

Review of: "[Commentary] Implications of HPV infectivity in early diagnosis and treatment of advanced/recurrent malignancies"

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Potential competing interests: No potential competing interests to declare.

“Abstract

Infection with HPV genotypes is a cause of cervical and pharyngeal cancer, etc. The amount of circulating HPV DNA in the blood is useful for detecting advanced/recurrent cancer earlier than the rise in tumor markers. Compared to HPV infection-negative cancer, cancer immunotherapy is more effective for HPV infection-positive cancer.

Short title: Diagnosis and treatment for HPV-positive malignancy”

Comment: The abstract is very brief and vague. I don't think “Etc.” is an appropriate abbreviation. The sentences seem to be unconnected, and the abstract does not convey the idea of the manuscript. The short title is unspecific.

“Human papillomavirus (HPV) is a virus that causes sexually transmitted diseases and skin diseases. The main route of transmission of HPV is sexual intercourse (sex, oral sex, anal sex) [1].”

Comment: The first sentence is imprecise. You failed to distinguish between different genera of HPV, as well as between low-risk and high-risk HPVs. If your manuscript is concerned only with cancer-causing types of HPV, then please write “high-risk HPVs”.

“Latent HPV infection is established when HPV enters the basal cells from a small wound on the genitals.”

Comment: Please remove “latent”. Also, “a microinjury of the epithelia” would be more correct.

“Sexually transmitted HPV infection is associated with the development of benign condyloma acuminata, as well as pharyngeal cancer, cervical cancer (including vaginal cancer), anus cancer, and penile cancer [1].”

Comment: Again, you didn't distinguish between low- and high-risk HPV.

“In most HPV-infected people, HPV is eliminated by the host immune system, which protects the body from foreign enemies. However, in rare cases, HPV infections have been observed to persist for long periods of time without the elimination of HPV.

Comment: “which protects the body from foreign enemies” and “without the elimination of HPV” are redundant

“The results of clinical research and basic medical research to date have revealed that normal cells gradually become cancerous due to persistent HPV infection.”

Comment: Needs further clarification.

“HPV vaccines prevent persistent infection with certain types of HPV. In clinical practice, three HPV vaccines are prescribed: the bivalent "Cervarix" (GlaxoSmithKline K.K., London, UK), the tetravalent "Gardasil" (Merck), and the nine-valent "Sylgard 9" (Merck KGaA, Darmstadt, Germany). In clinical trials conducted in various countries, it has been revealed that the development of pharyngeal, cervical (including vaginal), anal, and penile cancers, as well as the benign disease Condyloma acuminata, is prevented by the inoculation of the 4-valent HPV vaccine or the 9-valent HPV vaccine [2]. Globally, infections with HPV types 16 and 18 account for approximately 70% of all cervical cancers.”

Comment: This could be a good place to insert a commentary about why it is still important to research HPV-induced cancers.

“From the results of the cancer genomic tests, it was revealed that a positive HPV16 or HPV18 infection was detected in a total of 11 cases (11/36, 30.6%) of advanced pharyngeal cancer, 37 cases (37/104, 35.6%) of advanced cervical cancer, 8 cases (8/22, 36.4%) of advanced anus cancer, and 3 cases (3/10, 30.0%) of advanced penile cancer”.

Comment: Please paraphrase for clarity. I suggest “The results of the cancer genomic test revealed an HPV16 or HPV18 infection in a total of 11 cases (11/36, 30.6%) of advanced pharyngeal cancer, 37 cases (37/104, 35.6%) of advanced cervical cancer, 8 cases (8/22, 36.4%) of advanced anus cancer, and 3 cases (3/10, 30.0%) of advanced penile cancer”. Also, what kind of cancer genomic test?

“Previous clinical trials have investigated the efficacy of nivolumab in 11 cases of HPV-positive pharyngeal cancer and 25 cases of HPV-negative pharyngeal cancer.”

Comment: A few sentences about what nivolumab is and how it works are needed.

“It has been shown that the efficacy of immune checkpoint inhibitors such as nivolumab is significantly higher in malignant tumors with a high tumor mutation burden (TMB) or Microsatellite Instability (MSI) high.”

Comment: Citation needed.

“Based on these clinical findings, the clinical application of novel anti-tumor immunotherapy, which involves infecting malignant tumors with pseudoviruses and increasing anti-immunogenicity against malignant tumors, is being considered [5][6].”

Comment: Needs clarification and further expansion.

“Therefore, the infection rate of HPV16 or HPV18 in advanced cancer, as shown above, is different from the incidence of cancer due to HPV infection in Japanese people.”

Comment: Unclear what the authors wanted to convey. That the infection rate of HPV is somehow unrelated to the rate of HPV-induced cancers?

“However, if HPV vaccination becomes widespread among Japanese people, the prevalence of cancer caused by infection with HPV16 or HPV18 (i.e., pharyngeal cancer, cervical cancer, and anus cancer) is expected to decrease considerably. According to the results of clinical studies, the number of cases of HPV-infected pharyngeal cancer in men is approximately three times the number of cases of HPV-infected pharyngeal cancer in women. Therefore, HPV vaccination for men must also be widely available [7].”

Comment: I agree with the value of vaccine availability, but don't understand what it has to do with the rest of this paragraph.

“Recent clinical research results show that the recurrence of various malignant tumors can be detected earlier by detecting circulating DNA (cDNA) in the blood derived from malignant tumor cells, rather than by increasing the tumor marker values [8].”

Comment: I believe you mean “detected” rather than confirmed. Also, cDNA is already a well-known and used term for copy or complementary DNA, so I would suggest using the term circulating tumor DNA or ctDNA, as the authors of the paper you cited did.

“Figure 1. Early diagnosis of advanced/recurrent malignant tumors by the detection of circulating HPV DNA rather than elevated tumor marker values”

Comment: The figure should be described in more detail.

“Human oncogenes such as Kirsten murine sarcoma virus (KRAS) are well known as oncogenes derived from viral genes.”

Comment: The Kirsten murine sarcoma virus is not an oncogene; it is a virus.

“As described above, various malignant tumors caused by viral infection have been recognized.”

Comment: They have been recognized, but you haven't described them.

“Vaccination is effective in preventing viral infection. However, unlike bacteria, mutations in viral genes easily change the structure of the viral backbone proteins and structural proteins. Therefore, it has become a problem that the preventive

effect of vaccines against viral infections is reduced. Therefore, there is a need to produce vaccines that induce the production of antiviral antibodies that recognize the structural proteins of mutant virus variants.”

Comment: This paragraph is unnecessary as it has nothing to do with the proposed topic of the paper.

Overall comment: Not to be insensitive, but this paper reads like a first draft. It is unclear what the subject is because the authors introduce several without connecting them with a clear line of thinking. The paragraphs feel disconnected, there is no flow to the writing, and a number of concepts (and one figure) are introduced but not expanded on. I recommend rejection.