Chapter 8

High-Risk Human Papillomavirus and Colorectal Carcinogenesis

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Additional information is available at the end of the chapter

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Abstract

Colorectal, colon and rectal, cancer is the third most common malignancy in both men and women worldwide. Colorectal carcinogenesis is a complex, multistep process implicating environmental and lifestyle factors in addition to gene mutation and viral infections. On the other hand, it is well established that human papillomaviruses (HPVs) infection play a crucial role in certain types of human carcinomas including cervical and head and neck (HN); as roughly 96% and 30% of these cancers are positive for high-risk HPVs, respectively. Moreover, it has been reported that the presence of high-risk HPVs is associated with vascular invasion, lymph node metastases, and tumor size in cervical and HN cancers. Recently, several investigations pointed-out that high-risk HPVs are present in around 70% of human colorectal cancers. Likewise, our group has demonstrated that E6/E7 oncoproteins of HPV type 16 convert noninvasive and nonmetastatic human cancer cells to invasive and metastatic form. Accordingly, it is evident that high-risk HPVs are present in human colorectal cancers where they could play an important role in the development of these malignancies. In this chapter, we will discuss the presence and role of high-risk HPVs in human colorectal carcinogenesis and metastasis; particularly, the interaction between E5 and E6/E7 oncoproteins of high-risk HPVs in colorectal malignancies, which has been linked with the initiation and progression of these tumors.

Keywords: colorectal cancer, high-risk HPVs, E5 & E6/E7 oncoproteins, cancer initiation, cancer progression

1. Introduction

Colorectal cancers (CRCs) colon and rectal, are the most common malignancies, accounting for approximately 1.36 million new cases worldwide every year [1]. These cancers are characterized by a marked propensity for local invasion and lymph node metastases. Thus, the overall 5-year-survival rate for patients diagnosed with colorectal cancers is approximately 60% worldwide and has not significantly improved over the past decade [2]. Colorectal carcinogenesis is a complex, multistep process involving environmental, demographic, and lifestyle factors in addition to gene alterations and viral infections. The highest incidence of CRCs is observed in Western Europe, North America, Australia as well as in some Middle-Eastern countries [3, 4]. It is notable also that although the rate of this disease is relatively lower in sub-Saharan African communities, South America, and Asia; however, CRCs are gradually increasing due to assimilating life style and dietary habits of Western countries [3–5]. Additionally, around two-thirds of CRC patients will develop distant metastases during the course of their illness, which is the main cause of cancer-related death of this disease [6].

Although, human papillomaviruses (HPVs) have been established as etiological agents of invasive cervical cancer, as generally 96% of these cancers are positive for high-risk HPVs [7–9]. However, persistent infection with high-risk HPVs is necessary but not sufficient for the development of malignant lesions [10, 11]. Furthermore, it was pointed-out that high-risk HPVs have carcinogenic effects at several other anatomical sites in women and men such as head and neck (HN) as well as colorectal [12–15]. These studies and others showed that high-risk HPVs are present in roughly 30% and 70% of HN and colorectal cancers, respectively, especially in their invasive form [14, 15]. Accordingly, we recently investigated the incidence of high-risk HPVs in CRCs in the Syrian population; our data revealed that 54% of human CRCs in Syria are positive for high-risk-HPVs; this was accompanied by an expression/overexpression of Fascin, Id-1, and P-cadherin genes [16], which are major regulators of cell invasion and metastasis [17–19]. Meanwhile, we revealed that E5 and E6/E7 oncoproteins of high-risk HPVs could cooperate together to enhance cancer progression through the deregulation of several key controller genes of the epithelial–mesenchymal transition (EMT) event [7, 20, 21]. It is clear that CRCs and especially their invasive forms are major health problems wherein high-risk HPVs infection can play important roles in the development of these malignancies as well as their metastasis via EMT. In this chapter, we will overview the presence and contributions of high-risk HPVs in CRC initiation and progression.

2. Colorectal cancers

CRCs are the most prevalent cancers worldwide, along with lung and breast cancers, they are one of the deadliest diseases today [22]. For instance, in the United States, CRCs are the third leading cause of cancer death in both sexes and the second overall in men and women combined [23, 24]. At current rates, approximately 5–6% of individuals will develop colon or rectum cancer within their lifetime [23]. These malignances are most common in Europe with

432,000 new cases reported annually in men and women combined, and the second most common cause of cancer deaths in Europe [22, 25]. In general, it is the second leading cause of cancer-related mortality worldwide and the third most commonly diagnosed malignant disease [26].

The prognosis of patients with colorectal cancer has slowly but steadily improved during the past decades in many countries. A 5-year relative survival has reached almost 65% in high-income countries, such as Australia, Canada, the USA, and several European countries, but has remained less than 50% in low-income countries [27–29]. Relative survival decreases with age, and at young ages, it is slightly higher for women than for men [30]; taking into consideration that the stage at diagnosis is the most important prognostic factor.

Colorectal carcinogenesis is common in the elderly; as approximately 90% of new colorectal cancers are diagnosed in patients over 50 years with the median age of diagnosis being 69 years. Furthermore, the incidence of CRCs dramatically rises as one ages, regardless of sex and racial background [26]. Although, it is well-known that patients with colorectal cancer may have a range of symptoms that include occult blood loss, rectal bleeding, change in stool caliber, unintentional weight loss, or have signs of bowel obstruction or perforation.

There are many risk factors for the development of colorectal cancer, one of which is colonic polyps. Pathologic entities include tubular adenoma, tubulovillous adenoma, villous adenoma, hyperplastic polyp, sessile serrated adenoma, sessile serrated polyp, and traditional serrated adenoma. In addition, some hamartomatous polyps are considered premalignant lesions [31]. Among precancerous polyps adenomatous and advanced adenomatous polyps that have polyp size >10 mm, in addition to villous/tubulovillous histological features, or having high-grade dysplasia (HGD), are found to have an increased prevalence and incidence in the elderly [26], and have a potential to progress to invasive adenocarcinomas [26, 32]. HGD is associated with larger size, villous morphology, *TP53* mutation, and deletion of a region of chromosome 18q. Chromosomal instability can be demonstrated in late precursor adenomas. In this sequence, *APC* mutation is a common early event, while the serrated lesions commonly have *BRAF* or *KRAS* mutation [31]. Other risk factors include diet and lifestyle (such as consumption of red meat, smoking, excessive alcohol, weight gain, etc.) as well as advancing age [23, 26].

For the most part, colorectal cancer arises sporadically, however, few cases are associated with inherited syndromes such as familial adenomatous polyposis (FAP; <1% of CRC) where patients exhibit germline mutations in one allele of the adenomatous polyposis (*APC*) tumor suppressor gene, MUTYH-associated polyposis (MAP; rare recessive condition, carrier estimated at ~1%), and Lynch syndrome/hereditary nonpolyposis colon cancer (LS/HNPCC; 2–4% of CRCs) [7, 33].

The usual malignant tumor of the large bowel is a well-to-moderately differentiated adenocarcinoma secreting variable amounts of mucin [34]. In World Health Organization (WHO) classification, a number of histologic variants of this tumor are listed, such as mucinous adenocarcinoma, signet ring cell, medullary, micropapillary, serrated, cribriform comedotype, adenosquamous, spindle cell, and undifferentiated. The most widely used immunohis-

tochemical markers for colorectal adenocarcinoma are cytokeratin (CK) 20, CK7, and CDX2. The most common immunophenotype of colorectal adenocarcinoma is positivity for CK20 and negativity for CK7 [35]. The CRCs are divided in to four grades. G1 are well-differentiated tumors (usually adenocarcinomas) that have more than 95% glandular structures. Further, G2 are designated as moderately differentiated tumors with 50–95% gland formation. G3 are poorly differentiated tumors with 5–50% gland formation; whereas G4 are highly aggressive and undifferentiated tumors with less than 5% gland formation. Recently, WHO also suggests dividing CRCs into low grade (G1 and G2) and high grade (G3 and G4) categories. The diagnosis of G3 and G4 is relatively consistent, but differentiation between G1 and G2 is associated with a significant degree of inter-observer variability [36, 37] .

As we mentioned above, CRCs are characterized by a marked propensity for invasion and metastasis. About 20% of patients with newly diagnosed colorectal cancer present with distant metastases [38, 39]. The most common location is the liver [38, 40]; however, investigators identified lung metastases in 2·1% of patients newly diagnosed with CRC in a large cancer registry in France [41]. Frequency was nearly three times higher for patients with rectal cancer than for patients with colon cancer. Smaller studies [42–44] have shown isolated lung metastases in 9–18% of patients with rectal cancer; although distant metastases can be identified in other organs including the bone and the brain [38].

As we cited above, lifetime risk of CRCs is estimated to be 5–6% in the general population of Western countries [45, 46]. Although hereditary forms of CRC have been well established; however, most cases are sporadic [47]. Numerous epidemiological studies have identified lifestyle and environmental factors contributing to the occurrence of CRCs [48, 49]. In the past decades, *Helicobacter pylori* and Epstein Barr virus infections have been identified as potential causal factors of gastric cancer [50, 51] and personal communication. A number of studies aimed to assess the possible role of viral infections, such as infection with high-risk HPVs, human polyomaviruses, and human herpesviruses in colorectal carcinogenesis [7, 45, 52, 53]. Thus, in the next paragraph the presence and role of high-risk HPVs in human CRCs will be reviewed.

3. Human papillomaviruses (HPVs)

Papillomaviruses were first identified in rabbits in 1933, and they were found to be involved in transmissible growth of benign papillomas [54]. HPVs were first identified in 1956, and they were associated with a variety of benign growths in humans [55]. However, it was later observed that HPVs, a highly prevalent sexually transmitted infection, have potentially serious health consequences in males and females. HPV infections have received considerable attention in recent years. So far, more than 150 HPV types have been isolated and characterized. While the involvement of HPV in causing benign warts was already known, the first evidence of the association between human cancer and certain HPV types was proposed more than thirty years ago by zur Hausen and his colleagues [56].

The common mode of transmission and acquisition of HPV is by horizontal transmission consequent to sexual activity. Occasionally, HPV may be transmitted through modes other

than sexual activity [57–61]. Thus, prevalence sites of HPVs include the epithelium of the vagina, vulva, penis, anal canal, cervix, perianal region, crypts of the tonsils, and oropharynx. Persistent HPV infection is essential for the development of cervical precancerous lesions and cancer. However, this may take a long time, usually a decade or more after the initial infection [62].

HPVs are small, double-stranded DNA viruses that generally infect cutaneous and mucosal epithelial tissues of the anogenital tract. The HPV DNA genome encodes approximately eight open reading frames (ORFs) [52, 62]. It is divided into three functional parts: the early (E) region, the late (L) region, and a long control region (LCR). The E region is important for replication, cellular transformation, and for the control of viral transcription, whereas the L region encodes the structural proteins (L1-L2) that take part in assembly [12]. The LCR is necessary for viral DNA replication and transcription. The seven proteins of the E region are E1, E2, E3, E4, E5, E6, and E7. E1 is necessary for viral DNA replication, while E2 has a role in viral gene transcription and replication. The function of E3 is still not understood. On the other hand, E4 protein interacts with the keratin cytoskeleton and intermediate filaments. Moreover, it facilitates virus assembly and release. The E5 protein interacts with the receptors of growth factors and stimulates cellular proliferation and inhibits apoptosis. E6 induces DNA synthesis, prevents cell differentiation, and interacts with tumor suppressor proteins and repair factors. In fact, E7 induces cell proliferation and interacts with negative regulators of cell cycle and tumor suppressor proteins. E5, E6, and E7 proteins act as oncogenes which are associated with carcinogenesis [12, 20, 63–66] (please see below).

As we mentioned above, over 150 different viral types have been identified, and about one-third of these infect epithelial cells in the genital tract [67]. HPVs are classified as either high risk or low risk. Infections with low-risk types are generally self-limiting and do not lead to malignancy. However, infections with high-risk HPVs (type 16, 18, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, 73, 82, and 83) are associated with the development of cervical cancers since more than 96% of these cancers are positive for high-risk HPVs [7, 9, 68–70].

It is well known that high-risk HPV early proteins, including E5, E6, and E7 oncoproteins, increase cellular alteration and probably lead to HPV induced carcinogenesis [20, 71–73]. More specifically, the E5 oncoprotein interacts with EGF-R1 signaling pathways (MAP Kinase and P13K-Akt) and proapoptotic proteins [74–76]; and therefore, it can play an important role in cell transformation and tumor formation. On the other hand, E6 and E7 of the high-risk HPV types, such as HPV16, are thought to work together in lesions caused by this virus, since, the two proteins are expressed from bicistronic mRNA [77] and initiated from the viral early promoter (p97). These proteins have functions that stimulate cell cycle progression and both can associate with regulators of the cell cycle [70, 72, 78].

Several studies have shown that the viral E6 protein complements the role of E7 and is thought to prevent the induction of apoptosis in response to unscheduled S-phase entry mediated by E7 [70, 79]. The E6 protein is also involved in the inactivation of p53-mediated growth suppression and/or apoptosis and can also associate with other proapoptotic proteins including Bak [80] and Bax [81]. In addition, E6 stimulates cell proliferation independently from E7 through its C-terminal PDZ-ligand domain [70, 82]. E6-PDZ binding is sufficient to mediate

suprabasal cell proliferation [83, 84] and may contribute to the development of metastatic tumours by disrupting normal cell adhesion. On the other hand, the E7 viral is involved with members of the pocket protein family such as pRb, which is well documented. E7 binding to pRb displaces E2F, irrespective of the presence of external growth factors and leads to the expression of proteins necessary for DNA replication [70, 71, 78, 85].

To address the role of E6/E7 genes in high-risk HPV-associated carcinogenesis *in vivo*, transgenic mice have been developed expressing E6/E7 of HPV type 16 individually and together under the human K14 promoter [86, 87]. These transgenic mice developed skin tumors, in general, and cervical cancer with chronic estrogen administration [87, 88]. On the other hand, and to examine the oncogenic properties of E5 *in vivo,* K14-E5 transgenic mice were generated in which the expression of E5 was directed to the basal layer of the stratified squamous epithelia. These mice exhibited the epidermal hyperplasia, aberrant differentiation of the epithelium, and were susceptible to spontaneous skin tumors [89]. Recently, it was reported that K14-E6/E7 transgenic mice have high susceptibility to colorectal cancers and precancerous lesions after dimethylbenz[a]anthracene-treatment, which is a chemical carcinogen that is known to induce squamous cell carcinomas in other sites [90]. These studies show clearly that high-risk HPVs play an important role in cancer initiation and/or progression of several anatomical sites, which could include colorectal, through their E5, E6, and E7 oncoproteins.

4. High-risk HPVs in colorectal cancers

High-risk HPVs have been established as etiological agents of invasive cervical cancer, as more than 96% of these cancers are positive for high-risk HPVs which are the most common viral sexually transmitted infection worldwide [7–9]. Infection with high-risk HPVs is important for the development of premalignant lesions and/or progression of the disease [10, 11]. Additionally, it was revealed that high-risk HPVs have carcinogenic effects at several other anatomical regions in women and men such as HN as well as colorectal [12–15]. These studies showed that high-risk HPVs are present in roughly 30 and 70% of HN and colorectal cancers, respectively, especially in their invasive form [14, 15]. Therefore, several recent studies including one from our group pointed-out that high-risk HPVs are present in human CRCs, specifically types 16, 18, 31, 33, and 35 [7, 12, 15, 16, 52]. Moreover, six recent meta-analysis studies confirmed the presence of high-risk HPVs in human CRCs [70, 91–95]; however, the prevalence of high-risk HPVs varied from one geographic location to another [7, 52]. Meanwhile, it was stated that high-risk HPVs are present especially in the invasive form of these malignancies worldwide [15].

Nevertheless, it is important to mention that high-risk HPV infection alone is not sufficient to induce neoplastic transformation of human normal epithelial cells; the infected cells must undergo additional genetic changes and/or coinfection with another oncovirus to reach full transformation and consequently tumor formation. Based on this fact, we have developed a new model to study the cooperation effect between high-risk HPVs and other oncogenes in

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human carcinogenesis using human normal epithelial (HNE) cells. In this model, we established that E6/E7 oncoproteins of high-risk type 16 cooperate with the ErbB-2 receptor to induce cellular transformation of HNE cells; this was accompanied by a delocalization of β-catenin from the undercoat membrane to the nucleus in HNE cells. Furthermore, we reported that cyclin D1 is the target of E6/E7/ErbB-2 cooperation via the conversion of β-catenin's role from a cell–cell adhesion molecule to a transcriptional regulator [96]. In parallel, we revealed that D-type cyclins (D1, D2, and D3) are essential for cell transformation induced by E6/E7/ErbB-2 cooperation in human HNE and mouse normal embryonic fibroblast (NEF) cells [96, 97]. Finally, we were able to show that the cooperation effect of E6/E7 with ErbB-2, in human normal epithelial and cancer cells, occurs via β-catenin tyrosine phosphorylation through pp60 (c-Src) kinase activation [98, 99]. Thus, the cooperation between E6/E7 oncoproteins of high-risk HPVs and other oncogenes could occur in colorectal carcinogenesis.

On the other hand, and to determine the role of high-risk HPVs infection in human cancer cells, we examined the effect of E6/E7 of HPV type 16 in two noninvasive human breast cancer cell lines. We reported that E6/E7 of HPV type 16 induce cell invasive and metastatic abilities of the two cell lines *in vitro* and *in vivo*, respectively, in comparison with their wild-type cells [100]. This is accompanied by an overexpression of Id-1, a family member of helix-loop-helix transcription factors which regulates cell invasion and metastasis of human cancer cells [101, 102]. We also demonstrated that E6/E7 oncoproteins upregulate Id-1 promoter activity in human cancer cells. These data suggest that high-risk HPVs could play an important role in the progression of human carcinomas via Id-1 deregulation. Thus, we believe that E6/E7 oncoproteins of high-risk HPVs could play a similar role in the progression of human CRCs.

In order to investigate the role of high-risk HPV infection in human colorectal carcinogenesis, we examined the effect of E6/E7 of HPV type 16 in two human primary normal colorectal "mesenchymal" cell lines, NCM1 and NCM5, which were established in our laboratory [20].

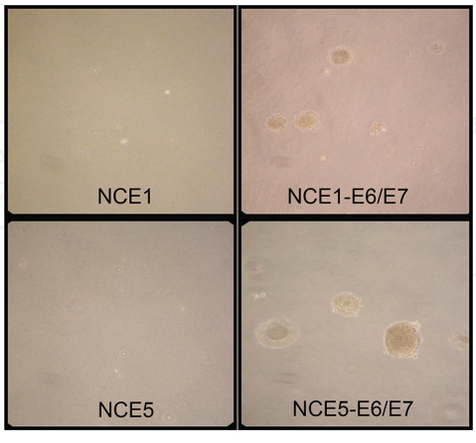

Figure 1. E6/E7 oncoproteins of high-risk HPV type 16 induce cellular transformation in human primary normal colorectal "mesenchymal" cell lines, NCE1, and NCE5 cells [103]. We note that NCE1 and NCE5 cells are unable to grow in soft agar. In contrast, NCE1 and NCE5 cells expressing E6/E7 oncoproteins form colonies in soft agar assay, which is an important characteristic of cancer cells.

We found that the expression of E6/E7 oncoproteins stimulate cell proliferation and induce cellular transformation (**Figure 1**) and migration of NCM1 and NCM5 cell lines. Moreover, our data revealed that E6/E7 of HPV type 16 provoke the upregulation of D-type cyclins and Cyclin E as well as Id-1 in these cell lines [103]. It is important to highlight that there are no other studies regarding the role of E6/E7 oncoproteins of high-risk HPVs in human colorectal cancers. Meanwhile, the function of E5 oncoprotein, in these malignancies, has not been investigated yet.

Additionally, we have recently investigated the incidence of high-risk HPVs in human CRCs in the Syrian population in a cohort of 78 cancer samples using PCR and tissue microarray analyses. We reported, for the first time, that high-risk HPVs are present in 42 samples (53.84%), which represent the majority of invasive colorectal cases; more significantly, our data pointed-out that the most frequent high-risk HPV types in the Syrian population are 16, 33, 18, 35, and 31, respectively. Furthermore, the expression of E6 oncoprotein of high-risk HPVs was found to be correlated with Fascin, Id-1, and P-cadherin expression/overexpression in the majority of cancer tissue samples, which are major regulators of cell invasion and metastasis [17–19, 52]. Our data imply that high-risk HPVs are present in human CRCs, and their presence is associated with invasive and metastatic phenotype [16, 52, 104]. Collectively, these data suggest that high-risk HPVs are present in CRCs and therefore could play an important role in the initiation and progression of these cancers. Thus, we believe that high-risk HPVs can be associated with a subset of colorectal cancers. However, future large-scale multicenter case–control studies with data on risk factors such as lifestyle and sexual behavior are needed; meanwhile, molecular and cellular studies are necessary to determine the role of E5 and E6/E7 oncoproteins in human colorectal cancer and normal cells since it was proposed that E5 can cooperate with E6/E7 oncoproteins to enhance cancer progression of other human malignancies via the EMT event [20, 52]. Thus, we believe that E5 and E6/E7 of high-risk HPVs can cooperate with other oncogenes and/or risk factors such as smoking or alcohol to initiate colorectal cancer; in addition, E5 could cooperate with E6/E7 to enhance cancer progression of this malignancy via the EMT event (**Figure 2**).

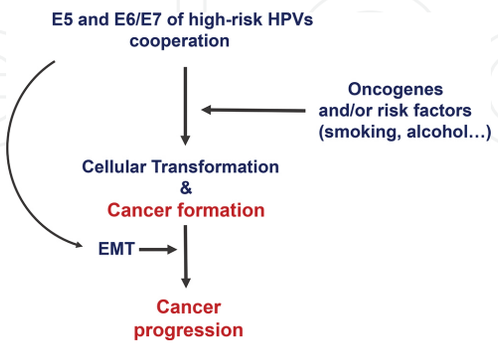

Figure 2. E5 and E6/E7 of high-risk HPVs cooperation and colorectal carcinogenesis. We believe that E5 and E6/E7 of high-risk HPVs can cooperate with other oncogene overexpressions that are linked to lifestyle or/and environmental factors to induce cellular transformation and consequently tumor formation. On the other hand, E5 and E6/E7 together can enhance cancer progression of colorectal cancer via the initiation of the epithelial-mesenchymal transition (EMT) event .

Finally, we think it is important to talk about the prevention strategy of HPV infections and their related cancers, which is essentially based on HPV vaccines. These vaccines are made of virus-like particles (VLPs) that contain inactive L1 HPV proteins—proteins from and specific to each type of HPV viruses [105, 106]. Thus, the quadrivalent vaccine Gardasil (Merck and Co) was developed and approved by the FDA in 2006 for protection against low-risk HPV types 6 and 11, which cause genital warts—and rarely, nongenital warts [107] and high-risk HPV types 16 and 18 [108]. The quadrivalent vaccine will not protect against anogenital disease other than HPV types 6, 11, 16, and 18 [109, 110]. In 2010, the FDA approved the quadrivalent vaccine for the prevention of CRC [106]. The efficacy of prevention of rectal intraepithelial neoplasia in some group of patients is 77.5% [111]. In 2009, a bivalent vaccine (Cervarix; GlaxoSmithKline) was approved for the prevention of HPV infections from high-risk types 16 and 18 [112]. On December 10, 2014, the FDA approved a 9-valent HPV vaccine (Gardasil-9; Merck and Co) that was approved to be given in three intramuscular doses to males 9–15 years of age and females 9–26 years of age [106, 113]. The 9-valent HPV vaccine targets high-risk HPV type 16 (responsible for 50% of cervical carcinogenesis) [114], high-risk HPV type 18 (detected in 20% of cervical cancers) [115], and types 31, 33, 45, 52, and 58, which are responsible for 25% of cervical cancers. Immunizations against low-risk HPV types 6 and 11, which cause genital warts, are also included in the 9-valent vaccine [106, 116]. Approval of the 9-valent vaccine was based on a randomized control study with 14,000 females 16–26 years of age; it noted efficacy of 97% [106]. Therefore, this vaccine will have an important role in preventing HPV infections and their related cancers including colorectal malignancies and their metastasis.

5. Conclusion and perspectives

This chapter presented substantial evidence that high-risk HPVs are present in human CRCs, thereby these viruses, through their E5 and E6/E7 oncoproteins, could play an important role in the initiation and progression of these malignances (Figure 2) [20, 100]. However, we believe that further studies are required to determine the function of E5 and E6/E7 oncogenes in human colorectal normal and cancer cells. Thus, developing new *in vitro* and *in vivo* models, such as cell lines and animal models, are necessary to identify the exact role of these oncoproteins and their potential cooperation in human colorectal carcinogenesis. Such studies can lead to the discovery of new targets to manage these malignances and other human carcinomas related to high-risk HPVs.

Alternatively, and with regards to colorectal malignancies as well as other human carcinomas prevention, we assume that the elimination of a number of known risk factors especially unprotected sexual activity, physical inactivity, smoking, alcohol, high consumption of red meat, and oncovirus infections such as high-risk HPVs could diminish the development of these malignancies and their metastases [20, 23, 26]. Additionally, prevention methodologies of high-risk HPVs using presently available vaccines could greatly reduce high-risk HPVs-associated cancers, including colorectal, and their progression to invasive form, which is responsible for the majority of cancer-related deaths.

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