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European Code against Cancer 4th Edition: Infections and Cancer☆

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ABSTRACT

Of the 2,635,000 new cancer cases (excluding non-melanoma skin cancers) occurring in the European Union (EU) in 2012, it is estimated that approximately 185,000 are related to infection with human papillomaviruses (HPVs), hepatitis B and C viruses (HBV and HCV), and *Helicobacter pylori* (*H. pylori*). Chronic infection with these agents can lead to cancers of the cervix uteri, liver, and stomach, respectively. Chronic infection with HCV can also lead to B-cell non-Hodgkin lymphoma. Human immunodeficiency virus (HIV) infection continues to be of major public health importance in several EU countries and increases cancer risk via HIV-induced immunosuppression. The fourth edition of the European Code Against Cancer presents recommendations on effective and safe preventive interventions in order to reduce the risk of infection-related cancers in EU citizens. Based on current available evidence, the fourth edition recommends that parents ensure the participation of their children in vaccination programs against HBV (for newborns) and HPV (for girls). In the 'Questions and Answers' (Q&As) section about vaccination and infections in the website for the European Code Against Cancer, individuals who are at risk of chronic HBV or HCV are advised to seek medical advice about testing and obtaining treatment when appropriate. Individuals most at risk of HIV are advised to consult their doctor or healthcare provider to access counselling and, if needed, testing and treatment without delay. Information about *H. pylori* testing and treatment is also provided as testing might currently be offered in some high-risk areas in Europe. The rationale and supporting evidence for the recommendations on vaccination in the European Code Against Cancer, and for the main recommendations on vaccination and infection in the Q&As, are explained in the present review.

1. Introduction

The population-attributable fraction (PAF) for cancer-related infections in more highly developed countries has been estimated to be 7.4% [1]. In 2012, approximately 195,000 of 2,635,222 new cancer cases (excluding non-melanoma skin cancers) occurring in the European Union (EU) [2] are estimated to be infection-related [1]. Human papillomaviruses (HPVs), hepatitis B virus (HBV), hepatitis C virus (HCV), and *Helicobacter pylori* (*H. pylori*) account for approximately 95% of these cases [1]. Because of the immunosuppression induced by human immunodeficiency virus (HIV), this virus should be also considered a cause of infection-related cancers in the EU. Current available evidence has been reviewed here to recommend – in the fourth edition of the European Code Against Cancer and related 'Questions and

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Answers' (Q&A) – effective and safe interventions for EU citizens to reduce their risk of infection-related cancers.

2. Human papillomaviruses

2.1. Role in cancer

Twelve HPV types – HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 – were classified by the International Agency for Research on Cancer (IARC) Monographs Program as Group 1 (i.e., firmly established) human carcinogens, and a few other types were classified as probably or possibly carcinogenic [3]. Cancers caused by HPV include all cancers of the cervix, most anal cancers (88%), and less well identified portions of vaginal (70%), vulvar (43%), penile (50%), and oropharyngeal cancers (26%) [1,4]. HPV16 and 18 account together for about 70% of cervical cancers in every world region [5]. In HPV-positive cancers of other anatomical sites, HPV16 is also the most common HPV type, being found in about 60% of vaginal [6], 80% of anal [7], 60% of penile [8] and 95% of oropharyngeal [9] cancers. HPV6 and 11 have been classified as Group 3 agents (i.e. "not classifiable as to its carcinogenicity to humans") by the IARC Monographs Program, but are responsible for almost 100% of genital warts and recurrent respiratory papillomatosis [3,10].

The natural history and molecular mechanisms involved in cervical carcinogenesis are well understood [10,11], and effective screening methods exist to detect precancerous lesions of the cervix (see Armaroli et al., 2015). HPV is considered a necessary cause of cervical cancer [3]. Cervical HPV infection is primarily transmitted by mucosal contact, usually during sexual intercourse. It is very common in young women after the onset of sexual activity, with peak prevalence among women under 25 years of age [11–13]. The majority of HPV infections, often associated with minor epithelial abnormalities, clear spontaneously within a few years [12,13]. Persistent HPV infection may lead to precancerous lesions – cervical intraepithelial neoplasia (CIN) 2 and 3 – around the mean age of 35–42 years, a proportion of which will progress, if not treated, to invasive cervical cancer over a period of 10–20 years [11–13]. The risk for persistence and progression to cancer precursor lesions varies by HPV type, host factors and the presence of cofactors [12,13]. Cofactors include smoking, immunosuppression, high parity and hormonal contraceptive use [3,14–16]. By specifically targeting women at the age of risk of developing CIN 2/3 and cervical cancers, well-organized cervical cancer screening programs have been able to prevent four out of five cervical cancers [17] (Armaroli et al., 2015).

Compared to other HPV-related cancers, cervical cancer is the most common [4]. It is the fourth most common cancer in women worldwide, with an estimated 528,000 new cases and 266,000 deaths in 2012, of which 87% occurred in the more poorly developed regions [18]. The estimated age-standardized mortality rate (ASMR) ranged from about 2/100,000 in developed regions (such as Western Europe[1]) to more than 20/100,000 in some less developed regions [18].

Cytology-based cervical cancer screening has resulted in a substantial reduction in cervical cancer incidence in the EU, with an age-standardized incidence rate (ASIR) in 2012 of 9.6/100,000 (33,679 new cases and 13,136 deaths). However, important regional disparities still exist, with high rates in Central and Eastern countries of the EU (ASIR 28.6 in Romania, 26.1 in Lithuania, 24.5 in Bulgaria, 16.1 in Slovakia and 12.2 in Poland) compared to other EU countries where the estimated ASIR was 10.6 (Denmark) or lower (Fig. 1) [18]. Mortality rates follow a similar pattern (Fig. 1) [18].

2.2. HPV vaccines

2.2.1. Scientific justification of the European Code Against Cancer recommendation

2.2.1.1. Efficacy and safety of HPV vaccines. Two prophylactic vaccines against HPV are currently marketed internationally and in the EU/European Economic Area (EEA) (which as of July 2013 includes EU-28 and Iceland, Lichtenstein and Norway); these include the bivalent vaccine produced by GlaxoSmithKline (Cervarix®), and the quadrivalent vaccine produced by Merck (Gardasil®), both of which originally had a three-dose schedule for girls (see below).

The two vaccines are based on virus-like particles (VLPs) produced by expression in insect cells (bivalent vaccine) or yeast (quadrivalent vaccine) of the HPV L1 gene, encoding the main component of the viral capsid. These VLPs are not infectious but are highly antigenic: they produce a strong antibody response that prevents infection by neutralizing infectious virions in the mucosa at the time of contagion [19]. The bivalent vaccine includes HPV16 and 18 VLPs and is produced with a complex adjuvant system (ASO4) consisting of monophosphoryl lipid A and alum. The quadrivalent vaccine, produced with alum adjuvant, includes HPV16 and 18 VLPs and also HPV6 and 11 VLPs.

For the first time in 2009, the World Health Organization (WHO) recommended the introduction of HPV vaccination into national immunization programs, targeting 9–13-year-old girls (i.e. before the onset of sexual activity) with a three-dose regimen [20]. Evidence available up to September 2008 from the three main randomized controlled trials (RCTs) at that time (i.e. FUTURE 1 and FUTURE 2 for the quadrivalent vaccine; PATRICIA for the bivalent vaccine) and immunobridging studies were used to support this recommendation. Immunogenicity studies showing that antibody response to the two licensed vaccines is stronger in adolescent girls (aged 10–14 years) than in young adult women (aged 15–25 years) [21–23] permitted bridging of efficacy data to adolescent girls. Recently, WHO updated its HPV vaccines position paper [24] to recommend a two-dose regimen with increased flexibility in the interval between doses (see below).

The evidence on HPV vaccination was updated in the European Code Against Cancer using the methodology described in greater detail in this issue (see Minozzi et al., 2015). The Medline, Embase, PsycINFO and Cochrane Library databases were searched to identify systematic reviews (SRs) on the efficacy and safety of HPV vaccines in women; two SRs were selected [25,26]. Additional scientific publications identified by the experts were also included (as detailed below) to complete the evidence. Due to the relatively low number of RCTs on efficacy and safety of HPV vaccines in men, individual studies on this topic were directly searched using the Cochrane Central Register of Controlled Trials (CENTRAL), and six articles [27–32] were selected from the publications retrieved.

In women, the totality of the evidence reviewed is in line with the WHO recommendation with regard to both efficacy and safety; both vaccines were shown to be safe, generally well tolerated, and almost 100% effective in preventing persistent cervical HPV16/18 infections and associated precancerous lesions – CIN2 or 3 (CIN2+) and adenocarcinoma in situ (AIS) – among young women (mean age of approximately 20–22 years) not previously infected at the time of vaccination [25,33–37]. No results from longitudinal

[1] As defined by the WHO, countries in Western Europe include: Andorra, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Spain, Sweden, Switzerland, and the United Kingdom. Countries in Central Europe include: Albania, Bosnia & Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Hungary, Former Yugoslav Republic of Macedonia, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia and Turkey.