FILE NAME: Talc (TALC)

DATE: 1997

DOC#: TALC027

DOCUMENT DESCRIPTION: Journal Letter to the Editor RE Perineal Powder Exposure and the Risk of Ovarian Cancer

American Journal of Epidemiology

Vol. 146, No. 9
Printed in U.S.A.

LETTERS TO THE EDITOR

RE: "PERINEAL POWDER EXPOSURE AND THE RISK OF OVARIAN CANCER"

Cook et al. (1) suggest that their data support the hypothesis that talcum powder use causes ovarian cancer. We believe that the current biologic and epidemiologic data do not provide strong evidence for a causal association. It is unknown how talcum powder could migrate to the ovaries, or whether the chemico-physical aspects of talcum powder can induce ovarian cancer. The cited paper by Egli and Newton (2) showed migration of carbon black particles from vaginal deposition to the oviducts in two of three patients. Different results were obtained by Deboer (3), who found carbon black translocation from the vagina to the uterus in only 2 of 37 surgical patients. Based on a previously published paper (4), the authors state that talc-like particles are found more frequently in ovarian tumors than in normal tissue. However, in that study, the amount of particles ranged from 6,900–55,100 /g wet tissue in tissues from three healthy ovaries to 6,400–24,500 /g wet tissue from three malignant ovaries (4). Further efforts are needed to determine whether and how talc-like particles can migrate up the reproductive tract, to confirm findings of talc particles in healthy and malignant ovarian tissue and to explore possible mechanisms of talc-induced ovarian carcinogenesis.

In epidemiologic studies of weak associations, dose-response trends are especially important to demonstrate causality (5). Cook et al. (1) found no trend in the odds ratios with increasing number of perineal applications despite a fivefold difference between the lowest and highest exposure categories. Other studies either did not determine the duration and frequency of perineal dusting (6–9), or showed no trend in risk with duration of exposure (9, 10), or a suggestive trend (11). The lack of a trend in several studies argues against a biologic effect. The modest positive findings may be due to greater awareness and recall among the cases. This seems possible given the numerous questions on talc use in these epidemiologic surveys and the considerable differences in exposure percentages between the control groups. Reliability studies on genital hygienic practices are needed.

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Joshua E. Muscat
Ernst L. Wynder
American Health Foundation
320 East 43rd Street
New York, NY 10017

Editor's note: *In accordance with* Journal *policy, Dr. Cook and her coauthors were given the opportunity to reply to the above letter, but they chose not to do so.*

RE: "ASSESSING THE DIRECTION OF CAUSALITY IN CROSS-SECTIONAL STUDIES"

We read with some concern the paper by Flanders et al. (1), in which they question the direct causality of the relation between dioxin exposure shown in studies (2, 3) that were carried out among veterans of Operation Ranch Hand who were participants in the ongoing Air Force Health Study (AFHS). As Flanders et al. correctly note in their first example, the exposed (E) and control (C) group triglyceride means are nearly identical in the AFHS. Therefore, we believe that any model relating triglyceride and dioxin in the AFHS should accommodate equal triglyceride group means.

Using the same notation used by Flanders et al., let Y_1, Y_2, and X denote the dioxin exposure level, the measured exposure level, and the triglyceride level, respectively. Without loss of generality, we have dropped the subject subscript from the notations. Then, a model to study triglycerides should accommodate the condition

$$\mu_C(X) = \mu_E(X), \quad (1)$$

where $\mu_C(X)$ and $\mu_E(X)$, respectively, are the overall triglyceride means for the control and exposed groups.

Flanders et al. consider two models. Their model 1 is a direct causation model to study the effect of dioxin exposure on health, and model 2 is a reverse causation model to study the effect of triglycerides on measured dioxin. In both models, they assume that the exposed group is stratified by dioxin categories: E_1, low; E_2, medium; and E_3, high; and

$$\mu_{10} < \mu_{11} < \mu_{12} < \mu_{13}, \quad (2)$$

diabetologists and in major medical centers where funduscopic examination is done routinely and competently. However, in the office of the primary care physicians, where most diabetics in this country receive much of their care, annual examination of the fundi through *dilated* pupils regrettably is performed infrequently if at all. Given that circumstance, an abnormal tourniquet test result demands a competent funduscopic examination to rule out proliferative retinopathy, often by referral to an ophthalmologist. I wish to emphasize that I am not advocating that the tourniquet test replace regular funduscopic examination.

If Drs Aaby and Zegarra have a cost-effective strategy to ensure adequate annual examination of the 11 million diabetics in the United States "by a physician who can recognize early proliferative diabetic retinopathy," I would happily endorse it and discard the tourniquet test; until then, the tourniquet test will identify nine of every ten patients with diabetic retinopathy who need to be referred to such a physician. Many of these patients' conditions are currently undiagnosed until loss of vision occurs.

Decrease in capillary fragility with improved diabetic control noted in several patients was not meant to imply regression of diabetic retinopathy. Histological study, however, may confirm that the tourniquet test does accurately reflect the progression or regression of diabetic dermal microangiopathy. At present, the vascular or platelet abnormality causing capillary fragility in diabetes is unknown. I am currently involved in a study correlating the tourniquet test with fluorescein retinal angiography in those patients who do not have identifiable diabetic retinopathy on ophthalmoscopic examination.

WILLIAM A. REYNOLDS, MD
Western Montana Clinic
Missoula

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Talc and Ovarian Cancer

To the Editor.—Cramer and co-workers[1] recently reported observing an association between talc use and risk of ovarian cancer. We therefore examined data on talc use that two of us (L.M. and L.P.L.) had collected as part of a case-control interview study of epithelial ovarian cancer conducted from 1974 to 1977 in the Washington, DC, area.[2] The cases were 197 women with pathologically confirmed primary epithelial ovarian cancers treated in participating hospitals. The controls were 197 women treated at the same hospitals for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy. The controls were frequency matched to the cases on age, race, and hospital. The interviewers asked questions about reproductive and sexual history, medical history, drug use, and other exposures. Questions about talc use were added to the questionnaire after the study began, so 135 cases and 171 controls were asked about talc exposure.

Estimated Relative Risk of Ovarian Cancer, According to Reported Use of Talc

	Cases	Controls	Estimated Relative Risk	95% Confidence Interval
No talc mentioned	62	61	1.0	. . .
Any talc mentioned	67	100	0.7	0.4-1.1
No diaphragm used	92	118	1.0	. . .
Diaphragm used, no talc	14	11	1.6	0.7-3.7
Diaphragm, with talc	25	41	0.8	0.4-1.4
No body talc	77	84	1.0	. . .
Some body talc	54	78	0.8	0.5-1.2
"All over"	37	57	0.7	0.4-1.2
Genital*	7	3	2.5	0.7-10.0
Legs only	1	0	. . .	. . .
Not genital	6	8	0.8	0.3-2.5
Unknown where	3	10	0.3	0.1-1.2

*On genitals, sanitary napkins, or underwear.

The reported talc use among cases and controls is given in the Table. We estimated the relative risk to talc users as 0.7 (95% confidence interval [CI]=0.4 to 1.1). The estimate was unaffected by adjustment for race, age, and gravidity. Neither women who used talc on their diaphragms nor those who used it as body powder seemed to be at excess risk. Women who used talc as a body powder were asked how they used it. Among the ten who specifically mentioned use on sanitary napkins, underwear, or the genital area, the relative risk was estimated as 2.5, but the small number of exposed women yielded an unreliable estimate (95% CI=0.7 to 10.0).

Our data thus indicate no overall association between talc use and risk of ovarian cancer. Although a small group of women who specifically reported genital use of body talcum powders showed an excess relative risk, use of talc on a diaphragm, which would be the closest exposure to the ovaries, did not seem to elevate risk.

Chance, bias in selection or observation, or confounding may have influenced these estimates. One important potential bias to consider in this and Cramer's study is a difference between cases and controls in recollecting or reporting talcum powder use, especially in the genital area. Talc exposure was not a major focus of this study, and few data are available to assess the likelihood of recall bias. Such a bias could stem from cases' heightened awareness or from the fact that controls were interviewed in the hospital while most cases were interviewed at home. On the other hand, the questions about talc use were rather simple and unambiguous. Also, we noted that cases and controls were equally likely to report douching. Since reporting of use of douches might be subject to the same recall biases as talc use, this observation suggests that little recall bias operated. Another possible interpretation of our findings of no apparent effect of using talc on the diaphragm but some effect of perineal use of powder is that talc itself does not increase risk of ovarian cancer but that patients with ovarian cancer have or perceive a greater need for using body powder in the genital area, for reasons related either to the biology of the disease or to life-style. We agree with Cramer and co-workers that other epidemiologic data will be useful.

PATRICIA HARTGE, MSc
ROBERT HOOVER, MD
National Cancer Institute
Bethesda, Md

LINDA P. LESHER, MPH
LARRY MCGOWAN, MD
George Washington University
Medical Center
Washington, DC

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