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by [Langseth H](#), [Kjærheim K](#)

**Affiliation:** Cancer Registry of Norway, Institute of Population-based Cancer Research, Montebello, N-0310 Oslo, Norway. [hilde.langseth@kreftregisteret.no](mailto:hilde.langseth@kreftregisteret.no)

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## Ovarian cancer and occupational exposure among pulp and paper employees in Norway

by Hilde Langseth, MSc,<sup>1</sup> Kristina Kjærheim, PhD<sup>1</sup>

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**Objectives** A cohort study of female pulp and paper workers in Norway has shown a significantly increased risk of ovarian cancer. Other than the involvement of hormonal and reproductive factors, little is known of the etiology of ovarian cancer. Asbestos and talc are two agents hypothesized to influence the development of the disease. The present study aimed to investigate the association between ovarian cancer and occupational exposure to asbestos, talc, and total dust among Norwegian pulp and paper workers.

**Methods** Forty-six cases of ovarian cancer, with four controls each, were included in the study. Occupational exposure was assessed by combining work histories from personnel files, questionnaire information about production processes, and exposure assessments from the mills. To obtain information about possible confounders, cases and controls were invited to participate in a personal interview.

**Results** The odds ratio for asbestos exposure was 2.02, 95% confidence interval 0.72–5.66. For talc exposure, the odds ratio was 1.10, and for ever exposure to total dust, it was below 1.00. The risk estimates did not essentially differ after adjustment for possible confounding variables.

**Conclusions** The results do not confirm an association between exposure to asbestos, talc, and total dust and ovarian cancer among Norwegian pulp and paper workers. However, the odds ratio for asbestos exposure was doubled, and control for established nonoccupational risk factors did not change the estimate. Therefore, the possibility that exposure to substances in the work environment contributes to the elevated risk cannot be rejected.

**Key terms** asbestos, cancer of the ovary, dust, female workers, nested case-control study, talc.

Ovarian cancer is one of the most common gynecological neoplasms among women today, especially in industrialized countries. Ovarian cancer is a hormone-related disease, and estrogens are known to have an adverse effect. This effect is supported by several studies showing that the inhibition of ovulation through child-bearing, oral contraceptive use, and breast-feeding reduces the risk (1). Inherited mutations in the breast cancer genes *BRCA-1* and *BRCA-2* account for approximately 5% of all cases (2).

Results from a study of 4247 Norwegian female pulp and paper workers showed a significantly increased risk of ovarian cancer (observed 37 cases, expected 24 cases, standard incidence ratio 1.5, 95% confidence interval 1.07–2.09), mainly among women working in the paper departments (3). The risk was highest in the younger age groups, whereas in the general Norwegian population the occurrence is highest among women aged 65 years or older (4).

Over the last decade, there has been a growing interest in the hypothesis that occupational and

environmental exposures may contribute to the development of ovarian cancer. Occupational groups of women who have been investigated and found at significant risk are, among others, women compensated for asbestosis in Italy (5), bookbinders in Russia (6), textile workers in the Nordic countries (7), and chicken farmers in Norway (8).

The role of asbestos in the causation of cancers other than those of the lung, pleura, and peritoneum is uncertain. Asbestos fibers are hypothesized to induce inflammation in the epithelium of the ovaries and further act as an initiator or promoter in the carcinogenesis of ovarian cancer (9). Asbestos fibers have been identified in tissue blocks from ovaries among women with both cancer and other diseases of the ovaries (10).

As early as 1960, it was found that women with pulmonary asbestosis tended to have ovarian and peritoneal neoplasms more often than other women (11). Increased mortality of ovarian cancer, as well as cancer of the lung and pleura, has been shown for asbestos-exposed gas-mask workers in two factories in

<sup>1</sup> Cancer Registry of Norway, Institute of Population-based Cancer Research, Oslo, Norway.

Reprint requests to: Ms Hilde Langseth, Cancer Registry of Norway, Institute of Population-based Cancer Research, Montebello, N-0310 Oslo, Norway. [E-mail: hilde.langseth@krefregisteret.no]

England (12), female gas-mask assemblers (13), and asbestos textile workers (14).

Talc is an agent with mineralogical similarities to asbestos, and it is often contaminated with asbestos (15). Results from several investigations have indicated that genital exposure to talc through its use on sanitary napkins or underwear, or by direct perineal application, increases the risk of ovarian cancer (16, 17). Furthermore, the risk seems to decrease among women who have undergone prior tubal ligation or hysterectomy (1). However, a recent meta-analysis concluded that no causal relation has been confirmed, and dose-response relationships have not been shown (18). Talc has been identified in tissue blocks from ovaries (19).

In the pulp and paper industry, relatively large quantities of asbestos have been used as an insulation material in boilers and in the breaks of slitter-winders and other rolling machines. Norwegian male pulp and paper workers had a significantly increased risk of pleural mesothelioma (20). This observation indicates that asbestos has been a considerable air pollutant in this industry. Talc has also been widely used as a coating agent—added in the paper mills.

Dust, especially paper dust, has been a main contaminant in the work atmosphere of female workers, and the dust may be a carrier of other air pollutants. Measurements of airborne dust in a Swedish soft paper mill showed that the dust also contained fibers other than cellulose (21).

A recent review of epidemiologic studies on occupational and environmental risk factors related to ovarian cancer concluded that current knowledge in this field is limited (22). We therefore found it worthwhile to investigate our observation among occupationally exposed women further. The aim of the study was to test the hypothesis that the increased risk of ovarian cancer among Norwegian pulp and paper workers was associated with exposure to asbestos, talc, and total dust.

### Study population and methods

Cases and controls were selected from the total cohort of 4247 female pulp and paper workers from 10 different mills. The cohort has been previously described in detail (3).

#### Selection of the cases and controls

The case group consisted of 46 persons with epithelial ovarian cancer, registered with the Cancer Registry of Norway and generated by the pulp and paper cohort during a follow-up period from 1953 to 1999. One person with a germ-cell tumor was excluded from the material. An experienced oncologist reviewed all the

histological records in the Cancer Registry for each case and an equal number of persons for the control group with ovarian cancer outside the pulp and paper industry. Eleven of the cases were tumors of borderline malignancy, mostly stage I, and 35 were invasive tumors, mostly stage III.

Four persons were drawn as controls for each case by incidence density sampling (ie, they had to be a member of the cohort at the time of diagnosis of the case). Each control was individually matched to a case by birth year  $\pm$  2 years. The controls had to be free of ovarian cancer and hold intact ovaries. Since the cohort consisted of many elderly persons, we expected a possible loss of available controls. We therefore selected two extra controls to be used if a person was dead or had emigrated and no relatives could be traced, if a person had a type of disease that made her unable to carry out an interview, or more than two controls for one case refused to participate. Five controls were excluded from the analyses because their ovaries were removed before the date of diagnosis of the case. The overall analyses included all 46 cases and 179 controls with complete work histories from the historical files. A description of the material used in the study is given in table 1.

#### Exposure assessments

Work history was obtained from the personnel files of each mill. Departments, job titles, and date of start and end of employment in specific work activities were registered for all the cases and controls. A questionnaire, including information about production processes, use of specific agents, and changes over the years, was filled out by industrial hygienists and

**Table 1.** Number of persons included as cases and controls in the overall analyses and the subanalyses according to the descriptive data.

Descriptive data	Cases (N)	Controls (N)
Observed	46	184
Excluded <sup>a</sup>	—	5
Included in overall analyses	46	179
Nonrespondents	11	77
Extra persons invited	—	33
Interviewed	—	19
Included in the subanalyses	35	121
Interview persons		
Self-respondents	10	90
Next of kin		
Spouse	3	6
Child, sibling	16	20
Other	6	5

<sup>a</sup> Excluded because their ovaries were removed before the cases diagnosis.

senior employees at each mill. Exposure assessments for the Norwegian mills were extracted from PAPDEM (pulp and paper department exposure matrix), an international database including measurements of 25 major agents in the pulp and paper industry in 15 countries (23). The assessment is specific to mill, work department, agent, and time period. Most of the measurements were from 1980 or later, and they were only used as exposure indicators.

Based on the questionnaire and PAPDEM information, table 2 shows the groups that were considered to have been exposed to asbestos, talc, and total dust in the pulp and paper industry and in work outside the industry. Separate analyses were carried out for the following five departments: (i) sulfite, sulfate and stock preparation departments (merged because of a small number of women in these departments), (ii) rayon plant (only one of the 10 mills included had rayon production), (iii) paper department, (iv) maintenance and laboratory department, and (v) clerical department. Duration of employment (<3, 3–5, and >5 years), time since first exposure to diagnosis of the case (<15, 15–30, and ≥30 years) and year of first exposure (before 1950, between 1950 and 1960, and after 1960) were used as indicators of occupational exposure.

#### Interview data

To collect information about possible confounders, all the persons in the case and control groups were invited to participate in a personal interview. The interview preferably took place in an office at the mills or, alternatively, in a private residence or institution or by telephone. Three specially trained professional female interviewers carried out the interviews. An informed consent form was signed before the interview started.

The interview included questions on complete occupational history, possible household asbestos exposure defined as having a husband or other members of the household ever employed as a plumber, stoker, insulation worker, machine worker on a boat, or other asbestos-related occupations. We also asked

**Table 2.** Job categories considered to result in exposure to asbestos, talc, or total dust.

Agent	Exposed in the pulp and paper industry	Exposed elsewhere
Asbestos	Maintenance workers, laboratory workers, chlorine plant workers	Electrical industry workers
Talc	Paper mill workers, sulfite mill workers, maintenance workers, stock preparation workers	Cosmetic industry workers rubber industry workers
Total dust	Paper mill workers, sulfite mill workers, stock preparation workers, storage workers	Paper workers in mills other than those included in the pulp and paper cohort

whether potential asbestos-exposed persons brought their workclothes home after work or not. Information about talc use on sanitary napkins, underwear, or diapers was obtained. Fertility pattern was registered as number of children, age at birth of first and last child, age at menarche and menopause, and oral contraceptive use. Hereditary variables were obtained by asking about ovarian and breast cancer among first- and second-degree relatives. Questions were asked about sterilization, hysterectomy, and operations in the abdominal cavity. Finally, information about smoking habits, height, and weight was obtained.

Eighty-eight persons initially refused to participate in the interviews because of old age or for medical or other reasons. Thirty-three controls from the additionally selected group were invited, and 19 were interviewed, giving a response rate of 76.1% for the cases and 65.7% for the controls. The analyses, including control for possible confounding variables, were based on 35 cases and 121 controls (table 1).

#### Statistical analyses

Odds ratios (ORs) and their 95% confidence intervals (95% CI) were derived from conditional logistic regression models using the statistical program package STATA (24).

The results have been presented according to two steps of analysis: first, for the full set of cases and controls, according to ever–never exposure to asbestos, talc and total dust based on occupational histories and, second, for the set of cases and controls who were interviewed, with adjustment for possible confounders, in addition to analyses of secondary asbestos exposure and hygienic talc use.

#### Results

Due to the small number of cases, all the histological types were merged in the analyses. Odds ratios were estimated for three exposure agents, asbestos, talc and total dust. A nonsignificant increased risk was found for ever asbestos exposure, with an odds ratio of 2.02. For talc exposure, the odds ratio was 1.10, and for ever exposure to total dust the odds ratio was 0.77 (table 3).

Six cases and twelve controls were considered to be exposed to asbestos. They were working as cleaners in the maintenance department, electricians, painters, chlorine plant workers, or viscose workers. Regarding asbestos exposure, the analyses of duration of work, time since first employment to cancer diagnosis, and time of first employment showed no clear trend in the risk estimates. For talc exposure, the risk was

**Table 3.** Odds ratios and 95% confidence intervals for the women exposed to asbestos, talc, and total dust in the Norwegian pulp and paper industry, for the full set of cases and controls.

Exposure	Number of exposed persons		Odds ratio	95% confidence interval
	Cases	Controls		
<b>Asbestos</b>				
Never	40	167	1.00	..
Ever	6	12	2.02	0.72–5.66
<b>Talc</b>				
Never	23	93	1.00	..
Ever	23	86	1.10	0.56–2.18
<b>Total dust</b>				
Never	12	38	1.00	..
Ever	34	141	0.77	0.35–1.68

highest for those with first employment before 1950 (not shown). The analyses did not show any trends in the odds ratios for the time variables for total dust exposure. The number of women exposed to any of the three exposure agents outside the pulp and paper industry were very low, and results are not presented.

The odds ratios for ever working in the paper departments and the maintenance and laboratory departments were 1.28 and 1.31, respectively (table 4). No increased risk was associated with work in the production departments, the rayon plant, or the clerical departments.

#### Interview data

Among those participating in the interview, the odds ratio for ever asbestos exposure was 2.18 (95% CI 0.53–9.05) (not shown). Adjustment for possible confounders such as number of children, breastfeeding, age at birth of first and last child, age at menarche and menopause, smoking habits, and family history of ovarian or breast cancer did not essentially change the risk estimates. The adjusted odds ratios for exposure to talc and dust were almost the same as the unadjusted ones (not shown). As a result of low statistical power, only one confounding variable was taken into the analyses at a time. Categories of unknown answers were excluded from the analyses.

#### Household exposure and hygienic talc use

Household exposure to asbestos through the husband or other family members living in the same house was reported for 16 cases and 70 controls. The conditional logistic regression analyses showed a lower risk among those exposed than among those not exposed (table 5). The risk was also lower for those whose family members brought their workclothes home after work. Use of talc on the genital area for personal hygiene gave an odds ratio of 1.15 (table 5).

**Table 4.** Odds ratios and 95% confidence intervals for the employees in five departments of the Norwegian pulp and paper industry, for the full set of cases and controls.

Department	Number of workers		Odds ratio	95% confidence interval
	Cases	Controls		
<b>Sulfite, sulfate and stock preparation</b>				
Never	43	168	1.00	..
Ever	3	11	1.05	0.26–4.17
<b>Rayon plant</b>				
Never	42	156	1.00	0.22–1.98
Ever	4	23	0.66	..
<b>Paper department</b>				
Never	21	91	1.00	..
Ever	25	88	1.28	0.65–2.50
<b>Maintenance and laboratory workers</b>				
Never	42	167	1.00	..
Ever	4	12	1.31	0.40–4.30
<b>Clerical workers</b>				
Never	30	116	1.00	..
Ever	16	63	0.97	0.47–2.00

**Table 5.** Odds ratios and 95% confidence intervals for household exposure to asbestos. Included in the table are also risk estimates for talc use for personal hygiene purposes. Only the set of cases and controls who participated in the interview are included.

Exposure indicators	Number of exposed persons		Odds ratio	95% confidence interval
	Cases	Controls		
<b>Asbestos</b>				
Household exposure <sup>a</sup>				
Never	13	45	1.00	..
Ever	16	70	0.82	0.35–1.91
Work clothes brought home <sup>b</sup>				
Never	20	71	1.00	..
Ever	12	49	0.86	0.38–1.98
<b>Talc</b>				
Talc use by personal hygiene <sup>c</sup>				
Never	7	42	1.00	..
Ever	12	53	1.15	0.41–3.21

<sup>a</sup> Women with household exposure to asbestos (husband or other family members occupationally exposed).

<sup>b</sup> Household-exposed women where workclothes were brought home by their husbands.

<sup>c</sup> Talc used on diapers, sanitary napkins, nongenital area or husband's use in genital area.

#### Discussion

Our study showed a nonsignificant odds ratio of 2.02 for asbestos exposure. The result remained stable after control for established nonoccupational risk factors. This finding indicates that asbestos exposure may be one contributing factor in the development of ovarian cancer among Norwegian pulp and paper workers. No associations were found between ovarian cancer and occupational exposure to talc or total dust.

The distinction between ovarian cancer and peritoneal mesotheliomas may be difficult to observe. To try to ensure that the included cases were correctly

diagnosed, we used an experienced gynecological oncologist to review all the histopathological records in the Cancer Registry. However, we cannot be sure that none of the ovarian cancer cases were peritoneal mesotheliomas, but we believe the possibility is very low.

Only a small proportion of the female pulp and paper workers had been directly occupationally exposed to asbestos, and it is difficult to demonstrate a true association between exposure and outcome in this specific study. The sample size of our study was small, and the statistical power was therefore low. A priori calculations showed a 53% probability of achieving a significant result at the 5% level if the odds ratio was 2.0. Our study was, however, based on a large cohort of female industrial workers, and we had complete job descriptions for all the workers, production data from the mills, and some exposure assessments. These data enabled us to estimate the risk related to specific work exposures. Earlier studies have focused on large occupational groups, being mainly based on census data, without specific exposure information.

Asbestos is known to cause cancer in wives and children of heavily exposed asbestos workers (25, 26). This association may indicate that even household exposures may play a role in the development of asbestos-related cancers. Furthermore, an association between environmental asbestos exposure and malignant mesothelioma of the pleura has been observed (27).

Results from British and Finnish studies have been contradictory with regard to the association between ovarian cancer and asbestos exposure. One explanation may be that different types of asbestos were used in the two countries, and these types of asbestos may have different effects on the target organ. One of the British studies found a significant association between crocidolite exposure and ovarian cancer, but no increased risk among chrysotile-exposed women (12). The Finnish study investigated women exposed to anthophyllite asbestos and found no increase in risk. This type of asbestos seems to have lower carcinogenic potential in mesothelial tissue than in lung tissue (28).

Women in pulp and paper mills have traditionally worked in the paper departments in the packing and sorting of paper or as clerical workers or cleaners, which are assumedly jobs without asbestos exposure. An international mortality study on asbestos exposure and pleural and lung cancer among pulp and paper industry workers emphasized that asbestos dust is not considered to be one of the main occupational exposures in this industry, although, on the other hand, it is not negligible. Of 24 pleural cancer cases, they considered 10 as never exposed and 14 as exposed to asbestos, and they expressed a concern that asbestos exposure may have been underestimated

and misclassified (29). Such misclassification and underestimation may also be the case in our study.

Talc-exposed women did not have an increased risk of ovarian cancer. One possible explanation for this finding may be that most of the talc used in Norwegian pulp and paper mills is not fibrous (ie, does not contain asbestiform fibers such as tremolite or anthophyllite). According to the data collected on the production processes at each mill, only one of the 11 mills used fibrous talc (unpublished observations).

Dust has been a common exposure in the paper departments that employed many of the women. In our study there was no significant association between total dust exposure and ovarian cancer. However, one Swedish study found a significantly increased risk of ovarian cancer among paper and packaging workers (30). Other studies have shown a nonsignificant increase in risk among paper workers (31, 32).

Among the interviewed persons, 71.4% of the patients and 28.6% of the controls were dead; therefore, much more information about the cases was collected from relatives than for the controls. This circumstance may have introduced problems with recall bias. Missing values with regard to household asbestos exposure may contribute to an underestimation of the association between household exposure and ovarian cancer. Experience from other studies has indicated that information obtained from relatives is generally valid, except for information on occupational exposure, which should be collected instead from colleagues or personnel departments (33).

The questions on hygienic talc use resulted in many missing values among the proxy respondents. Thus the odds ratios for some of the variables were the highest in the unknown categories, indicating a possible uncertainty in the results.

The importance of including job history and exposure measurements in the study of the relationship between women's occupational exposure and health effects has recently been emphasized (34). In the case of asbestos, one should bear in mind that, even though the use of asbestos has decreased in developed nations, it is still widely used in developing countries (35). The focus on asbestos as a health hazard is therefore still a necessity in research. Future research to investigate an association between asbestos and other occupational and environmental exposures and ovarian cancer should be done among large groups of women with considerable exposure.

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