Asbestos Exposure and Ovarian Cancer – a Gynaecological Occupational Disease. Background, Mandatory Notification, Practical Approach

Ovarialkarzinom durch Asbest – eine gynäkologische Berufskrankheit. Hintergrund, Meldepflicht, praktisches Vorgehen

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ABSTRACT

In 2017, ovarian cancer due to asbestos exposure was designated a new, and thereby the first, gynaecological occupational disease in Germany. Asbestos is a naturally occurring mineral fibre with an annual usage in Germany of 160 000–180 000 metric tonnes in the 1960s and 1970s. The carcinogenicity of asbestos for the target organs lungs, larynx, pleura including pericardium, and peritoneum including tunica vaginalis testis has been clearly established for many years. Recent meta-analyses of data from cohort studies have demonstrated that the risk of ovarian cancer roughly doubles in women with occupational exposure to asbestos. Since the group of people with double the risk of developing lung cancer due to work-related asbestos exposure has a 2.25-fold increased risk of mortality from ovarian cancer on average, work-related ovarian cancer has been assigned the same recognition requirements as in occupational lung (and laryngeal) cancer. Thus, gynaecologists must obtain a thorough history of occupational exposure to asbestos, even if it may have taken place long in the past. The law mandates that suspected such cases must be reported to the Statutory Accident Insurance carrier or the State Occupational Safety and Health Agency.

ZUSAMMENFASSUNG

Seit 2017 gibt es eine neue, die erste gynäkologische Berufskrankheit, das Ovarialkarzinom durch Asbest. Asbest ist ein natürlich vorkommender mineralischer Faserstoff mit einem Verbrauch von 160 000–180 000 Tonnen jährlich in den 1960er- und 1970er-Jahren in Deutschland. Die Karzinogenität von Asbest für die Zielorgane Lunge, Larynx, Pleura einschließlich Perikard sowie Peritoneum einschließlich Tunica vaginalis testis ist seit vielen Jahren eindeutig gesichert. Neuere Metaanalysen von Daten aus Kohortenstudien zeigen, dass sich das Ovarialkarzinomrisiko bei Frauen etwa verdoppelt,

die beruflichen Umgang mit Asbest hatten. Da die Personengruppe, bei der das Verdoppelungsrisiko für die Entstehung eines Lungenkarzinoms durch arbeitsbedingte Asbestexposition gegeben ist, ein im Mittel 2,25-fach erhöhtes Risiko für die Mortalität an einem Ovarialkarzinom aufweist, wurden für das berufsbedingte Ovarialkarzinom dieselben Anerkennungsvoraussetzungen wie für das berufsbedingte Lungen- (und Larynxkarzinom) festgelegt. Somit muss der Gynäkologe eine Arbeitsanamnese bezüglich langjährig zurückliegender beruflicher Asbestexposition erheben. Eine Meldepflicht des Verdachts an Unfallversicherungsträger oder Staatlichen Gewerbearzt ist gesetzlich vorgeschrieben.

Introduction

In 2017, ovarian cancer due to asbestos exposure was designated a new gynaecological occupational disease. This paper aims to outline the scientific background and describe for the gynaecological community the practical approach in patients with ovarian cancer. In part, close reference is made to the Scientific Rationale of this occupational disease, which one of the authors (DN) was involved in drafting [1].

First, here is the German legal definition of occupational disease: “Occupational diseases are diseases which the Federal Government of Germany with the consent of the Federal Council of Germany designates as occupational diseases by statutory order and which insured persons suffer as a result of an activity giving rise to insurance cover under Article 2, 3 or 6” (Article 9 [1] Social Security Code VII). “The Federal Government shall be empowered to designate as occupational diseases in the statutory order those diseases which, according to the findings of medical science, are caused by special effects to which certain groups of persons, as a result of their insured activity, are exposed to a substantially higher degree than the rest of the population” (Article 9 [1] Social Security Code VII). In practice, this is often based on a doubling of the relative risk (i.e., the morbidity of the exposed group relative to the comparison group without exposure).

Risk Factors and Pathomechanisms of Ovarian Cancer

One established risk factor is the familial clustering of certain tumours, which is often associated with an earlier age of onset than in the normal population. The majority of genetic changes in familial breast and ovarian cancer syndrome are seen in the BRCA1 and BRCA2 genes, but there are also other – less common – risk genes such as RAD51C as well as BRIP1 and others.

Obesity, peri- and postmenopausal hormone therapy and infertility also increase the risk of developing ovarian cancer. Oral contraceptives and sterilisation by tubal ligation reduce the risk, while parity and lactation correlate inversely with the risk of serous ovarian cancer [2].

The pathomechanism of ovarian cancer development is based on activation of oncogenes, non-response to growth-inhibiting cellular signals, survival of apoptotic processes, and cellular immortalisation. Angiogenesis, invasive growth and metastasis are early events [3]. Every ovulation involves cytokine mediated inflammatory processes, which also play a role in tissue repair – in this respect, inflammatory processes probably play a role in the genesis of ovarian cancer [4]. The role of inflammatory processes in tumour development is supported by the observation that women on anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs, are less likely to develop ovarian cancer [5].

Histopathology differentiates five different subgroups of ovarian cancer: high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous. Epithelial tumours of the peritoneum (type Müller) are differentiated as low- and high-grade serous carcinomas.

Asbestos as a Naturally Occurring Fibrous Mineral Material

Asbestos (in ancient Greek ἄσβεστος, “unquenchable”), is a collective term for various naturally occurring, fibrous crystallised silicate minerals which, when processed, yield technically usable fibres of varying lengths. The fibre of crocidolite from the hornblende group (also known as blue asbestos) is bluish, while the chrysotile fibre (serpentine group) is white or green. Chrysotile, also called white asbestos, saw the widest technical usage. The occupational use of asbestos is discussed below in the practice-related section “Possible occupational exposure that the gynaecologist must thus inquire about when taking the medical history of patients with ovarian cancer”.

Asbestos Usage and Ban in Germany

After World War II, asbestos usage in the Federal Republic of Germany rose steeply from a very low level to a maximum of around 180 000 t/year by the end of the 1960s, remained at a high level of around 160 000 t on average until the end of the 1970s, and then declined very steeply. In contrast, the decline in usage in the German Democratic Republic (GDR) in the 1980s was much more moderate. There are important differences in the use of asbestos in the two German states in those days; in the GDR, sprayed asbestos was only used until 1969 and then almost exclusively in shipbuilding. Only in a few exceptional cases was sprayed asbestos still used later as fire protection for steel girder constructions in public buildings (e.g., in the “Palace of the Republic”). Since sprayed asbestos was not used in private housing, no floor coverings containing asbestos were installed there. In the meantime, the 1993 ban on the use of asbestos in Germany has reduced asbestos usage here to practically zero. Today, asbestos materials are essentially only handled during demolition, renovation and maintenance work [6].

In 1983, Iceland was the first country in the world with a national ban on all types of asbestos – 10 years before Germany. Since then, more than 50 other countries have issued similar bans.

In recent years, however, the pace of these additional national asbestos bans has slowed. Some emerging countries have reversed their asbestos bans, while others have transition periods that are far too long. Nine of the ten most populous countries in the world have not banned asbestos. As a result, the protection of the world's population from the health effects of asbestos exposure is low; protection is primarily provided in the developed countries.

The above ban on the use of asbestos in Germany preceded the ban in the European Union (EU) by 12 years. It is estimated that, compared to the rest of the EU, this earlier ban on asbestos use in Germany prevented more than 20 000 lung cancers and mesotheliomas and saved the lives of almost as many people.

Pathomechanism of Asbestos Effects in Humans, Especially in the Ovary Target Organ

Inhaled asbestos fibres have proven fibrogenic effects in humans as well as local tumourigenic characteristics. The carcinogenicity for the target organs lungs, larynx, pleura including pericardium, and peritoneum including tunica vaginalis testis has been clearly established for many years [7]. It is only in the last few years that the data have become more conclusive to the effect that ovarian cancer is also caused by asbestos [8].

Asbestos fibres are primarily inhaled with the air we breathe. Mucociliary clearance transports most of the deposited fibres first into the gastrointestinal tract and parts of it from there apparently into the abdominal cavity. In addition, lymphogenic and haematogenic transport as well as the penetration of asbestos fibres into the serous cavities of the chest and abdominal cavity are under discussion. The body's own defensive reaction of coating the incorporated fibres with ferroproteins sometimes leads to the formation of asbestos bodies [9]. These can be detected not only in the lungs but also in numerous extrapulmonary and extrathoracic organs [10].

Since two studies saw the use of talcum powder (formerly often containing asbestos) in perineal powder associated with a significantly increased odds ratio of 1.33 (95% CI 1.16–1.45) [11], and 1.24 (95% CI 1.15–1.33) [12] respectively for the development of ovarian cancer, direct transvaginal incorporation of asbestos fibres can also be speculated. However, neither of these studies found a significant dose-response correlation. Other authors therefore doubt a causal connection [13]. Schildkraut et al. [14] reported an increased odds ratio for ovarian cancer of 1.44 (95% CI 1.11–1.86) in black American women with their more common use of perineal and body powder compared to the white population, and a positive dose-response correlation. To what extent a recall bias (better memory of those exposed, especially when it comes to compensation claims) plays a role [15] or whether a heightened readiness for inflammatory reactions of the body (e.g. [16]) contributed to the observation of Schildkraut et al. [14] in Black Americans compared to the white population remains unclear at present.

Saad et al. [3] saw the carcinogenicity of talcum powder (in the sense of talcum containing asbestos) and asbestos as also mediated by inflammatory processes, although there is no animal model for this.

Epidemiological Data on Ovarian Cancer by Asbestos Exposure

In its monograph 100 C, the International Agency for Research on Cancer (IARC, Lyon) of the World Health Organisation (WHO), after reviewing the published literature, concluded more than 10 years ago that there was sufficient evidence for the carcinogenicity of asbestos in humans to cause ovarian cancer (meeting on 17–24 March 2009, [7]). This assessment was based on 11 cohort studies in 13 populations, 10 of them with occupational asbestos exposure, and 3 others with environmental exposure, plus one case-control study. This assessment by the IARC [7] did not include a meta-analysis.

In addition, there was a meta-analysis by Camargo et al. [8] on the question of the association between occupational exposure to asbestos and the development of ovarian cancer. The authors evaluated 18 cohort studies of occupationally exposed women and also performed a meta-analysis on the association between occupational asbestos exposure and ovarian cancer, with mortality being the target criterion in 17 studies and incidence in one.

While preparing the scientific rationale to designate "ovarian carcinoma by asbestos exposure", the systematic reviews of Reid et al. [17] and Bounin et al. [18] were also considered, and one of the authors (DN) screened the scientific literature for new publications on the topic as of September 2016. Each of the studies available up to this point was critically evaluated; for details, please refer to the detailed scientific rationale [1].

Finally, the Medical Expert Advisory Board on Occupational Diseases at the Federal Ministry of Labour and Social Affairs (BMAS) conducted its own meta-analysis of all studies (led by M. Möhner, as of September 2016).

This resulted in the following (▶ **Fig. 1**).

Meta-analysis of all studies using a random effects model yielded an overall SMR of 1.88 (95% CI 1.47–2.39).

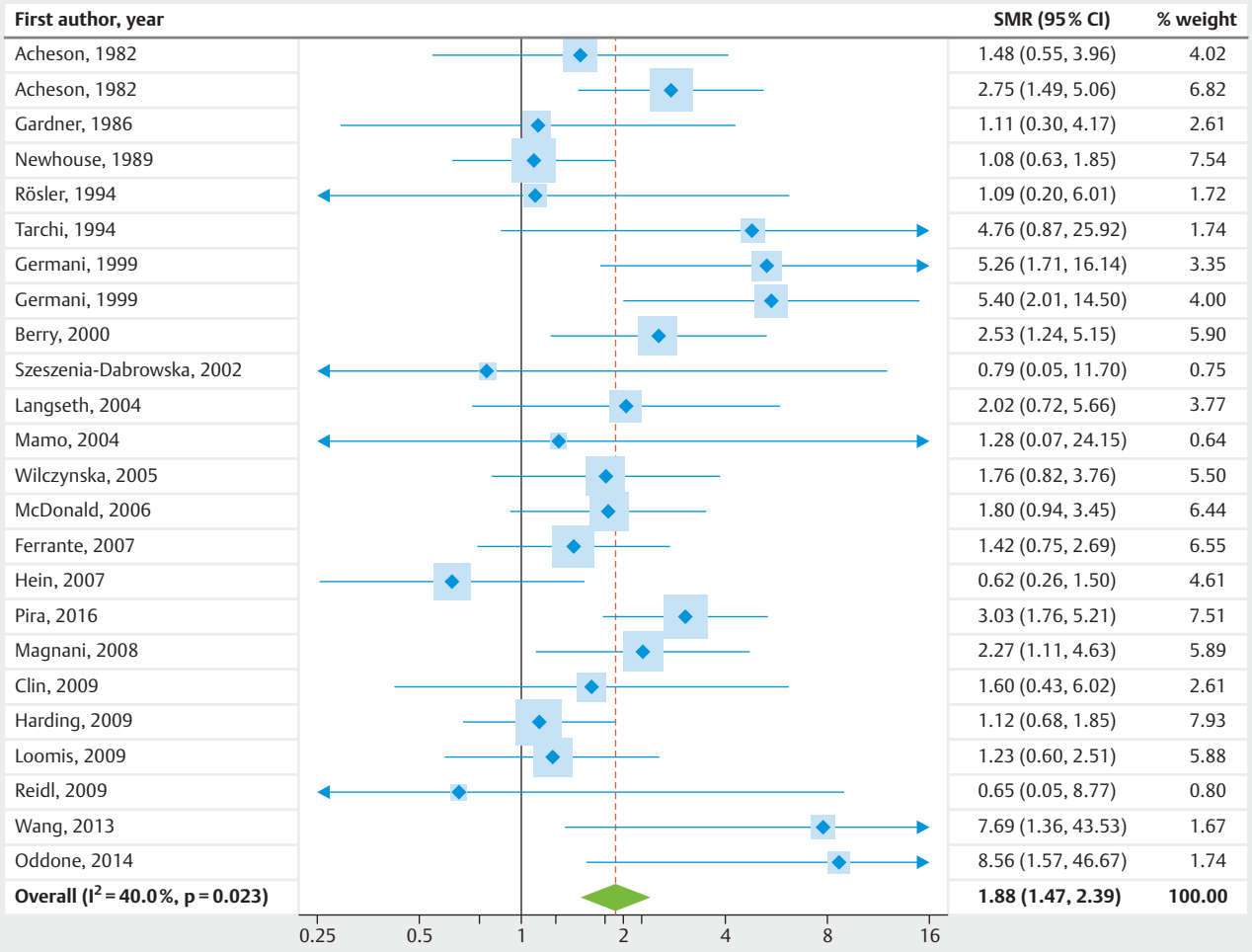
If the distinction is made according to "ovarian cancers confirmed", as in Reid et al. [17], a pooled effect estimate of 1.89 (95% CI 1.40–2.55) is obtained for the studies without histological verification of ovarian cancer and a pooled effect estimate of 1.98 (95% CI 1.32–2.97) for those with histological confirmation of ovarian cancer. The difference is thus negligible ($p > 0.8$).

Note

In summary, women with a history of occupational asbestos exposure have about double the risk of dying from ovarian cancer compared to those without such exposure.

Doubling of the risk of ovarian cancer in workers with occupational exposure to asbestos is reached or exceeded in particular in the following cases:

- Participants in European studies (SMR 1.95, 95% CI 1.51–2.51),
- Subgroups with an SMR for lung cancer greater than 2.0 (SMR 2.25, 95% CI 1.64–3.07)
- Participants in the groups with the highest exposure (SMR 2.78, 95% CI 1.36–5.66)



Note: Weights are from random effects analysis.

▶ **Fig. 1** Meta-analysis on the association between occupational exposure to asbestos and ovarian cancer, based on Camargo et al. (2011) and additional consideration of data from Langseth et al. (2004), Ferrante et al. (2007), Wang et al. (2013) and Oddone et al. (2014), replacement of Pira et al. (2007) with Pira et al. (2016). From [1].

Procedure for Extending the Current Occupational Disease 4104 to Include Ovarian Cancer

Assessing the risk of ovarian cancer from asbestos exposure requires the calculation of a cumulative asbestos fibre dose, above which the risk of disease doubles. Once this dose is exceeded, the percentage of occupational asbestos exposure in causing a disease would be more than 50%. The studies included by the IARC [7] and Camargo et al. [8] to assess the risk of ovarian cancer from asbestos exposure, as well as more recent publications, did not allow precise quantitative calculation of such a dose. However, it was deemed obvious to fall back on previous German work that affirmed risk doubling for the development of lung cancer in the sense of occupational disease no. 4104 under three conditions: In the regulations governing occupational diseases in Germany, the following applied until 2017:

- in conjunction with asbestos dust lung disease (asbestosis),
- in conjunction with disease of the pleura caused by asbestos dust or
- evidence of exposure to a cumulative workplace dose of asbestos fibre dust of at least 25 fibre years (25×10^6 [(fibres/m^3] × years]).

(Only one of the three criteria mentioned in the bullet points must be fulfilled – the first two findings are radiological diagnoses, the third is a cumulative dose measure to be reconstructed by the Statutory Accident Insurance carrier from an occupational point of view. One fibre year corresponds to the product of the concentration of one million asbestos fibres of critical dimensions per cubic metre of air in the workplace over a period of 240 working days).

The data of Camargo et al. [8] showed that those with a doubled risk of developing lung cancer due to work-related asbestos exposure had a mean 2.25-fold (95% CI 1.64–3.07) increased

mortality risk from ovarian cancer. Therefore, it seemed scientifically legitimate and justified to link the recognition of ovarian carcinoma as an occupational disease due to occupational asbestos exposure to the same medical and occupational requirements that are demanded for the claim of asbestos-related lung cancer. When this occupational disease (No. 4104) was introduced, the focus was also on the doubling of the risk of developing lung cancer (later also laryngeal cancer) due to occupational exposure to asbestos.

The legal definition of occupational disease no. 4104, which was expanded in 2017 to include ovarian carcinoma, is therefore:

DEFINITION

Lung cancer, laryngeal cancer *or ovarian cancer*

- in conjunction with asbestos dust lung disease (asbestosis)
- in conjunction with disease of the pleura caused by asbestos dust or
- evidence of exposure to a cumulative workplace dose of asbestos fibre dust of at least 25 fibre years (25×10^6 [{fibres/m^3} × years])

Accordingly, Chapter 5.2 "Ovarian carcinoma as a notifiable occupational disease" was included in the S3 guideline "Malignant ovarian tumours" with questions on medical history and exposure as well as the procedure for notification (S3 guideline Diagnostics, therapy and follow-up of malignant ovarian tumours, https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Ovarialkarzinom/Version_4/LL_Ovarialkarzinom_Langversion_4.01.pdf).

Doctors are generally legally required to report any suspected presence of occupational disease to the Statutory Accident Insurance carrier or to the state authority responsible for occupational health and safety (Article 202 of the German Social Security Code, Book VII). Thus, if the medical history of a patient with ovarian cancer suggests occupational exposure to asbestos, her physician is legally required to report the reasonable suspicion of occupational disease to the State Occupational Safety and Health Agency or the respective Statutory Accident Insurance carrier.

Possible Occupational Exposures Gynaecologists Must Therefore Inquire About When Obtaining the Medical History of Patients with Ovarian Cancer

In the Federal Republic of Germany, which had been importing asbestos in the past, numerous products were manufactured from raw asbestos. Examples include the asbestos cement industry; friction liner industry; rubber-asbestos (CAF) industry; asbestos paper, board, gasket, and filter industry; asbestos textile industry; and the asbestos plastics industry.

In addition, products containing asbestos are or were used in a wide variety of industries, e.g., in certain activities in structural and civil engineering; automobile industry; insulation; heating, air conditioning, heating and ventilation; as well as in vehicle construction.

Since the latency between the onset of exposure and disease are likely to be around 30 to 50 years on average, it is essential to obtain a work history covering decades.

Important sources of danger for the inhalation of asbestos dust are or were in particular:

- Asbestos processing. In this process, either parent rock containing asbestos is crushed and/or raw asbestos loosened into more strongly disaggregated fibres in pan, impact or beater mills.
- Manufacture and processing of asbestos textile products such as yarns; twines; tapes; cords; ropes; hoses; cloths; wrappings; clothing, etc. This involves activities such as filling; weighing; mixing; carding; spinning; twisting; braiding; weaving; and cutting to size. The wearing of uncoated asbestos containing protective work clothing must also be taken into account where appropriate.
- Industrial manufacture and processing of asbestos cement products, especially weather-resistant sheets and building materials including prefabricated moulded elements, e.g., for roofing; façade constructions; structural fire protection; etc.
- Processing and repair of the asbestos-cement products listed above, e.g., activities such as sawing, drilling, grinding, etc., in the building and building materials industry.
- Industrial manufacture and processing of friction linings containing asbestos, especially clutch and brake linings.
- Replacement of such friction linings, e.g., activities such as turning, grinding, drilling, milling of brake linings in automotive repair shops, etc.
- Manufacture, application, repair and disposal of sprayed compounds containing asbestos for thermal, sound and fire insulation.
- Manufacture, processing and repair of acid- and heat-resistant seals, packings, etc., e.g., in pipeline construction in the chemical industry.
- Manufacture, treatment and processing of rubber-asbestos (CAF) products.
- Manufacture, treatment and processing of paper, cardboard and felt materials containing asbestos.
- Use of asbestos as an additive in the manufacture of paints; floor coverings; sealants; rubber tyres; thermoplastics; plastic resin moulding compounds; and the like.
- Removal, e.g., by demolition work, repairs etc., and removal of the asbestos-containing products above.

In addition, various minerals, e.g., soapstone (talc), gabbro, diabase, etc. contain small amounts of asbestos, such as tremolite and actinolite. As a result, they can pose asbestos risks through exposure to mixed dust.

The occupational history regarding occupational asbestos exposure can be shortened significantly if the patient is asked to go through a detailed list of possible occupational exposures available on the Internet: https://www.tumorzentrum-muenchen.de/fileadmin/Downloads/Patientenseite/Experten_Service/Fragebogen_Berufl._Risikofaktoren_2017.pdf

If necessary, the support of the local university institutes of occupational medicine with outpatient clinics can also be called upon.

Note

If the work history of a patient with ovarian cancer is positive with regard to one of the above or similar activities, this suspicion must be documented in an occupational disease report.

This is done on the official form: https://www.dguv.de/medien/formtexte/aerzte/f_6000/f6000.pdf

If the patients have had computed tomography chest scans, it is helpful if the radiologist reading these scans looks for typical signs of asbestos inhalation sequelae (asbestosis, frequently pleural plaques), as these bridge findings facilitate recognition as an occupational disease. Otherwise, the Statutory Accident Insurance carrier will have to investigate whether the cumulated dose fulfils the 25 fibre years requirement. The fibre year report 1/2013 [6] contains detailed measurements, including those from historical workplaces.

Rationale of the Notification Requirement

Apart from the legal requirement to report any suspicion, experience has shown that physicians and those affected often ask themselves what the point of reporting the disease is for the patient.

Here, a formal distinction must be made between insured event and benefit. The insured event is defined as a disease of an insured person which fulfils the criteria of an occupational disease (here no. 4104) resulting from an insured activity. Benefits are payable if the insured person requires treatment or is partially or completely unable to work. Ovarian cancer as an occupational disease will almost always be an insured event but will also result in benefits payable. In addition to prevention measures, the catalogue of the statutory Accident Insurance carriers includes the following:

- Medical treatment
- Rehabilitation benefits
- Measures supporting the resumption of work
- Measures to participate in life in the community
- Benefits in case of nursing care dependency

In addition, the statutory Accident Insurance covers financial benefits during inability to work and pays injury compensation or transition allowances. In ovarian cancer, it is almost always the case that the patient will have reduced earning capacity on the general labour market, and therefore the insured person can expect to receive a pension once the occupational disease has been recognised. In addition, the insurance provides for survivors' benefits.

With regard to the practical workflow in the occupational disease process including expert assessment, see [19] for a detailed description. Further information on the topic of occupational diseases may also be found in Nowak [20] and Nowak and Ochmann [21].

Consistent reporting of suspected cases can also contribute in the long run to answering the important practical question of preventive adnexectomy in asbestos-related pleural mesothelioma: There is no data to date on how many patients with pleural mesothelioma develop ovarian cancer. Therefore, no general recommendation for preventive adnexectomy can be given at present. This recommendation currently applies only to BRCA1 and BRCA2 and other high-risk genes. Therefore, the current recommendation for gynaecologists can only be to inquire about asbestos exposure and in case of ovarian cancer to report it as a justified suspicion of occupational disease in order to obtain further data and, if necessary, to be able to answer the above question.

Finding Cases of "Ovarian Cancer from Asbestos Exposure"

The studies on which the newly recognised occupational disease "ovarian carcinoma from asbestos exposure" was based often had limitations such as poor histological validation or small patient numbers. For further refinement of the occupational disease, an even more precise specification of a dose-response relationship would have been desirable. Supported by the German Statutory Accident Insurance (DGUV), a pilot study was therefore conducted to test the feasibility of a large-scale epidemiological study to investigate even more precisely the quantitative relationship between occupational asbestos exposure and ovarian cancer. At the same time, this way of "active case finding" should try to transfer as many such patients as possible from the collective health care system (GVS) to the occupational disease care system. Out of a total of 16000 insured female workers registered with the Gesundheitsvorsorge (GVS) c/o Berufsgenossenschaft Energie Textil Elektro Medienerzeugnisse (BG ETEM) who had been exposed occupationally to asbestos, a total of 1000 insured women were randomly drawn by the GVS between December 2017 and April 2018 and invited to participate in the study. Those who agreed to participate were then interviewed by telephone. The questionnaire used was the same as the one to be used in the main study. The feasibility of the project was verified on the basis of precisely defined criteria. The criteria related to the expected willingness to participate; the expected number of cases; the possibility of detailed fibre-year calculations based on the asbestos exposure data collected by questionnaire; and the availability of significant medical records (imaging studies, medical reports, histological specimens). At 17%, the willingness to participate was significantly lower than the targeted number (60%). With six suspected cases of ovarian cancer, of which two diagnoses were considered confirmed based on medical documentation, the number of cases was within the expected range. Fibre-year calculations were performed with the help of the questionnaire data in 29% of the respondents, but among them only for one of the suspected cases. Medical records were available for very few of the participants. Thus, only the feasibility criterion of the expected number of cases was met. The results of this pilot study therefore indicate that due to the limited willingness to participate the intended project is only feasible to a rather limited extent [22].

Since a "nationwide" survey of women with occupational exposure to asbestos, who are registered with the GVS, does not appear to make sense due to inadequate participation rates, the responsible collection of asbestos history and reporting of suspected occupational diseases by each gynaecologist is of particular importance. This paper would like to contribute to this.

Conflict of Interest

The authors declare that they have no conflict of interest.

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