaborative re-analysis of the world's date, but they unfairly neglect to mention the studies that did not find an increase in the risk of breast cancer with postmenopausal hormone therapy, including recent reports.[9,10] There are more than 60 case-control and cohort studies in the literature, and the results are not uniform, but in fact negative results outnumber the positive reports.[11]

The conclusions in this new report are biologically plausible and the link with duration of use gives strength to the observations. However, where the case numbers are reasonably large the odds ratios are weak, and where the odds ratios are large, the case numbers are small. So, are we seeing a small increase in the risk of breast cancer associated with postmenopausal hormone therapy or are we seeing the effect of hormone exposure on pre-existing tumors? We don't know the answer, an answer that can only be provided by a large, randomized clinical

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Table

Risk of Breast Cancer Associated With Lifetime and Recent 5-Year HRT by Type of Breast Cancer

	Cases	Controls	Odds Ratio & CI
Current Use			
Estrogen Only (E-O)	132	111	1.17 (0.85-1.80)
Current Use, E-P*	112	74	1.49 (1.04-2.12)
Recent 5-Year Use			
E-O for 60 mos.	35	22	1.84 (1.04-3.27)
Estrogen-Progestin for 57+ mos.	83	56	1.70 (1.15-2.50)
Sequential E-P, 36+ mos.	58	40	1.82 (1.03-2.55)
Continuous E-P, 20+ mos.	17	11	1.85 (0.81-4.21)

	LOBULAR	***DUCTAL***
	Cases/Controls, OR (CI)	**Cases/Controls, OR (CI)**
Current Use		
E-O	21/111; 1.98 (1.04-3.78)	111/111; 1.08 (0.78-1.50)
E-P	26/74; 3.91 (2.05-7.44)	86/74; 1.25 (0.86-1.61)
Recent 5-Year Use		
E-O, 60 mos.	8/22; 3.68 (1.46-9.25)	27/22; 1.60 (0.87-2.93)
E-P, 57+ mos.	17/56; 3.07 (1.55-6.06)	65/56; 1.52 (1.01-2.29)
Seq. E-P, 36+ mos.	10/40; 2.64 (1.14-8.08)	48/40; 1.49 (0.93-2.39)
Cont. E-P, 11+ mos.	8/19; 6.07 (2.13-17.3)	18/19; 1.19 (0.58-2.43)

* — Estrogen-Progestin

trial. Hopefully, the answer will emerge from the Women's Health Initiative in 2006 and the European WISDOM trial in 2011. Until then, another case-control study and another report from a cohort study will bring no further clarity to this issue.

I think it is appropriate to point out to patients that we have more than 60 studies with no uniform, consistent conclusion—an indication that the association is either due to confounding problems or it is a small one. It is also time to bring the message to our patients, that users of postmenopausal hormone therapy who develop breast cancer have a reduced risk of dying of breast cancer, because their tumors are better differentiated, lower stage, lower grade disease.

Points to be Made with Patients

- Some epidemiologic case-control and cohort studies conclude that long-term (5 or more years) of current use of postmenopausal hormone therapy is associated with a slight increase in the risk of breast cancer. This conclusion might be due to confounding biases, particularly detection/surveillance bias;
- All epidemiologic studies fail to find an increased risk of breast cancer associated with short-term (less than 5 years) use or past use of postmenopausal hormone therapy;
- The epidemiologic data do not agree that the addition of a progestin to the treatment regimen increases the risk observed in individual studies;
- The epidemiologic data indicate that a positive family history of breast cancer should not be a contraindication to the use of postmenopausal hormone therapy;
- Women who develop breast cancer while using postmenopausal hormone therapy have a reduced risk of dying from breast cancer. This is because of 2 factors: 1) increased surveillance and early detection; and 2) acceleration of tumor growth so that tumors appear at a less virulent and aggressive stage. ❖

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Empiric Vaginal Metronidazole in the Management of the ASCUS Pap Smear

ABSTRACT & COMMENTARY

Synopsis: *Empiric vaginal metronidazole should not be used in the management of patients with ASCUS Pap smears.*

Source: Connor JP, et al. *Obstet Gynecol*. 2002;99: 183-187.

THE PURPOSE OF THIS STUDY WAS TO DETERMINE whether women with ASCUS Pap smears who had no evidence of bacterial vaginosis had fewer abnormal

repeat smears if empiric treatment with vaginal metronidazole was prescribed. Conner and associates mention that the practice of using a vagina antibiotic following a minimally atypical Pap smear is widespread. They also had reviewed the literature and found no evidence to support such therapy. The only prospective randomized trial in the literature compared use of vaginal triple sulfa cream to no treatment. Vaginal metronidazole had not previously been used in a placebo-controlled trial.

One hundred ninety-seven women were eligible for consideration for entry into this study. The population was chosen from an inner-city gynecologic clinic. In order to be a study participant, the woman had an ASCUS Pap smear, was 18 years of age or older, had no other abnormal cytology in the prior year, had no history of lower genital tract infection in the past month, had no antibiotic use in the past month, and was not pregnant. After the study was discussed with the potential participants, each underwent a speculum examination. Proper techniques were used to exclude the presence of bacterial vaginosis, trichomonas, or candidiasis. One hundred six women met entry criteria and were not excluded by initial examination. Each received either metronidazole vaginal cream or a placebo in an unmarked tube. Neither the study participants nor the physicians knew which tubes contained the active ingredient.

Demographic variables were virtually identical for the treatment and placebo groups. Eighty-four women (41 metronidazole and 43 placebo participants) returned for repeat Pap smear. Fifty of these 84 had normal cytology and 34 had persistent abnormal findings. Fifty-four percent of the women who received the active ingredient and 65% of those who received placebo had a repeat normal cytology. Women in both groups who had abnormalities on the repeat smear were referred for cytology. There were no differences in the findings of CIN between the 2 groups among those women who appeared for colposcopy.

Conner et al conclude that there is no role for the empiric use of vaginal metronidazole following an initial ASCUS Pap smear.

■ COMMENT BY KENNETH L. NOLLER, MD

For more than 25 years, I have had a referral colposcopy practice. During that time I have heard an unbelievable wide array of tests and procedures that were performed prior to the patient being sent to me. Among those women who had repeat minimal abnormal smears (previously Class II and now ASCUS), the one constant has been that most had received some type of antibacterial vaginal cream prior to their repeat Pap smear. In years past the cream of choice was a triple sulfa preparation, and more recently it has been either metronidazole or clindamycin vaginal cream.

I have always wondered why such treatment is so common, since there is no literature to support the practice. I strongly suspect that it goes back to the old Papanicolaou classification system of Pap smears in which a "Class II" smear was more or less equated with "inflammation." Perhaps clinicians think that by using an antibiotic cream the inflammation resolves and the Pap smear will more frequently revert to normal. Although the change to the Bethesda system took inflammation out of the category of squamous abnormalities (and inflammation should not be the cause of an ASCUS smear), I suspect that old habits are hard to break. Unfortunately, a lot of young practitioners also routinely use vaginal antibiotic cream after a minimally atypical Pap smear.

I firmly believe that the results of this study, and the previous study using triple sulfa cream, should convince even the most skeptical clinician that there is no place for the empiric use of vaginal antibiotic creams in an attempt to revert a minimally atypical Pap smear to normal. The practice is costly, inconvenient, and potentially dangerous. ❖

Findings in Female Offspring of Women Exposed In Utero to Diethylstilbestrol

ABSTRACT & COMMENTARY

Synopsis: *Not one of 28 third-generation DES-exposed women had lower genital tract changes.*

Source: Kaufman RH, Adam E. *Obstet Gynecol*. 2002; 99:197-200.

In 1974, the National Cancer Institute funded a large multicenter project with the purpose of identifying, examining, and following women whose mothers had taken DES while they were in utero (DESAD Project). Many of these women had epithelial and structural changes in the lower (and upper) genital tract. Because of the results of several animal studies that suggested that the effects of DES may be multigenerational, Kaufman and Adam contacted women who had enrolled in the DESAD project who were known to have daughters older than 15 years of age and requested that the daughters (third generation, granddaughters) appear for pelvic and colposcopic examination.

A total of 28 third-generation daughters were exam-

ined. At the time of examination, they averaged 20 years of age. Not one of these women was found to have any of the epithelial or structural changes that had been seen in their mothers and other women exposed in-utero to DES. A total of 61.5% of the mothers of the women examined in this report had been noted to have vaginal and/or cervical epithelial and/or structural abnormalities.

Kaufman and Adam conclude that it is unlikely that third-generation DES daughters will have the same problems that have been reported in their mothers. However, rare events, such as vaginal adenocarcinoma, cannot be excluded.

■ **COMMENT BY KENNETH L. NOLLER, MD**

This is an extremely important article for the approximately 2 million women who were exposed in utero to DES. Most of these women have now completed their families and many of their daughters are teenagers or older. Many of the mothers who had DES abnormalities have asked questions about the chances that their daughters would have similar problems. This article shows convincingly that the epithelial and structural abnormalities seen in their mothers either do not occur at all, or occur with low frequency.

It may never be possible to determine whether or not the third-generation women have an increased risk of vaginal adenocarcinoma as it is such a rare condition even among women exposed in utero. Certainly there will be an occasional case of vaginal clear cell cancer in third-generation women, just as there are occasional cases in the general population. I just hope that the first reported case does not cause a national scare the way the original report did. ❖

Intraperitoneal Chemotherapy for Ovarian Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Although prolonged survival was observed in selected patients receiving IP platinum-based therapy, it is not possible to determine the contribution of IP therapy to survival in this study.*

Source: Barakat RR, et al. *J Clin Oncol*. 2002;20: 694-698.

Barakat and colleagues from Memorial Sloan-Kettering Cancer Center reviewed the records of 433 patients who received intraperitoneal (IP) therapy for ovarian cancer between 1984 and 1998; follow-up data were available for 411 patients. IP therapy was provided as consolidation therapy (n = 89), or for treatment of persistent (n = 310) or recurrent (n = 12) disease after surgery and initial systemic therapy; therapy usually consisted of platinum-based combination therapy. The mean age of patients was 52 years (range, 25-76 years). Distribution by stage and grade was as follows: stage I, 7; II, 24; III, 342; IV, 52; not available (NA), 8; and grade 1, 30; 2, 99; and 3, 289; NA, 15. The median survival from initiation of IP therapy by residual disease was none, 8.7 years; microscopic, 4.8 years; less than 1 cm, 3.3 years; more than 1 cm, 1.2 years. In a multivariate analysis, the only significant predictors of long-term survival were grade and size of residual disease at initiation of IP therapy. Barakat et al concluded that, although prolonged survival was observed in selected patients receiving IP platinum-based therapy, it is not possible to determine the contribution of IP therapy to survival in this study. A relationship between size of disease at the initiation of IP therapy and long-term survival was demonstrated.

■ **COMMENT BY DAVID M. GERSHENSON, MD**

Ovarian cancer remains a challenging disease. Despite a high response rate to postoperative chemotherapy after primary cytoreductive surgery—on the order of 80%—most patients with advanced-stage disease will ultimately relapse. Therefore, several strategies have been studied as consolidation therapy for patients in remission and for patients with persistent disease after primary therapy—further systemic chemotherapy, radiation, intraperitoneal chemotherapy (as in this study), and high-dose chemotherapy with stem cell support. The group from Memorial Sloan-Kettering has focused much of their efforts on IP chemotherapy. Several other groups have also studied IP therapy over the past 2 decades or so, and it has found its way into clinical practice in some sectors without any clear information suggesting benefit. Unfortunately, as Barakat et al themselves acknowledge, it is difficult if not impossible to interpret the true value of this approach without conducting a randomized trial. Distinguishing the biologic behavior of the tumor from the influence of the intervention is the challenge in studies such as this. IP therapy has been tested in 3 major randomized trials as part of primary treatment, and the data thus far suggest a slight but real benefit in terms of progression-free survival or overall survival for IP therapy compared with intravenous therapy. Nevertheless, this approach has not been widely embraced, most likely related to the technical difficulties and skepticism regarding the true benefits. ❖

Special Feature

MORE Data, MORE Questions

By Sarah L. Berga, MD

I REMEMBER WHEN I USED TO EAGERLY TURN BACK THE cover of *JAMA* in anticipation of that week's medical findings. I still have the anticipation, but the sense of potential enlightenment has been replaced by a more utilitarian goal, that of making sure I am up-to-date on the latest in confusing information. I want to make sure that I will be able to explain the most recent report to my patients trying to decide about whether to start or remain on hormonal therapy. Typically, patients hear a sound bite on the radio or read a small blurb in the newspaper. Naturally, if the findings are ambiguous, as they mostly are, the patients are worried and want to know what I think. I can't blame them. I also want to know what I think. Thus, I am compelled to turn pages. Last week's *JAMA* was a case-in-point. The lead article (Barrett-Connor E, et al. Raloxifene and cardiovascular events in osteoporotic women. *JAMA*. 2002;287:847-857) reported the effect of raloxifene use in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial upon cardiovascular events. The abstract suggested that raloxifene conferred cardioprotection for those most at risk for CVD. I was surprised because I knew that cardiovascular events were not one of the end points of the trial in question. So I read more, hoping for some clarification. Here is what I learned.

The MORE trial was a double-blind, placebo-controlled trial of 7705 postmenopausal women with osteoporosis that was conducted from 1994 to 1999. The mean age of participants was 67 years. The rate of cardiovascular events and mortality was about half of that reported for women in the general US population, so the number of events for the entire cohort during the 4 years was small (272), ie, 3.5% of the cohort. Overall, there was no difference in cardiovascular events among the 3 groups, which were those treated with placebo, raloxifene 60 mg/d, and raloxifene 120 mg/d. But in a subset of 1035 women at increased risk of cardiovascular disease, there was a decreased risk of cardiovascular events after the first year of raloxifene use. However, this decrease was statistically significant only in the group treated with the 60-mg daily dose of raloxifene and not in the group treated with the 120-mg raloxifene dose. The number of events in this subset of 1035 "high-risk" women was tiny, only 55 coronary events and 41 cerebrovascular events over the entire 4 years. Only in the discussion do Barrett-Conner and colleagues point out that the reduction in risk of cardiovascular events did not translate into a reduction in risk of death from cardiovascular disease. Further, the analysis was by intention-to-treat and 26% of the participants in each arm dropped out, mostly due to adverse events, the nature of which are not disclosed in the manuscript. Barrett-Conner et al do note that the trial was not designed to look at cardiovascular events, so the data on death and events are from the safety end points, rather than from direct prospective ascertainment. The groups differed from the outset in terms of diabetes and use of lipid-lowering agents, both of which were higher in the raloxifene groups. Thus, one wonders if the raloxifene group might have received more intensive medical care unrelated to the study. There also tended to be fewer women with a prior history of myocardial infarction or having had a coronary artery bypass graph (CABG) in the 60-mg/d raloxifene group.

I must acknowledge that I started to read the article in my customary (skeptical) frame of reference. However, the introduction was succinct and made a good case for the hypothesis. I started to become hopeful that the results would be convincing. The description of the methods was thorough and detailed, lending the impression that the study design might be adequate for the query under examination. But as I read a little more, the troublesome details began to emerge. In the end, I felt betrayed. After wading through 10 pages of fine print, I concluded that the study was so problematic that the results could not be trusted. I also felt that the positive aspects of the study had been highlighted in the abstract while the negative or problematic details were buried in the back. Further, while estrogen was not one of the study arms, sprinkled throughout the discussion were references as to how the present results compared to results obtained in postmenopausal women using conventional estrogens. Although the data do not permit such conclusions, the implication was that raloxifene might be better than estrogen for cardioprotection.

Why am I harassing you with these details? In part, I aim to sound a cautionary note about the reliability of the results of a study likely to receive more attention than it deserves. I would also like to point out the obvious, if only to make it more so. The company that makes the drug in question funded the study. This is not optimal. The study was conducted by a group of clinical investigators at reputable academic institutions. This is good. But why are distinguished clinical investigators doing a study funded by a pharmaceutical house? Because there is almost no money available from other sources for clinical investigations of this type. When the federal government undertook a similar study, the Women's Health Initiative, they too

asked for and received free drugs, thus becoming unwitting handmaidens of the drug makers. It is not that the pharmaceutical industry is intrinsically evil; their representatives are trying to let us know the most favorable points about the products that they sell. If we are ever to get the kind of reliable information we need to make informed decisions about the array of available products, then we will have to find a way for adjudicators (clinical investigators) to have the resources required for conducting head-to-head comparisons free of commercial bias. ❖

Reader Questions

Question: *Dear Editor, In a recent edition of OB/GYN Clinical Alert, Dr. Noller stated that there is no longer any indication for the use of 5-FU in the lower genital tract. In 1999 we published a randomized controlled trial of the use of 5-FU in HIV-positive women with significant intraepithelial neoplasia. Those women who received the active agent after ablative or excisional therapy had more and longer disease-free intervals than those who received the placebo (Obstet Gynecol. 1999;94:954-961). We believe that there is a place for the use of this agent in this select population. Can you comment?* — Mitchell Maiman, MD, Chairman, Dept. of Ob-Gyn, Staten Island University Hosptial, NY

Kenneth Noller, MD responds: Dr. Maimon's article did indeed demonstrate that 5-FU can be useful for HIV-positive women who have been treated for intraepithelial neoplasia. As I have previously indicated in these pages, a few women who have condylomatous colpitis as a result of immunosuppression (usually iatrogenic) also can benefit from careful use of small amounts of intravaginal 5-FU. As far as I know, these are the only examples of proven benefit from the use of this caustic agent in the lower genital tract. Unfortunately, I continue to see women who have been injured by this drug, the majority of whom have used it on the vulva. ❖

CME Questions

12. Which one of the following statements is true regarding the association of breast cancer with postmenopausal hormone therapy?

a. Case-control studies on this issue find it difficult to compare cases to identical controls.
b. Past users of combined estrogen and progestin have an increased risk of breast cancer.
c. Postmenopausal hormone users who are diagnosed with breast cancer have less aggressive tumors.
d. More than 60 observational studies do not give a consistent, clear-cut result.

13. In the multivariate analysis from the study by Barakat et al on intraperitoneal (IP) chemotherapy for ovarian cancer, the only significant predictors of long-term survival were which of the following?

a. FIGO stage and histologic type
b. Histologic grade and residual disease at start of IP therapy
c. Age of the patient and response to prior therapy
d. Age of the patient and FIGO stage
e. Histologic grade and age of the patient

14. Which of the following statements concerning the Connor et al report on the use of empiric vaginal metronidazole for ASCUS Pap smears is true?

a. A larger percentage of women in the placebo group had normal repeat Pap smears than the metronidazole group.
b. The use of vaginal metronidazole did not result in more normal Pap smears at follow-up.
c. The rate of CIN was found to be the same in both the metronidazole and placebo groups.
d. All of the above

15. In the article by Kaufman and Adam, what was the rate of cervical and vaginal epithelial and structural abnormalities identified among 28 DES granddaughters?

a. 0%
b. 12.6%
c. 41.3%
d. 61.5%

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We look forward to hearing from you. ❖

In Future Issues:

Oral Contraceptives and Ovarian Cancer

PHARMACOLOGY WATCH

GlaxoSmithKline Withdrawals Lymerix: Company 'Cuts Losses' on Controversial Lyme Disease Vaccine

Citing poor sales, GlaxoSmithKline has announced that it is withdrawing Lymerix, the Lyme disease vaccine, from the market. The vaccine was the first, and only, Lyme disease vaccine on the market. Lymerix generated $40 million in sales in 1999, its first year on the market, but sales have fallen steadily since. The vaccine has also been plagued by controversy regarding side effects claimed by patients—side effects that seem to mimic Lyme disease and include arthralgias, fatigue, and neurocognitive symptoms. The FDA reviewed a study of 10,000 patients (5000 active vaccine, 5000 placebo) and found no increase in side effects with the vaccine. But because of continued complaints by consumers, the Centers for Disease Control (CDC) independently reviewed more than 900 reported side effects. In a report issued in January, the CDC declared that the vaccine was not associated with unexpected events. Despite the report and statistics that show Lyme disease cases reaching record highs, Glaxo has decided to cut their losses and is pulling the vaccine from the market.

Measles Vaccine Weathers Storm in Europe

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PHARMACOLOGY WATCH

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