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Original scientific paper

The Role of Polio-Vaccine in Pleural Mesothelioma – An Epidemiological Observation

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A B S T R A C T

From the Croatian Cancer Registry (period 1991–1997) 194 malignant pleural mesothelioma patients were collected. According to participation in polio vaccination mass campaign in 1961 that covered the entire Croatian population aged 3 months to 20 years, mesothelioma patients were divided in vaccinated (N=58), and non-vaccinated (N=136) subjects. Significantly higher percentage of those with a history of occupational exposure to asbestos was found in vaccinated (79%) compared to non-vaccinated group (63%). This is the opposite to what would be expected if potential SV40 contamination of polio vaccine used had a causative role in the development of the tumour. On the other hand, shorter latency period reflected by very high percentage of 45-year-old or younger mesothelioma patients in vaccinated group (15 out of 58), with all of them having a history of occupational asbestos exposure, raises a question for a possible enhancing effect of the vaccine used to asbestos exposure, if it was contaminated with SV40.

Key words: *poliovirus vaccine, Simian virus 40, mesothelioma, pleura, asbestos, occupational exposure*

Introduction

Since the link between malignant pleural mesothelioma and asbestos was first suggested in South African asbestos miners[1], exposure to asbestos has been considered as the main etiological factor in the development of this tumour. Simian virus 40 (SV40), as another potential factor, came into focus of attention when it was discovered as a contaminant of poliovirus vaccines in the early 1960s. It may be assumed that between 1955 and the beginning of year 1963 millions of subjects throughout the world had been treated with contaminated vaccines. About 98 millions children and adults received inactivated polio-vaccine in USA during that period. The proportion that was actually infected by SV40 was estimated at 10% to 30%[2]. Although cell culture and animal studies argued against a role for SV40 in human disease, recently a number of reports have implicated SV40 in the aetiology of 40% to 60% of human mesotheliomas, based on detection of DNA sequences encoding the SV40 large – T antigen and/or its protein expression in such tumours[3–7]. In 2005 an article was published with evidence against a role for SV40 in human mesothelioma[8]. In that study, none of 69 tumours, in which a single copy gene was readily amplified, contained detectable SV40. Kidney, a known reservoir of SV40 in monkeys, from some of these individuals was also negative for SV40 large – T antigen sequences. In a more recent study on the frequency of SV40 infection in Japanese malignant mesothelioma cases, the presence of SV40 large T antigen in 35 mesothelioma samples was not found, as well[9]. Nevertheless, epidemiological evidence in literature regarding the association between SV40 and the occurrence of mesothelioma is rather limited. Only a few period-cohort studies were carried out, either on mortality or incidence rates of cancer in the search for an effect due to treatment with polio-vaccine in 1955–1963[10–12]. In these studies no significant increase in the occurrence of mesothelioma has been observed.

Some years ago we performed a study on malignant pleural mesothelioma in Croatia, its geographical distribution, and the occupations of the patients[13]. Age-standardized incidence rates (period 1991–1997) was 0.74/100,000 (men 1.34 and women 0.27). Recorded cases of mesothelioma ranged from 20 in 1991, 23 in 1992, 37 in 1993, and 34 in 1994, up to 43 in 1995, 48 in 1996, and 43 in 1997. About two-thirds of patients with this tumour

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were occupationally exposed to asbestos. The remaining third of patients, whose occupation was not related to asbestos exposure, still had the tumour incidence about two per million per year. An explanation of this finding could be in non-occupational exposure to asbestos. However, there was also a possibility of involvement of SV40 as one of the etiological factor. Namely, the incidence of poliomyelitis in Croatia had progressively increased since 1945. There were serious epidemics with 388 cases in 1953, and 563 in 1960. In order to protect the age groups of greatest risk a mass vaccination campaign was carried out with Koprowski live virus vaccine in the early spring of 1961, covering the entire population aged 3 months to 20 years[14]. Altogether 1,339,244 persons were given type 1 (CHAT strain), and 1,287,909 received type 3 (W-Fox). During this first phase of vaccination against polio there was a possibility of SV40-contamination of polio-vaccine used, although this could not be confirmed at that time. Later than 1963, measures were applied to prevent the contamination of vaccines with SV40.

The purpose of this study was to evaluate the role of poliovirus vaccine used, potentially contaminated with SV40, in the development of mesothelioma.

Subjects and Methods

The study was performed in 194 subjects with malignant pleural mesothelioma recorded by the Croatian Cancer Registry over seven years (1991–1997). With the use of a short questionnaire sent to the patients' families additional information on their occupation (possible exposure to asbestos) were obtained. In the study were included only registered patients with the tumour for whom the additional questionnaire was answered: 194 out of 248 malignant pleural mesothelioma patients recorded by the Registry (78% response).

In connection with the mentioned mass vaccination campaign with polio-vaccine potentially contaminated with SV40 carried out in 1961[14], subjects selected for the study were divided into two groups. One group consisted of 58 subjects whose age ranged between 3 months and 20 years at the time of vaccination. As vaccination was compulsory, it is reasonable to assume that they received vaccine against poliovirus. The other group consisted of 136 non-vaccinated subjects who were older than 20 years of age at the time of vaccination campaign.

Results

In the group of vaccinated during the mass vaccination campaign in 1961, out of 58 subjects only 6 (10.3%) were women and 52 (89.7%) men. Median age of vaccinated patients was 48,5 years (range 35–56 years).

In the group of non-vaccinated patients there were 36 (26.5%) women and 100 men (73.5%). Median age was 64 years (range 53–84 years).

Table 1 shows the proportion of asbestos-exposed subjects by age in vaccinated and non-vaccinated groups.

TABLE 1
VACCINATED AND NON-VACCINATED SUBJECTS EXPOSED TO ASBESTOS BY AGE GROUPS

Age group	Vaccinated		Non vaccinated	
	Women	Men	Women	Men
35–40		3		
41–45		16		
46–50		8		
51–55	1	18		
56–60				23
61–65			9	15
66–70				17
71–75				15
76–80				7
81–85			1	

Of all subjects in the vaccinated group, 15 (28.8 %) were younger than 45 years, and all had a history of occupational exposure to asbestos. The youngest patient was a 35-year-old man. Based on the questionnaire data, he had a history of occupational exposure in an asbestos processing plant in another country. Among the youngest patients, a 38-year-old man had been engaged in machine maintenance on ships. Other patients from the vaccinated group younger than 45 years were exposed to asbestos in shipbuilding industry (3 workers), asbestos-cement industry (3 workers), insulation and asbestos textile industry (4 workers), and in construction industry (3 workers).

In the non-vaccinated group the youngest patient was a female administrative worker (aged 53) without the history of occupational exposure to asbestos. Table 2 and 3 show the occupation of vaccinated and non-vaccinated subjects with pleural mesothelioma, according to the questionnaire.

As seen from Table 2, among vaccinated subjects only one women (out of 6) had a work history with exposure to asbestos, while 45 men – including 8 construction workers – were occupationaly exposed to asbestos. In the non-vaccinated group 8 women (out of 36) and 77 men – including 20 construction workers – (out of 100) were exposed to asbestos (Table 3).

Comparison between the analysed groups, taking men and women together, shows that in vaccinated subjects there was significantly higher percentage of those with a history of occupational exposure to asbestos (including presumably asbestos-exposed in construction industry) than in non-vaccinated subjects (79%:63%; Chi square=4.44; p=0.0351). Presumably exposed to asbestos in construction industry, due to increased use of asbestos-based construction material, were similarly distributed in both groups compared (14%:15%). When construction industry workers in both vaccinated and non-vaccinated groups were excluded, the difference was still significant (Chi square=4.33; p=0.0376).

TABLE 2
OCCUPATION OF PATIENTS WITH PLEURAL MESOTHELIOMA, VACCINATED AGAINST POLIOVIRUS, ACCORDING TO THE QUESTIONNAIRE

	Shipbuilding industry	Asbestos-cement production	Other jobs with exposure to asbestos*	Construction industry	Agriculture	Other†	Total
Women	0	0	1	0	1	4	6
Men	13	7	17	8	0	7	52
Total	13	7	18	8	1	11	58

*Insulation workers (n=1), asbestos processing (n=7), asbestos textile workers (n=4), maintenance and repair of machines and items containing asbestos (n=3), naval machinists (n=1), history of work in asbestos processing plant abroad (n=1), transportation and storage of asbestos (n=1)
†Blue collar workers (n=2), technicians (n=1), administrative staff (n=2), persons with university education (n=1), miscellaneous (n=2), housewives (n=3)

TABLE 3
OCCUPATION OF NON-VACCINATED PATIENTS WITH PLEURAL MESOTHELIOMA, ACCORDING TO THE QUESTIONNAIRE

	Shipbuilding industry	Asbestos-cement production	Other jobs with exposure to asbestos*	Construction industry	Agriculture	Other†	Total
Women	2	0	8	0	9	17	36
Men	41	5	11	20	8	15	100
Total	43	5	19	20	17	32	136

*Insulation workers (n=4), asbestos processing (n=1), asbestos textile workers (n=2), maintenance and repair of machines and items containing asbestos (n=1), history of work in asbestos processing plant abroad (n=3), naval machinists (n=2), transportation and storage of asbestos (n=5), asbestos-cement workers wife (n=1)
†Blue collar workers (n=7), technicians (n=1), administrative staff (n=8), persons with university education (n=3), miscellaneous (n=2), housewives (n=11)

Higher percentage of patients whose occupation was not related to asbestos exposure was observed in non-vaccinated (37%) than in vaccinated group (21%).

Discussion

As shown in the results, vaccinated subjects had significantly higher percentage of those with a history of occupational exposure to asbestos when compared to non-vaccinated subjects. On the other hand, in subjects whose occupation was not related to asbestos exposure, higher participation in non-vaccinated than in vaccinated group was observed. These findings do not indicate a causative role of potentially SV40-contaminated polio-vaccine used. However, another explanation could lie in non-occupational exposure to asbestos, as pointed earlier. Our previous studies[15, 16] indicated the importance of asbestos emissions in the environment around asbestos processing and asbestos-cement plants for the development of lung tumours, including pleural mesothelioma. Environmental exposure to asbestos may also be involved in enhancing the risk of respiratory tract tumours, particularly in jobs involving outdoor work (agriculture, construction) in areas contaminated by asbestos emitted from industrial sources. Housewives involved in farming or gardening, which is rather common in the areas with asbestos processing and asbestos-cement plants, were also among them. Our study of the incidence of malignant plural mesothelioma in coastal and continental Croatia[13] shows that standardized incidence of this tumour by residence and sex was 0.38/100,000 for women in the coastal area, while in the continental area it was 0.24/100,000, and in the city of Zagreb 0.18/100,000, but these differences were not statistically significant. Exposure to non-identified or less identified sources of asbestos has also to be considered. For example, the same study showed that age-standardized incidence of malignant pleural mesothelioma in males, was only slightly (with marginal significance) higher in the coastal area with numerous identified exposure sources of asbestos than in the city of Zagreb, as a large urban area without particularly identified sources of exposure to asbestos.

Our results show that, apart from age differences in tumour cases, there was also a gender difference. Among those who had asbestos exposure history in the vaccinated group, there was only one woman out of six with mesothelioma. In the non-vaccinated group, 10 of 36 women had a history of occupational exposure to asbestos. This ratio is closer to the ratio of tumour incidence generally observed in earlier studies[13], which is approximately four times higher in men than in women. It may be worth to note that before asbestos ban, certain jobs in shipbuilding and asbestos-cement industry, which were important sources of occupational exposure to asbestos, were occupied almost exclusively by men.

Although a causative role of polio-vaccine potentially SV40-contaminated could not be implied by our data, interesting observation regarding age, and consequently

latency period for the onset of the disease, has to be pointed out. It is known that higher cumulative exposure to asbestos generally correlates with the increased risk of malignant mesothelioma, although studies have revealed that the tumour may develop from short-term exposure and lower exposure levels, as well[18]. Supporting this generally accepted experience is a study on patients with malignant pleural mesothelioma treated between 1991–2000 at the Split University Hospital[17]. It showed that only 5.6% of patients developed mesothelioma after 10–20 years of exposure, 9.9% after 21–30 years of exposure, while 85.5% developed the tumour after 31–40 years of exposure or even longer. Coming back to age and latency period, in a study on 343 mesothelioma cases in Croatia for a period of 10 years (1989–1998) which included 194 subjects dealt in our study, 7.8% of the total number of registered patients were 44 years old or younger[19]. On the other hand, a study performed in Australia for a three year period (1997–1999), significantly lower percentage of mesothelioma patients in the same age group was registered, that is 1.8% to 2.6% out of total number of registered mesothelioma patients[20]. In a study on the incidence of malignant mesothelioma (period 1980–1990) performed in the province of Brescia (Italy), out of 190 cases registered only 10 (5.2%) were younger than 45 years, with only one subject occupationally exposed to asbestos[21]. In a study on mesothelioma epidemic in Western Europe during the period 1990–1999 which dealt with males only, in the age group of 40 to 54 years the number of deaths from pleural cancer, expressed as percent from total number of pleural cancer deaths in according country, ranged between 10.6% to 13.1% (France 10.6%, Italy 11.6% and Germany 13.1%)[22]. For comparison, in our present study we found even 29% of mesothelioma patient of the same age group. The increase in mesothelioma incidence during the period of observation, namely in the years 1993–1997, as noted in the Introduction, could be at least partly explaned by increase of tumours in younger subjects with shorter exposure to asbestos involved in tumour development.

Since all of our mesothelioma patients younger than 45 years (15 out of 58 vaccinated) were vaccinated with incriminated polio-vaccine, and all of them had a history of occupational asbestos exposure, a question may be raised for a possible enhancing effect of SV40 and asbestos in development of mesothelioma. Hypothetically, there is a possibility that SV40 acts as a co-carcinogen to asbestos in the occurrence in human mesothelioma. In some of the published observations such an assumption has been mentioned[4]. A recently published molecular epidemiologic case-control study[23], which following such assumption has to be emphasized, was dealing with the hazard ratio of developing mesothelioma in exposure to asbestos alone, SV40 alone, and to asbestos exposure plus SV40 infection. Asbestos exposure alone was associated with mesothelioma, while SV40 alone was not. The contamination with SV40 plus asbestos exposure revealed significantly greater risk of developing mesothelioma compared to asbestos exposure alone.

Conclusion

Although a number of cases of malignant pleural mesothelioma cannot be etiologically explained, the results of this epidemiologic observation do not suggest a causative role of potentially SV40-contaminated polio-vaccine used. However, based on high percentage of mesothelioma patients younger than 45 years in our study, with all of them being vaccinated with polio-vaccine potentially contaminated with SV40 and having a history of occupational exposure to asbestos, a question may be raised for a possible enhancing effect of SV40 and asbestos in development of mesothelioma. Nevertheless, the lack of evidence concerned with the contamination of the vaccines used does not allow a firm conclusion.

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ULOGA POLIOVAKCINE U NASTANKU MEZOTELIOMA POPLUĆNICE – EPIDEMIOLOŠKO OPAŽANJE

S A Ž E T A K

Godine 1961. provedeno je u Hrvatskoj masovno cijepljenje protiv poliovirusa, kojim je bila obuhvaćena cijela populacija u dobi od 3 mjeseca do uključivo 20 godina života. Da bi se ispitala moguća veza između upotrebljenog cjepiva i razvoja malignog mezotelioma poplućnice, iz podataka Hrvatskog registra za rak (razdoblje 1991.–1997.) izdvojene su 194 osobe s mezoteliomom od kojih su 58 bile cijepljene 1961. godine, a 136 su bile necijepljene. Temeljem podataka dobivenih anketom (heteroanamneza), u skupini cijepljenih registriran je značajno veći postotak osoba, koje su bile profesionalno izložene azbestu u odnosu na necijepljene (79% : 63%). Takav nalaz govori protiv pretpostavljene uloge provedene vakcinacije u razvoju mezotelioma. Međutim, u skupini cijepljenih s mezoteliomom 15 (od ukupno 58) bili su mlađi od 45 godine s time što su svi bili profesionalno izloženi azbestu. Znatno kraće latentno razdoblje od očekivanog u tih cijepljenih osoba ujedno izloženih azbestu, upućuje na mogućnost da je korišteno cjepivo pridonjelo razvoju tumora. Sigurniji zaključak, ipak, nije moguć budući da ne raspolažemo podatkom da li je upotrebljeno cjepivo bilo doista onečišćeno virusom SV40.