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REVIEW

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Advances in early diagnosis of cervical cancer based on biosensors

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Abstract

Human papillomavirus (HPV) is a causative agent of cervical cancer among women worldwide. Serological and molecular tests are commonly used to detect and identify HPV, but all the detection methods for HPV have some limitations. Nowadays, considerable advancements in nanosensors have enabled monitoring of hybridization procedures dynamically for HPV detection. Biosensors, as effective, quick, economical, and highly sensitive tools, can be used in the diagnosis of HPV as an alternative technique instead of other detection methods. Biosensor detection methods of HPV in use from 2000 to 2021 were investigated using several databases such as Google Scholar, Scopus, PubMed, and the Scientific Information Database. Furthermore, a manual search of the references of the retrieved articles was performed. On analyzing the most recently developed biosensors for HPV identification, we observed that three biosensor systems, electrochemical, optical, and piezoelectric systems, are the main transducers used in the development of HPV biosensors. The aim of this review is to examine recent research on biosensors for the detection of HPV and perform a comparison with other diagnostic methods. Considering the importance of rapid HPV detection in the control of infection and development of public health measures, improvement of biosensors as an economical and quick method can be very useful in the diagnosis of HPV.

KEYWORDS

biosensor, cervical cancer, human papillomavirus, molecular methods

1 | INTRODUCTION

Cancer is a large group of diseases and is the second most common cause of death globally. Lung, colorectal, prostate, bladder, liver, and stomach cancers are reported as the most common types of cancer in men, while breast, colorectal, lung, thyroid, and also cervical cancers are the most common types of cancer in women (Barani, Hosseinikhah, et al., 2021). At present, different treatment approaches, including surgical resection combined with chemotherapy, nanotherapy, radiotherapy, and immunotherapy, are utilized as conventional treatments for people with cancer (Arshad, Fatima, et al., 2021; Laraib et al., 2021).

Cervical cancer is the fourth most common type of cancer that occurs in women, and it is caused by human papillomavirus viruses (Jalil & Karevskiy, 2020). The World Health Organization considers cervical cancer as one of the main causes of abnormalities and death in women (Liverani et al., 2020). It has been estimated that there are approximately 1.4 million women with cervical cancer worldwide (Naz et al., 2018). HPV is one of the most important human viruses that is transmitted sexually worldwide. Although the immune system of most patients with HPV infection can spontaneously clear it, recurrent infections may be observed in immunocompromised patients. HPV infection

can remain asymptomatic in some individuals, resulting in the persistence of HPV in latent form (Okunade, 2020).

HPV is a small and nonenveloped DNA virus that can infect mucosal cells or skin. HPVs are classified into low- and high-risk groups (Singh et al., 2020). More than 150 types of HPV are recognized worldwide, and approximately 10 types have been reported in cervical cancers (Jalil & Karevskiy, 2020). The most common types of HPV have been reported in cervical cancer (HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-45, HPV-52, and HPV-58) and the less common types of HPV are HPV-39, HPV-51, HPV-56, and HPV-59. Both HPV-16 and HPV-18 types, which are part of the high-risk group, are reported in about 70% of cases of cervical cancers. It has been reported that HPV-16 is the most carcinogenic type of HPV and HPV-18 is the second most carcinogenic type of HPV (Wu et al., 2006; Zhou et al., 2018). HPV-18 is known to be present in approximately 37% of adenocarcinomas as well as 12% of squamous cell carcinomas of the cervix worldwide (Chen et al., 2015).

Currently, polymerase chain reaction (PCR) is the most widely used diagnostic test. Although it is an effective tool for the detection of etiological agents of diseases, and can also detect different types of viruses, it has some disadvantages; for example, it is a complicated and costly procedure (Rahman et al., 2016; Zandi, Zandi, et al., 2021). Therefore, it is necessary to develop an easy to use, economical, rapid, and sensitive method.

2 | DETECTION TECHNIQUES FOR HPV IN CERVICAL CANCER

Several screening methods are used for the identification and detection of high-risk HPV types in cervical cancer; the common ones include pap smear, liquid-based cytology, and visual inspection with acetic acid (Catarino et al., 2015; Mahmoodi et al., 2019).

The Pap smear test is one of the most commonly used methods of screening precancerous changes in squamous cervical cancer (Mayer & Budh, 2020). In this test, cells are collected from the cervix of women and examination is performed under a microscope to identify abnormalities. The false-positive and false-negative rates for pap smears are 0%–14% and 13%–70%, respectively (Rezaee Azhar et al., 2022; Vassilakos et al., 1999). The second most commonly used cytology technique is liquid-based cytology. The advantages of the Pap smear method are that more homogeneous samples are obtained, an improved method exists for propagating slides, there is improved adoption of sample standardization, and it has more sensitivity. On the other hand, the main disadvantage of the liquid-based cytology method is that it is not an economical test, as it is more costly than the pap smear test. Also, only a trained person can conduct this test, and it is also not appropriate for use on a sample with limited resources (Karnon et al., 2004; León-Ordóñez et al., 2019; Soltani et al., 2021). Visual inspection with acetic acid is the third most commonly used conventional technique that is carried out in low-resource settings; in addition, its specificity is limited (Mahmoodi et al., 2019). The main limitation of this test is its lack of reliability in the area of cervical cancer precursors in postmenopausal women (Git et al., 2010).

The molecular methods in HPV diagnosis lead to true detection and also typing of HPVs. These techniques include quantitative reverse transcription-PCR, microarray, and next-generation sequencing (Shah et al., 2016). Quantitative reverse transcription-PCR can be considered the gold standard and a suitable technique because it has high specificity and sensitivity (Hammond, 2006). This technique is performed according to TaqMan or SYBR Green methods and fluorescence signal measurements of the amplicon; thus, it cannot be considered an economical test (Git et al., 2010). Microarray is another technique that is used to identify HPV DNA. It screens the expression of microRNAs and DNA in single testing. In this technique, the product of PCR is hybridized by probe amplification into a chip, followed by a washing step. Hybridized signals are imaged using a DNA chip scanner (Hammond, 2006). Overall, serological techniques and tissue cultures cannot be used to detect HPVs. Therefore, in most laboratories, molecular techniques are applied for the diagnosis of high-risk HPVs. Early diagnosis is important for effective treatment in the fight against cervical cancer. Traditional cervical cancer diagnostic tools present limitations that make early detection difficult; thus, nanobiosensors have revolutionized the era of diagnosis and treatment of cancer (Arshad, Fatima et al., 2021).

3 | BIOSENSORS

Biosensors, as portable analytical devices, are made up of at least one biological molecule (Fani et al., 2020; Zandi & Fani, 2022). The strategies to develop this measurement system combine the analytical capacity of transduction methods with the specificity of biological components (Caygill et al., 2010; Mehrvar & Abdi, 2004). Furthermore, materials at the nanometer scale such as nanofibers, nanotubes, and nanoparticles have been used to achieve the nano-structures of these devices (Frías et al., 2015; Sargazi, Mukhtar, et al., 2022). Generally, these measurement systems can detect biomolecules such as proteins, nucleic acids, and also cells that are related to diseases. Biological components such as antibodies, nucleic acids, and enzymes are used to detect biomolecules (Arshad et al., 2021b; Barani, Zeeshan, et al., 2021; Barani, Mukhtar, et al., 2021; Sabir et al., 2021; Xiang et al., 2011). These devices are used to detect biomolecules that are associated with diseases at the clinical level (Barani, Sargazi, et al., 2021; Fatima et al., 2021). Biosensors can detect the biochemical markers of a disease, which can be found in different body fluids, such as urine, blood, or saliva. Biosensors can be classified according to the different types of biological components or type of physicochemical transduction (Kamali et al., 2021; Karunakaran et al., 2015; Zandi, Rasooli, et al., 2021). Based on the transducer, these systems can be classified into optical, piezoelectric, magnetic, and electrochemical biosensors; in addition, fluorescence-based assays, electrochemical-based assays, enzyme-linked immunosorbent assays, and mass-based detection are the current methods used for detecting tumor markers (Laraib et al., 2021; Mukhtar et al., 2021;

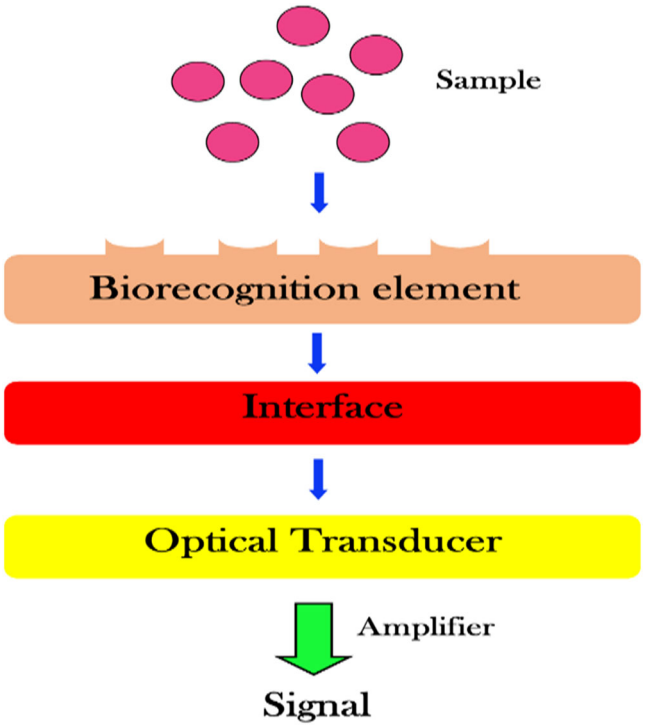

FIGURE 1 Schematic presentation of an optical biosensor

Rocha-Santos, 2014; Sargazi, Fatima, et al., 2022). The current review aims to provide an overview of the advances in the field of biosensors for the diagnosis and detection of HPV as the causative agent of cervical cancer. In addition, we compared different platforms of biosensors such as optical, piezoelectric, magnetic, and electrochemical ones to identify the best platform to detect HPV in a quick, simple, economical, and also accurate diagnostic manner.

4 | OPTICAL BIOSENSOR

An optical biosensor is a compact analytical tool that includes a biorecognition sensing component incorporated into an optical transducer system (Damborský et al., 2016) (Figure 1). Optical detection is carried out on the basis of the interaction between a biorecognition element and the optical field. There are two general modes of optical biosensing: label-based and label-free. Optical-based techniques are used to detect pathological infections (Peltomaa et al., 2018). In the Pap smear test, optical methods such as microscopy are used to detect the causative agents of cervical cancer (Mitchell et al., 1999; Rao et al., 2007). The fluorescent in situ hybridization technique is commonly utilized to detect HPV. This method provides the possibility to check the tissue sample in which the specific DNA region is signaled by a fluorescent label probe for which it was designed at the same time (Frías et al., 2015) (Table 1). Fluorescent-based bioprobes have been utilized to develop highly sensitive nanobiosensors for detecting various chemical and biological agents because of their properties such as good selectivity, sensitivity, high surface-to-volume ratio, and versatile electronic and optical features (Sargazi, Fatima, et al., 2022; Sargazi, Mukhtar, et al., 2022).

Recently, Espinosa et al. developed an electrochemical resistive DNA biosensor to identify HPV-16. They immobilized a DNA probe onto a screen-printed gold electrode; the limit of detection for this biosensor was reported to be 2.39nM (Espinosa et al., 2021). In 2020, He et al. fabricated a selective and ultrasensitive label-free homogeneous electrochemical biosensor for the quantitative determination of the E6 and E7 oncogenes of HPV-16. This biosensor combined the ability of superior recognition of entropy-driven amplification with the high signal amplification capability of hyperbranched rolling circle amplification (He et al., 2020; Sabir et al., 2021). In one study, researchers reported that multiplex detection of HPV-18 and HPV-16 was carried out using a sandwich assay, and the limits of detection for this method were 0.78 and 0.17nM, respectively (W. Wang et al., 2014). The biotinylated capture probe HPV DNA strands were coated with avidin-coated silica nanoparticles. Then, they were mixed with 64-base HPV-16 and HPV-18 target strands of DNA. Target strands of DNA were selectively captured on the nanoparticles after hybridization, and then the fluorescein amidite and 6-carboxyl-X-rhodamine-labeled specific probes of HPV-18 and HPV-16 were incubated to identify target DNA strands with particles (W. Wang et al., 2014).

In another study, Chan et al., in 2007, utilized organic nanometer-sized crystals as labels to quantitatively detect different genotypes of HPV including HPV-16, HPV-18, and HPV-45. Fluorescein diacetate was ground into a nanocrystals platform, and consequently, they were adsorbed with streptavidin human papillomavirus DNA. The fluorescence signal was proportional to the amplicon concentration in 10^3–10^5 copies/μl (Chan et al., 2007).

Yue et al., in another project, encoded a combination of various spectral microbeads for multiplex detection of HPV-16 and HPV-18 targets of DNA. A single-layer array of microbeads was advanced with specific DNA of HPV capture probes in a microfluidic structure. After hybridization of probe DNA with biotinylated target DNA in the microfluidic platform, a fluorescent label was presented in a microchannel and then a fluorescent signal measured the HPV DNA down to 25 pM (Yue et al., 2014).

In another project, Brandstetter et al. used a polymer-based DNA platform to detect high- and low-risk HPV types. Using an ultraviolet-irradiation procedure, researchers printed 36 DNA probes on a substrate in a microarray pattern with polydimethyl acrylamide. This chip showed the diversity of genotypes of HPV in samples down to 10^4 copies (Brandstetter et al., 2010).

In addition, Palantavida et al., using the ultra-bright fluorescent process, detected HPV-16 inside infected epithelial cells by utilizing mesoporous silica nanoparticles. For specifically targeting folate receptors of folate in malignant cells, nanoparticles were functionalized with folic acid. Then, the nanoparticles were incubated with the sample for a short time, after which, infected cells with HPV-16 were distinguishable. This method presented better sensitivity than what was reported (95%–97%), and also presented better sensitivity than cell pathology and HPV DNA tests (Palantavida et al., 2013).

Li et al. used a single-molecule imaging system to detect HPV-16 target DNA in a capillary channel. They hybridized an HPV DNA

TABLE 1 Biosensor methods for the detection of HPV

Method	Sensor platform	Detection range	HPV types	Response time	Reference
Current relaxation	Screen-printed gold electrode	5–20 nM	16	35 min	Espinosa et al. (2021)
Hyperbranched rolling circle amplification	Methylene blue	0.1 fM to 10 pM	16	-	He et al. (2020)
Fluorescence spectroscopy	Silica nanoparticle	0–0.78 nM	16 and 18	90 min	W. Wang et al. (2014)
PCR	Aqueous solution/particle-based conjugates	-	16, 18, and 45	10 min	Chan et al. (2007)
PCR	Microfluidic-based microbead array platform	-	6, 11, 16, and 18	30 min	Yue et al. (2014)
PCR	Biochip platform	-	12 different types	20 min	Brandstetter et al. (2010)
Fluorescence microscopy	Silica nanoparticle	-	16	15	Palantavida et al. (2013)
Optical signal	In situ histological sample	-	16	24 h	Li et al. (2006)
PCR	Glass	1.44–7000 copies/cell	16	16 h	Lee et al. (2007)
Quartz crystal microbalance	Biotinylated HPV probe	-	16 and 18	-	Dell'Atti et al. (2007)
Quartz crystal microbalance	Biotinylated HPV probe	-	11 different types	-	Parsongdee et al. (2008)
Quartz crystal microbalance	HPV probes with a disulfide group	-	6, 11, 16, and 18	-	Fu et al. (2004)
Magnetic	GMR biochip	-	18	1 h	Xu et al. (2008)
Magnetic	GMI-based microchannel system	-	16 and 18	Less than 2 h	H. Yang et al. (2010)
EIS	SWCNT/gold nanoparticles	1–1 μM	16	2 h	S. Wang et al. (2013)
CV	Gold surface/capture oligonucleotides	-	21 different types	2–8 h	Vernon et al. (2003)
DPV	PGE	2–8 nM	16	15 min	Souza et al. (2014)
CV	SPE/carbon-based electrode	-	16 and 18	30 min	Bartosik et al. (2016)
Impedimetric	GCE/Gold nanosheet	1 μM to 1 pM	16	2 h	Karimizefreh et al. (2017)

Abbreviations: CV, cyclic voltammetry; DPV, differential pulse voltammetry; EIS, electrochemical impedance spectroscopy; GCE, glassy carbon electrode; GMI, giant magnetoimpedance; GMR, giant magnetoresistance; HPV, human papillomavirus; PCR, polymerase chain reaction; PGE, pencil graphite electrode; SPE, screen-printed electrodes; SWCNT, single-walled carbon nanotube.

probe labeled with a fluorescent HPV DNA target. The resultant fluorescent signal was reported down to 0.7 copies per infected cell (Li et al., 2006). Lee et al. (2007) used a dual-probe technique for the identification of HPV-16.

5 | PIEZOELECTRIC BIOSENSORS

The principle of piezoelectric biosensors involves affinity interaction recording. The platform of the piezoelectric biosensor is based on the principle of changing oscillations because of a mass bound on the piezoelectric crystal surface (Pohanka, 2018). This method has advantages including high sensitivity, simplicity, low cost, label-free detection, and possibility for real-time detection (Tombelli et al., 2005).

Dell'Atti et al. constructed a tool based on long-term stable anchoring between streptavidin and biotin to detect HPV types. It enabled real-time monitoring of hybridization via frequency alterations, which in turn enabled differentiation of HPV type. The biosensor could identify PCR-amplified short DNA strands within a 50nM detection limit (Dell'Atti et al., 2007).

In another study, researchers performed the same examination by immobilizing biotinylated probes for 11 high-risk HPV types. This method presented optimal sensitivity of up to 10^3 copies/μl from PCR products (Parsongdee et al., 2008).

Fu et al. fabricated HPV nanosensors using QCM piezoelectrics to identify different types of HPV from pathologic biopsy samples. The method involved the adsorption of HPV oligonucleotides functionalized with groups of disulfide on the surface of a QCM disc (Fu et al., 2004). The biosensor showed optimal sensibility (25 μM), which is comparable to the result achieved by the combination of dot-blot and PCR methods (Fu et al., 2004).

6 | MAGNETIC BIOSENSORS

Biosensors based on magnetic materials labels represent specific alternatives for the detection of causative agents (Llandro et al., 2010) such as different genotypes of HPV (Figure 2). A specific biological probe is immobilized on the surface of the magnetic material to interact with its counterpart found on a sample suspected to comprise biological traces of the agent (S.-Y. Yang et al., 2008). In a study, researchers presented a multilayered system to identify some HPV types including 16, 18, 33, and 45. Xu et al reported that the HPV DNA target was identified from a concentration as low as 10 mp using a giant magnetoresistive biochip (Xu et al., 2008). In addition, in another study, researchers used a similar method with a giant magnetoimpedance-based biosensor, wherein impedance changes on the magnetic sensor instead of resistance changes as with the giant magnetoresistance sensor were utilized to diagnose the presence of magnetic labels. Using this platform, the target DNA of HPV-16 and HPV-18 were evaluated in samples (H. Yang et al., 2010).

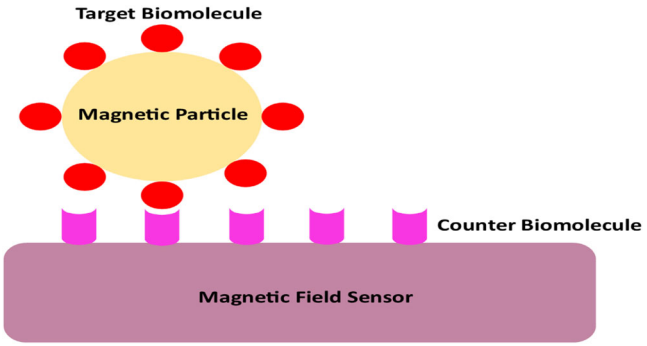

FIGURE 2 Schematic diagram of a magnetic biosensor

7 | ELECTROCHEMICAL BIOSENSORS

Electrochemical biosensors are one of the most common sensing devices involving transduction of the biochemical procedures to electrical signals (Thévenot et al., 2001). An electrode is used as the main component as a solid support to immobilize biomolecules and electron movement in this type of biosensor (Figure 3). Due to the features of electrochemical biosensors including simplicity, low-cost instrumentation, and also quick response, it is an excellent tool for the diagnosis of HPV.

In a study, Wang et al. developed an electrochemical sensor with high sensitivity. They deposited immobilized single-stranded probe DNA and Au nanoparticles on a single-wall carbon nanotube platform. This sensor was utilized to identify the sequence concentration of HPV-16 DNA from 1 aM to 1 μM (S. Wang et al., 2013).

In another study, Vernon et al. fabricated a bioelectronic tool to detect 21 types of HPV. They deposited a monolayer of immobilized oligonucleotides, which were specific for different HPV genotypes, on a gold electrode. In this process, two hybridization phases were carried out in the mentioned platform separately: the first hybridization process was between the capture probe and the target, and the second hybridization process was between the ferrocene-labeled signal probe and an adjacent region of the target (Vernon et al., 2003). Souza et al. developed a pencil graphite working electrode to detect the E1 gene in HPV-16. They utilized methylene blue to record the signals. The limit of detection for the mentioned method was 1.49 nM (Souza et al., 2014).

In a study, researchers developed an SPE electrode assembled with streptavidin-modified magnetic beads and a DNA capture probe labeled with digoxigenin for the detection of DNA of HPV-16. The range of detection for this assay is reported to be 1 pM to 1 nM (Bartosik et al., 2016).

A research group created a modified glassy carbon electrode with gold nanosheets labelled with hexacyanoferrate to detect HPV type 16 DNA. It is reported that the limit of detection for this biosensor was 0.15pM and also, this tool could respond to target DNA with a range from 1 μM to 1 pM (Karimizefreh et al., 2017).

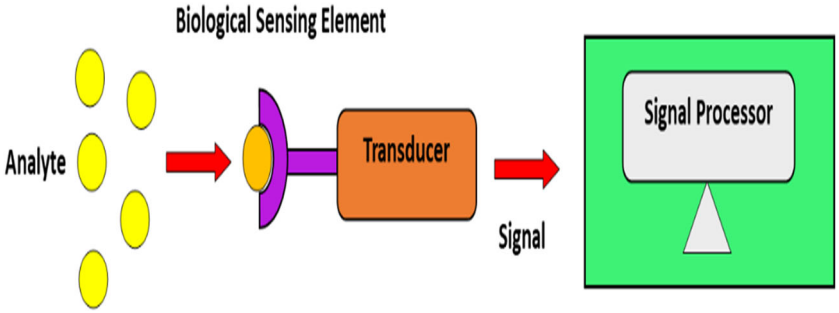

FIGURE 3 Schematic diagram of an electrochemical biosensor

8 | CONCLUSIONS

Significant efforts are being made aimed at the prevention and treatment of HPV infection. However, there is a high prevalence of human papillomavirus infection in both developing and developed countries. The Pap test is considered the key method to identify the primary lesions of cervical cancer. Molecular tests, in conjunction with the Pap test, increase the sensitivity of HPV detection, particularly in terms of the capability of diagnosing high-risk oncogenic types. The diagnosis of HPV infections to prevent cervical cancer is still essential. From previous studies, it is clear that quick, simple, economical, and also accurate diagnostic techniques need to be developed in tune with technological advancements; thus, in this review, we focus on EIS, fluorescent spectroscopy, and QCM methods for the diagnosis of HPV infection. The rapid regeneration of the substrate following a diagnosed sample is of great importance and can directly affect the development cost. Nitrocellulose and QCM substrates have achieved more than 12 diagnoses without losing sensitivity in this regard. On the other hand, investigation of the biosensors' performance in biological samples, such as blood, urine, and other body fluids, will confirm the real potential of these novel molecular approaches to confirm the clinical diagnosis of HPV.

AUTHOR CONTRIBUTIONS

Hadi Esmaeili Gouvarchin Ghale and Mahdieh Farzanehpour were responsible for conceptualization of this study and final data interpretation and presentation. The manuscript was drafted by Hadi Esmaeili Gouvarchin Ghale and Morteza Izadi. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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