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Robert B. Armstrong, MD
Vice President, Regulatory & Medical Affairs
Fax: 908-904-3480
Email: Rarmstr1@cpcus.jnj.com

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Board of Scientific Counselors
National Toxicology Program
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Board Members,

My name is Dr. Robert B. Armstrong, and I am Vice President of Regulatory & Medical Affairs at Johnson & Johnson Consumer Products Worldwide.

The enclosed document was prepared by Dr. Judith K. Jones to assess the epidemiologic evidence considered by the NTP as part of the risk assessment of talc. I believe her report raises important caveats about the association between ovarian cancer and use of talc products.

Thank you for consideration of this analysis. Please feel free to contact me if additional information is needed.

Sincerely,

[redacted]

Robert B. Armstrong, MD

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Review and Critique of Epidemiology Studies of Talc and its Relationship to Ovarian Cancer

Judith K. Jones, MD, PhD

The Degge Group, Ltd.
Suite 1430, 1616 N. Ft. Myer Drive
Arlington, VA USA

November 27, 2000

Critique of Epidemiology Studies of Talc and its Relationship to Ovarian Cancer

Executive Summary

The National Toxicology Program(NTP) has recently raised the concern that talc may be carcinogenic, based upon their assessment that it is related to asbestos, and that several epidemiological studies have suggested an elevated risk of ovarian cancer associated with use of talc.

This report builds upon the many reviews of the epidemiology studies of ovarian cancer, in particular those that examine the role of talc as a risk factor.

All epidemiology studies that in any way examine the role of talc and ovarian cancer are reviewed. The specific findings relative to talc exposure variables are summarized and critiqued. Studies were examined with respect to the following criteria:

- Quality of the epidemiological study
- Definition and quantification of the talc exposure variable
- Definitions of the ovarian cancer cases and their classification
- Control or consideration of confounding variables

The results of this evaluation are then considered in light of standard criteria for epidemiologic causality.

The result of this review reveals several studies that show an elevated relative risk for talc exposure and the development of ovarian cancer, and several that show no elevated risk. Remarkable in most of the studies that do demonstrate risk is a lack of either a dose and/or time related effect of talc exposure. Other limitations on exposure ascertainment and definitions also exists in many of the studies independent of results. Recent studies suggest absence of risk for ovarian cancer as a whole, but find increased risk for one or another subtypes (serous or mucinous). This apparent specificity is clouded by the considerable differences of opinion in the pathological classification of ovarian cancers and raises significant concerns regarding misclassification and case definition. This is also potentially confounded by any bias that might arise with the selection of patients able and willing to participate in these studies compared with those who are unable to participate due to advanced disease.

Finally, recent research clearly underlines the role of genetic factors, such as the BRCAI /II genes in predisposing to some ovarian cancers. This serves as one additional reminder that it is likely that a number of risk factors are not yet accounted for and these may further confound any findings such as of talc exposure.

In summary, although there are some studies suggesting an increased risk of ovarian cancer after exposure to talc, the risk estimates are almost all borderline or not significant. Further, they are based on relatively imprecise measures of exposure that do not show a dose-reponse relationship, and do not typically take all risk factors into consideration. This, coupled with recent careful studies such as that of Whittemore et al, and Gertig that show no overall significant risk bring one to conclude that there is not sufficient evidence based on the available data that talc in fact poses a risk for ovarian cancer.

Critique of Epidemiology Studies of Talc

and its Relationship to Ovarian Cancer

The National Toxicology Program (NTP) has recently again raised the concern that talc may be carcinogenic, based upon their assessment that it is related to asbestos, and that several epidemiological studies have suggested an elevated risk of ovarian cancer associated with use of talc. Hearings to review the evidence on talc and other substances will be held December 13-14, 2000.

This report examines the available epidemiology studies that examine exposure to talc and its relationship to ovarian cancer, and builds upon the many extant reviews of this topic to summarize the strength of the evidence for this association.

History and Background

Concern about the possibility of talc serving as a risk factor for ovarian cancer became evident in the 1970's medical literature. Hendersen et al (1971) found talc in ovarian tumors and noted the relationship of talc to asbestos. In 1976, the Cosmetic, Fragrance and Toiletry Association established guidelines to assure that cosmetic talc was free of asbestos contamination (Harlow et al, 1992). In 1979, an article in Lancet (Longo and Young, 1979) reviewing this topic called for further examination of the possible role of talc in ovarian cancer. Cramer et al (1982) published the initial epidemiological study that examined exposure to talc and reported an association of ovarian cancer with use of talc. By 1994, a number of epidemiological studies had followed this effort, which showed either no increased risk or a modest increased risk overall or in some exposure groups (Hartge et al, 1983; Whittemore et al, 1989; Harlow and Weiss, 1989; Booth et al,1989; Harlow, Cramer et al, 1992 and Rosenblatt et al, 1992. These were reviewed by the NTP in 1994.

Two detailed critiques examined the studies and other data in detail. Gross (1994) in his report conducts a summary analysis (a crude "meta-analysis" that he qualifies as limited in its validity) to find a slight increased combined risk of 1.25 (95% confidence interval, 1.08-1.47). However, he noted that

> "*while this result is barely statistically significant, one cannot conclude the existence of an association between an increased risk of ovarian cancer in women who use talc in their perineal region,*"

and further points out that the meta-analysis result is based upon unadjusted odds ratios, the issue of selection and differential biases are not explicitly addressed in the studies, and that unpublished studies should be sought to address publication bias.

Dr. Ronald Ross, another epidemiologist also provided a detailed critique of each study (Ross, 1994) and concluded:

> "*Epidemiologic studies to date have been unable to disprove that perineal talc exposure is associated with a small increase in ovarian cancer risk (i.e., to fully*

exclude the null hypothesis of no association). However existing epidemiologic evidence is highly unconvincing that any association represents a cause-effect relationship."

Dr. Ross goes on to support this conclusion by noting:

- The low magnitude risk estimates, almost always below 2.0, with insufficient power to examine subgroups;
- Substantial inconsistencies among studies in the types of exposure conveying an increase in risk;
- Since all exposure classifications are based upon self-reports, there is a very real possibility of recall bias (i.e., cases remembering better or over-reporting past exposures because of greater motivation or in an attempt to explain why they became ill);
- The evidence for a dose-response is weak, at best, even in the Harlow study that attempts to factor in anovulatory time which he questions;
- That although a biological mechanism has been proposed, it is not clearly established in man, and may not be relevant to current (post 1976) exposure.
- The absence of consistent efforts in the different studies to control for confounding.
- Several potential problems with controls in some studies that could introduce bias, and explain some of the deviations from the null.

However, a number of additional epidemiological studies of the association of talc with ovarian cancer have subsequently been published. These have actively responded to the prior studies and have added fuel to the current active discussions relating to theories on the etiological factors for ovarian cancer.

These etiological theories, roughly divided into the gonadotrophic overstimulation mechanism, the ovulatory activity mechanism and the environmental exposure factors have formed the basis for most examinations for causes and risk factors. More recently, with the emergence of a growing number of tools for genetic studies, the specific roles of the BRAC1 and 2 genes and other genetic factors have gained more prominence in the discussions of etiologies. To date, they have only been thought to account for ~ 4.5% of all ovarian cancers (Whittemore et al, 1997). Other forays into possible etiologies have examined the roles of drug exposure, including fertility drugs, tranquilizers and analgesics and anti-inflammatory drugs (Tzounou, 1993, Harlow and Cramer, 1995). In addition, diet (notably lactose-containing diets, Cramer et al, 1989) has been explored and these findings have been incorporated into the major theories.

More recently, Ness et al (2000) has proposed an additional theory relating to inflammation of the ovary as a potential factor. This might link to the environmental exposure theory and provide an explanation for a protective effect of analgesics and a finding of a thyroid risk factor (as a marker of autoimmune disease). Talc has been implicated in both the environmental as well as the inflammatory theory. Thus is predicated on the implicit or explicit acceptance of early studies demonstrating movement of particles from the vagina to

the fallopian tube tract (Egli and Newton, 1961), and the assumptions since talc chemically resembles asbestos, it can also cause inflammatory responses and predispose to tumors.

This review will focus more upon the more recent studies and following consideration of the strengths and weaknesses of these efforts, will return to the criteria for causality in epidemiological studies, and specifically, the theories of etiology for ovarian cancer.

Review of Studies

All of the epidemiology studies that examine the role of talc and ovarian cancer were reviewed for this report. Studies were examined with respect to the following criteria:

- Quality of the epidemiological studies
- Definition and quantification of the talc exposure variable
- Definitions of the ovarian cancer cases and their classification
- Control or consideration of confounding variables

Methodology and quality of the studies.

The salient epidemiology studies are briefly summarized in **Table 1**. These illustrate that the question of talc exposure has now been explored in a diverse array of populations from several countries spanning exposures that potentially extend into the 1960s or before (Cramer, 1982, Whittemore et al, 1989, Hartge et al, 1989, Gertig et al, 2000). The later studies mostly relate to the post 1976 period where talc purity was increased (Ness, 2000, Purdie, 1995, Chang, 1997, Godard, 1998 and Cramer, 1999).

Limitations in Case Selection. Other than the cohort from the Nurses Health Study by Gertig and colleagues (2000) all of the studies have utilized a case-control methodology. Identification of cases has been population-based in some studies (Ness et al, 1999), whereas other cases have been drawn from convenience samples of cases presented to specific hospitals. For the most part, a moderately high (~70%) proportion of eligible cases were accessed for the studies. However, in almost all cases, due to the nature of ovarian cancer, available cases represent those with the less extensive disease. This has been noted by several authors in consideration of limitations. When overall risk for any epithelial ovarian cancer is considered, this is likely less of a limitation; however, in recent studies, attempts have been made to evaluate tumor type. In this case, the loss of cases might be a further limitation if aggressive disease is more commonly associated with one or another cell type.

Control selection trade-offs. Selection of controls has varied considerably in the studies, and as noted by Ross (1994) this may be a clear source of bias. Hartge et al (1983), Booth et al (1989), Rosenblatt et al (1992) and Wong et al (1999) all selected controls in the hospital with non-gynecologic diseases and made efforts to eliminate those with history of oophoectomy. Wong and colleagues utilized patients with other cancers, and this has been

critiqued in the literature as a major concern due to the likelihood of confounding at least in the colon cancer cases (Cramer, 1999; Piver, 1999). However, it may have other advantages, as discussed below. Whittemore et al utilized both hospital and community controls.

The remaining case-control studies have sought women from the community selected from random-digit dialing in the same region or from electoral rolls in Australia (where registration is mandatory) and town rolls in Massachusetts. Although hospital controls have the advantage of potentially addressing the issue of recall bias (e.g., the need to consider possible explanations for the illness, particularly in controls with cancer), there is a clear potential for confounding in this "medicalized" hospital population that is best offset by use of community controls. A further trade-off with community controls, however, can be related to the way in which exposure information is obtained, as discussed below.

Study design, analysis and adjusted estimates of risk. The various investigators designing studies to evaluate this question have clearly compared their results with those of colleagues conducting studies in other populations. Accordingly, it is notable that there has been no attempt to standardize almost any of the methods used to facilitate comparison of results in different populations. Although almost all of the studies examine relatively similar variables, with addition of some such as diet or medication in selected studies(Tzounou et al, 1993), it is notable that the manner for defining variables often varies, and analysis of the data through multivariate modeling also appears to vary considerably. This is most significant in defining exposure, discussed below. Although this variation in analysis in part may be due to type of data and the manner in which it is collected, it would appear to preclude any effort at careful comparison, much less a rigorous meta-analysis of many risk factors. This is of particular concern since the reviews to date suggest that ovarian epithelial cancer is likely associated with multiple, possibly interacting risk factors, including age, family and genetic history, parity, oral contraceptive use, and hysterectomy and tubal ligation (Tortolero-Luna and Mitchell, 1995; Westhoff, 1996, Daly and Obrams, 1998). Other factors, including body mass index, postmenopausal hormone therapy, breast-feeding duration also appear to play a role based upon some, but not all studies. If these factors are not consistently accounted for in risk adjustment models, then analysis of moderate or small subgroups relative to an exposure may be expected to yield varying results.

Ascertainment of Exposure in the Studies

All of the studies cited here have ascertained exposure through questionnaires that are either:

- Self-administered (Gertig, et al, 2000; Wong et al, 1999),
- Structured questionnaires/instruments administered by interviewers who query the patient and controls in person (Cramer et al, 1982, Hartge et al, 1983, Whittemore et al, 1989, Harlow and Weiss, 1989, Harlow, Cramer et al, 1992, Tzounou et al, 1993, Purdie et al, 1995, Chang et al, 1997, Cook et al, 1997, Ness et al, 1999),

though some studies included some patients interviewed by telephone (Rosenblatt et al, 1992; Godard, et al, 1998). Booth, et al (1989) did not designate the method for obtaining patient and control information.

Although the interview instrument was not described in detail except by Rosenblatt et al (1992) who included the questionnaire in the appendix, review of the articles suggested that although the interviewers covered some of the same general questions, there was only partial uniformity in the questions asked and thus the exposure information sought. This is illustrated in part in **Figures 1A, 1B and 1C** that summarize the different categories of exposure in six of the studies that examined diverse types of talc exposure.

It is quite possible that some biases may have been operating at the interview level for both in-person and likely telephone interviews. First, although Whittemore et al (1989) specifically refer to trained interviewers, other descriptions of the interview methods do not mention this, although it might be generally assumed. However, the questions include relatively sensitive questions that some (particularly healthy controls with no necessary interest in exploring such details) might prefer to avoid, making well-trained interviewers a critical element. None of the methods note that the reviewers are blinded to the hypothesis, a preferred practice; again, it is possible that this was an unpublished standard practice that helps avoid interviewer and recall bias. Some investigators detailed specific methods to aid in recall, such as calendars for menstrual and pregnancy history and pill charts though this was likely not standardized. No mention was made of any efforts to structure questionnaires to disguise the hypothesis.

There are two further areas in the ascertainment of exposure that raise the most questions methodologically. First is the reliance on a response to a single interview set of questions to establish not only short-term exposure (which is likely relatively reliable) but of greater concern, to estimate long-term and lifetime exposure. This measure of long-term exposure can at best be only approximate, is certainly non-standardized and is of unknown reliability. Thus, it is not surprising that there is little difference in estimates of risk for short and long term use, as illustrated in examples from two studies (**Figure 2**). This likely imprecision in estimating long-term exposure calls into question the practice in two of the Brigham and Women's research group's papers (Cramer et al, 1998; Harlow , Cramer et al, 1992) to not only conduct statistical analysis on estimates of up to >10,000 applications, but to censor estimated time in pregnancy and on oral contraceptives and recalculate this long-term exposure.

The second reason builds upon this concern because it can certainly lead to serious recall bias. The patients with ovarian cancer who are interviewed have recently experienced a serious, life-threatening disease onset and at interview, may often be undergoing active treatment, or at minimum, active surveillance. Even if the hypothesis relating to talc is not stated, the detailed queries on talc use can reasonably lead to presumption that the questions may relate to suspected causation. As noted by Ross in his 1994 critique, it seems plausible that these patients will be quite willing to scour their past history for explanations for their illness. Control patients, on the other hand, except for those in the Roswell Park study (Wong et al, 1998) who did have other cancers and might also be searching in their past for possible "causes," might be much less attentive or interested in accurate responses to the necessarily detailed and sensitive questions on genital talc use and contraceptive practices. This study, incidentally, did not find any difference, but it was also based upon routine questionnaires.

Thus, in the study of this question with the interview methodology, there is a very likely possibility that significant recall bias that might well contribute to the magnitude of increase in risk consistently seen in these studies. It is quite analogous to the methodological construct that faces those conducting birth defect case-control studies. In these studies, the current usual practice is to have children with diverse other birth defects serve as controls for a defect of interest, due to the marked recall bias for women with children suffering a birth defect versus those with normal pregnancy outcomes (MacKenzie, et al, 1989; Werler et al, 1989a; Werler et al, 1989b; Bryant et al, 1989; Mitchell, A,). As detailed in these and a further study by Michell et al (1986), the impact of question specificity in exposure history was found to be critical in these epidemiological studies.

It is not clear if there would be a time-related effect of this recall bias but if it were true that case women and control women approached equivalence in their long-term recall of exposure, this might help explain the negative dose and time effects seen in the studies that examined this, and as illustrated as an example in **Figure 3** for the studies of Ness et al (1999) and Chang and Risch (1997).

The one cohort study in this group of studies, that conducted within the Women's Health Study (Gertig, et al, 2000), avoids any recall bias since questions are answered at the time of the routine questionnaire, independent of and usually prior to the diagnosis of ovarian cancer, although this study only queried limited information on talc exposure. It found no significant increase in risk (see **Table 1**).

Definitions of the ovarian cancer cases and their classification

The Gertig et al cohort study (2000) did, however, identify an increased risk associated with talc exposure in the subgroup of women with serous invasive cancers, but not all serous cancers, nor in other cell types. As summarized in **Table 2**, this finding of increased risk in serous invasive tumors was also found by Cramer et al (1999) in their more recent study, and in invasive tumors by Chang and Risch (1997) in their study. However, in contrast, Harlow and Cramer (1992) found endometroid tumors, not serous, to be associated with increased risk, and Cook et al (1997) found <u>both</u> serous and other tumors to be associated with increased odds ratios. These varied findings could be explained in various ways. At this point, given the differing results between studies and the relatively low level of increased risk of talc exposure for any of the cell types, it is questionable whether the findings can be related at present to any biological mechanism.

This conclusion is also due to the fact that the pathology of ovarian tumors can be ambiguous and lead to a significant degree of misclassification. For example, in the Ness et al study (1999), in an effort to validate tumor type, a central pathologist agreed with 95% of the invasiveness diagnoses, but only 82% of the original pathology diagnoses. Young (1993) provides a detailed elaboration of different cell types and how they may resemble other cell types. For example, some serous carcinomas may resemble endometrioid or clear cell carcinomas, and in less common circumstances, mucinous carcinomas may be difficult to distinguish from endometrioid carcinomas. Hendrickson and Longacre (1993) provide further extensive elaboration on the classifications and Gore (1994) has recommended that if a patient is to be included in a protocol, histologic material should be reviewed by a referee, citing a critical review that found an agreement rate of 72% for serous and endometrioid, 86% for mucinous and 100 for clear cell carcinoma. Analogous disagreement was found in a

Japanese study where in only 53% of tumors did all observers agree upon the diagnoses (Sakamoto et al (1994).

Controls for Confounding Factors

It has long been recognized that there has been the possibility that the low level risk or no increased risk associated with talc exposure found in these epidemiological studies related to unknown confounding factors that related to both risk and talc use. Rosenblatt et al (1998) in a cross-sectional study examined certain demographic and behavioral factors that related to perineal application of powders. Drawing upon controls in three case-control studies in the western Washington State three county area, 1206 controls were questioned in person about their use of genital powders. Use was associated with douching, alcohol consumption, smoking and women in the highest body mass index category were more likely to have used genital powder (OR=1.6, 95% C.I. 1.1, 2.5), and more prone to have used a greater number of applications (P<0.002). Although another study (Harlow et al, 1992) found no relationship of body mass index to powder use, this factor has not been examined in most of the other studies, but could be a significant confounder.

What is the basis for a causal relationship of talc and ovarian cancer?

Talc has now been hypothesized to be associated with ovarian cancer for almost 30 years and has now been the topic of a number of epidemiological studies and supportive physiological studies to attempt to characterize and quantify this association. Strom (2000) in his textbook on pharmacoepidemiology, summarized the original Bradford Hill criteria for causality as applied to smoking and lung cancer as:

1. The coherence of the association with existing information (biological plausibility)
2. The consistency of the association
3. The temporal sequence
4. The specificity of the association
5. The strength of the association, including
    - Quantitative strength
    - Dose-response or time duration relationship
    - Study design.

These criteria will be considered briefly here.

First, the <u>coherence, or biological plausibility</u> of the association of talc with ovarian cancer would require that certain conditions be met:

1. *Talc can reach the ovary (usually through the vaginal tract, although this may not be the only route).* This issue remains controversial. A very early study showed transport of carbon black particles from the posterior cul de sac to the fallopian tubes in two of three women undergoing gynecological surgery (Egli and Newton, 1961). However, Deboer (1972) found only 2/37 patients demonstrated transport from the vagina to the uterus. Further, Wehner et al (1985, 1986) utilized cynomulgus monkeys (who have reproductive tracks roughly similar to humans) in a similar experiment with multilabeled carbon black particles and was unable to demonstrate transport. However, several studies have identified talc in the human ovary, both normal and tumorous (Henderson et al, 1971). Surprising was the finding by Heller et al, (1996) that ovaries contained talc whether or not there was any history of exposure.

2. *Talc, once in contact with the ovary, can stimulate malignant transformation and development of cancer.* Talc does not typically stimulate an inflammatory response in the ovary based upon the findings above. Although theories as to how this might occur have been offered, clear explanations were not found. In most cases, authors have analogized talc to asbestos to explain this phenomenon, despite their very different crystal structure.

3. *A further biological component would be that it could stimulate one or another specific tumor type*, but the pathology is too murky for consideration of this, as discussed above.

Second, the *consistency of the association*. As discussed above, presented in Table 1 and also discussed extensively in other reviews of the topic, the association has not been consistent in all studies, nor has it been consistent with respect to exposure type (sanitary napkin, vs. genital powdering vs. deodorant spray), or pathology (see Table 2).

Third, the *time sequence* of the association. This has not been clearly evaluated, in part because of the limitations of the exposure ascertainment.

Fourth, the *specificity* of the association. Epithelial ovarian cancer of any of the pathology types are not appearing in any specific fashion in association with talc use.

Fifth, the *strength* of the association, based upon:

- *Quantitative strength.* All studies have shown a weak or non-existent association, where even lower confidence intervals for significant values seldom exceed 1.10.

- *Dose – response relationship.* Almost all of the studies where either a dose response or dose-duration relationship was examined have failed to show any increase in risk of tumor.

- *Study design.* As detailed above, although the overall study designs have been good, a number of details in exposure ascertainment, in particular, may have limited the strength of the findings.

Therefore, based upon these criteria, and despite the continuing contention in the literature that talc must be associated with a measurable risk of ovarian cancer based upon the reviewed epidemiological studies, this review found that the weak and often non-significant association of talc with ovarian cancer, in many populations in both a cohort and several case-control studies, coupled with a lack of dose-response or dose-duration effects and a questionable credible effort to tie risk to a specific tumor type make the likelihood of a true

significant biological association unlikely at present. The real likelihood of a significant recall bias in the designs used could explain some of the positive associations. If further understanding of this association is to be pursued, it would be better served by exposure ascertainments that could be standardized, that could be designed to minimize recall bias and optimize control participation, by consistent adjustments for major risk factors in analysis, and by standardizing pathology type in a formal methodology to address the variability in diagnosis.

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Table 1. Epidemiological Studies of Talc Exposure and Ovarian Carcinoma: A Review

Author	Year	Country	Study Type	Dates of Study	Case definition	Case Participation Rate	Control Selection	Match	Interview	Other variables	Cases	Controls	Talc Measures and results	Comments
Cramer DW, et al	1982	U.S.	Case-control	11/78-9/81	English-speaking women with ovarian CA identified through pathology logs or hospital tumor boards in 12 Boston hospitals	86% of identified eligible interviewed; 18 cases eliminated as non-ovarian primaries, leaving 215, including 39 with borderline	From Mass town books	Matched by precinct, race and 2 year age group. Did exclude prior bilat. SaO, but not other pelvic surgery.	In person interview	Menstrual, reproductive history, family history, environmental exposure, and details of contraceptive practices	215	215	For any perineal exposure (case, control Ns=92/61), Adjusted (for parity and menopausal status) R.R. was 1.92 (1.27-2.89); and the **maximum likelihood estimate adjusted for religion, marital status, education, ponderal index, age at menarche, parity, OC or hormone use and smoking was 1.61 (1.04-2.49).** Analysis of exposure strata for exposure on either sanitary napkins (crude RR=1.58) or as dusting powder only (crude RR=1.52), resulted in an adjusted R.R.=1.55 (0.98-2.47). For use of both (case/control Ns=32/13), adjusted RR=3.28 (1.68-6.42).	Case-control study, roughly population based. Details of interview sketchy in published report. Found increased risk with perineal use, but not diaphragm use with talc (All users, case/control Ns=40/40) adjusted R.R. =1.56 (0.62-3.88).
Hartge P et al	1983	U.S. Washington DC area	Case-control	1974-1977	Women with epithelial ovarian cancers in local hospitals	135 or 197 cases interviewed due to adding talc questions after study began	From patients in same hospitals treated for non-gynecologic conditions	Frequency matched on age, race and hospital	Interview	Reproductive, sexual Hirose, medical history, drug use and other exposures	135	171	**Found no increased risk with any talc use, R.R.0.7 (0.4-1.1), unaffected by adjustment for race, age and gravidity.** Point estimate for diagragm with no talc higher than with, but neither significant. In the 7 cases vs 3 controls who related genital use, R.R. was 2.5 (0.7-10), not significant. Authors discuss possible role of recall bias but note equal reports of douching in both cases and controls (numbers not provided).	
Whittemore et al	1988	Northern California	Case-Control	1/83-12/85	Residents of N. California diagnosed with primary epithelial ovarian cancer at one of 8 hospitals	No data	Two control groups: (1) women hospitalized at one of the hospitals; (2) RDD of regional population	Age within 5 years, race	Structured in-home interviews by trianed interviewers	Menstrual, reproductive history, family history, coffee use, smoking, alcohol, medical history, and if talc use, details.	188	280 hospital, 259 community	**Although RR for any use was 1.40 (p=0.06), there was little difference between cases and controls in use of talc on sanitary pads and diaphragms (RR's = 0.93, p=0.76 and 0.95, p=0.86, respectively).** There was also n increasing dose-response pattern. Risk was lower in those with hysterectomy regardless of talc use.	Detailed case-control study with detailed assessment of risk factors, including talc use. Notes that though trend of increased risk with increased frequency of exposure, it is not statistically significant, and there was no trend with duration of exposure, concluding that though data don't exonerate talc, they also don't provide strong evidence to implicate it.

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Harlow and Weiss	1989	Western Washington State	Case-control	1980-85	Residents of three urban counties of western Washington State with serous or mucinous borderline ovarian tumors from the Puget Sound cancer registry.	68%	Random digit dialing for controls "similar" to cases	Not described	In person interview	Reproductive, sexual history, medical history, and information on perineal exposure to talc	116	158	Found adjusted (age, parity, use of Ocs) R.R. =1.1 (0.7-2.1). Risk for use of talc or cornstarch on sanitary napkins was 2.2 (0.8-19.8), and no increased risk was seen for long-term or frequent use. Found elevated risk (2.8 (1.1-11.7) for deodorizing powders with/without baby powder (case N=14) and deodorizing powder only RR=3.5 (1.2-28.7) case N=10. In light of this being the only risk, concern is raised over deodorizing powders.	Study focuses on type of powder with finding of few differences and no signficant increased risk, except for deodorizing powder. Numbers in strata are generally small.
Booth et al	1989	London School of Hygiene	Case control	10/78-2/83	Women age <65 with diagnosis of epithelial ovarian CA in 13 London and 2 Oxford hospitals	No data	Inpatient females at the same hosptial (where possible) without gynecologic or malignant conditions	age matched, hospital matched (some)	Questionnaire - administration method not specified	Detailed information on reporductive and menstrual history, contraception, talc use, sexual activity	235	451	Found a RR of 2.0 (1.3-3.4) Case N=57, P=0.007, but for dailing use RR was 1.3 (0.8-1.8), case N=71. Authors note no consistent trend of increasing risk with increasing frequency of talc use, and no significant difference between percent of cases (86%) and controls (81%) who had used and kept diaphragm in talc.	
Rosenblatt et al	1992	Baltimore (Johns Hopkins Hospital)	Case-control	1981-85	Newly diagnosed cases of epithelial ovarian cancer at Johns Hopkins Hospital	77%	Inpatient females without gynecologic or conditions that could relate to oral contraceptive use	5 year age, race, within 1 year of diagnostic admission [not all cases matched so 13 cases excluded	Questionnaire by phone and in hospital, plus medical records	Focus on "mineral fiber" exposure in any form (talc on body, genitals, napkins; asbestos in occupation, fiberglass), tobacco use, Reproductive, weight history, family history, prior cancer, marital, religious status, contraceptive practices	77	46	Found overall high level of exposure to genital fiber (91% of controls) and was not related to ovarian CA. (RR=1.0 (0.2-4.0). Assessed "dose" of genital fiber with R.R. of 2.4 (1.0-5.8) [median length, excluding time after hysterectomy/tubal ligation =37.4 years]. Found increased risk with exposure to talc on sanitary napkins (RR=4.8, 1.3-18, case N=21), but no significant risks for genital bath talc, diaphragm use or condom use. Also found no increase with respiratory fiber exposures (environmental).	Small case-control study in one hospital. Controls were difficult to find, resulting in exclusion of some cases. Investigators provide instrument for ascertaining exposure which reveals relatively general questions.
Harlow BL, Cramer DW et al	1992	Boston metropolitan area	Case-control	7/84-9/87	Residents of Boston metropolitan area diagnosed with borderline or malignant epithelial ovarian CA at one of ten participating hospitals	69%	From Mass town books	2 year age match, race without history of bilat oophorectomy	In-person interview	Demographic, occupational, medical, reproductive histories, pregnancies, hormones, dietary, smoking, hygienic practices, focusing on talc exposure.	235	239	**Found adjusted (age, parity, education, marital status, religion, use of sanitary napkins, douching and weight) OR=1.5 (1.0-2.1) for any genital talc application.** Use on sanitary napkins, underwear NS, but perineal use was (OR=1.7, 1.1-2.7). Use before 1960 had increased risk (1.7,1.1-2.7) vs. after OR=1.1, 0.6-2.1. Highest association was with use in prior 6 months (OR=2.3, 1.3-4.0) vs. prior times (NS).	Case control study analysis that is one of a series by this group of investigators. Many results have lower confidence interval at 1.0 and paper considers results significant. Analysis considers multiple scenarios (e.g. table 3) and arrives at one significant trend for increased risk with >10,000 applications. Not all results are biologically consistent within study and other results (e.g., tumor type).

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Tzonou A et al	1993	Greece	Case-Control	6/89-3/91	Residents of greater Athens who underwent surgery for epithelial ovarian CA	90%	From visitors to patients in same hospital	Not described	Interview by 2 medical residents in wards	Reproductive, sexual history, medical history, drug use and other exposures	189	200	**Finding of no increased risk associated with talc use (Multivariate R.R. = 1.05 (0.28-3.98) N=183 cases;** however, paper's discussion notes limitations of this small study and biass and that results also not incompatible with findings of increased risk.	Small case-control study of convenience sample, +/- population based with limited information on method of assessment to talc.
Purdie et al	1995	Australia	Case-Control	9/90-12/93	All histologically confirmed incident cases of primary epithelial ovarian cancer from all major gyn-onc centers in Victoria, NSWales and Queensland	Of 915 eligible cases, 824 (90%) interviewed	From electoral rolls in same geographic region	Approx. age match	In clinic (most cases), in-home (a few cases, all controls)	Marital status, demographics, smoking, occupation, family history, reproductive, OC history, talc, childhood mumps, diet.	824	860	Finding of increased risk with **OR (adjusted for parity) of 1.27 (1.04-1.54)** with 56.7 (N=467) cases affirming some use. Noted only briefly in paper's discussion.	Large case-control study, but details of talc exposure not described /obtained. Effect size much smaller than family history of ovarian cancer (OR=4.48), increased BMI (>85 percentile OR=1.97).
Chang S & Risch HA	1997	Ontario, CAN	Case-Control	11/1/89-10/31/92	Histologically confirmed primary, invasive or borderline epithelial ovarian tumors	71.3 % (no proxy interviews)	Geographic population based	15 Yr Age match (but age also as contin. Variable in models	In-person, in-home	Pregnancies, menses, hormone, OC use, breastfeeding & duration, tubal ligation, hysterectomy, family history	450	564	**Any talc exposure:OR=1.420 (1.08-1.86)** -Sanitary Nap:1.262 (0.81-1.96) -After bath (all): 1.312 (1.00 1.73) Date Before 1970: 1.090 (0.98-1.22) -----after 1970: 1.095 (0.89-1.35), Before tubal ligation: 1.105 (0.99-1.24) After tubal ligation: 1.031 (0.82-1.29) **See also Figures (Chang Figs 1,2,3 for frequency & duration of talc exposure that show no intensity or duration**	Large study, with sufficient cases/controls for talc exposure subgroups. Type of tumor showed significant association with invasive, not borderline (opposite of Harlow who found strongest association with endometriod and borderline tumors. Agreed with Cooks finding of no inc. risk in mucinous tumors; another study found no variation in risk by subtype (Cramer et al, 1982)
Cook, LS, Kamb ML, Weiss NS	1997	Western Washington state	Case-control	1986-1988	White women only; Invasive or borderline epithelial CA from Cancer Surveillance System of W. Washington, grouped by ICD9CM codes, including unclassified.	64.30%	Random-digit dialing of counties	5 Yr age match, white only	In-person, in-home	Details of genital powder exposure, education, household income, marital status, BMI, pregnancies, including full-term births	313	422	**Any talc exposure (154 cases, 256 controls): OR=1.5 (1.1-2.0)** - Sanitary Nap(12 cases, 10 controls):1.5 (0.6-3.6) -Perineal dusting (55 cases, 48 controls): 1.8 (1.2-2.9) Diaphram storage in powder only: (22 cases, 35 controls) 0.8 (0.4-1.4) Genital deoderant spray only (18 cases, 28 controls): 1.5 (0.8-3.0)	Authors conclude risk of talc exists, though except for deodorant sprays, no dose or time effect is seen (See Cook Figs 1-4), and adjusted risks are not significant. Exposure and case categories are not always well-defined. Muscat and Wynder (Am J Epi., Letter:1997; 146:786) critique weak association, lack of dose effect, and recall bias in cases due to intense questioning.

Table 1. Epidemiological Studies of Talc Exposure and Ovarian Carcinoma: A Review

Author	Year	Country	Study Type	Dates of Study	Case definition	Case Participation Rate	Control Selection	Match	Interview	Other variables	Cases	Controls	Talc Measures and results	Comments
Godard B, et al	1998	Montreal	Case-control (convenience sample)	1995-96	Cases from Gyn clinics in Montreal teaching hospitals	87% of eligible living patients	Random-digit dialing from same page in phone book	1 year age match	In clinic (70% of cases), telephone (30% of cases, all controls)	57 questions, including menarche age, pregnancies, menses, hormone, OC use, breastfeeding & duration, tubal ligation, hysterectomy, family history, smoking, alcohol, education	170	170	**Perineal talc use: p=0.064** (10.6% of cases, 4.7% of controls), perineal talc use in cases: sporadic vs familial: P=0.79 (compares the means of the sporadic with the familial case patients. In multivariate analysis, tubal ligation or hysterectomy was protective (RR 0.51, P =0.16) and use at any time of talc in the perineal region was a positive risk factor (RR=2.49, P = 0.064, NS).	Authors note elevated R.R. for talc but question significance. Trend for ligation and talc was similar for familial and nonfamilial cases.
Cramer DW, et al	1999	Eastern Massachusetts and New Hampshire	Case-Control (population based)	5/92-3/97	Cases identified from hospital tumor boards and state CA registries	70% of eligible living	RDD matching 1st 5 digits of case	4 year age match	In-person interview, details not provided	Details of queries not provided, but included medical history and details of powder use by female and spouse	563	523	**Any personal genital exposure to body powder Adjusted OR = 1.60 (1.18 2.15)**; see also Cramer Figures 1-	Authors conclude their study comfirms talc as a risk factor that may contribute to at least 10% of ovarian cancers. Their biological plausibility argument relies on Venter and Iturralde's 1979 work, acceptance of an analogy of cosmetic talc to asbestos, and their finding of increased risk associated with spouse use of genital talc.
Wong C, Hempling RE, Piver M, Natarajan N, Mettlin, CJ	1999	Roswell Park NY Patients	Case-control, convenience sample	10/82-10/95	Cases from Roswell Park Tumor Registry	Unknown	Patients in Roswell Park Tumor registry with nongynecologic tumors	5 year age match	Self-administered questionnaire provided on admission to Roswell park	Baseline medical history, including social history, parity, mentrual history, use of hormones, ODCs, and personal hygiene and occupational history	499	753	**Found no difference in talc use between cases and controls**. Sanitary napkin use N=20 cases): OR=0.9 (0.4-2.0); Genital/thigh area use (N=223 cases) 1.0 (0.8-1.3), or both (N=68) OR = 1.1 (0.7-1.7). Multiple logistic regression adjusting for age at diagnosis, parity, OC use, smoking, family history of ovarian CA, age at menarche, menopausal status, income, education, geography, history of tubal ligation/hysterectomy failed to shown an association of talc with ovarian CA (OR=0.92 (0.24-3.62).	Authors conclude their study fails to find an association of talc with ovarian CA and not that despite several positive studies, their results concur withthose of Booth, Rosenblatt, Tzounou, and Whittemore's review. They also identify limitation in Cook's study (high proportion of likely familial CA with high proportion of younger patients, number of borderline CA). This study has the limitations that it is an unsupervised questionnaire so that answers to questions are not probed; also, controls are cancer patients with chronic illness who might both be at risk for ovarian CA(e.g., colon CA in familial cancer).

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Ness, et al	1999	Delaware Valley-39 hospitals	Case cont	1994-1998	Cases diagnosed with epithelial ovarian CA within 6 months before interview	767 eligible= 61% of potentially eligible and 88% of potentially eligible incident cases	RDD matching 1st 3 digits of case	5 year age match	In person, in-home interviews	Extensive 1.5 hour interview of reproductive history, medical history, personal and spouse talc use and duration. Central path. Review of 120 cases (agreement on invasiveness=95%, cell type=82% so used original path dx.	616 invasive, 151 borderline	1367	Study finds elevated risks for genital/rectal (OR=1.5 (1.1-2.0), sanitary napkin (OR=1.6 (1.1-2.3), underwear (OR=1.7 (1.2-2.4), and foot (OR=1.4 (1.1-1.6) talc use, but no increased risk by years of use (See Ness Figures 1,2).	Data presented shows modest increased OR without increase with prolonged use; no effect seen with diaphragm use, or use by male partner. OR by pathology strata not presented. Tubal ligation found protective (OR=0.5 (0.6-1.1).
Gertig DM et al	2000	Nurses Health Study Cohort	Prospective Cohort Study	1982-6/1/96	Cases from cohort in 11 larger states	Unknown	Remainder of eligible cohort of 78,630 women	5 year age match	Biyearly mailed questionnaires	Extensive data on cohort, plus, medical records(including pathology reports) on those where requested.	307 (984, 212 Person-years)		**No overall association with ever use talc and epithelial ovarian CA (R.R.:1.09 (0.86-1.37)**, no increase with frequency of use (See Gertig Figure 1); did find "modest increase in risk" for serous invasive CA (RR=1.40 (1.02-1.91) but not for all serous cancers.	Authors conclude their study fails to find an overall association of talc with ovarian CA. The strength of their cohort study is that recall and selection bias are avoided; however, their questionnaire was did not ascertain age at first use, lifetime use and current vs ever use. Although tubal ligation did not change risk: R.R. 0.97 ((0.71-1.32 for never tubal ligation), query may have had lower response (no N provided). is based upon data from an unsupervised mailed questionnaire and pathology reports (albeit independently reviewed without knowledge of the hypothesis).

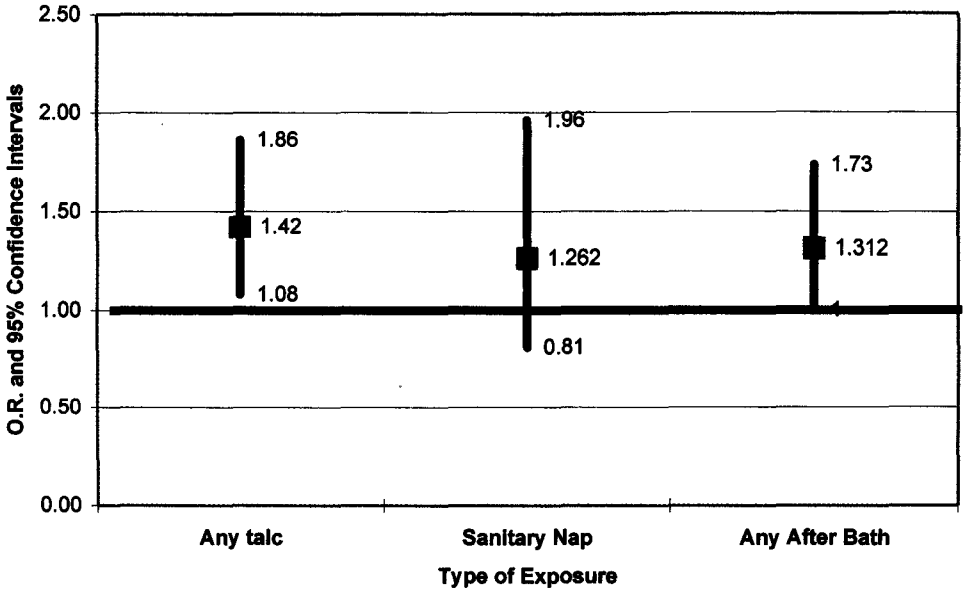
Table 2. Epidemiological Studies of Talc Exposure and Ovarian Carcinoma: Summary of Risks Associated with Different Pathology Types*

Author	Institution	Year	Country	Total InvasiveTumor Risk O.R.(95% CI) (Number of cases)	Total Borderline Tumor Risk O.R.(95% CI) (Number of cases)	Serous Tumor Risk O.R.(95% CI) (Number of cases)	Mucinous tumor Risk (O.R.(95% CI) (Number of Cases)	Endometroid tumor Risk (O.R.(95% CI) (Number of Cases)	Other tumors (O.R.(95% CI) (Number & type)
Harlow BL, Cramer DW et al	Brigham & Women's Hospital	1992	Boston metropolitan area			1.4 (0.9-2.2), adjusted N=60	1.2 (0.6-2.5) (N=17)	**2.8 (1.2-6.4)** (N=18)	OR=1.6 (0.8-3.3) (N=19)
Chang S & Risch HA	Yale	1997	Ontario, CAN	**1.513 (1.13-2.02)** N = 367	1.237 (0.76-2.02) N = 83	1.336 (0.96-1.83) N=254	1.585 ((0.97-2.58) (N=80)	1.671 (1.00-2.79) (N=74)	
Cook, LS, Kamb ML, Weiss NS	U. Wash	1997	Western Washington state			**1.7 (1.1-2.5)** N=71	0.7 (0.4-1.4) (N=14)	1.2 (0.6-2.3) (N=17)	**1.8 (1.1-2.8)** N=57, including 17 clear cell, 2 undiff., 83 unclassified
Cramer DW, et al	Brigham & Womens and Dartmouth	1999	Eastern Massachusetts and New Hampshire	Serous Invasive Adjusted OR=**1.70 (1.22-2.39)** (N=229)	Serous Borderline: Adjusted OR=1.38 (0.82-2.31) (N= 86)	See other data on serous	0.79 (0.44-1.40), adjusted (N=83)	1.04 (0.67-1.61), Adjusted. Endometroid and clear cell	1.44 (0.67-3.08), adjusted Undifferentiated
Wong C, Hempling RE, Piver M, Natarajan N, Mettlin, CJ	Roswell Park	1999	Roswell Park NY Patients			1.2 (0.7-2.1), Serous cystadenocarcinoma	1.5 (0.6-4.0)	1.4 (0.7-2.7), endometroid; Clear cell CA OR=1.6 (0.6-4.3)	1.00 (0.6-1.6) Undifferentiated
Gertig DM et al	Brigham & Women's, Harvard	2000	Nurses Health Study Cohort	Serous Invasive Ever Use: Multivariate Adjusted RR=**1.40 (1.02-1.91)** (N=76)		1.26 (0.94-1.69) Multivariate R.R., all serous (N=84)	0.93 (0.53-1.66), Multivariate R.R. Mucinous (N=20)	.0.91 (0.49-1.87), : Multivariate R.R , Endometroid(includes clear cell, other types) (N=16)	

* **Significant Associations Bolded**

Figure 1A. Studies of Ovarian Cancer and Talc Use: Findings for Different Exposures-Chang et al and Cook et al.

Chang Fig 1: Talc Exposure and Ovarian CA: Ontario Case Control Study (Chang & Risch, 1997)



Cook Fig 1: Talc Exposure and Ovarian CA: Western Washington Case Control Study (Cook, Kamb & Weiss, 1997)

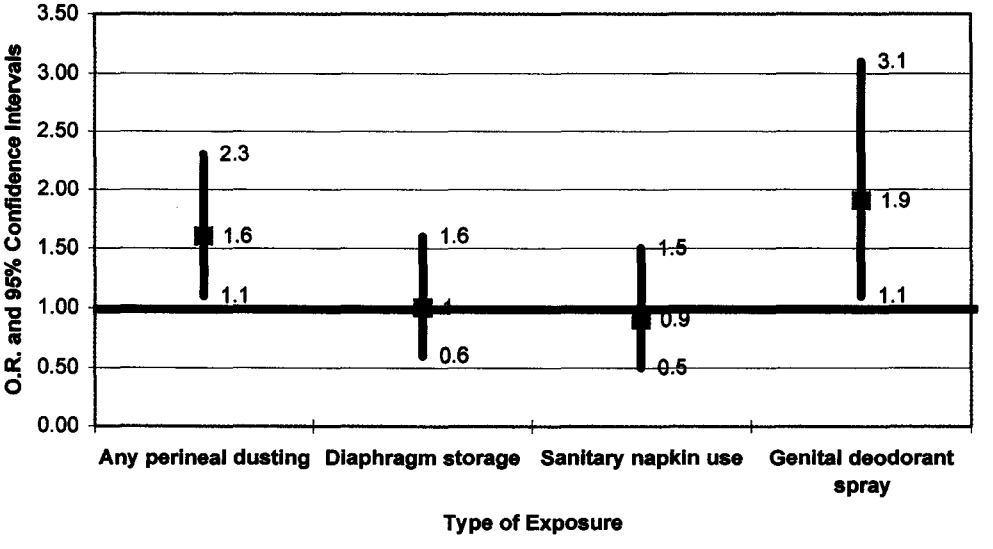
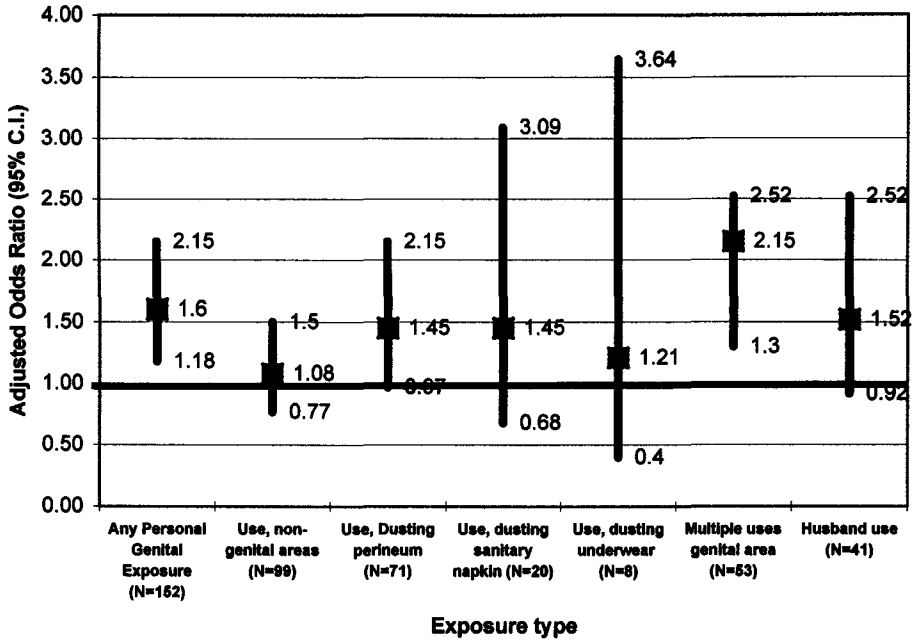


Figure 1 B. Studies of Ovarian Cancer and Talc Use: Findings for Different Exposures - Harlow et al, and Gertig et al.

Cramer Fig 1: Body Powder and Risks of Ovarian Cancer: Cramer et al, 1999



Gertig Fig 1: Talc Use and Risks of Ovarian Cancer-Women's Health Study: Gertig et al, 2000

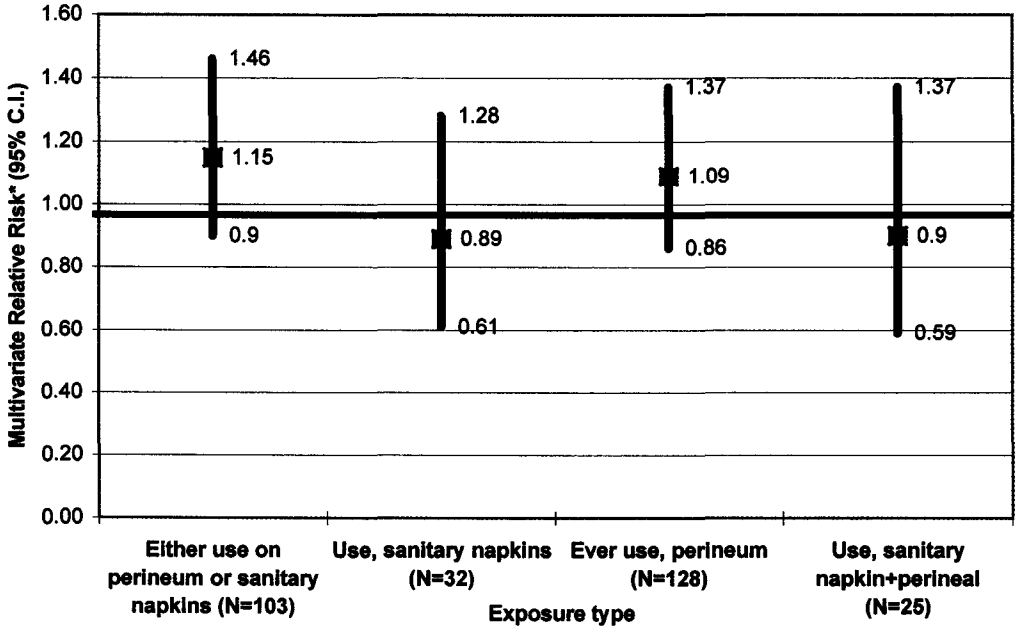
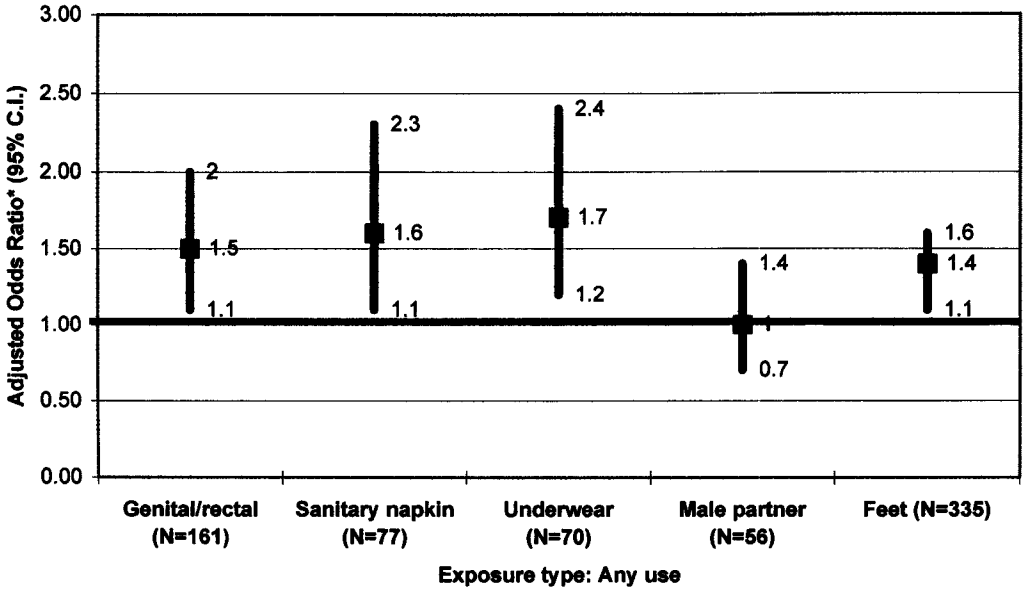


Figure 1C. Studies of Ovarian Cancer and Talc Use: Findings for Different Exposures- Ness et al, and Whittemore et al

Ness Fig 1: Talc Use and Risks of Ovarian Cancer-Delaware Valley Case Control Study: Ness et al, 1999



Whittemore Fig 1: Talc Use and Risks of Ovarian Cancer-N. California Case-Control Study: Whittemore et al, 1988

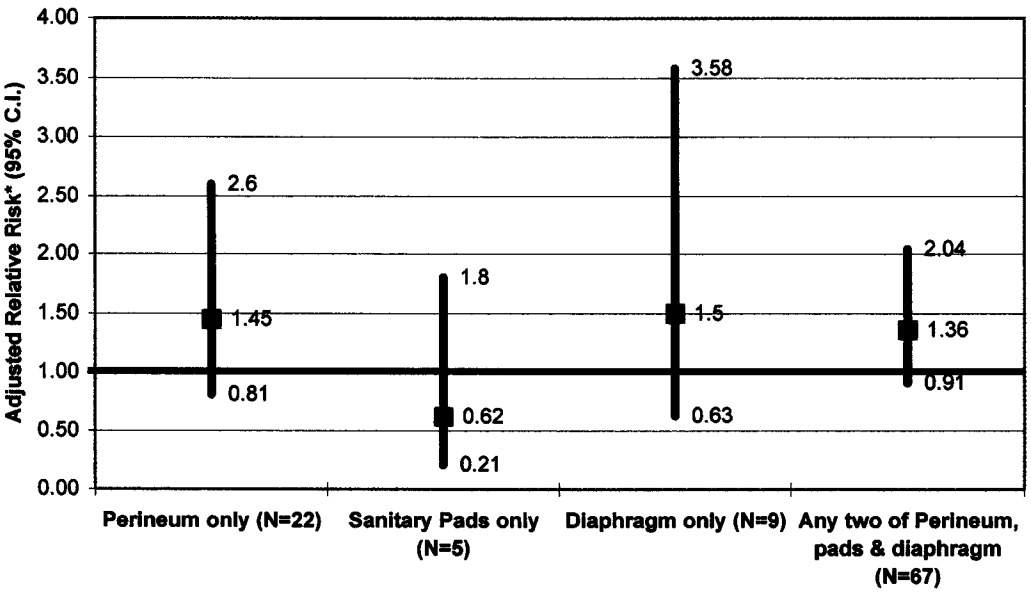
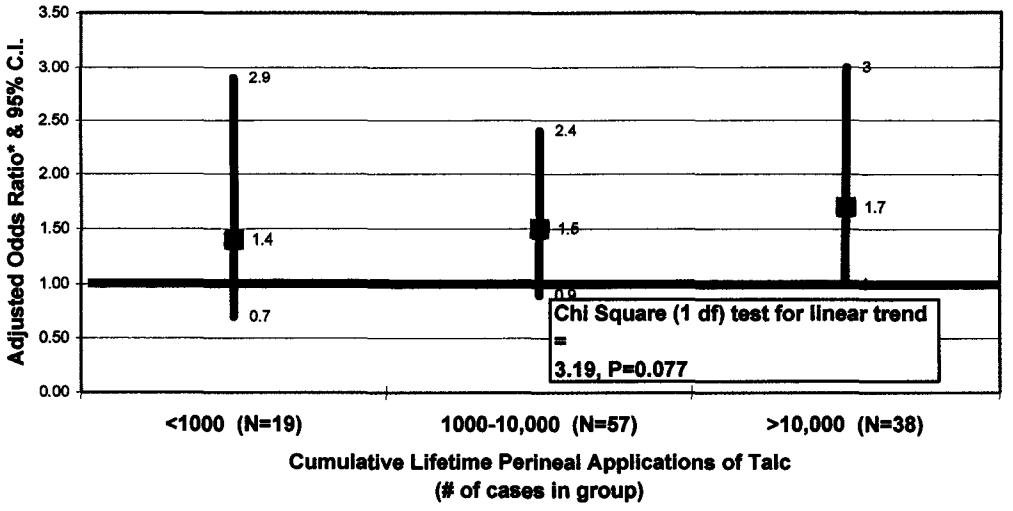


Figure 2. Estimates of Risk from Lifetime Cumulative Exposure: Results from Harlow et al and Cook et al Studies

Harlow Fig 4: Talc and Ovarian CA: Boston Area Case-Control Study: Estimated Total Lifetime Applications of Talc: Harlow et al, 1992



Cook Fig 2: Talc and Ovarian CA: Cumulative Lifetime Days of Use: Cook, Kamp & Weiss, 1997

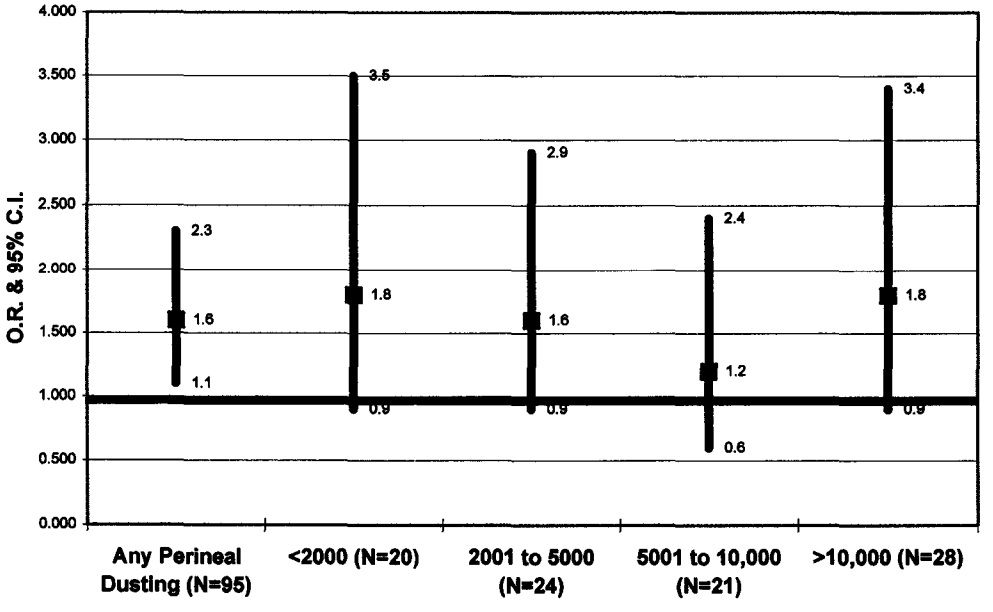
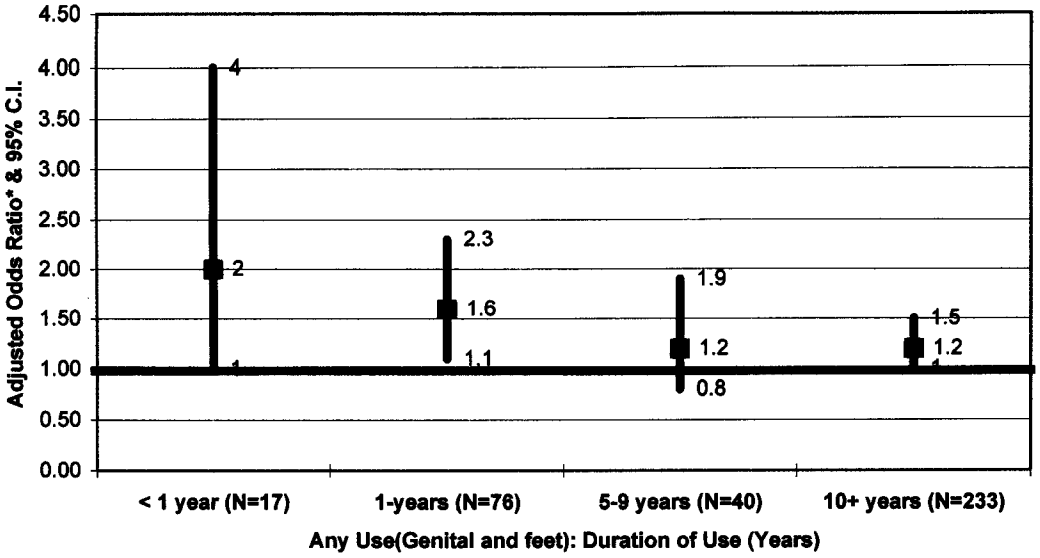


Figure 3. Estimates of Risk by Years of Exposure to Talc: Data from Ness et al and Chang et al studies

Ness Figure 2: Talc and Ovarian CA: Delaware Valley Case Control Study- Duration of Any Use (years) : Ness et al, 1999



Talc and Ovarian CA: Intensity of After Bath Use Years of Use: Chang & Risch, 1997