

Review

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Review

Human Papillomaviruses and Malignant Neoplasms of the Female Upper Reproductive Tract: A Comprehensive Review of the Literature

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Abstract: Malignancies of the female upper reproductive tract, especially endometrial and ovarian cancers, consist a significant burden for women worldwide. The possible etiopathogenetic role of chronic human papillomavirus (HPV) infection in the female upper genital tract carcinogenesis is neither clearly established nor completely understood. Therefore, we performed a literature review through PubMed and SCOPUS electronic databases about the prevalence of HPV DNA in endometrial, primary fallopian tube, ovarian and primary peritoneal cancers, as well as uterine sarcomas. The present investigation covered 35 studies from different countries of various continents. Overall, HPV prevalence was approximately 15% in all the above cancers. HPV DNA was isolated from 11%, 0%, 0% and 14% of endometrial carcinomas, uterine sarcomas, primary fallopian tube cancers and ovarian malignant neoplasms, respectively. No relevant studies on primary peritoneal cancers were retrieved. The predominant HPV strain from all tumors of the upper female reproductive tract, regardless of the tumor site, was mostly HPV-16, followed by HPV-18. HPV DNA was identified exclusively from subtypes HPV-6, HPV-11, HPV-16, HPV-18, and HPV-33, which are responsible for the development of not only cervical cancer, but also of condylomata acuminata. The findings of the present review indicate that HPV vaccination might prove to be a useful strategy in the prevention HPV-related carcinomas of the upper genital tract in women.

Keywords: human papillomavirus; endometrial cancer; uterine corpus cancer; uterine sarcoma; fallopian tube cancer; ovarian cancer; primary peritoneal cancer

1. Introduction

The female upper reproductive tract consists of the cervix, uterus, fallopian tubes and ovaries[1]. Malignant transformation in these structures could occur on each of the above sites, leading to the development of cancer, i.e. cancer of the cervix uteri[2], cancer of the corpus uteri[3], uterine sarcoma[4], primary fallopian tube cancer, ovarian cancer, and primary peritoneal cancer[5], respectively. The global burden of these diseases is significantly high. According to the Global Cancer Observatory (GLOBOCAN) of the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), a total of 662,301 new cervix uteri cancer cases were newly diagnosed in 2022, and a total of 348,874 deaths were attributed to this malignancy, whereas the global incidence and mortality of corpus uteri cancer in 2022 was 420,368 new cases and 97,723 deaths, respectively. Regarding ovarian cancer, 324,603 new cases were diagnosed in 2022 and 206,956 women died of the disease the same year, respectively[6].

The role of chronic human papillomavirus (HPV) infection in the development of cervical cancer has been strongly proven and clearly established since more than two decades ago. A seminal study published in 1999 from The Netherlands by Walboomers et al., demonstrated that high-risk HPV DNA could be detected in nearly all (approximately 99.7%) cervical cancer cases worldwide, thus establishing HPV as a necessary cause of invasive cervical cancer[7]. Moreover, it was also later the same year when German virologist Harald zur Hausen published a comprehensive review of the evidence linking HPV infection to cervical carcinogenesis. zur Hausen's pioneering work in the field laid the groundwork for future research, confirming the causal role of HPV in cervical cancer development[8]. Although HPV DNA has even been isolated from cancerous tissues of human body sites which are neither directly nor obviously linked to sexual intercourse, such as lungs (non-small cell lung cancer, NSCLC)[9] and brain (glioblastoma multiforme, GBM)[10], the possible detrimental contribution of HPV infection to the tumorigenesis in the female upper genital tract at an anatomical level higher than the cervix uteri still remains controversial, as the current published literature is divergent[11,12].

The aim of this comprehensive review is to address the prevalence of HPV DNA isolated from malignant neoplasms of the uterus, fallopian tubes, ovaries and peritoneum and attempt to correlate the presence of the HPV strains identified in these sites with the histopathology of the above malignancies, according to data obtained from individual studies.

2. Materials and Methods

This is a comprehensive review of the literature aiming to summarize the current evidence regarding the prevalence of HPV DNA isolation from malignant tumors of the female upper reproductive tract, excluding cervix uteri, i.e. epithelial and mesenchymal tumors of the corpus uteri, fallopian tube tumors, ovarian tumors and primary peritoneal tumors[13]. The present review was conducted following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) recommendations[14].

2.1. Data Sources and Search Strategy

A search of the literature was conducted on 22 April 2025 through PubMed and SCOPUS electronic databases and designed using the "Systematic Review Accelerator"[15]. The literature search was performed regarding the period from 1 January 1985 to 22 April 2025 for finally published, full-text English journal articles including human adult female individuals of >19 years of age. The searching strategy was formed by combining appropriate MeSH terms and keywords, with the help of the Boolean operators "OR" and "AND". The reference lists of pertinent articles were further manually searched for potentially eligible results. The "Related Citations" tool in PubMed was also applied whenever a suitable article was included. Table 1 presents the exact search string for each database and each cancer site.

Table 1. Electronic databases search string per cancer site.

Malignancy site	PubMed	SCOPUS
Endometrial cancer	(("human papillomavirus viruses"[MeSH Terms] OR "human papillomavirus"[Title/Abstract] OR "HPV"[Title/Abstract]) AND ("endometrial neoplasms"[MeSH Terms] OR "endometrial neoplasms"[MeSH Terms] OR ("endometrial"[All Fields] AND "neoplasms"[MeSH Terms]) OR "endometrial cancer*"[Title/Abstract] OR "endometrial carcinoma*"[Title/Abstract] OR	(INDEXTERMS("human papillomavirus viruses") OR TITLE-ABS("human papillomavirus") OR TITLE-ABS(HPV)) AND (INDEXTERMS("endometrial neoplasms") OR INDEXTERMS("endometrial neoplasms") OR (ALL(endometrial) AND INDEXTERMS(neoplasms)) OR TITLE-ABS("endometrial cancer*") OR TITLE-ABS("endometrial carcinoma*") OR (ALL(endometrial) AND TITLE-

	<p>("endometrial"[All Fields] AND "malignant neoplasm*"[Title/Abstract]) OR "endometrial ca"[Title/Abstract])) AND ((excludepreprints[Filter]) AND (fft[Filter]) AND (humans[Filter]) AND (female[Filter]) AND (1985/1/1:2025/1/1[pdat]) AND (english[Filter]) AND (alladult[Filter]))</p>	<p>ABS("malignant neoplasm*") OR TITLE-ABS("endometrial ca")) AND PUBYEAR > 1985 AND PUBYEAR < 2026 AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (PUBSTAGE,"final")) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (LANGUAGE,"English"))</p>
Uterine sarcoma	<p>(("human papillomavirus viruses"[MeSH Terms] OR "human papillomavirus"[Title/Abstract] OR "HPV"[Title/Abstract]) AND (((uterin"[All Fields] OR "uterines"[All Fields] OR "uterus"[MeSH Terms] OR "uterus"[All Fields] OR "uterine"[All Fields]) AND "sarcoma"[MeSH Terms]) OR "uterine sarcoma*"[Title/Abstract])) AND ((excludepreprints[Filter]) AND (fft[Filter]) AND (humans[Filter]) AND (female[Filter]) AND (1985/1/1:2025/1/1[pdat]) AND (english[Filter]) AND (alladult[Filter]))</p>	<p>INDEXTERMS("human papillomavirus viruses") OR TITLE-ABS("human papillomavirus") OR TITLE-ABS(HPV)) AND ((ALL(uterin) OR ALL(uterines) OR INDEXTERMS(uterus) OR ALL(uterus) OR ALL(uterine)) AND INDEXTERMS(sarcoma)) OR TITLE-ABS("uterine sarcoma*") AND PUBYEAR > 1984 AND PUBYEAR < 2026 AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (PUBSTAGE,"final")) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (LANGUAGE,"English"))</p>
Fallopian tube cancer	<p>(("human papillomavirus viruses"[MeSH Terms] OR "human papillomavirus"[Title/Abstract] OR "HPV"[Title/Abstract]) AND ("ovarian neoplasms"[MeSH Terms] OR "ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] OR "ovarians"[All Fields]) AND "neoplasms"[MeSH Terms] OR "ovarian cancer*"[Title/Abstract] OR "ovarian carcinoma*"[Title/Abstract] OR "ovarian malignant neoplasm*"[Title/Abstract] OR "ovarian ca"[Title/Abstract])) AND ((excludepreprints[Filter]) AND (fft[Filter]) AND (humans[Filter]) AND (female[Filter]) AND (1985/1/1:2025/1/1[pdat]) AND (english[Filter]) AND (alladult[Filter]))</p>	<p>INDEXTERMS("human papillomavirus viruses") OR TITLE-ABS("human papillomavirus") OR TITLE-ABS(HPV)) AND INDEXTERMS("fallopian tube neoplasms") OR TITLE-ABS("fallopian tube cancer*") OR TITLE-ABS("fallopian tube carcinoma*") OR ((INDEXTERMS("fallopian tubes") OR (ALL(fallopian) AND ALL(tubes)) OR ALL("fallopian tubes") OR (ALL(fallopian) AND ALL(tube)) OR ALL("fallopian tube")) AND TITLE-ABS("malignant neoplasm*")) AND PUBYEAR > 1995 AND PUBYEAR < 2022 AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (PUBSTAGE,"final")) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (LANGUAGE,"English"))</p>
Ovarian cancer	<p>(("human papillomavirus viruses"[MeSH Terms] OR "human papillomavirus"[Title/Abstract] OR "HPV"[Title/Abstract]) AND ("ovarian neoplasms"[MeSH Terms] OR "ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] OR "ovarians"[All Fields]) AND "neoplasms"[MeSH Terms] OR "ovarian cancer*"[Title/Abstract] OR "ovarian carcinoma*"[Title/Abstract] OR "ovarian malignant neoplasm*"[Title/Abstract] OR "ovarian ca"[Title/Abstract])) AND ((excludepreprints[Filter]) AND (fft[Filter]) AND (humans[Filter]) AND (female[Filter]) AND (1985/1/1:2025/1/1[pdat]) AND (english[Filter]) AND (alladult[Filter]))</p>	<p>INDEXTERMS("human papillomavirus viruses") OR TITLE-ABS("human papillomavirus") OR TITLE-ABS(HPV)) AND INDEXTERMS("ovarian neoplasms") OR INDEXTERMS("ovarian neoplasms") OR ((ALL(ovarian) OR ALL(ovarians)) AND INDEXTERMS(neoplasms)) OR TITLE-ABS("ovarian cancer*") OR TITLE-</p>

	<p>"ovarian carcinoma*"[Title/Abstract] OR "ovarian malignant neoplasm*"[Title/Abstract] OR "ovarian ca"[Title/Abstract])) AND ((excludepreprints[Filter]) AND (fft[Filter]) AND (humans[Filter]) AND (female[Filter]) AND (1985/1/1:2025/1/1[pdat]) AND (english[Filter]) AND (alladult[Filter]))</p>	<p>ABS("ovarian carcinoma*") OR TITLE-ABS("ovarian malignant neoplasm*") OR TITLE-ABS("ovarian ca")) AND PUBYEAR > 1986 AND PUBYEAR < 2026 AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (PUBSTAGE,"final")) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (LANGUAGE,"English"))</p>
Primary peritoneal cancer	<p>((("human papillomavirus viruses"[MeSH Terms] OR "human papillomavirus"[Title/Abstract] OR "HPV"[Title/Abstract]) AND (((("primaries"[All Fields] OR "primary"[All Fields]) AND ("peritoneally"[All Fields] OR "peritoneum"[MeSH Terms] OR "peritoneum"[All Fields] OR "peritoneal"[All Fields] OR "peritonism"[All Fields] OR "peritonitis"[MeSH Terms] OR "peritonitis"[All Fields]) AND "neoplasms"[MeSH Terms] OR ("primaries"[All Fields] OR "primary"[All Fields]) AND ("peritoneally"[All Fields] OR "peritoneum"[MeSH Terms] OR "peritoneum"[All Fields] OR "peritoneal"[All Fields] OR "peritonism"[All Fields] OR "peritonitis"[MeSH Terms] OR "peritonitis"[All Fields]) AND "carcinoma"[MeSH Terms]) OR "primary peritoneal cancer*"[Title/Abstract] OR "primary peritoneal carcinoma*"[Title/Abstract] OR ("primaries"[All Fields] OR "primary"[All Fields]) AND ("peritoneally"[All Fields] OR "peritoneum"[MeSH Terms] OR "peritoneum"[All Fields] OR "peritoneal"[All Fields] OR "peritonism"[All Fields] OR "peritonitis"[MeSH Terms] OR "peritonitis"[All Fields]) AND "malignant neoplasm*"[Title/Abstract])) AND ((excludepreprints[Filter]) AND (fft[Filter]) AND (humans[Filter]) AND (female[Filter]) AND (1985/1/1:2025/1/1[pdat]) AND (english[Filter]) AND (alladult[Filter]))</p>	<p>(INDEXTERMS("human papillomavirus viruses") OR TITLE-ABS("human papillomavirus") OR TITLE-ABS(HPV)) AND (((ALL(primaries) OR ALL(primary)) AND (ALL(peritoneally) OR INDEXTERMS(peritoneum) OR ALL(peritoneum) OR ALL(peritoneal) OR ALL(peritonism) OR INDEXTERMS(peritonitis) OR ALL(peritonitis)) AND INDEXTERMS(neoplasms)) OR ((ALL(primaries) OR ALL(primary)) AND (ALL(peritoneally) OR INDEXTERMS(peritoneum) OR ALL(peritoneum) OR ALL(peritoneal) OR ALL(peritonism) OR INDEXTERMS(peritonitis) OR ALL(peritonitis)) AND INDEXTERMS(carcinoma)) OR TITLE-ABS("primary peritoneal cancer*") OR TITLE-ABS("primary peritoneal carcinoma*") OR ((ALL(primaries) OR ALL(primary)) AND (ALL(peritoneally) OR INDEXTERMS(peritoneum) OR ALL(peritoneum) OR ALL(peritoneal) OR ALL(peritonism) OR INDEXTERMS(peritonitis) OR ALL(peritonitis)) AND TITLE-ABS("malignant neoplasm*")))) AND PUBYEAR > 1986 AND PUBYEAR < 2026 AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (PUBSTAGE,"final")) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (LANGUAGE,"English"))</p>

2.2. Eligibility Criteria

The inclusion criteria were: i) prospective and retrospective randomized control trials (RCTs), cohort studies, case-control, case series and case report studies, ii) human female adult patients aged >19 years histologically diagnosed with upper female reproductive tract cancer, irrespective to tumor stage, grade and histologic type; iii) HPV DNA extracted from the tumors and detected by polymerase chain reaction (PCR).

2.3. Exclusion Criteria

The exclusion criteria were: i) books or book chapters, conference abstracts, theses, press articles, expert reviews, narrative reviews, systematic reviews and meta-analyses, medical hypotheses; ii) animal studies, in vitro studies, abstract- or protocol-only publications and video reports; iii) non-English articles and published abstracts without full-text manuscripts; iv) presence of concomitant disease site(s) with precancerous or cancerous lesions; v) HPV genome extracted from samples other than upper female genital tract malignant tissues, such as blood; vi) patients and/or non-patients with prior neoplasia, surgery for malignancy, radiation or cytotoxic therapy; vii) co-presence of other oncogenic viruses; and viii) HPV presence detected by methods other than PCR.

2.4. Study Screening and Selection Process

Two authors, CK and IL, independently selected the articles which fulfilled the inclusion criteria. Once the initial title and abstract screening was completed, the full texts of the included studies from that stage were reviewed by the aforementioned investigators to determine if they should be included. Discrepancies were resolved by consulting a third author, SP. The aforementioned stage was completed with the assistance of the automation tool "Systematic Review Accelerator"[15].

2.5. Data Extraction

Study characteristics and data outcomes from each study were recorded in a data extraction form. Data extraction was independently conducted by two researchers, CK and EAA. A third and a fourth researcher, CMS and GMS, were consulted to resolve disagreements through open discussion. The following data regarding study characteristics and outcomes were extracted from every included study: First author, publication year, type of study, malignant neoplasm(s) histopathologic type(s), HPV DNA positivity and HPV subtypes isolated from the tumors by PCR. The flowcharts of study selection for each malignancy site are presented in Figures 1 to 5.

Human papillomaviruses (HPVs) and endometrial cancer (EC)

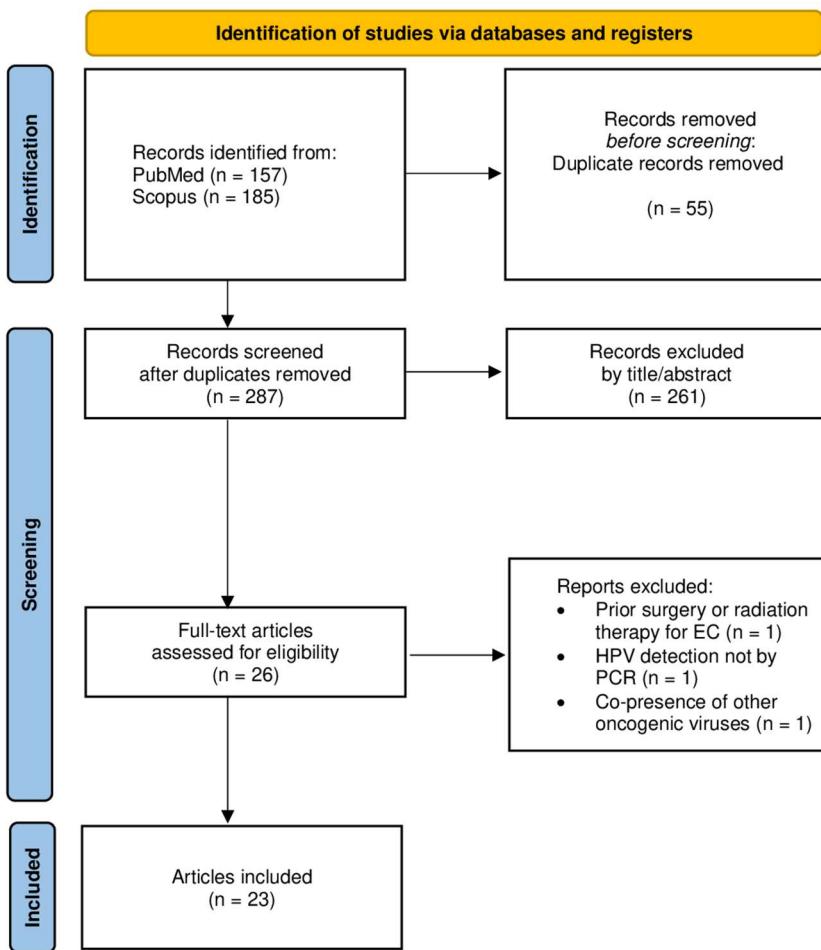


Figure 1. Flowchart of study selection for endometrial cancer.

Human papillomaviruses (HPVs) and primary fallopian tube cancer (PFTC)

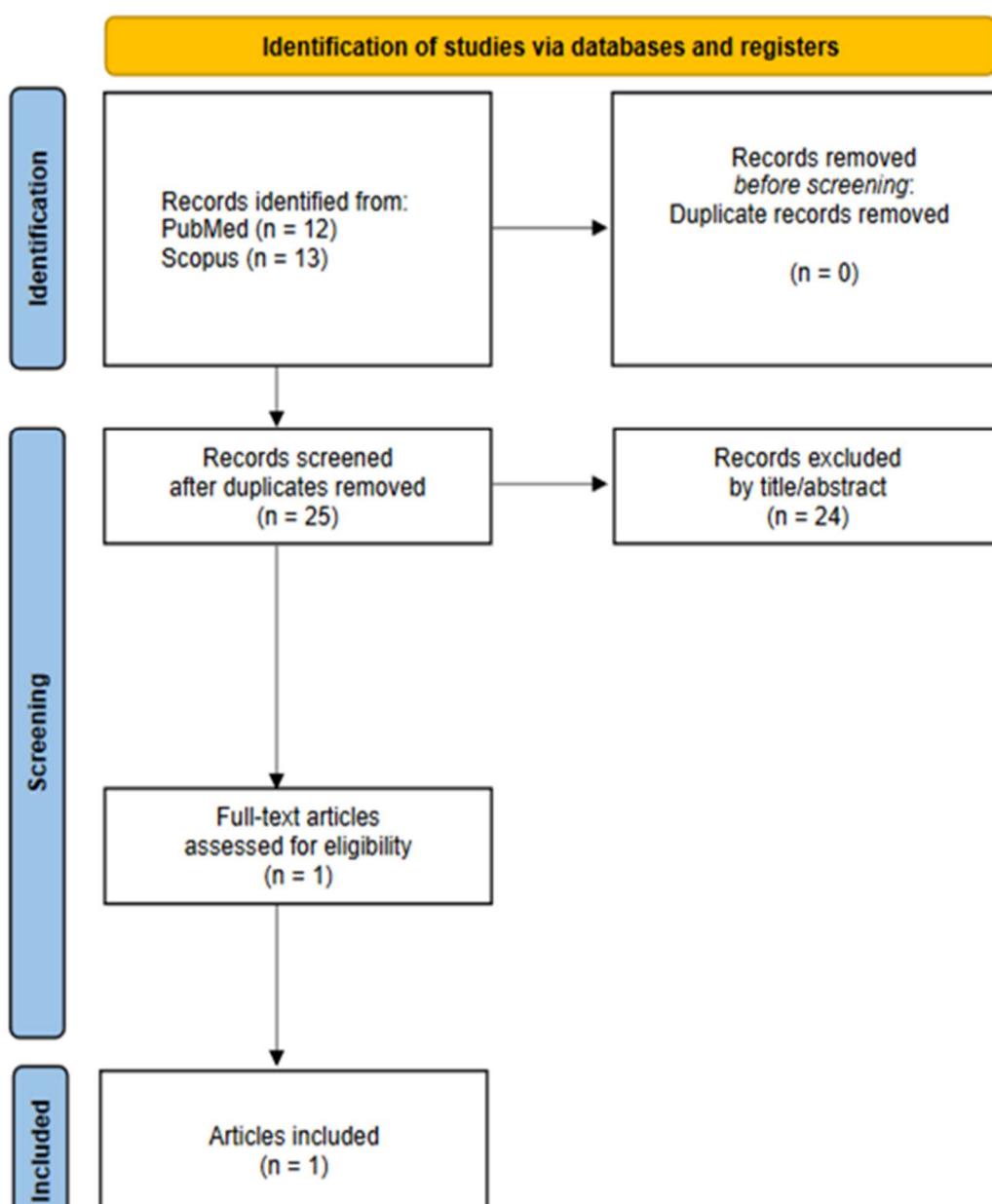


Figure 2. Flowchart of study selection for uterine sarcoma

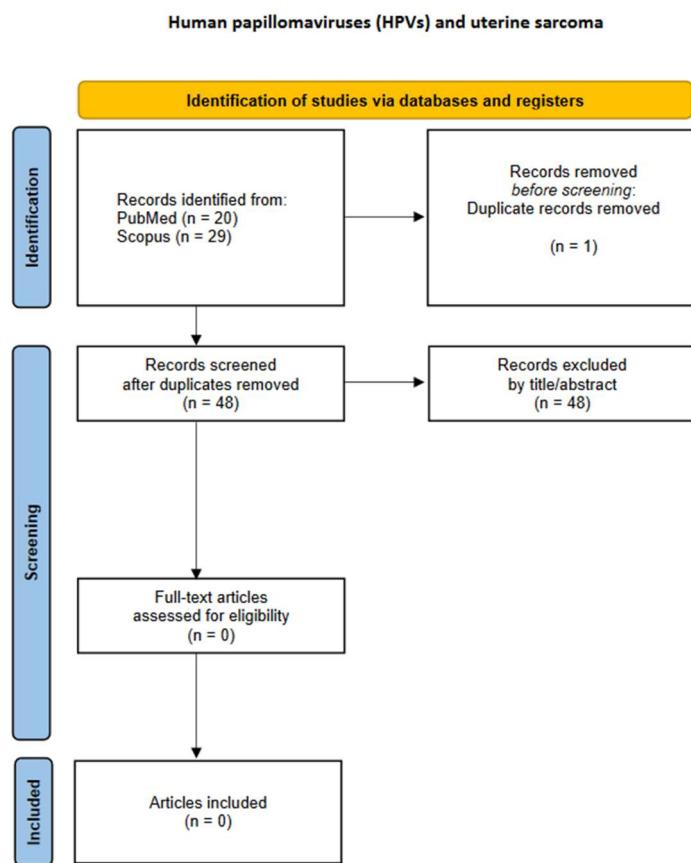


Figure 3. Flowchart of study selection for primary fallopian tube cancer.

Human papillomaviruses (HPVs) and ovarian cancer (OC)

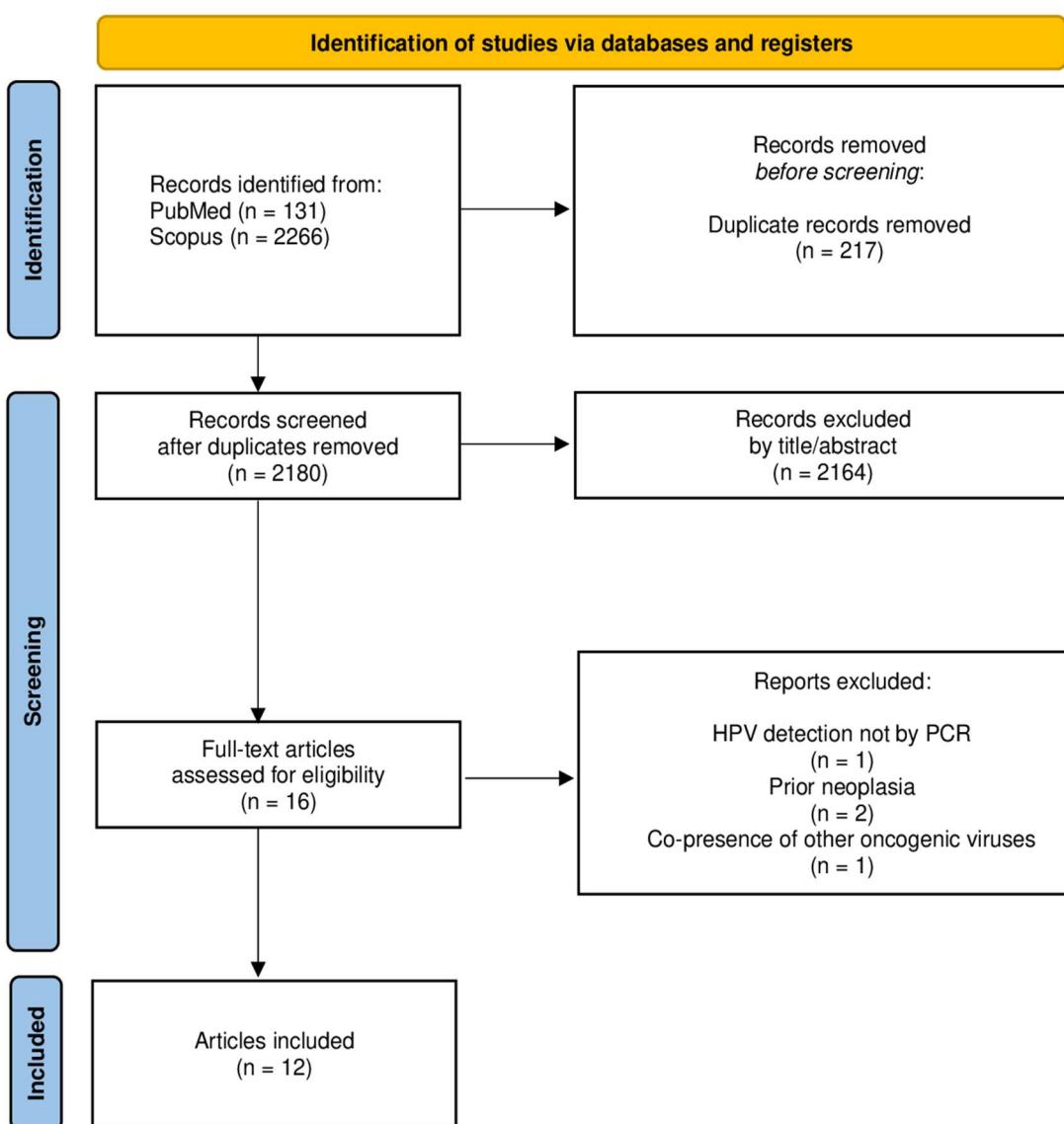


Figure 4. Flowchart of study selection for ovarian cancer.

Human papillomaviruses (HPVs) and primary peritoneal cancer (PPC)

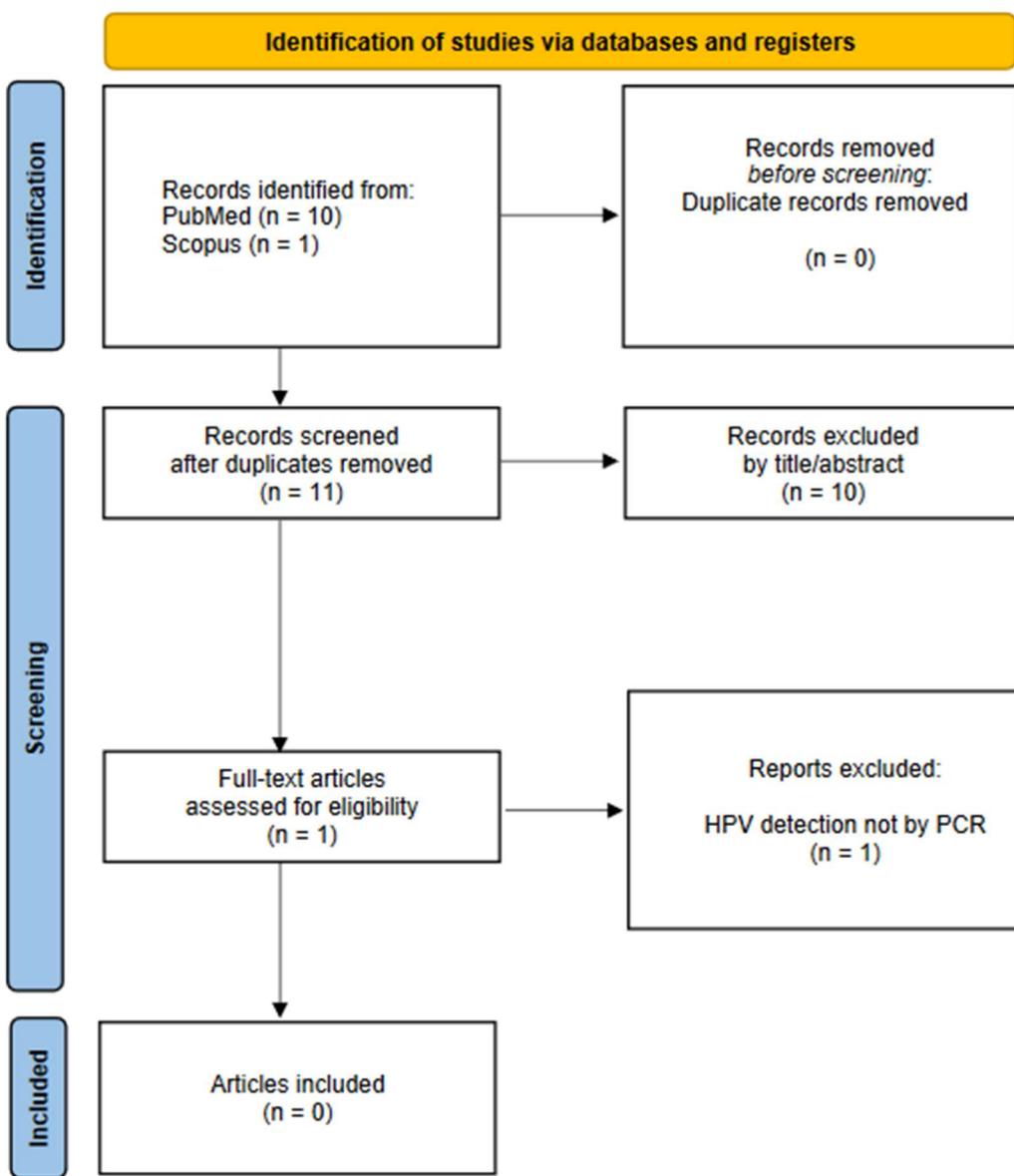


Figure 5. Flowchart of study selection for primary peritoneal cancer.

3. Results

An overview of all selected studies is presented in Table 2. A total of 35 articles, published from 1992 up to 2024, meet the eligibility criteria for the present comprehensive review. These consist of 8 case-control studies[16–23], 25 case series[11,12,24–46] and 2 case reports[47,48]. HPV DNA has been isolated from 222 specimens out of 1,666 malignant neoplastic tissues (222/1,666; 13%). All 222 specimens originate exclusively from 101 endometrial and 189 ovarian carcinomas, as no HPV DNA has been isolated from uterine sarcomas, primary fallopian tube carcinomas, or primary peritoneal carcinomas. Although various commercially available kits capable of identifying DNA from several different HPV strains have been deployed for the isolation of viral DNA from the above tumors, HPV DNA was found only from subtypes HPV-6, HPV-11, HPV-16, HPV-18, and HPV-33. In general, the predominant HPV strain from all tumors of the upper female reproductive tract, regardless of the tumor site, was mostly HPV-16 (145/222; 65%), followed by HPV-18 (48/222; 22%).

3.1. Endometrial Cancer (EC)

The presence of HPV DNA in EC was examined in 24 studies, i.e. 5 case-control studies[16–19,22], 17 case series[24–38,40,46] and 2 case reports[47,49], which included a total of 668 patients with EC. Endometrioid endometrial carcinomas were the most frequent histological type. Viral DNA was detected in 15 of 24 studies (62%), including 74 patients (74/668; 11%). HPV DNA positivity ranged from 0 to 100%. DNA from HPV-16 was isolated from 29 patients, which was the most common HPV subtype (29/74; 39%). The rest HPV strains detected were HPV-6, HPV-18, HPV-33, HPV-11 and HPV-31 in 20, 12, 8, 3 and 2 EC specimens, respectively.

3.2. Uterine Sarcomas

Only one leiomyosarcoma was identified from a case series published in 1994 by *Koffa* et al., from which no HPV DNA was isolated[40].

3.3. Primary Fallopian Tube Cancer (PFTC)

In a case series of 7 PFTCs published in 1996 by *Runnebaum* et al., no HPV DNA was identified in these relatively rare malignant neoplasms[39].

3.4. Ovarian Cancer (OC)

The presence of HPV DNA in OC was examined in 16 studies, i.e. 4 case-control studies[20–23] and 12 case series[11,12,24,32,33,36,40–45], which included 996 patients with OC in total, and confirmed in 13 of 16 studies (81%) and 148 patients (148/996; 15%). Ovarian serous adenocarcinomas were the most frequent histological type in both HPV DNA positive and negative ovarian malignant neoplasms, accounting for more than half of all cases (542/996; 54%). HPV DNA positivity ranged from 0 to 62%[45]. DNA from HPV-16 was isolated from 116 patients, which was the most common HPV subtype (116/148; 78%). The rest HPV strains detected were HPV-18 and HPV-33 in 26 and 1 OC specimens, respectively.

3.5. Primary Peritoneal Cancer (PPC)

A study by *Gatalica* et al. published in 2008 described a case of low-grade peritoneal mucinous carcinomatosis containing high-risk HPV sequences (HPV-16, 18, 31, 33, 35, 39, 51, 52, 56, 58, and 66)[50]. However, it did not pertain to the eligibility criteria and, thus, had to be excluded, because the HPV presence was not confirmed by PCR, but by *in situ* hybridization, without exact HPV genotyping. Therefore, our search retrieved no relevant results.

Table 2. Studies on HPV DNA presence in malignancies of the upper female reproductive tract.

First author, year, reference	Study type	Malignant neoplasm histopathologic type	HPV positivity
Anwar et al., 1996[24]	Case series	15 endometrial carcinomas	• 2/15 (13%) HPV-18 • 5/15 (33%) HPV-33
		3 ovarian carcinomas	None
		20 endometrial adenocarcinomas	2/20 (10%) HPV-11
O'Leary et al., 1998[25]	Case series	41 endometrial adenocarcinomas with squamous metaplasia	• 19/41 (46%) HPV-6 • 2/41 (5%) HPV-16 • 1/41 (2%) HPV-18 • 2/41 (5%) HPV-33
		2 adenosquamous endometrial carcinomas	1/2 (50%) HPV-6 & HPV-33 (same patient)
		4 endometrioid endometrial adenocarcinomas	• 1/4 (25%) HPV-11 • 1/4 (25%) HPV-18

Abu-Lubad et al., 2020[16]	Case-control study	36 endometrial carcinomas 5 primary squamous cell carcinomas of the endometrium	3/20 (15%) HPV-18
Bures et al., 2013[27]	Case series	8 endometrioid endometrial carcinomas	None
Fedrizzi et al., 2009[17]	Case-control study	50 endometrial carcinomas	<ul style="list-style-type: none"> 3/50 (6%) HPV-16 1/50 (2%) HPV-18 & HPV-31 (same patient)
Fujita et al., 1995[28]	Case series	85 endometrial adenocarcinomas	8/85 (9%) HPV-16
Giordano et al., 2006[30]	Case series	2 mucinous microglandular endometrial adenocarcinomas	None
Giordano et al., 2005[47]	Case report	1 primary squamous cell endometrial carcinoma	None
Hachisuga et al., 1996[29]	Case series	30 endometrial carcinomas	None
Hording et al., 1997[31]	Case series	23 endometrial carcinomas	None
Ip et al., 2002[32]	Case series	55 endometrial adenocarcinomas	5/55 (9%) HPV-16
		60 primary epithelial ovarian carcinomas	6/60 (10%) HPV-16/18
		4 mucinous borderline ovarian tumors	3/60 (5%) HPV-16 1/60 (2%) HPV-18
		1 clear cell ovarian adenocarcinoma	1/60 (2%) HPV-16
		1 mucinous ovarian adenocarcinoma	1/60 (2%) HPV-16
Karadayi et al., 2013[18]	Case-control study	30 endometrial adenocarcinomas	None
Kataoka et al., 1997[49]	Case report	1 primary squamous cell carcinoma of the endometrium	1 (100%) HPV-31
Lai et al., 1994[33]	Case series	18 epithelial ovarian adenocarcinomas, of which: 9 serous 7 mucinous 2 undifferentiated adenocarcinomas	9/18 (50%) HPV-16 3/18 (17%) HPV-18
		18 endometrial adenocarcinomas, of which: 10 adenocarcinomas 6 adenosquamous carcinomas 1 clear cell carcinoma 1 undifferentiated carcinoma	8/18 (44%) HPV-16 3/18 (17%) HPV-18
Mariño-Enríquez et al., 2008[34]	Case series	5 primary transitional cell carcinomas of the	None

		endometrium and endometrial carcinomas with transitional cell differentiation	
Park et al., 2004[35]	Case series	10 endometrial adenocarcinomas	None
Plunkett et al., 2003[19]	Case-control study	50 endometrial carcinomas, of which: 38 endometrioid villoglandular 1 serous papillary 7 mixed adenocarcinomas 1 adenosquamous	1/50 (2%) HPV-16
Yang et al., 2003[36]	Case series	46 endometrioid endometrial carcinomas 14 endometrioid ovarian carcinomas 21 serous ovarian carcinomas 11 mucinous ovarian carcinomas 6 clear cell ovarian carcinomas 4 undifferentiated ovarian carcinomas	Endometrial carcinomas: 7/46 (15%) HPV-16 Ovarian carcinomas: 18/56 (32%) HPV-16 1/56 (2%) HPV-18
Zielinski et al., 2003[37]	Case series	20 endometrial adenocarcinomas	None
Brewster et al., 1999[38]	Case series	58 endometrioid endometrial carcinomas 4 adenosquamous endometrial carcinomas 3 malignant mixed mesodermal tumors of the endometrial cavity 1 squamous cell carcinoma of the endometrial cavity	None 1/4 (25%) HPV-16 None 1 (100%) HPV-18
Wong et al., 1993[46]	Case series	22 endometrial adenocarcinomas	1/22 (5%) HPV-16
Runnebaum et al., 1996[39]	Case series	7 primary fallopian tube adenocarcinomas	None
Koffa et al., 1994[40]	Case series	14 endometrial adenocarcinomas 1 clear cell endometrial carcinoma 1 uterine leiomyosarcoma 5 ovarian adenocarcinomas 1 ovarian serous cystadenocarcinoma 1 borderline mucinous ovarian tumor	5/14 (36%) HPV-? (11/16/18/33) None None None None None

		1 Krukenberg tumor	None
Runnebaum et al., 1995[41]	Case series	20 ovarian serous cystadenocarcinomas	None
		2 ovarian endometrioid adenocarcinomas	None
		2 ovarian mucinous cystadenocarcinomas	None
		1 ovarian mixed (endometrioid and serous) cystadenocarcinoma	None
		1 heterologous malignant mixed Müllerian ovarian tumor	None
		1 undifferentiated ovarian carcinoma	None
		1 granulosa cell ovarian tumor	None
Chen et al., 1999[42]	Case series	20 ovarian carcinomas	None
Alavi et al., 2012[20]	Case-control study	43 ovarian serous cystadenocarcinomas	2/43 (5%) HPV-? (16/18)
		7 ovarian mucinous adenocarcinomas	1/7 (14%) HPV-? (16/18)
Ingerslev et al., 2016[11]	Case series	146 ovarian serous adenocarcinomas	1/146 (1%) HPV-18
		10 ovarian mucinous adenocarcinomas	None
		12 ovarian endometrioid adenocarcinomas	None
		6 ovarian clear cell carcinomas	None
Dadashi et al., 2017[21]	Case-control study	25 ovarian carcinomas	25/70 (36%) HPV-16
Hassan et al., 2017[43]	Case series	100 ovarian carcinomas	5/100 (5%) HPV-16 4/100 (4%) HPV-18 1/100 (1%) HPV-33
Kisseljova et al., 2020[12]	Case series	29 ovarian serous adenocarcinomas	18/34 (53%) HPV-16
		2 ovarian mucinous adenocarcinomas	
		3 ovarian endometrioid adenocarcinomas	
Yang et al., 2020[44]	Case series	310 ovarian carcinomas, of which: 208 serous ovarian adenocarcinomas 48 mucinous ovarian adenocarcinomas	78/310 (25%) HPV-?
Jarych et al., 2024[45]	Case series	33 serous ovarian adenocarcinomas	14/46 (30%) HPV-16 9/46 (20%) HPV-18

		5 borderline ovarian tumors 3 clear-cell ovarian adenocarcinomas 3 mucinous ovarian adenocarcinomas 2 other types of epithelial ovarian adenocarcinomas	7/46 (15%) HPV-16+18
Lai et al., 1992[22]	Case-control study	11 epithelial ovarian carcinomas, of which: 7 serous ovarian carcinomas 3 mucinous ovarian carcinomas 1 mixed ovarian carcinoma	2/11 (18%) HPV-16 3/11 (27%) HPV-18
		8 endometrial adenocarcinomas	2/8 (25%) HPV-16
Mohamed et al., 2024[23]	Case-control study	47 epithelial ovarian carcinomas, of which: 15 high grade serous carcinomas 11 papillary serous adenocarcinomas 10 endometrioid adenocarcinomas 4 undifferentiated carcinomas 2 squamous cell carcinomas 2 mucinous borderline tumors (atypical proliferative mucinous tumors) 2 adult type granulosa cell tumors 1 mixed malignant mullerian tumor	6/47 (13%) HPV-16 1/47 (2%) HPV-18 5/47 (11%) HPV-?

4. Discussion

4.1. General Considerations

Evidence from existing literature of the last forty years shows a very wide heterogeneity in the prevalence of HPV DNA isolation from malignant tissues of the upper female genital tract, ranging from 0[11] to 100%[38]. Of note, there are neither narrative nor systematic reviews focused exclusively on examining the potential role of HPVs to the development of uterine sarcomas, primary fallopian tube carcinomas, or primary peritoneal cancers, most probably due to the relative rarity of these malignant neoplasms in comparison to endometrial and ovarian cancer. The most frequently identified HPV subtype for all HPV DNA-positive malignancies studied was HPV-16, regardless of the geographical region from which the samples were collected, which comes in agreement with several meta-analyses published from different researchers in different years[51–54]. Geographical differences in the prevalence of HPV DNA might be attributed to geographical and biological

interactions between HPV subtypes and the host immunogenetic factors, such as HLA (human leukocyte antigen), GST (glutathione-S-transferase), FAS (fatty acid synthase) gene promoter-670, MDM2 (Mouse double minute 2 homolog), and p53 codon 72 polymorphisms[55]. Moreover, HPV DNA prevalence can vary according to the tissue type (for example, frozen tissues versus formalin-fixed paraffin-embedded tissues, FFPE) and the detection method (for example, PCR versus in situ hybridization; PCR is considered as the most sensitive method in HPV detection[51]) used in each study among the included ones. In a meta-analysis from Denmark by *Svahn* et al. published in 2014, HPV prevalence was slightly higher in frozen tissues than FFPE tissues, but this difference was not statistically significant[51]. Paraffin-embedded tissues amplify DNA products less efficiently than fresh tissues, due to loss of DNA integrity, especially when fixation protocols including non-buffered formalin are implemented[51,54]. A long fixation time with formalin can be responsible for a cross-linking of nucleic acids and proteins, as well as random breaks in nucleotide sequences. Additionally, carryover contamination could occur if FFPE blocks were not strictly processed, thus leading to false positive results[54].

4.2. HPV and Endometrial Cancer

In the present review, endometrial cancer prevalence, regardless of type, was approximately 11%, ranging from 0% to 100%. Endometrioid EC was the most common histological type and HPV-16 was the most frequent HPV subtype. According to a systematic review and meta-analysis from Denmark published by *Olesen* et al. in 2014, including 1026 cases of EC in 29 studies, the HPV DNA prevalence varied from 0% to 61% and the pooled prevalence of HPV DNA was 10%. The majority (97%, n=761/1026) of endometrial carcinomas were Type 1 (endometrioid, endometrioid with squamous differentiation, villoglandular, secretory, ciliated cell and mucinous)[52].

An important aspect of HPV-related endometrial carcinogenesis involves the route of HPV transmission from the lower female genital tract to the upper female reproductive tract. The former includes the vagina and the ectocervix, is covered with multiple layers of stratified squamous epithelia and is often exposed to pathogens. The latter, which includes the uterus, endometrium and endocervix, consists of a single layer of columnar epithelium that maintains a relatively sterile environment, with intermittent ascending microorganisms from the lower female genital tract. The endocervix functions as an interface between the relatively sterile upper female reproductive tract and the non-sterile lower female genital tract. It is hypothesized that HPVs could ascend to the endometrium from the vagina and the ectocervix, through the endocervix, and infect the squamous epithelium in the endometrium also, in a similar fashion that HPV infects the basal cells of the squamous epithelium in the cervix[52].

4.3. HPV and Ovarian Cancer

The first report on HPV infection in OC was published in 1987 by *Kaufmann* et al., whose research team had used southern blot hybridization[55], and the first report of HPV-related primary ovarian squamous cell carcinoma was published by *Mai* et al. in 1996[56]. Thereafter, several reports have examined the HPV DNA prevalence in OC. In a meta-analysis by *Svahn* et al., HPV prevalence in ovarian carcinomas ranged from 2% to 67% and the pooled prevalence was approximately 16%. HPV-16, which was the most frequently isolated HPV subtype, was found in serous, mucinous and endometrioid ovarian malignant tissues[51]. Moreover, in a meta-analysis from Brazil published by *Rosa* et al. in 2013, 17.5% of OC cases reported HPV infection. HPV-16 was also the most common strain, followed by HPV-18. Only subtypes 6, 16, 18 and 33 were identified[53]. Furthermore, a more recent meta-analysis by *Ibragimova* et al., which included 14 studies with a total number of 1163 OC samples, revealed a low risk of OC development with HPV infection. The prevalence of HPV in OC averaged 22%, ranging from 0% to 90%[54]. Similar were the findings of a meta-analysis from Berlin, Germany by *Cherif* et al., which was published in the same year, and included 2280 cases of OC, in which the prevalence of detection ranged from 0% to 81% and the overall pooled prevalence of HPV was approximately 16%[55].

A variety of possible transmission pathways have been hypothesized for the detection of HPV DNA in ovarian malignant tissues, such as: i) an ascending infection from the lower genital tract-as

the endometrium and oviducts are an anatomical continuation of the endocervix[53], ii) semen containing HPV DNA and spermatozoa in contaminated semen absorbing HPV DNA and transmitting it to ovarian tissues, or iii) lymphocytes transporting HPV to the ovaries. In each of the cases above, after the virus reaches the ovaries, the disruption of ovarian epithelium during ovulation, could facilitate ovarian HPV infection[51]. HPV prevalence is significantly higher in the squamous cell cervical tissues rather than the glandular tissues of the ovaries, thus indicating the possibly greater affinity of HPV for the former anatomical site[51]. Moreover, the cervical transformation zone (TZ) might be vulnerable to HPV infection, because the TZ consists of cuboidal epithelial cells, reserve cells, or potentially embryonal stem cells, which are possible targets of HPV, whereas similar target cells have not been described in the ovaries, thus somehow explaining the overall lower HPV DNA prevalence in OC compared to cervical cancer and “protecting” the ovaries from HPV DNA integration into the ovarian cells’ genome [55].

5. Limitations

The present comprehensive review implements a systematic way to retrieve as much evidence as possible published in the last four decades on the issue. However, it has several limitations. First, it does not include older studies published prior to 1992. Second, only two electronic databases (PubMed and SCOPUS) have been searched. Third, three of the included studies[23,40,44] do not clearly state which HPV subtype was isolated from the malignant tumors that were analyzed. Fourth, only 7 out of the 35 included studies were case-control studies. Therefore, it was not feasible to distinguish the possible differences between malignant neoplasms and healthy tissues serving as controls. Fifth, not all studies reported which HPV strains were detected in the malignant tumors by their histological type. Sixth, the samples of some of the included studies were obtained from fresh-frozen paraffin-embedded tissue block, while the samples from other included studies were collected from fresh tissues. Seventh, possible contamination from the cervix of examined malignant tissues could not be totally excluded in every included study, especially in cases where no HPV detection isolated from the cervix has been carried out. Eighth, it was the possible presence of HPV DNA and not of HPV mRNA that was performed in the included studies. HPV mRNA marks transcriptionally-active HPV infection[57], while HPV DNA shows the mere presence of the virus. Ninth, no studies for primary peritoneal cancer have been included in the present review. Last, but not least, there are no information on HPV vaccination status of patients and/or controls, especially in newer included studies.

6. Implications for Practice and Future Research

HPV DNA isolation from the upper female genital tract varies widely among the published studies. Nevertheless, the presence of both high-risk and low-risk HPV subtypes in anatomical sites above the cervix implicates their potential role in the development of cancer at these sites. However, a more sensitive detection method, based on mRNA HPV oncogene expression instead of HPV DNA isolation, could compare viral oncogene expression in malignant tissue samples and adjacent healthy tissues, thus further clarifying the potential role of HPVs in upper female reproductive tract tumorigenesis. Moreover, there is no strong evidence whether HPV vaccines could lower the incidence of these malignant neoplasms. Not only prospective multicenter studies on the incidence of HPV DNA-positive malignant tumors in HPV-vaccinated versus HPV-unvaccinated women, but also retrospective studies with large samples on the prevalence of HPV vaccination in HPV DNA-positive malignancies of the upper female reproductive tract, could shed further light on the potentially protective role of HPV vaccines against carcinogenesis in the corpus uteri, adnexa and peritoneum.

7. Conclusions

The present comprehensive review demonstrated that HPV DNA can be found in both endometrial carcinomas and ovarian cancer cases. Highly oncogenic HPV-16 and HPV-18 were the most common HPV strains in the majority of the studies. Therefore, the necessity for HPV vaccination

of both women and men remains imperative, so as a significant reduction in the incidence and burden of HPV-related malignancies of the upper female genital tract is achieved worldwide.

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Abbreviations

The following abbreviations are used in this manuscript:

DNA – Deoxyribonucleic Acid

EC – Endometrial Cancer

FAS – Fatty Acid Synthase

FFPE – Formalin-Fixed, Paraffin-Embedded

GBM – Glioblastoma Multiforme

GLOBOCAN – Global Cancer Observatory

GST – Glutathione S-Transferase

HLA – Human Leukocyte Antigen

HPV – Human Papillomavirus

IARC – International Agency for Research on Cancer

MDM2 – Mouse Double Minute 2 homolog

mRNA – Messenger Ribonucleic Acid

NSCLC – Non-Small Cell Lung Cancer

OC – Ovarian Cancer

PCR – Polymerase Chain Reaction

PFTC – Primary Fallopian Tube Carcinoma

PPC – Primary Peritoneal Carcinoma

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT – Randomized Controlled Trial

TZ – Transformation Zone

WHO – World Health Organization

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