The mutual interplay between NTRK fusion genes and human papillomavirus infection in cervical cancer progression (Review)

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Abstract. Cervical cancer is a significant global health concern, with a substantial portion of cases attributed to human papillomavirus (HPV) infection. Recent advancements in molecular profiling have identified distinct subtypes of cervical cancer based on their genomic alterations. One such subgroup is neurotrophic tropomyosin receptor kinase (NTRK) fusion-positive cervical cancers, characterized by gene fusions involving the NTRK genes. Although both NTRK fusion genes and HPV infections are independently recognized as significant risk factors in cervical cancer, their interplay and mutual effects on cancer progression are not yet fully understood. The present review is the first of its kind to explore the potential interplay between NTRK fusion genes and HPV infections. It surveys in detail how their combined effect can influence the signaling pathways during cervical cancer development and progression. Moreover, the present study discussed the clinical features, histopathological examinations, treatment procedures and follow-up outcomes of NTRK-fusion gene-positive cervical cancer. The present review may help in the understanding of the management and treatment of such rare, lethal and resistant cervical cancers.

Contents

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1. Introduction

Cervical cancer (CC) is one of the most common cancers in women of reproductive age, with 342,000 deaths and 604,000 new cases in 2020. Nearly 90% of these deaths occur in middle- and low-income nations (1). The primary cause of CC is the chronic persistent infection of high-risk human papillomavirus (HPV), which is present in over 90% of cases. However, it is important to note that only 1% of high-risk HPV-infected women develop CC (2). This indicates the presence of additional factors, such as gene mutations and chromosome rearrangements, that contribute to the development of CC. Numerous studies have identified genetic alterations, such as mutations and amplifications, that contribute to the oncogenic process in HPV-positive CC. For example, recent observations have shown that HPV integration leads to various genomic changes in cervical adenocarcinoma (3). Similarly, a previous study identified the FGFR3-TACC3 fusion in HPV-positive CC (4). Therefore, it is urgent to gain a deeper understanding of new fusion genes responsible for molecular heterogeneity in HPV-related CC for improved clinical outcomes.

The neurotrophic tyrosine receptor kinase (NTRK) genes encode tropomyosin receptor kinases (TRK). NTRK genes are essential for nerve cell development and function and may fuse with different genes. When NTRK genes fuse, they produce constitutively activated chimeric TRK receptors. These receptors can lead to cancer invasion, angiogenesis, growth, survival and activate the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways (5). NTRK1-3 fusions have now been recognized in multiple cancer types. They are highly prevalent (~90%) in some rare cancers such as mammary analogue secretory carcinoma, secretory breast carcinoma and congenital infantile fibrosarcoma, and less common (<1%) in numerous types of adult cancers including salivary gland cancers, thyroid, colorectal and non-small cell lung cancers (6). The prevalence of NTRK fusion genes in

CC is low (0.36-1.88%). However, NTRK-fusion gene positive cancers caused by these genetic alterations have a different tumor microenvironment and do not respond to conventional treatments like radiotherapy/chemotherapy (7). Therefore, there is a dire need for in-depth studies of NTRK-fusion positive CC to identify more potent signaling molecules associated with dysregulation of immune cells and activation of oncogenic pathways.

The role of HPV infection in the development of NTRK fusion genes is unknown. Both factors independently contribute to the risk of developing CC and contribute to CC heterogeneity. The authors' hypothesis is that CC that is positive for NTRK fusion genes and has HPV infection may have more severe outcomes and require more effective treatments. Therefore, it is crucial to review the interaction between HPV and NTRK fusion genes in CC. The present review is pioneering because it focuses on the combined effect and interaction of HPV and NTRK fusion genes in the progression of CC.

2. NTRK fusion genes

The NTRK1, 2 and 3 genes are located on chromosomes 1q21-q22, 9q22.1 and 15q25, respectively. They code for TRKA (140 kDa), TRKB (145 kDa) and TRKC (145 kDa) proteins, respectively. Despite their different positions on different chromosomes and different mechanisms of activation and regulation, they are highly homologous and have similar structural domains, including intracellular kinase domains and extracellular ligand binding (8). The extracellular domain contains two immunoglobulin-like (Ig1-2) high-affinity receptors that interact with cognate ligands, predominantly via Ig-2. Specifically, TRK proteins have three leucine-rich 24-residue motifs that are flanked by two cysteine clusters (C1-2). Meanwhile, the intracellular domain contains a kinase domain and is linked to the extracellular domain through a transmembrane structure (9) (Fig. 1A).

The fusion of NTRK1-3 genes is a common occurrence that leads to the oncogenic activation of TRK. This happens when the 3' region of the NTRK gene combines with a 5' sequence of a fusion partner gene through rearrangement, either within the same chromosome or between different chromosomes (Fig. 1B and C). In all TRK oncogenic fusions, the TRK protein kinase domain is always present. Therefore, TRK fusion proteins always contain the TRK kinase domain. As a result, the resulting protein from the fusion, known as a chimeric oncoprotein, is characterized by continuous activation and overexpression of the TRK protein kinase, independent of any ligand (10). Because of their strong oncogenic effects and potential for targeted therapy, TRK fusions have received significant attention as promising therapeutic targets in cancer treatment (11).

3. TRK signaling pathways

Binding of ligands to extracellular domains of Ig receptors leads to autophosphorylation of intracellular tyrosine (Y) residues. The most common ligand for TRKA is nerve growth factor (NGF), while brain-derived growth factor and neurotrophin (NT)-4/5 bind to TRKB, and NT-3 binds to TRKC. NGF binding to TRKA triggers receptor homodimerization and transphosphorylation of crucial tyrosine residues (Y496, Y676, Y680, Y681 and Y791) (Fig. 2A). Specifically, Y496 and Y791 serve as phosphorylation-dependent binding sites for adaptor proteins with phosphotyrosine binding or src homology 2 (SH2) domains, such as GRB2-associated-binding protein 1 (GAB1), phospholipase C-γ (PLCγ) and SHC adaptor protein 1. Other adaptor proteins involved are insulin receptor substrate (IRS)1-2, growth factor receptor bound protein 2 (GRB2), SH2B and fibroblast growth factor receptor substrate 2 (FRS2). Multiple studies have suggested that RAS or GAB1 activates the PI3K signaling pathway, although other mechanisms may also activate it (12). Once activated, the three wildtype TRK family members commonly activate multiple downstream signaling pathways, including PI3K-AKT, PLCγ-PKC, or SHC-RAS-MAPK, depending on which docking protein(s) are bound to phosphorylated Y496 and Y791 (12). Activation of these molecular pathways leads to various cellular processes, such as transcriptional regulation, neurite outgrowth, synaptic plasticity, cellular proliferation, repair or prevention of neurodegeneration, maintenance of sensory neurons, or apoptosis (Fig. 2B) (12). Previous studies have also revealed that the reduced isoforms of TRK proteins can act as active signaling molecules by recruiting scaffolding proteins like Rho GDP-dissociation inhibitor 1 and GRP1-associated scaffold protein (13).

4. TRK activation in cancer

TRK proteins can be activated through various mechanisms, including somatic NTRK mutations, activation of NTRK splice variants and TRK overexpression. Somatic NTRK mutations have been observed in different types of tumors, such as colorectal cancer, lung cancer, acute myeloid leukemia and melanoma. Studies have investigated mutations affecting Ig2, kinase activity, activation loop residues and inhibitor efficiency (14). The exact role of NTRK mutants in cancer development remains unclear. However, the NTRK1 splice variant (TRKAIII) and a genomic in-frame deletion mutant (ΔTRKA) are known to be oncogenic. Both variants lack glycosylated regions in the ligand binding domain and have a constitutively active kinase domain (14). Additionally, TRKA-C is overexpressed in various cancers and is associated with tumor aggressiveness. In breast cancer models, for instance, TRKA overexpression leads to increased tumor cell migration, invasion and proliferation through activation of the PI3K and MAPK pathways. Overexpression of TRKB and/or TRKC has also been observed in patients with cylindroma, as well as in sporadic basal cell carcinomas (14).

5. TRK fusions oncogenic activation

In fusion biology, it is observed that upstream gene partners in NTRK fusion events often possess WD repeats, zinc finger domains, or oligomerization domains such as coiled-coil domains. These domains are crucial for the full activation of downstream kinase. Most NTRK fusion partners typically have oligomerization domains, although there are exceptions in which fusion partners do not possess known dimerization domains (15). In such cases, it remains unclear how the upstream partner contributes to the downstream TRK kinase

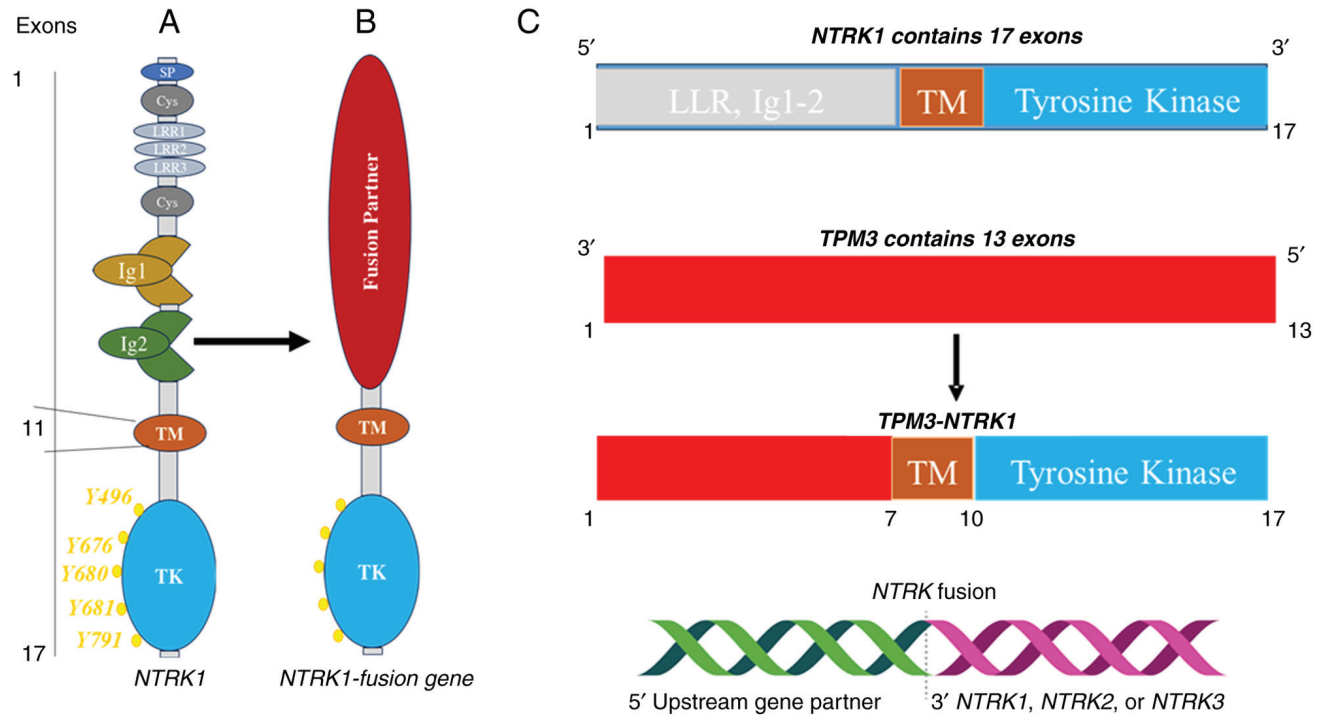


Figure 1. (A) NTRK1 gene, (B) NTRK1-fusion gene and (C) TPM3-NTRK1 formation (10,11). NTRK1, neurotrophic tropomyosin receptor kinase 1; Cys, cysteine-rich clusters; LRR, leucine-rich motifs; SP, signal peptide; TK, tyrosine kinase; TM, transmembrane; Y, tyrosine residue. Microsoft PowerPoint (Office 365; Microsoft Corporation) was used for figure creation.

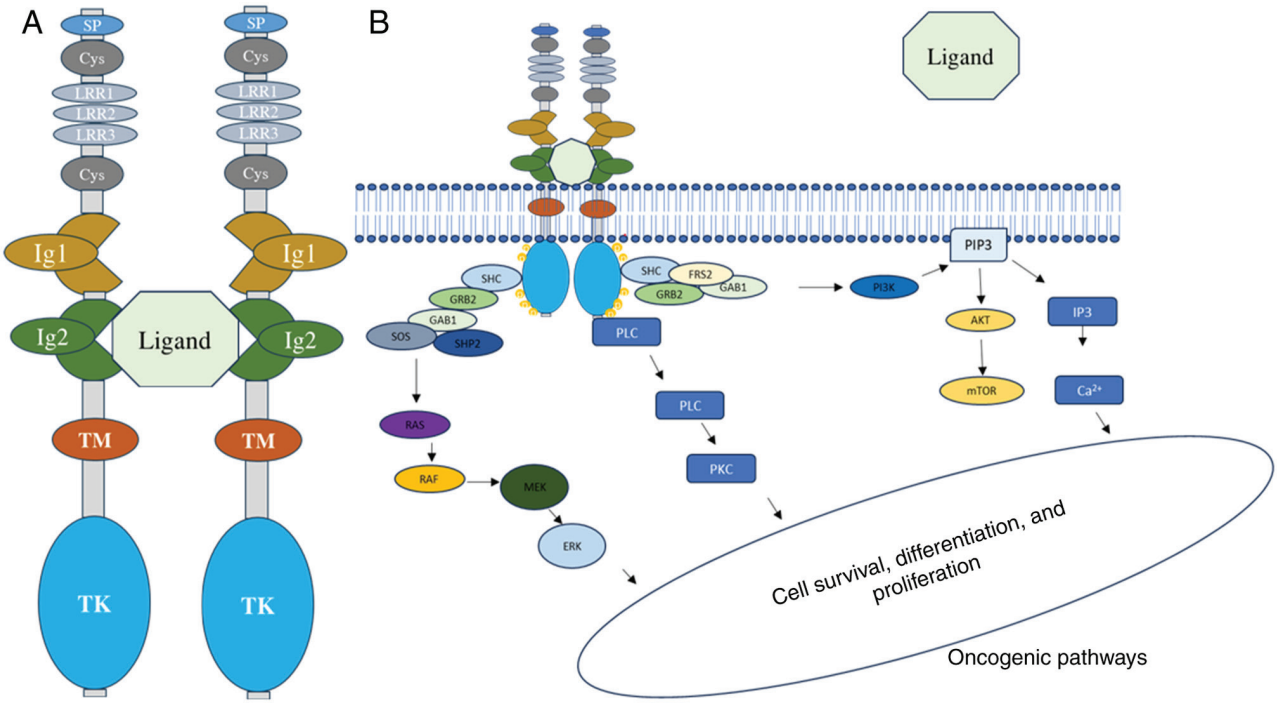


Figure 2. (A) NTRK genes interaction with ligand and (B) TRK signaling pathways (10). NTRK1, neurotrophic tropomyosin receptor kinase 1; Cys, cysteine-rich clusters; LRR, leucine-rich motifs; SP, signal peptide; TK, tyrosine kinase; TM, transmembrane. Microsoft PowerPoint (Office 365; Microsoft Corporation) was used for figure creation.

activation. Immunohistochemical analyses of tumors with NTRK fusions suggest that the fusion protein's subcellular localization can be determined by the kinase partner. This emphasizes the varied and crucial roles of upstream partners in the oncogenic activation of various TRK fusion proteins. These fusion proteins, even without ligand signaling, can

still activate the same downstream pathways as full-length TRK proteins. For instance, fusion oncoproteins, tropomyosin 3 (TPM3)-TRKA and translocated promoter region (TPR)-TRKA, were able to bind SHC, IRS1, IRS2, FRS2 and FRS3, similar to the full-length TRK protein (16). Moreover, such activated adaptors facilitate the recruitment of p85, SH2 domain containing protein tyrosine phosphatase (SH-PTP2) and GRB2, leading to PI3K and MAPK signaling network activation (16). Although TRK fusions signal through the same pathways as full-length TRK proteins, the downstream signaling can also be affected by the subcellular localization of TRK receptors driven by the fusion partner and the specific histology of the tumor tissue (14).

6. Mutations in NTRK fusion gene and drug resistance

The kinase domains of NTRK exhibit structural flexibility and undergo various conformational transitions that directly affect how inhibitors bind. These domains primarily exist in two conformations, which are determined by the position of three specific residues: Aspartic acid (D), phenylalanine (F) and glycine (G)-known as the DFG motif. This activation loop in the kinase domain is flexible and determines whether the kinase is in an active state (in conformation) or an inactive state (out-conformation) (7). Crucial mutations in the catalytic region of the kinase domain have been identified through clinical screenings. These mutations can occur in the solvent front of the ATP-binding pocket (solvent-front mutations), the amino acid preceding the activation loop DFG motif (xDFG mutation), or the gatekeeper residue (a conserved hydrophobic amino acid in the active site). Somatic point mutations at these sites in the NTRK kinase domain led to resistance against inhibitor drugs such as larotrectinib and entrectinib (7). These mutations often impede inhibitor binding and boost catalytic function by reducing the KM value for ATP, thus increasing rivalry between inhibitors and ATP. For example, the TPM3-NTRK1 fusion includes G595R, F589L, as well as G667C mutations, while the ETV6-NTRK3 fusion contains G623R, F617L and G696A (7,17).

The aforementioned data showed that somatic NTRK mutations and gene fusions play a crucial role in activating TRK proteins in a cancerous manner. Furthermore, these mutations and fusions can significantly change the 3D structure of the kinase domain. This change not only affects the recruitment of adaptor proteins, which leads to false signals and the activation of cancer-causing pathways, but also reduces the binding of TRK inhibitor drugs, resulting in increased drug resistance (7). However, current research does not fully understand how different mutations and NTRK gene fusions contribute to the activation of cancer-causing pathways. Therefore, further research is needed to investigate their role in CC and identify the most promising abnormalities that can be targeted for therapy.

7. NTRK fusion genes and cervical cancer

NTRK gene fusions occur in various tumors in both children and adults, across different tissues and cell lineages. A recent study analyzed >295,000 patients with cancer and found NTRK gene fusions in 889 cases, representing a prevalence of 0.30% across 45 different tumor types. The prevalence of NTRK gene fusions varied significantly depending on age, cancer type and histology. These fusions were commonly found in both adult and pediatric tumors, with NTRK1 and NTRK3 being the most frequent partner genes and the ETV6-NTRK3 fusion being the most frequently observed (6).

A total of 23 published case reports of NTRK fusion genes in patients with CC (59 individuals) were obtained through a literature survey conducted in December 2023 (Table I). Among the 59 cases, 35 cases (59.32%) were reported in the United States of America, 9 cases (15.25%) were reported in China, 8 cases (13.56%) were reported in France and only 2 (3.39%) cases were reported in Japan. Australia, Canada, Switzerland, the United Kingdom and New Zealand each reported 1 case (1.7%) (Fig. 3A). The highest number (41; 69.49%) of fusions were observed with NTRK1, with TPM3 being the most frequent partner of NTRK1 in 26 cases (63.41%), followed TPR (10 cases; 24.39%). C16orf72 and IRF2BP2 were each observed in 2 cases (4.87%). NTRK3 fusions were observed in 16 cases (27.12%), with the partner genes sperm antigen with calponin homology and coiled-coil domains 1-like (SPECC1L), EMAP like 4 (EML4), ETS variant transcription factor 6 (ETV6), RNA-binding protein with multiple splicing (RBPMS), trafficking from endoplasmic reticulum to Golgi regulator (TFG) and KH RNA-binding domain containing, signal transduction associated 1 (KHDRBS1) in 4, 4, 2, 1, 1 and 1 case, respectively. However, 3 cases showed NTRK3 rearrangements, but no fusion partner was mentioned. There were only 2 (3.39%) reported cases of NTRK2 fusions, 1 case of discs large MAGUK scaffold protein 2 (DLG2) and 1 case of WW domain-containing oxidoreductase (WWOX) (Fig. 3B). The average age (38.18 years), size of tumor (6.05 cm) and a high recurrence rate among 18 (30.51%) individuals were observed. The expression levels of different proteins and other clinical characteristics are revealed in Fig. 3C.

8. HPV and cervical cancer

HPV is a virus that belongs to the *Papovaviridae* family and has a double-stranded DNA. It has a small, highly conserved DNA with ~8,000 base pairs (bp), which is divided into three regions. The genome encodes eight open reading frames that are arranged on one DNA strand. These include six early proteins, three regulatory proteins (E1, E2 and E4), and three oncoproteins (E5, E6 and E7). These proteins, which are encoded in 4,000 bp, play a role in viral replication and cell transformation. An additional 3,000 bp region of the DNA molecule encodes two structural proteins, L1 and L2, which make up the capsid of the virus. The replication and transcriptional regulatory elements of the viral DNA are controlled by a long control region that is encoded within a 1,000 bp region (Fig. 4A) (18). More than 200 HPV types have been recognized, with over 40 types that can colonize the genital tract. HPV infection types are categorized into high and low risk groups based on their ability to cause cancer. It is well established that HPV-16 and 18 are the most dangerous high-risk genotypes, responsible for ~70% of all cases of invasive CC worldwide.

Multiple studies have confirmed that oncogenic HPV infection is the main risk factor for the development of cervical intraepithelial neoplasia (CIN). CIN can range from low-grade squamous intraepithelial lesions (SIL) to high-grade SIL and cancer. Persistent HPV infection can cause cellular changes in

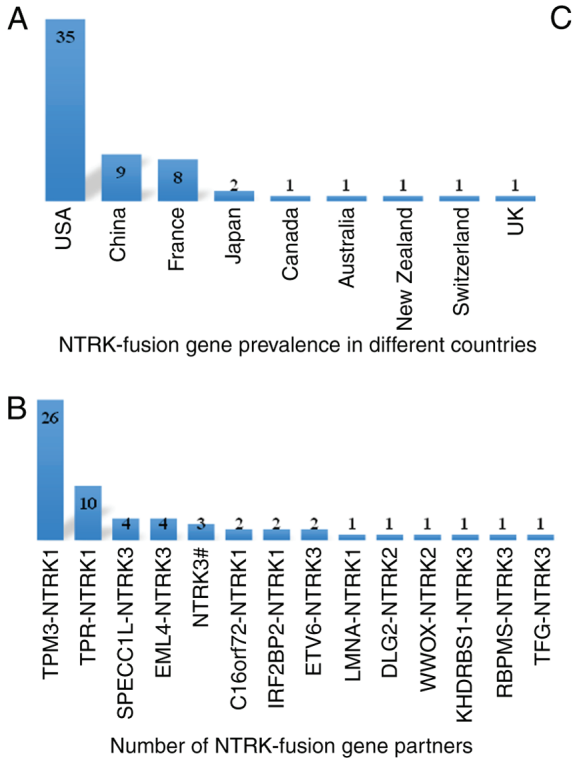
Table I. List of included articles.

First author, year	Region	Cases	Case number	Age	Fusion type	(Refs.)
Boyle *et al*, 2020	UK	1	1	42	TPM3-NTRK1	(26)
Chiang *et al*, 2018	USA	4	2	46	RBPMS-NTRK3	(27)
			3	27	TPR-NTRK1	
			4	47	LMNA-NTRK1	
			5	42	TPM3-NTRK1	
Costigan *et al*, 2022	USA	13	6	35	C16orf72-NTRK1	(28)
			7	35	TPM3-NTRK1	
			8	47	TPR-NTRK1	
			9	30	TPR-NTRK1	
			10	39	TPM3-NTRK1	
			11	16	TPR-NTRK1	
			12	26	EML4-NTRK3	
			13	26	TFG-NTRK3	
			14	61	SPECC1L-NTRK3	
			15	24	TPM3-NTRK1	
			16	42	TPR-NTRK1	
			17	46	IRF2BP2-NTRK1	
			18	26	TPM3-NTRK1	
Bühler *et al*, 2023	Switzerland	1	19	24	TPM3-NTRK1	(29)
Wells *et al*, 2019	USA	1	20	30	TPM3-NTRK1	(30)
Croce *et al*, 2019	France	8	21	39	TPM3-NTRK1	(31)
			22	44	TPM3-NTRK1	
			23	26	EML4-NTRK3	
			24	23	TPM3-NTRK1	
			25	30	TPM3-NTRK1	
			26	60	TPM3-NTRK1	
			27	33	TPM3-NTRK1	
			28	23	TPM3-NTRK1	
Dang *et al*, 2022	China	1	29	33	EML4–NTRK3	(32)
Devereaux *et al*, 2021	USA	9	30	39	TPM3-NTRK1	(33)
			31	66	TPM3-NTRK1	
			32	30	TPM3-NTRK1	
			33	32	TPM3-NTRK1	
			34	21	TPM3-NTRK1	
			35	40	TPR-NTRK1	
			36	37	IRF2BP2-NTRK1	
			37	35	C16orf72-NTRK1	
			38	24	SPECC1L-NTRK3	
Fang *et al*, 2023	China	1	39	49	NTRK3#	(34)
Gatalica *et al*, 2019	USA	1	40	NK	TPM3-NTRK1	(35)
Goulding *et al*, 2021	New Zealand	1	41	13	TPM3-NTRK1	(36)
Xiaoqing *et al*, 2023	China	2	42	55	KHDRBS1-NTRK3	(37)
			43	46	TPR-NTRK1	
Wong *et al*, 2020	Australia	1	44	31	NTRK3#	(38)
Tsai*et al*, 2022	China	2	45	47	TPM3-NTRK1	(39)
			46	53	TPM3-NTRK1	
Takahashi *et al*, 2018	Japan	1	47	44	ETV6-NTRK3	(40)
Rabban *et al*, 2020	USA	3	48	24	TPM3-NTRK1	(41)
			49	30	TPR-NTRK1	
			50	49	TPR-NTRK1	
Nilforoushan *et al*, 2022	USA	2	51	54	SPECC1L-NTRK3	(42)
			52	52	TPM3-NTRK1	

Table I. Continued.

First author, year	Region	Cases	Case number	Age	Fusion type	(Refs.)
Munkhdelger *et al*, 2021	Japan	1	53	72	DLG2-NTRK2	(43)
Moh *et al*, 2021	USA	1	54	69	WWOX-NTRK2	(44)
Hanhan *et al*, 2021	China	1	55	33	ETV6-NTRK3	(45)
Xiaoqi *et al*, 2023	China	2	56	21	EML4-NTRK3	(46)
			57	28	NTRK3#	
Hodgson *et al*, 2021	Canada	1	58	60	SPECC1L-NTRK3	(47)
Hartmaier *et al*, 2017	USA	1	59	-	TPR-NTRK1	(48)

NTRK1, neurotrophic tropomyosin receptor kinase 1; NTRK3#, NTRK3 rearrangements.



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Characteristics	Detail (No. of cases)
No. of published studies	23
Total cases	59
Fusions	NTRK1 (41), NTRK2 (2), NTRK3 (16)
Age (years) [min (average±SD) max]	13(38.18±13.39)72
Outcome	Alive (42), Died (7) Lost follow up (10)
Size (cm) [min (average±SD) max]	1.30(6.05±3.57)16.3
Stage	IA (11), IIA (2), IB (17), IIB-IIIB (4), NK (24)
Recurrence	No (29), Yes (18), NK (12)
CD10	Negative (14), Positive (10), NK (35)
Vimentin	Negative (1), Positive (6), NK (52)
Cytokeratins	Negative (3), Positive (2), NK (54)
Desmin	Negative (36), NK (23)
SMA	Negative (16), Positive (6), NK (37)
Caldesmon	Negative (5), Positive (2), NK (52)
ALK1	Negative (7), NK (52)
S100	Negative (7), Positive (36), NK (16)
SOX10	Negative (18), NK (41)
cKIT	Negative (1), NK (58)
DOG1	Negative (1), NK (58)
CD21	Negative (1), NK (58)
CD23	Negative (1), NK (58)
PR	Negative (24), Positive (9), NK (26)
ER	Negative (29), Positive (5), NK (25)

Figure 3. (A) NTRK fusion gene prevalence in different countries, (B) number of NTRK-fusion genes and their partners and (C) clinical characteristics of patients with cervical cancer. NTRK, neurotrophic tropomyosin receptor kinase. Microsoft excel (Office 365; Microsoft Corporation) was used for figure creation.

the cervix, leading to precancerous lesions known as CIN, which are classified into three grades: CIN1, CIN2 and CIN3. If left untreated, CIN3 can progress to invasive CC. The VIVIANE study found that HPV33 and HPV16 pose the highest risk for developing CIN, followed by HPV18, HPV31 and HPV45 (19). Additionally, HPV testing has proven to be effective in detecting precancerous cervical lesions, particularly in population-based cervical screening programs (20). The role of different HPVs in the progression of CC has been recently reviewed in studies (21,22).

9. HPV activates the same oncogenic pathways as NTRK fusion genes

The main reason why HPV is considered oncogenic is due to the expression of viral oncoproteins E5, E6 and E7. These oncoproteins disrupt normal cellular functions and promote malignant transformation (18). The role of E6 and E7 oncoproteins in the development of HPV-associated CC has been extensively studied. It has been observed that the E6 and E7 proteins interact with various intracellular signaling pathways, leading to induced carcinogenesis. The viral oncoprotein E6 interacts with the tumor suppressor protein p53, causing its degradation and inhibiting apoptosis. Similarly, the E7 protein binds to and inactivates the tumor suppressor retinoblastoma protein (pRb), promoting cell cycle progression and genomic instability. HPV infection leads to cell immortalization and transformation, primarily through the viral oncogenes E6, E7 and E5. These oncogenes have various effects on cellular processes, such as inhibiting p53 and pRb (23), altering the expression of numerous genes (~4% of the genes

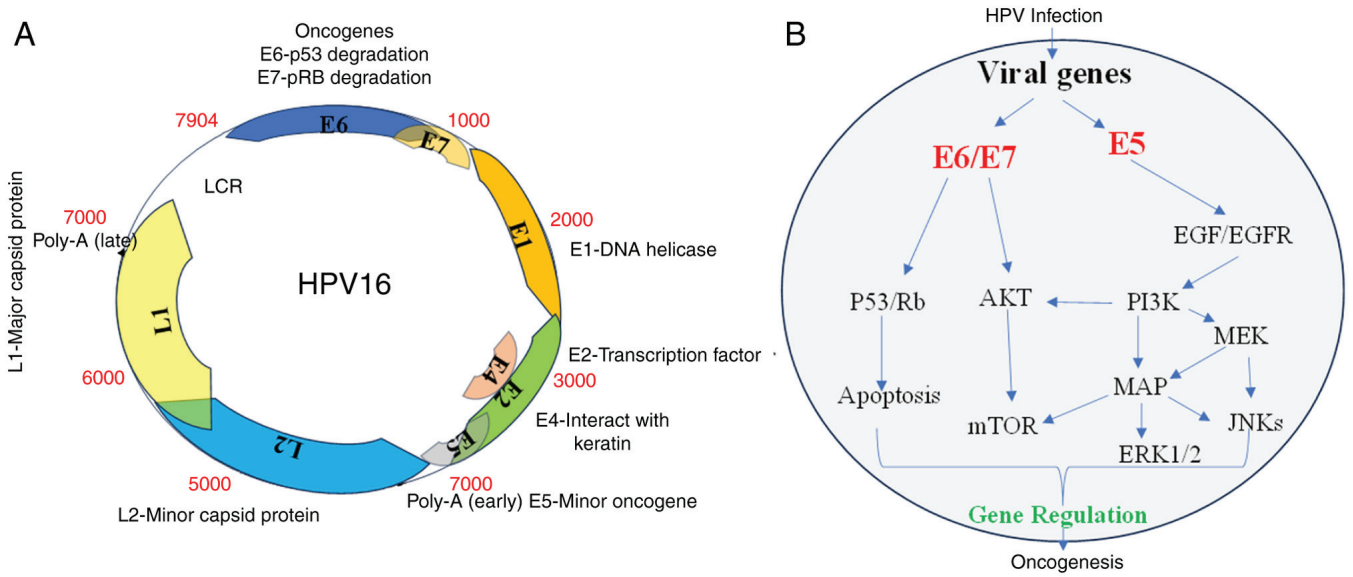

Figure 4. (A) HPV16 genome (21) and (B) HPV-induced oncogenesis (23). HPV, human papillomavirus. Microsoft PowerPoint (Office 365; Microsoft Corporation) was used for figure creation.

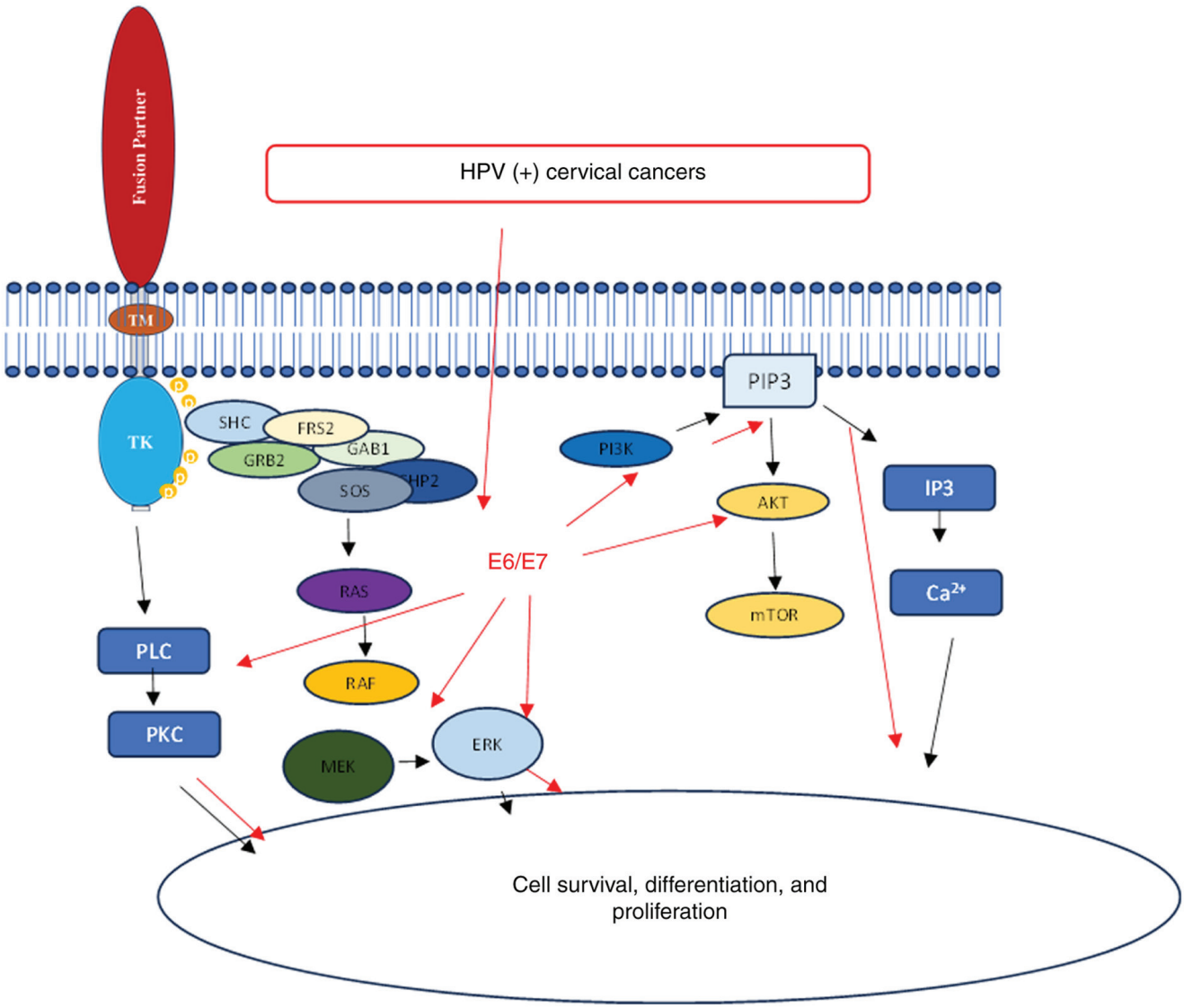

Figure 5. Supposed interplay between HPV and NTRK-induced signaling pathways. HPV, human papillomavirus; NTRK, neurotrophic tropomyosin receptor kinase. Microsoft PowerPoint (Office 365; Microsoft Corporation) was used for figure creation.

on the array) (24), and activating signaling pathways. The virus utilizes various pathways (PI3K/Akt, Wnt/β-catenin, ERK/MAPK and JAK/STAT) that transmit signaling through active molecules such as MEK, ERK and Akt. Ultimately, all these developments increase cell proliferation, leading to carcinogenesis (18,23,25) (Fig. 4B).

10. Conclusion

The aforementioned data suggested that both NTRK-fusion genes and HPV regulate CC through the same signaling pathways. The development of HPV-induced CC involves multiple steps, including the accumulation of genetic and epigenetic alterations in cervical cells. In cases of persistent HPV infection, viral oncoproteins E6 and E7 contribute to the progression of precancerous lesions and CC. Therefore, the presence of NTRK-fusion genes in HPV-induced CC could potentially enhance the impact on downstream signaling pathways, affecting cellular functions such as cell survival, differentiation and proliferation, and ultimately lead to oncogenesis. A hypothetical mechanism, suggesting the existence of a synergistic relationship between NTRK fusion genes and HPV, is demonstrated in Fig. 5. This emphasizes the complexity of this scientific problem and highlights the need for further in-depth research.

Based on the aforementioned literature surveys, it was hypothesized that treating HPV-positive CC with NTRK fusion genes may present more challenges. However, despite extensive searches in online databases, data correlating HPV with NTRK fusion genes could not be found. This further emphasizes the novelty of the present review. One limitation of the present review is the absence of statistical analysis or correlation due to the unavailability of relevant data. Therefore, further investigation is necessary to explore this area and contribute to the development of personalized treatment strategies for patients with NTRK fusion and HPV-positive CC. This could potentially lead to improved patient outcomes and a reduction in mortality rates.

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Availability of data and materials

Not applicable.

Authors' contributions

AURA conceptualized the study, developed methodology, performed software analysis and wrote the original draft. JZ and CZ curated and validated data. XY and DW supervised the study, acquired funding, and wrote, reviewed and edited the manuscript. DW conducted project administration. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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