



Editorial

Cervical cancer: From Hippocrates through Rigoni-Stern to zur Hausen

On September 5, 2008, the Warren Alpert Foundation announced that Harald zur Hausen and Lutz Gissmann had won the Foundation's 20th annual prize. In the 1980s, zur Hausen and Gissmann provided the first concrete evidence that specific Human Papillomavirus (HPV) types were linked to cancer of the cervix [1,2]. That was the prelude to assignment of the Nobel Prize to the German scientist. "Dr. zur Hausen went against current dogma by postulating that the virus caused cervical cancer," said the Karolinska Institute in Stockholm, in the statement explaining the reasons for the assignment of the prize.

More than 2000 years have elapsed since the first description of cervical cancer by Hippocrates [3].

Aretaeus (Ἀρεταῖος), one of the most celebrated of the ancient Greek physicians, who probably practised in the first century after Christ, described uterine cancer as superficial and deep ulcers, which later infiltrate the uterus. He also described another type of cancer, which does not present ulcers, but is rather a growth in the uterus [3].

Although in 1991 Griffiths [4] did not recognize the importance of Rigoni-Stern as a pioneer in the perception of the pathogenetic mechanism of cervical cancer, Rigoni-Stern's work is mentioned in almost 70 papers published from 2000 to 2008 [5]. In the literature, Rigoni-Stern appears as an epidemiologist ahead of his time. Indeed, the Royal Society of Epidemiology was founded in London in 1850. A surgeon in Padua in the mid-19th century, Rigoni-Stern appears to have had an amateur interest in epidemiology, and observed that cancer of the uterine cervix rarely occurred among celibate nuns [6].

Epidemiologists working in the early 20th century noted that: cervical cancer was common in female sex workers [7], it was more common in women whose husbands had a high number of sexual partners or were regular customers of prostitutes [8], and it was rare in Jewish women [9].

Other important milestones in the prevention of cervical cancer were: the invention of the colposcope in 1925, the development of the Pap technique by Papanicolaou, the launch of Pap screening by Papanicolaou and Traut [10] and the invention of a specific spatula to scrape the cervix by Ayre [11]. Another important achievement was the standardization of screening results by the Bethesda System in 1988 [12]. However, in 1976 zur Hausen and Gissmann had already found HPV DNA in cervical cancer and warts [13].

In 1983 zur Hausen, Gissmann and their co-workers identified HPV 16 in precursor lesions of genital cancer. In 1985 they demonstrated the presence of HPV DNA in cervical cancer cells [2]. The findings of the two scientists created the basis for subsequent studies, which led to the development of two preventive vaccines:

Gardasil® and Cervarix®. Both vaccines are effective in protecting against cervical lesions due to HPV 16 and 18, and Gardasil® also protects against HPV 6 and 11, which are responsible for 90% of genital warts.

HPV 16 and 18 are responsible for 70% of cervical cancer worldwide. From a global perspective, each year about 500,000 new cases occur and 270,000 women die of cervical cancer [14]. Furthermore, it has been estimated that 33,386 new cases of cervical cancer occurred in Europe in 2002 and that the disease caused 14,638 deaths [15]. In Italy there are 3500 new cases/year and 1500 deaths [16,17].

Clinical trials have proved that the above-mentioned vaccines are immunogenic and effective against mild and severe cervical lesions. Furthermore, both vaccines have proved to be safe and well tolerated [18,19]. Currently available in various parts of the world, these two vaccines have recently been approved by regulatory authorities: only Gardasil® by the FDA in the US and both by the EMEA in the EU.

Several nations have introduced HPV vaccination, such as the US [20], Canada [21] and Australia [22]; the European Centre for Disease Control (ECDC) has also recommended its use in the countries of the European Union [23]. In the US, the ACIP recommends routine vaccination of females aged 11–12 years with 3 doses of quadrivalent HPV vaccine. The course of vaccination can be started as early as the age of 9 years. Vaccination by means of a catch-up strategy is also recommended for females aged 13–26 years.

The Canadian National Advisory Committee on Immunization advises vaccination for the following groups of people: (1) Females between the ages of 9 and 13 years who have not yet become sexually active; (2) Females between the ages of 14 and 26 years, even if they have become sexually active, as they would also benefit from the vaccine; (3) Females between the ages of 14 and 26 years who have had previous Pap abnormalities, including cervical cancer, or have had genital warts or known HPV infection, as they could still benefit from the vaccine (they may not have been infected with the HPV types covered by the vaccine).

Since April 2007, the Australian Government has provided the new vaccine free of charge to all women and girls aged between 12 and 26 years, through the National HPV Vaccination Program. Among developed countries, only Austria offers vaccination to young boys, too. In Germany, vaccination is offered to 12–17-year-old females, and in France to 14-year-old females and to 15–23-year-old virgins or girls who have become sexually active within the previous 12 months [24].

In September 2008, Scotland was the first of the four UK countries to start a programme of vaccination against HPV, at the

beginning of the new school year [25]. The policy of the UK Department of Health is to vaccinate 12–13-year-old schoolgirls, and to implement a 2-year catch-up programme for those who will turn 18 by 2009 [26].

In Italy, the HPV vaccination campaign started in March 2008, and the various regions offer the vaccination free of charge at least to 11-year-old girls [27]. The question of how best to improve the Italian vaccination policy is currently the subject of lively debate [28]; a recent study [29] has suggested that, in the short period, the best choice would be to temporarily increase the cohorts to whom the vaccination is offered by including 14-, 15- and 16-year-old girls.

Nevertheless, important questions remain open, such as, for instance, the duration of protection, the best policy in the different epidemiological contexts, and how to vaccinate women in developing areas of the world, where cervical cancer kills more females than any other cancer [30].

In any case, the introduction of a vaccine which protects against a necessary cause of cancer is an epochal moment in medical science; a new era of cancer prevention has undoubtedly begun.

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