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Environmental risk factors for prevention and molecular intervention of cervical cancer

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Abstract

Cervical cancer (CC) is potentially the most preventable and treatable cancer in human but it is a leading cause for cancer morbidity and mortality in women around the world. Therefore, more innovative prevention and treatment protocols need to be developed and implemented. With better understanding of the etiology of the disease, specific prevention protocols that involve life-style modifications to minimize the impact of environmental risk factors can be developed. It may be necessary to implement unique modification protocols for different countries. In addition, antiviral vaccine is a highly promising prevention approach. With respect to therapy, the development of more specific protocols that have fewer side effects is needed. With the availability of sophisticated molecular techniques, a new generation of targeted approach that has the potential to generate outstanding efficacy is being tested. Using the siRNA technology against the expression of human papillomavirus oncogenes, specific biological pathways that are essential to the growth and survival of the CC cells can be interrupted. Another promising approach is the molecular intervention of the estrogen pathway by blocking the expression of estrogen receptors. These molecular techniques may work by reactivating endogenous regulatory processes, e.g., the core apoptotic machinery, that can cause self-destruction of the CC cells, thus providing potentially effective molecular therapy. These topics are discussed in this review.

Keywords: Cervical cancer; HPV infection; Cigarette smoking; SiRNA; Estrogen; Cancer prevention; Dominant negative estrogen receptor; Molecular therapy; Gene therapy

Introduction

Cervical cancer (CC) is a leading cause of cancer morbidity and mortality for women around the world. In 2005, the American Cancer Society estimated that more than 10,000 cases of invasive CC were diagnosed and 3710 women died from the disease in the US (www.cancer.org). However, approximately 85% of the incidence and mortality from CC occurs in developing countries, amounting to approximately 500,000 cases and 275,000 deaths (www.WHO.org; Parkin, 2001; Fig. 1) on a yearly basis. For some developing countries,

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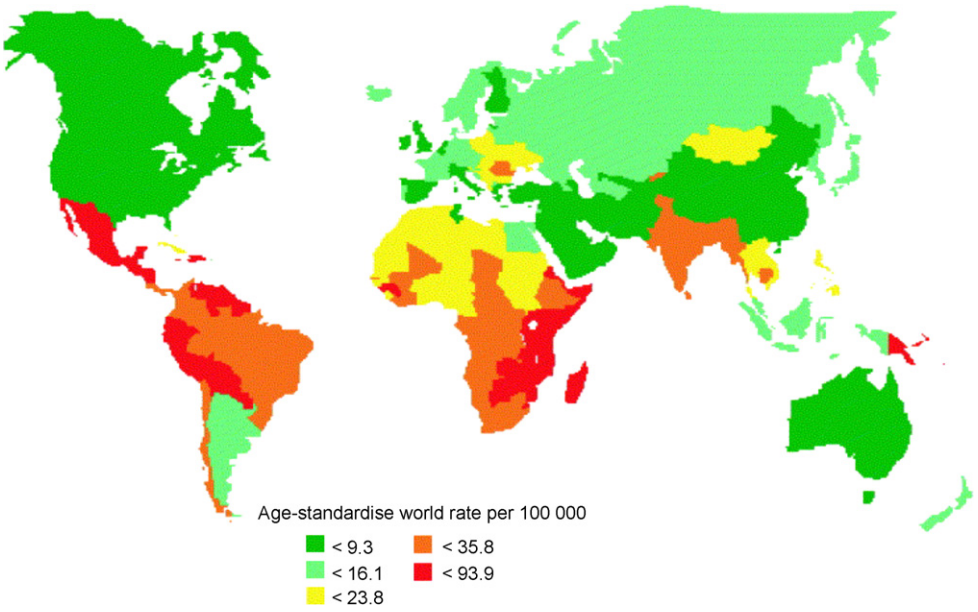

Fig. 1. Estimated age standardized by world standard incidence rates, by country: cancer of the cervix uteri. (Reprinted from Parkin, 2001 with permission from Elsevier).

therefore, CC is the number one cause of cancer-related deaths in women. On the other hand, CC is potentially one of the most preventable and treatable cancer types in the population; therefore, such extensive human sufferings are inconceivable.

Many reviews have been written on CC. However, most of them have been concentrated mainly on topics such as human papilloma virus (HPV) etiology, prevention, screening, pathology, therapy, management and social–economic concerns. In this review, we will focus on the identification of environmental risk factors that are causally related to the development of CC and on how such information can be used to develop disease prevention and molecular intervention strategies.

CC – problems and opportunities

Among sexually active females, the risk for contracting HPV is exceedingly high, which translates to a lifetime risk of approximately 80% (Baseman and Koutsky, 2005). With such high infection rate, it becomes clear that the development of CC is still a rare event among HPV-infected women. Since significant increase in CC incidence occurs first in young adult females, the evidence indicates that, after infection with high risk HPV, it takes approximately 10 years for cancer to develop. The most common histological type of CC is the squamous cell carcinoma (SCC) and the second common type is the adenocarcinoma (www.cancer.org; reviewed by Snijders et al., 2006). The development of CC takes on a series of developmental changes. The development begins usually with the presence of non-invasive squamous lesions that are known as cervical intraepithelial neoplasias (CINs) or squamous intraepithelial lesions (SILs). These lesions are further staged as CIN 1 (or LSIL) for low grade lesions, CIN 2 and CIN 3 for medium to high grade lesions (or HSIL) and to carcinoma in situ. Interestingly, the low grade lesions may regress spontaneously leading to no serious consequences. When the carcinoma becomes invasive it can cause very serious consequences. Clinical management of these various lesions/carcinomas typically requires a combination of surgical and/or chemo- and radio-therapy protocols.

Although the risk factors, clinical features and stages for CC have been clearly identified, major questions remain to be resolved. Some questions are posted here. Why does a common and mostly benign infection process result in malignancy? Why are some individuals susceptible to the infection and/or development of the disease, and others are resistant? What mechanisms trigger the progression of the disease from one stage to another? How can one use the current knowledge to these questions to develop precise and effective prevention and intervention strategies? Some possible answers to these questions are discussed in this review.

Environmental factors for the development of CC

Approximately 90% of CC is associated with HPV infection, particularly with high risk HPV types such as HPV 16 and 18 (reviewed by Baseman and Koutsky, 2005). In addition, infection with high risk HPV can cause oncogenic transformation of cells in vitro (Chen