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# Cigarette Smoking, Asbestos Exposure, and Malignant Mesothelioma[1]

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## ABSTRACT

**In a hospital-based case-control study of 124 (105 male and 19 female) histologically confirmed malignant mesothelioma cases and age- and sex-matched controls, the role of cigarette smoking and the risk of asbestos exposure was investigated. Exposure to asbestos for at least 1 year was likely for 78% of male cases and 16% of female cases, and 90% of males were possibly exposed. Male cases worked predominately in the shipbuilding industry, construction, or insulation trades. Elevated risks were found for males employed in asbestos-related industries [odds ratio (OR) 8.1; 95% confidence interval (CI) 4.9–13.5], *e.g.*, shipyards (OR 82.9, 95% CI 25.5–269.1), construction/maintenance (OR 8.3, 95% CI 4.6–14.8), and other asbestos-related jobs (OR 3.2, 95% CI 1.4–7.2), and for males who self-reported exposure to asbestos or insulation (OR 50.9, 95% CI 21.7–119.8). A statistically significant trend was found for the risk of mesothelioma with increasing years employed in non-shipyard asbestos-related occupations. Among women, only one case worked in an asbestos-related industry and two reported domestic contact with asbestos. No association between cigarette smoking and mesothelioma was found for either men or women. We also report the occurrence of mesothelioma in occupations which have not been previously reported.**

## INTRODUCTION

Studies by Selikoff *et al.* (1), Doll (2), and others (3) have shown a synergistic effect of cigarette smoking with asbestos-related lung cancer. However, the role of cigarette smoking in the development of malignant mesothelioma has not been as clearly established. Investigators have found little or no association (4–10) (Table 1), although the interpretation of the findings were limited by some methodological and statistical concerns including (*a*) validity of death certificate data, (*b*) small sample sizes, and (*c*) control groups with smoking-related conditions. Since the causes of some mesotheliomas remain unknown, it seems worthwhile to more rigorously examine cigarette smoking as a possible cause.

Since the first large scale study by Wagner *et al.* (11) that related asbestos exposure to mesothelioma in 1960, numerous case reports, hospital reviews, and epidemiological studies have examined the association of asbestos with mesothelioma in specific occupational cohorts and environmental settings. The percentage of mesothelioma cases that have been reported to have been exposed to asbestos has ranged from 10 to 99% (12, 13). This wide variation has resulted from differences in study design, occupational cohorts, methods of classifying and ascertaining exposure to asbestos and job histories, and uncertainty or bias in diagnosis.

This report describes a case-control study that quantifies the association of cigarette smoking and asbestos exposure and their interaction with the risk of malignant mesothelioma.

## PATIENTS AND METHODS

All patients entering Memorial Sloan-Kettering Cancer Center in New York City and other hospitals[3] between 1981 and mid-1990 with a primary diagnosis of histologically confirmed malignant mesothelioma were interviewed. Hospitalized controls with non-tobacco-related diseases were eligible for the study. Among males, 14% had colon cancer, 8.9% had bone or spinal conditions, 8.9% had cancer of the prostate, 8.2% had cancer of the rectum, and 5.9% had sarcomas. Among females, 25.6% had breast cancer, 17.6% had colon cancer, and 8.1% had ovarian cancer. Two male controls were randomly matched to each male case by hospital, age (±5 years), race, and month of interview. Four female controls were matched to each female case by the same criteria. Incomplete matching occurred for 16 male cases (one control/case) and one female case (2 controls/case).

Trained interviewers used a structured questionnaire that had detailed questions concerning demographic factors and history of smoking, occupation and self-reported exposures to asbestos fibers, fiberglass, metal dust, wood dust, insulation materials, chemicals, and other substances. From 1985 to 1990, a more detailed questionnaire was used to obtain data concerning the type and duration of the 6 occupations that cases and controls held the longest, for at least 1 year each. Subjects were considered occupationally exposed to asbestos if they had worked in jobs or industries described in the medical or government literature as having likely or probable asbestos exposure (7, 14–22). These include shipyard employment, construction (*e.g.*, electricians, carpenters, plasterers, painters, cement finishers, plumbers, pipe fitters, insulators, building maintenance), railroad workers, rubber plant workers, firemen and fire chiefs, merchant seamen, mine operatives, textile operatives, auto and heavy equipment mechanics, tobacco packers, and other trades. The duration of self-reported exposure to asbestos, insulation, and other substances listed above was also obtained when the exposures occurred for at least 8 h/week for 1 year, either on the job or as a hobby.

Crude ORs[4] were calculated as estimates of relative risk, and 95% CIs were calculated by the method of Miettenen (23). Odds ratios were calculated for 3 types of occupational categories: shipyard employment, construction, and other jobs involving asbestos exposure. Odds ratios were adjusted for potentially confounding variables using the Mantel-Haenszel statistic (24). The Mantel $\chi^2$ extension test was calculated to assess a dose-response relationship between duration of exposure and case-control status (25).

## RESULTS

The 124 cases and 267 controls had very similar ages (Table 2). Only 3 cases and 4 controls were black or Asian. A greater proportion of male controls attended college and were Jewish

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[3] Other hospitals include New York University, Long Island Jewish Medical Center, Nassau County Medical Center, Jefferson Medical College, University of Pennsylvania Medical Center, Loyola University Medical Center, and Henry Ford Hospital; 78% of subjects were Memorial Hospital patients.

[4] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 *Summary of studies of cigarette exposure and mesothelioma*

| Authors; study design; location | # subjects; methods of interview; criteria | Results | Comments |
|---|---|---|---|
| Tagnon *et al.* (8); case-control study of shipbuilding industry in Tidewater, VA | 56 white male cases and 236 matched non-respiratory-diseased controls, selected from hospital discharge diagnoses, pathology files, and tumor registries. | 4% of cases smoked >2 packs/day *vs.* 19% of controls. Decreased risk among heavy smokers. | Information concerning exposures obtained from relatives. Some controls include tobacco-related diseases. No women studied. |
| McDonald and McDonald (7); case-control study in United States and Canada | 668 cases and single matched controls with nonpulmonary tumors, selected from pathologists from Canadian pathological societies and U.S. Armed Forces Institute of Pathology relatives interviewed. | No association found between cigarette smoking and mesothelioma among males. Elevated risk among female heavy smokers. | Information concerning exposure obtain from relatives. Some controls included tobacco-related disease. |
| Hammond *et al.* (4) and Selikoff (6); cohort study in United States and Canada. | 17,800 male Insulation Union workers and 73,763 controls with a history of occupational exposures. | Among male never smokers, 8 deaths from mesothelioma *vs.* 8 expected. | Histological confirmation not available. Sample size was too small to evaluate effects of smoknig. No women studied. |
| Zielhuis *et al.* (5); case-control study in Amsterdam | 67 cases and age- (±3 yr) and sex-matched controls with cardiovascular conditions; obtained from pathology reports. Personal interview of relatives, neighbors, employees, or patients (if alive). | No increased risk of mesothelioma found with smoking. | Controls included tobacco-related conditions. Exposure information obtained from relatives. |
| Selikoff *et al.* (10); standardized mortality ratio study in New Jersey | 933 amosite asbestos workers, followed up for 20 yr. | Observed and expected death rate from mesothelioma: 9 *vs.* 14.8 among smokers, for never smokers, 3 *vs.* 3.0. | No women studied. |
| Berry *et al.* (9); standardized mortality ratio study in London | 3700 male and female asbestos factory workers followed up 16–47 yr. | Among female and male smokers, observed to expected ratio mortality was similar for smokers and nonsmokers. | Too few male nonsmokers to evaluate. |

Table 2 *Sociodemographic characteristics of cases and controls*

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases ($n$ = 105) | | Controls ($n$ = 193) | | Cases ($n$ = 19) | | Controls ($n$ = 74) | |
| | No. | % | No. | % | No. | % | No. | % |
| Age (yr) | | | | | | | | |
| <44 | 8 | 7.6 | 19 | 9.8 | 1 | 5.3 | 9 | 12.2 |
| 45–54 | 23 | 21.9 | 37 | 19.2 | 4 | 21.1 | 18 | 24.3 |
| 55–64 | 39 | 37.1 | 78 | 40.4 | 9 | 47.4 | 26 | 35.1 |
| 65–74 | 30 | 28.6 | 54 | 28.0 | 4 | 21.1 | 15 | 20.3 |
| >75 | 5 | 4.8 | 5 | 2.5 | 1 | 5.3 | 6 | 8.1 |
| Education (yr) | | | | | | | | |
| 1–8 | 7 | 6.7 | 16 | 8.3 | 1 | 5.3 | 10 | 13.5 |
| 9–12 | 52 | 49.5 | 66 | 34.2 | 11 | 57.9 | 32 | 43.2 |
| 13–15 | 36 | 34.3 | 63 | 32.6 | 6 | 31.6 | 19 | 25.7 |
| >16 | 10 | 9.5 | 48 | 24.9 | 1 | 5.3 | 13 | 17.6 |
| Religion | | | | | | | | |
| Protestant | 40 | 38.1 | 46 | 23.8 | 7 | 36.8 | 9 | 12.2 |
| Catholic | 48 | 45.7 | 88 | 45.6 | 10 | 52.6 | 50 | 67.6 |
| Jewish | 14 | 13.3 | 49 | 25.4 | 2 | 10.5 | 14 | 18.9 |
| Other | 2 | 1.9 | 4 | 2.1 | 0 | 0.0 | 1 | 1.4 |
| None | 1 | 1.0 | 6 | 3.1 | 0 | 0.0 | 0 | 0.0 |

than cases ($P < 0.05$); they were more likely to have worked in professional or managerial jobs. A larger proportion of female controls were Catholic and Jewish than female cases. Most subjects lived the majority of their adult lives in New York, New Jersey, Pennsylvania, and Illinois. Controls were more likely than cases to have lived in New York. Residency was further classified by urban density: city, >250,000 persons; town, 50,000–250,000 persons; village or suburb, 2,500–49,999 persons; and rural area, <2,000 persons. More cases resided in suburban or rural areas than controls: males, 56 *versus* 40.4% (test for trend, $P < 0.02$); females, 73.3 *versus* 37.9% ($P < 0.01$).

The site of mesothelioma was known for 84 cases; 82 (97%) had pleural mesothelioma and 2 (3%) had peritoneal mesothelioma. Histopathological subtyping was reported for 75 cases. Sixty-one (81.3%) had epithelial mesothelioma, 9 (12%) had sarcomatous tumors, and 5 (6.7%) had biphasic or tumors of mixed histology. Of 70 male cases, 44 (63%) had a primary tumor of the right pleura compared to 8 of 17 women (47%) (OR 2.0, 95% CI 0.7–5.5).

Among male cases, 82 men (78%) were considered exposed to asbestos; 72 men (69%) were employed in asbestos-related industries and 59 of these 72 also self-reported asbestos exposure. Ten men (9.5%) reported asbestos exposure but worked in jobs that are not considered asbestos-related industries, including 2 policemen, 3 Navy seamen, one school teacher, one potter, one environmental consultant, one insurance salesman, and one plant manager. The potter reported working with an asbestos-lined kiln, and the teacher reported friable asbestos leaking from his classroom ceiling, although he stated anecdotally that he had also worked 2 months previously in an asbestos factory. One Navy ensign reported exposure on a Navy ship. The plant manager reported workplace exposure. One policeman reported domestic exposure during childhood.

Among the 72 men who worked in asbestos-related occupations, 18 worked in shipyards during World War II as pipefitters, electricians or insulators; 5 were subsequently employed in other asbestos-related occupations. Forty-three men worked in construction and 11 were employed in other asbestos-related jobs.

Among women, only one (5%) case worked in an asbestos-related industry as a textile operative for 27 years. Three females (16%) self-reported exposure to asbestos: the textile worker, a bank teller who was exposed during extensive home renovation, and an executive director who was exposed during childhood.

The mean latent period between the first year employed in an asbestos-related occupation and diagnosis of mesothelioma was 38.4 years (±1.4 years) for male cases and 36.6 years (±1.4 years) from first self-reported exposure. Only one case developed mesothelioma within 10 years of initial exposure (5 years).

Twenty-three male cases (22%) and 16 female cases (84%) never worked in an asbestos-related industry or self-reported exposure to asbestos. Five of these males worked in occupations with possible sources of asbestos exposure including tire recap-

Table 3 *Case-control status, years of non-shipyard occupational exposure, and year of birth among men*

| | Cases | | Controls | | Crude | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | OR | 95% CI |
| Exposure (yr) | | | | | | |
| 0 | 33 | 37.9 | 152 | 79.2 | 1.0[a] | |
| 1–9 | 12 | 13.8 | 13 | 6.8 | 4.3[a] | 1.9–9.7 |
| 10–19 | 11 | 12.6 | 11 | 5.7 | 4.6[a] | 2.0–10.9 |
| 20–29 | 9 | 10.3 | 5 | 2.6 | 8.3[a] | 3.0–22.8 |
| 30+ | 22 | 25.3 | 11 | 5.7 | 9.2[a] | 4.4–19.9 |
| Year of birth | | | | | | |
| 1910–1919 | 25 | 64.0[b] | 41 | 24.4 | 5.5[c] | 1.5–15.8 |
| 1920–1929 | 42 | 90.5[b] | 78 | 23.1 | 31.7[c] | 10.0–100.7 |
| 1930–1939 | 26 | 69.2[b] | 45 | 24.4 | 7.0[c] | 2.5–19.6 |
| 1940–1949 | 7 | 85.7[b] | 18 | 22.2 | 21.0[c] | 1.9–229.4 |

[a] Trend $\chi^2 = 44.2$, $P < 0.01$.
[b] Exposed.
[c] For self-reported or occupational exposure.

ping, carpet installation, jewelry manufacturing, ironwork, and steel mill inspection. One woman was married to an automobile mechanic, indicating possible domestic contact with asbestos.

Forty-one male controls (21%) worked in asbestos-related industries: one in a shipyard, 24 in construction, and 16 in other asbestos-related jobs. Seven of these 41 men (17%) reported asbestos exposure on the job. Three females worked as textile operatives (4%) but did not report asbestos exposure.

Risk estimates for mesothelioma were computed for men who worked in asbestos-related occupations (OR 8.1, 95% CI 4.9–13.5). Shipyard workers had the largest elevated risk (OR 82.9, 95% CI 25.5–269.1), followed by construction/maintenance workers (OR 8.3, 95% CI 4.6–14.8) and other asbestos-related occupations (OR 3.2, 95% CI 1.4–7.2) The duration of employment in these occupations was similar between cases and controls (19.7 ± 1.9 *versus* 20.0 ± 2.5 years). However, shipyard cases were employed for a much shorter duration than other cases (2.7 ± 0.6 *versus* 24.8 ± 2.1 years). This large difference likely reflected a greater intensity of asbestos exposure in the shipyards. There were very few miners, millers, or manufacturers (other occupations thought to entail heavy asbestos exposure) among other subjects. The risk of mesothelioma was subsequently examined among non-shipyard cases and controls. Subjects who never worked in an asbestos-related industry were used as a reference group, and a significant trend was found for the number of years employed in asbestos-related occupations (Table 3).

There was a large increased risk for men who self-reported exposure to asbestos (OR 50.9, 95% CI 21.7–119.8). The duration of employment was 14.4 ± 1.8 years for these cases, compared to 18.6 ± 3.7 years for controls. The risk for men who were employed in asbestos-related occupations or reported asbestos exposure was 13.2 (95% CI 7.8–22.5).[5] Men who were born between 1920 and 1929 and reached working age during World War II had the highest risk of asbestos-associated mesothelioma (Table 3).

The risk estimates of mesothelioma by tobacco smoking is shown in Table 4. Among men, cases and controls had almost identical smoking habits. Approximately 25% of both groups reported currently smoking cigarettes, and 25% never smoked tobacco products. Among current smokers, no differences were found by the number of cigarettes smoked/day. For ex-smokers, cases and controls reported similar durations of years since quitting. The risk among pipe and cigar smokers was elevated but not statistically significant. The mean number of years that pipes and cigars were smoked was similar for cases and controls. Among women, there was a similar proportion of those who had never smoked for cases and controls. There was a small but nonsignificant risk for current cigarette smokers, whereas ex-smokers had a nonsignificant decrease in risk.

A synergistic effect was not found among males who currently smoked cigarette and who were also exposed to asbestos. The excess risk for men with both exposures is not greater than the sum of the risk differences for each separate exposure (Table 5).

The risk for mesothelioma among men who reported exposure to other fibers or chemicals is shown in Table 5. Although some substances were significantly associated with mesothelioma, the adjusted odds ratio shows the confounding effects of asbestos.

## DISCUSSION

Asbestos exposure was ascertained for 78% of male cases and 16% of female cases. The very large risk of mesothelioma among men formerly employed in the shipyard industry supports previous findings by Tagnon *et al.* (8) and Kolonel *et al.* (26) and confirms projections of high mortality in this group (27). A significant trend was found in the relative risks when stratified by duration of non-shipyard employment. Other investigators (6, 16, 28) have also found trends for duration of employment. This study has also shown that mesothelioma is occurring among persons employed in occupations which have not been previously examined for excess risk. Only one female case worked in an asbestos-related occupation, although the findings provide further evidence that domestic contact with relatives exposed to asbestos carries a risk.

More cases than controls lived the greater part of their adult lives in suburban or rural areas and outside of New York state. This reflects a selection bias since the participating hospitals are cancer referral centers. Selection bias may have resulted in the low percentage of cases that were black. In 1987, the age-adjusted incidence rates for mesothelioma were 1.4/100,000 for white men and 0.7/100,000 for black men (29). Although race has not been shown to be a risk factor for mesothelioma, these study results should be generalized only to white populations.

The smaller ORs for occupational exposure compared to self-reported asbestos exposure suggest that recall bias or wish bias influenced the responses from cases (30). Since interviewers were aware of case-control status and cases were likely to have been knowledgeable regarding the carcinogenic potential of asbestos, misclassification may have elevated the ORs. Sixty-six % of male cases self-reported asbestos exposure, compared to 4% of controls, although the mean duration of employment in asbestos-related jobs and self-reported exposure was very similar between cases and controls. We believe that recall or wish biases were likely to inflate the ORs for self-reported asbestos exposure but not for asbestos-related occupations.

An estimated 70–80% of mesotheliomas are caused by asbestos exposure in the general population of adults (31). In this study 78% of the male cases, which represents a cross-section of different occupations, were ascertained to have been exposed to asbestos. However, the early version of the questionnaire (1980–1985) obtained information concerning only the most usual occupation. The more recent questionnaire revealed that

[5] Some studies suggest an association of asbestos with colon cancer. When controls with colon cancer are excluded, the odds ratios for occupational, self-reported, or any asbestos exposure were 7.8, 59.2, and 12.7, respectively. The data from this study indicate that colon cancer is not related to asbestos exposure.

Table 4 *Relative risk estimates for mesothelioma by cigarette smoking history*[a]

| | Males | | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases ($n$ = 10) | | Controls ($n$ = 193) | | OR | Adjusted | Cases ($n$ = 19) | | Controls ($n$ = 74) | | |
| | No. | % | No. | % | (95% CI) | OR[b] | No. | % | No. | % | OR |
| Never | 26 | 24.8 | 48 | 24.9 | 1.0 | 1.0 | 9 | 47.4 | 34 | 46.0 | 1.0 |
| Current (no./day) | 25 | 23.8 | 50 | 25.9 | 0.9 | 1.0 | 7 | 36.9 | 16 | 21.6 | 1.7 |
| 1–20 | 12 | (48.0) | 26 | (52.0) | (0.5–1.8) | (0.5–2.3) | 6 | (85.7) | 12 | (75.0) | (0.5–5.3) |
| ≥21 | 13 | (52.0) | 24 | (48.0) | | | 1 | (14.3) | 4 | (25.0) | |
| Ex-smoker (yr) | 46 | 43.8 | 86 | 44.6 | 1.0 | 1.0 | 3 | 15.8 | 24 | 32.4 | 0.5 |
| 1–20 | 31 | (67.4) | 61 | (70.9) | (0.5–1.8) | (0.5–1.9) | 2 | (66.7) | 18 | (75.0) | (0.1–1.9) |
| 21–40 | 14 | (30.4) | 22 | (25.6) | | | 1 | (33.3) | 6 | (25.0) | |
| >40 | 1 | (2.2) | 3 | (3.5) | | | | | | | |
| | | | | | | 2.6 | | | | | |
| Pipe/cigar | 8 | 7.6 | 9 | 4.7 | 1.6 | 2.6 | | | | | |
| | | | | | (0.6–4.8) | (0.8–8.8) | | | | | |

[a] Risks are relative to those who never smoked cigarettes.
[b] Adjusted for occupational exposure to asbestos. Adjustment for self-reported exposure or any exposure resulted in virtually identical adjusted ORs.

Table 5 *Relative risk estimates for mesothelioma by exposure to asbestos and current cigarette smoking and other substances*

| | Cigarette smoking | | | | |
|---|---|---|---|---|---|
| | Yes | | No | | |
| | No. | OR | No. | OR | Risk difference[a] |
| Asbestos exposure | | | | | |
| Yes | 27 | 13.9 | 96 | 13.9 | |
| No | 48 | 1.2 | 127 | 1.0[b] | 0.2 |
| Risk difference | | | | 12.9 | |

| | % exposed | | Crude | | Adjusted | |
|---|---|---|---|---|---|---|
| | Cases | Controls | OR | 95% CI | OR[c] | 95% CI |
| Benzene | 5.7 | 4.2 | 1.4 | 0.5–4.2 | | |
| Cotton fiber | 1.0 | 1.0 | 0.9 | 0.1–10.2 | | |
| Cutting oil | 12.4 | 4.7 | 2.9 | 1.2–6.8 | 1.4 | 0.4–3.9 |
| Fiberglass | 13.3 | 2.6 | 5.8 | 2.2–15.0 | 1.5 | 0.6–3.7 |
| Metal dust | 11.4 | 5.2 | 2.4 | 1.0–5.6 | 2.3 | 0.6–8.5 |
| Wood dust | 13.3 | 4.7 | 3.1 | 1.4–7.3 | 1.5 | 0.9–3.6 |
| X-rays | 1.0 | 1.0 | 0.9 | 0.1–10.2 | | |

[a] Excess relative risk, 12.9; sum of risk differences, 13.1.
[b] Reference group. Asbestos exposure is for occupational or self-reported exposure.
[c] Adjusted for self-reported exposure to asbestos.

many subjects worked in several occupations and were exposed to asbestos in secondary jobs. Twelve of 24 male cases (50%) interviewed prior to 1986 were considered exposed to asbestos, compared to 70 of 81 (86%) male cases interviewed after 1986. This difference shows the need to obtain a detailed, lifelong history of occupational exposures.

Extrapolating the differences in exposure percentages between the 2 questionnaires (86 − 50% = 36%), we estimate that an additional 8 male cases interviewed before 1986 were possibly exposed to asbestos. Potentially 95 (90.4%) male cases were exposed to asbestos if these 8 cases and the 5 male cases with possible asbestos exposure (*e.g.*, tire recapper) are included.

Cigarette smoking was not found to be a risk for mesothelioma among men or women. Hammond *et al.* (4) and Selikoff (6) reported no effect of cigarette smoking on male death rates for pleural mesothelioma. McDonald and McDonald (7) found no association among male cases, whereas female cases were somewhat heavier current smokers. A higher proportion of female cases were employed outside the home. Tagnon *et al.* (8) found a deficit of heavy male smokers among cases of mesothelioma, although they attributed this to competing causes of respiratory mortality (*i.e.*, lung cancer) among shipyard workers. Zielhuis *et al.* (5) found no association among men.

Asbestos products and materials have been manufactured since the early 20th century in surfacing material; preformed thermal insulating products; textiles such as cloth, blankets, felt, sheets, cord, rope, tape, and curtains; concrete and paper products; electrical wiring; roofing felts; putty; plaster; vinyl products; wallcovering; and paints. Asbestos is usually bound in materials such as cement, magnesium carbonate, calcium or sodium silicate, cotton, asphalt, clay, and linseed and other oils (32). Future studies should consider all direct and secondary sources of exposures and other substances which could induce mesothelioma. However, precautions must be taken to limit interviewer and wish biases and interpret findings based on minimal asbestos exposure.

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