บทความพิเศษ

Special Article

Susceptibility Factors in the Genesis of Mesothelioma

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★★The Academy of Science, The Royal Society of Thailand, Bangkok, 10300
★Presented at the Annual Conference of the Interdisplinary Networks Section of the Royal Society of Thailand at Impact Building, Muangtongthani, July 6, 2016
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Mesothelioma is a disease that starts in cells linings certain organs of the body, especially the pleura, peritoneum, pericardium and tunica vaginalis testis. The tumors can be benign or malignant at the start.

Mesothelioma is a rare disease. The incidence of mesothelioma in the United States was about 3,000 new cases diagnosed each year, while in Thailand it was only 81 cases reported in the period from 1928 to 2015. The incidence of this disease has leveled off and even declined slightly in developed countries, probably owing to changes in workplace exposures to asbestos, whereas the incidence is increasing in underdeveloped and developing countries. The prevalence of mesothelioma is lower in women than men and much more common in older people; for pleural mesothelioma, the average age at the time of diagnosis is 69 years.

In terms of race, mesothelioma is more common in whites and Hispanics/Latinos than in African Americans or Asian Americans.

The main risk for mesothelioma is exposure to asbestos, usually from high levels of exposure in the workplace; as such, it mostly affects miners, factory workers, insulation manufacturers and installers, railroad and automotive workers, ship builders, gas mask manufacturers, plumber, and construction workers. The general population is also exposed to very low levels of naturally occurring asbestos in outdoor air as the mineral is contained in dust that come from rocks and soil containing asbestos; particles of asbestos somehow escape into the air, such as when building materials begin to decompose over time, or during remodeling or removal. Unfortunately, the risk posed by mesothelioma does not decline over time following one's exposure to asbestos; the risk remains a lifelong one.

The risk of developing mesothelioma is loosely related to how much asbestos a person is exposed to and how long the contact lasts at specific sites. It is known that most people exposed to asbestos, even in large amounts, do not get mesothelioma; other factors, such as a person's genes, may make that person more or less likely to develop mesothelioma following exposure to asbestos. However, mesothelioma is not caused by exposure to asbestos alone. Other minerals chemically related to asbestos, such as zeolites, are known to cause mesothelioma. Zeolites are common in rocks and soil in some parts of the world; one such mineral known as erionite is common in Turkey and is believed to be the cause

of high rates of mesothelioma rates in such areas. Zeolite are common also in China, the Republic of Korea, Jordan, Slovakia and the United States. There are some rare reports of mesothelioma developing in people who had been exposed to high doses of radiation to the chest or abdomen as a treatment for a different form of cancer.

Researchers have found several other factors that increase a person's risk of mesothelioma, apart from age, gender and race.

Smoking is a potential confounding factor, which is not a risk factor in mesothelioma. However, the patterns of deposition and retention of asbestos fibers after inhalation are important in its pathogenesis. Most asbestos fibers deposited in the tracheobronchial airways are carried proximally on the surface of mucus to the larynx to be swallowed. For non-smokers, the residence time for such fibers on the surface of the tracheobronchial region is too short for any significant change to take place in the size or composition of the fibers. For smoker, there may be bronchial airway surfaces that are denuded of cilia where fibers can be deposited and accumulate, which would account for the greater incidence of lung cancer in smokers than in non-smokers due to increased residence time of fibers in the lung.

Opportunistic infection with simian virus 40 (SV40) might increase the risk of developing mesothelioma in asbestos-exposed persons, such as the possible incidence from injectable contaminated polio vaccines administered between 1955 and 1963 . There is evidence of correlation between SV40 large T-antigen (SV40LTAg) and p53 tumor suppressor proteins in mesothelioma, which in turn offer support for the hypothesis that SV40 contributes to malignancy by binding and inactivating p53 and other nuclear proteins.

When cells in the body suffer damage to their DNA, which is the chemical molecule in each of the cells that makes up genes – the instructions for how the cells function. Some genes control when cells in the body grow, divide into new cells, and die at the right time (apoptosis). Changes in these genes may cause cells to grow out of control and lead to the formation of a tumor.

Asbestos is the main cause of mesothelioma; when it is breathed in, the asbestos fibers travel to the deepest parts of the air passages and pleura where they can cause inflammation, scarring and damage to the DNA of cells, causing changes that result in uncontrolled cell growth. However, owing to the fact that most exposed people do not get mesothelioma, other factors, such as a person's genes, may make that person more susceptible to the development of mesothelioma.

Molecular genetic analysis has revealed several key genetic alterations which are responsible for the development and progression of mesothelioma, including cyclin-dependent kinase inhibitor 2A alternative reading frame (CDKN2A/ARF), neurofibromatosis type 2 (NF2) and BRCA1-associated protein-1 (BAP1) genes, which are the most frequently mutated tumor suppressor genes in mesothelioma cells. BAP1 is the gene that normally keeps cell growth under control; it is involved in histone modification and its inactivation induces the disturbance of global gene expression profiling and mesothelioma susceptibility.

DNA methylation is essential for normal development; however, it is also implicated in many pathologies including cancer. Up-regulation of epidermal growth factor receptor (EGFR) plays an important role in the development of malignant pleural mesothelioma.

Conclusions

Only a fraction of subjects exposed to asbestos develop mesothelioma, suggesting that additional

factors may render some individuals more susceptible, apart from ages, sex, race, and the smoking of tobacco. Somatic and epigenetic alterations in mesothelioma cells, associated with altered expression and activation or inactivation of critical genes, are important in oncogenesis.

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