

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2020 June 7; 26(21): 2682-2888



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The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for WJG as 3.411 (5-year impact factor: 3.579), ranking WJG as 35<sup>th</sup> among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Yu-Jie Ma*

Proofing Production Department Director: *Xiang Li*

Responsible Editorial Office Director: *Ze-Mao Gong*

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Subrata Ghosh, Andrzej S Tarnawski

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

June 7, 2020

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**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Importance of investigating high-risk human papillomavirus in lymph node metastasis of esophageal adenocarcinoma

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**Author contributions:** All authors equally contributed to this paper with conception and design of the study. Sharma P did the literature review and analysis. All authors equally contributed to the drafting, critical revision, editing and approval of the final version.

**Conflict-of-interest statement:** No potential conflicts of interest.

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**Manuscript source:** Invited manuscript

**Received:** January 30, 2020

**Peer-review started:** January 30, 2020

**First decision:** March 15, 2020

**Revised:** March 18, 2020

**Accepted:** May 21, 2020

**Article in press:** May 21, 2020

**Published online:** June 7, 2020

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### Abstract

High-risk human papillomavirus has been suggested as a risk factor for esophageal adenocarcinoma. Tumor human papillomavirus status has been reported to confer a favorable prognosis in esophageal adenocarcinoma. The size of the primary tumor and degree of lymphatic spread determines the prognosis of esophageal carcinomas. Lymph node status has been found to be a predictor of recurrent disease as well as 5-year survival in esophageal malignancies. In human papillomavirus driven cancers, *e.g.* cervical, anogenital, head and neck cancers, associated lymph nodes with a high viral load suggest metastatic lymph node involvement. Thus, human papillomavirus could potentially be useful as a marker of micro-metastases. To date, there have been no reported studies regarding human papillomavirus involvement in lymph nodes of metastatic esophageal adenocarcinoma. This review highlights the importance of investigating human papillomavirus in lymph node metastasis of esophageal adenocarcinoma based on data derived from other human papillomavirus driven cancers.

**Key words:** Esophageal cancer; Esophageal adenocarcinoma; Metastasis; Lymph nodes; Human papillomavirus

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**Core tip:** Esophageal adenocarcinoma (EAC) is one of the fastest growing cancers in the western world. EAC has been associated with high-risk human papillomavirus and has

**P-Reviewer:** Bratlie SO, Iwaya Y**S-Editor:** Zhang H**L-Editor:** A**E-Editor:** Ma YJ

been shown to grant a positive prognosis in EAC. In some human papillomavirus (HPV) driven malignancies (*e.g.*, cervical and head and neck tumors), associated lymph nodes with a high viral load suggest metastatic lymph node involvement. Therefore, HPV is a potential marker of micro-metastases. This review highlights the importance of investigating HPV in lymph node metastasis of EAC based on data derived from other HPV driven malignancies.

**Citation:** Sharma P, Gautam SD, Rajendra S. Importance of investigating high-risk human papillomavirus in lymph node metastasis of esophageal adenocarcinoma. *World J Gastroenterol* 2020; 26(21): 2729-2739

**URL:** <https://www.wjgnet.com/1007-9327/full/v26/i21/2729.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v26.i21.2729>

## INTRODUCTION

The incidence rates for esophageal adenocarcinoma (EAC) has rapidly risen in the western world<sup>[1-7]</sup>. EAC has a high mortality rate with a 5-year survival of less than 15%<sup>[8,9]</sup>. Even patients (< 50%) considered fit for surgery (with neo-adjuvant therapy) and a curative intent, the outcome remains poor with a 5-year survival rate of < 45%<sup>[10,11]</sup>. This is predominantly because esophageal cancer often proliferates through the lymphatic system. Lymph node metastasis (LNM) is the most crucial prognostic factor in esophageal carcinoma, whereby the number of lymph nodes (LN) is directly correlated with disease progression<sup>[12-21]</sup>. The extent of the primary tumor and lymphatic spread determines the prognosis of esophageal carcinoma. In particular, it has been found that LN status is a predictor of recurrent disease as well as 5-year survival<sup>[19,20,22]</sup>.

Over 200 years ago, LeDran *et al*<sup>[23]</sup> first observed the difference in prognosis in breast cancer patients with metastatic spread of tumor cells to regional lymph nodes (RLNs) and patients without spread. Ever since, several studies have focused on the mechanisms involved in this phenomenon. Tumor cells migrate to regional lymph nodes through systematic circulation. Nearly all types of cancers involve circulating tumor cells<sup>[24]</sup>. Few studies supporting the intravasation of these tumor cells into blood vessels have been reported. LNM is a well-established prognostic factor in breast cancer, head and neck cancer, colorectal cancer and prostate cancer. However, the methods of vascular invasions (lymphatic invasion, hematogenous dissemination, *etc.*) vary in different cancers<sup>[25-29]</sup>. Hosch *et al*<sup>[30]</sup> classified esophageal carcinoma as an immunogenic tumor. Mechanisms reported include immune evasion due to functional suppression of cytotoxic T-lymphocytes by DNA methylation in MHC class I phenotype esophageal cancers and hypercoagulation<sup>[30-33]</sup>.

Human papillomavirus (HPV) has been associated with tumorigenesis of several cancers including cervical, anal, head and neck, oral and oropharyngeal squamous cell carcinomas<sup>[34-37]</sup>. The presence of HPV DNA in the RLNs has been associated with disease recurrence and early signs of metastasis<sup>[20,38-43]</sup>.

HPV is a non-enveloped, double-stranded DNA virus from the papillomavirus family. It is approximately 8kB in size with its genome encoding for at least 8 proteins of which 2 oncoproteins E6 and E7 are of importance. The E6 oncogene causes disruption to the p53 pathway with ultimate degradation of the cell. The E7 oncogene binds and inactivates the retinoblastoma protein (pRb) which is responsible for the major G1 checkpoint that blocks the S-phase entry and cell growth phase transition, thereby upregulating p16 expression<sup>[44,45]</sup>.

HPV can be classified into high risk type *i.e.* HPV type 16 and 18 that causes cervical malignancy and head and neck cancers and low-risk type *e.g.* HPV type 6 and 11 which are linked to genital warts and benign changes in the cervix. The causal link between high-risk human papillomavirus (hr-HPV) infection and cervical malignancy, anogenital, and a subset of oropharyngeal squamous cell carcinoma has been well established by molecular and epidemiological investigations<sup>[46-50]</sup>.

HPV detection in these cancers has been undertaken using a combination of techniques: Polymerase chain reaction (PCR), in-situ hybridization (ISH) and p16<sup>INK4A</sup> expression. Detection of both high-risk and low-risk HPV types in tumor samples has been performed by nested PCR. The PCR amplifies the L1 gene of HPV using MY09 and MY11 and GP5+ and GP6+ primers. PCR products were then separated on 2% agarose gel and sequencing performed to determine the genotypes. Viral load has



been calculated by real-time PCR assay method. It measures E6 and E7 copy numbers using genotype-specific HPV-16 and HPV-18 primers. Hr-HPV16 and 18 E6/E7 mRNA has been determined by RT-PCR and/or RNA ISH, which are considered the gold standard for detection of transcriptionally active hr-HPV. p16<sup>INK4A</sup> expression has been assessed by immunohistochemical staining on FFPE (formalin fixed paraffin-embedded) tumor biopsies and controls. These techniques have been widely used in all the HPV driven cancers<sup>[50-53]</sup>.

Currently, Barrett's esophagus (BE) is the only recognized visible precursor lesion for EAC<sup>[54,55]</sup>. It has been proposed that a metaplasia – dysplasia – cancer sequence exists<sup>[56,57]</sup>, whereby patients with BE (no dysplasia) undergo dysplastic transformation (low- and high-grade dysplasia) before cancer development. Although, the cancer risk in BE gets progressively downgraded, the exponential rise in EAC continues unabated<sup>[58,59]</sup>.

Syrjanen reported the association of HPV with esophageal squamous cancer for the first time in 1982<sup>[60,61]</sup>. In 2010, Rajendra *et al*<sup>[62]</sup> hypothesized that HPV could be a common denominator in the pathogenesis of EAC due to similar immunogenetics of BE and cervical neoplasia. Later in 2013, they provided world first evidence for a strong association of transcriptionally active hr-HPV with EAC<sup>[52,63]</sup>. Hr-HPV has now been proposed as one of the risk factors for esophageal adenocarcinoma<sup>[64]</sup>.

Despite the suggested association of HPV with Barrett's dysplasia and EAC, a few studies found contradictory results. A study by Antonsson *et al*<sup>[65]</sup> found no evidence of HPV in 233 formalin-fixed EAC tissue specimens > 10 years old. In another case-control study by Serag *et al*<sup>[66]</sup>, no viral presence was detected in 127 patients with BE in a US cohort, as the virus is not associated with metaplastic tissue. Rai *et al*<sup>[67]</sup> again confirmed the virtual absence of HPV infection in Barrett's metaplasia in the UK population. Iyer *et al*<sup>[68]</sup> found no statistical difference in the HPV prevalence between BE (27.4%), EAC (31%) and controls (20.7%) and thus concluded that it was of no etiologic significance. Cross-contamination may explain their results. Plausible reasons for negative studies in EAC include limited sample size, geographical location of patient cohorts, racial disparity, methods of HPV detection especially as the viral load in esophageal tissue is low, sample collection, storage, age of specimens and poor tissue classification. HPV detection by PCR is an extremely sensitive assay. Thus, quality of tissue samples, storage conditions and contamination can all adversely affect the assay. For example, the PCR primers MY09/MY11 might not amplify the 450 bp target area on the biopsy tissues collected over 10 years ago. Also, HPV detection is significantly superior in fresh-frozen samples than in the paraffin embedded tissues<sup>[34,69]</sup>.

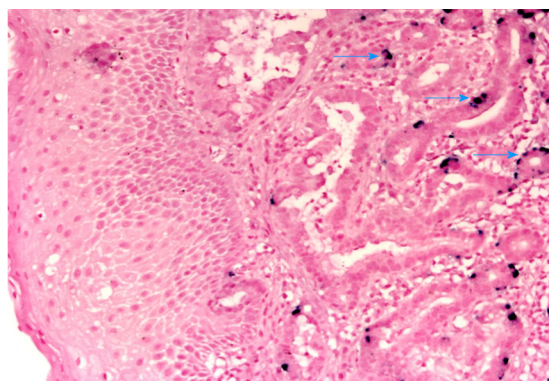
A systematic review has reported HPV prevalence rates of 35% in EAC ( $n = 174$ ), which is not much different to our findings. Another systematic review which included 19 studies concluded that the pooled prevalence of HPV in EAC was 13%. The authors suggested that the low prevalence rate may have been caused by small sample sizes and compromised detection methods<sup>[34,69]</sup>. Increasing hr-HPV viral load and integration status has been linked with more severe disease along the Barrett metaplasia-dysplasia-adenocarcinoma sequence. In situ-hybridization (ISH) demonstrated for the first time that the hr-HPV genome is present in BE, BD and EAC cells but not the squamous epithelium (Figure 1)<sup>[70]</sup>. The presence of HPV oncogene E6/7 mRNA was also observed in the BD and EAC (Figure 2)<sup>[51]</sup>.

Moreover, treatment failure after endoscopic ablation of Barrett's dysplasia (BD) or EAC is predicted by persistent hr-HPV infection and overexpression of the p53 gene (TP53)<sup>[71]</sup>. Epidemiological data indicate various other risk factors for EAC including Caucasian race, gender, age, obesity and smoking<sup>[72-74]</sup>.

HPV-16 DNA has been detected in the cervical lymph nodes of esophageal squamous cell carcinoma (ESCC)<sup>[42]</sup>. Currently no studies have been reported regarding HPV involvement with LNM in EAC. This review will therefore emphasize the significance of conducting such an investigation.

## ASSOCIATION OF HPV INFECTION AND LYMPH NODE METASTASIS IN VARIOUS CANCERS

Cervical cancer is the archetypal HPV driven malignancy. This has led investigators to examine HPV involvement in other less common cancers which involve the transformation zone and/or the genital area. Examples are head and neck tumors which have a physiological transformation zone rather an anatomical one, esophageal adenocarcinoma (anatomical transformation zone), penile, vulvar and anal carcinomas. Summarized below, we review LNM in the HPV driven cancers.



**Figure 1** DNA *in-situ* hybridization showing high-risk human papillomavirus DNA in Barrett's dysplasia /esophageal adenocarcinoma tissue only. (Adapted from: Al-Haddad *et al*<sup>[70]</sup>, 2014)

### Anogenital cancer

**Cervical cancer:** More than 90% of cervical cancer cases are caused by untreated HPV infection<sup>[75-77]</sup>. The presence of HPV DNA in lymph nodes ranges between 40%-99.7% and has been linked to early signs of metastasis with poor prognosis. The disparity in results can be due to technical differences and variations in patient cohorts<sup>[20,38,43,78-84]</sup>. Although, there is a more apparent correlation of HPV-16 and LNM, both hr-HPV types 16 and 18 have been reported to be predictive of LNM in cervical cancer thus affecting prognosis<sup>[82,85,86]</sup>.

Early detection of epithelial cells containing transcriptionally active HPV in lymph nodes has been proposed as a marker for metastases<sup>[87,88]</sup>. In 2012, Zhang *et al*<sup>[89]</sup> reported hr-HPV positivity in 95.8% metastatic lymph nodes with same HPV type as in the primary lesion. Thus, testing for HPV DNA in pathologically negative lymph nodes could be a crucial marker of micro-metastases<sup>[89]</sup>. About 15% of cervical cancer cases have non-metastatic lymph nodes and detection of HPV in negative lymph nodes has been indicated as a marker of micro-metastasis<sup>[87,90]</sup>. HPV positive DNA in pelvic lymph nodes has been found in 25%-80% of women in early stages cervical cancer<sup>[83,91]</sup>. In contrast to the above findings, few studies reported no correlation between HPV positivity and LNM<sup>[92-94]</sup>.

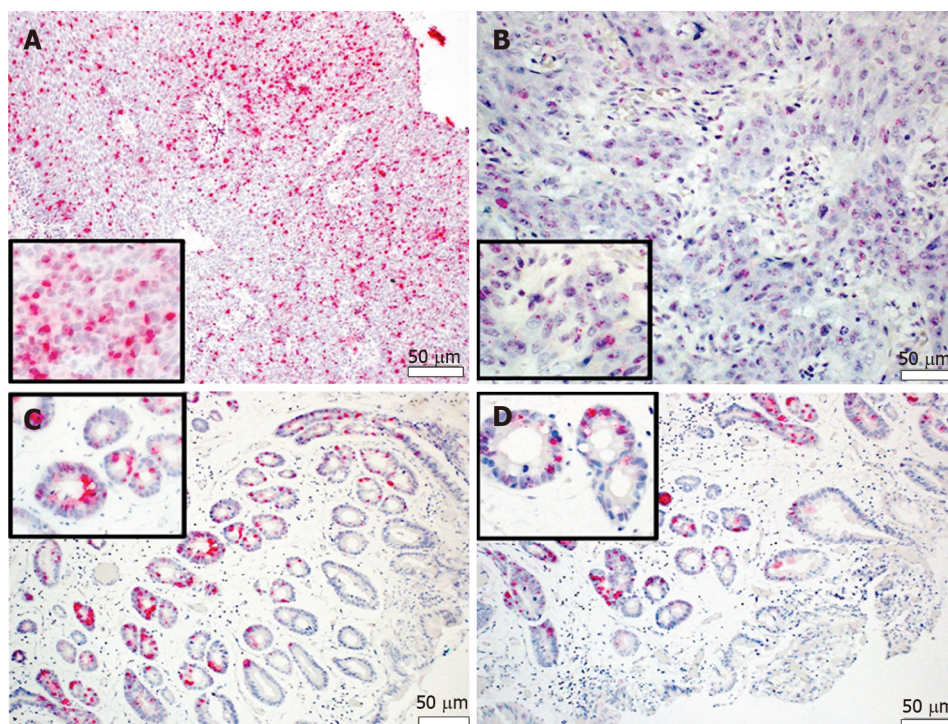
While, some studies associate HPV-positive lymph nodes with higher risk of disease recurrence and lower overall survival<sup>[88,81]</sup>, others find no notable differences in these parameters between HPV positive and negative lymph node status<sup>[93,94]</sup>. Coutant *et al*<sup>[91]</sup> reported no correlation between the HPV status in pelvic lymph nodes and overall prognosis. These disparities could be due to limited sample size and DNA detection methods. A study by Lukaszuk *et al*<sup>[41]</sup> concluded that LNM detection is significantly more accurate by ascertaining HPV status than normal histopathological testing.

**Anal, penile and vulvar cancers:** The incidence of penile and vulvar cancers is highest in some developing countries. HPV has been linked with the pathogenesis of a subset of these cancers<sup>[95-98]</sup>. Studies have reported the overall prevalence of HPV DNA in other anogenital cancers as: Penile cancer (15%-71%); anal (80%) and vulvar (40.1%) cancers have been reported to be HPV-associated<sup>[95,99]</sup>. These prevalence rates are obviously dependent on the methods of DNA detection, patient cohort selection as well as sample handling and processing.

Hr-HPV 16 and 18 has been detected in penile and vulvar cancer tissues using polymerase chain reaction, Southern blot and in-situ hybridization techniques<sup>[100,101]</sup>. The prevalence of HPV DNA has been reported higher (> 55%) in basaloid and warty penile cancers as compared to verrucous and keratinizing cancers (< 10%)<sup>[95]</sup>. Involvement of inguinal lymph node in penile cancer is an unfavorable prognostic indicator<sup>[102]</sup>. In a study by Picconi *et al*<sup>[103]</sup>, 71% of cases were positive for HPV DNA. The positivity was consistent in both the primary tumor and lymph node metastasis. Also, HPV positivity was found in histologically normal lymph nodes which could indicate early metastasis and disease recurrence<sup>[103]</sup>.

In regard to the prevalence of HPV and location in the transformation zone, anal cancer mimics cervical malignancy better than other HPV associated anogenital cancers. Using the PCR detection technique, HPV positivity has been found in up to 89% of the squamous cell anal carcinoma cases. HPV 16 is the most prevalent high-risk type<sup>[104,105]</sup>.





**Figure 2** *In-situ* hybridization detection of transcriptional activity of high-risk human papillomavirus types 16 and 18 E6/E7 mRNA. A: HPV16 cervical squamous cell carcinoma; B: HPV16 head and neck squamous cell carcinoma; C: HPV16/18 positive EAC; D: Barrett's esophagus with HGD. (Adapted from: Rajendra *et al*<sup>[71]</sup>, 2015).

### Head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) is the fifth most common cancer worldwide<sup>[106]</sup>. Most of the primary tumors detected in HNSCC are of unknown primary origin and are found in the oropharynx. Cervical LNM in oropharyngeal squamous cell carcinoma (OSCC) has been linked to regional recurrence and decreased overall survival<sup>[106-109]</sup>. Lymph node metastasis has been described as an independent prognostic factor in head and neck cancers<sup>[108,110,111]</sup>.

Around 80-90% oropharyngeal tumors are associated with hr- HPV<sup>[112-115]</sup>. Of all high-risk types, HPV-16 is the most frequent genotype. HPV driven HNSCCs have considerably superior prognosis and superior chemo- and radio-sensitivity than the typical non-HPV related HNSCC. Normally, HNSCC is keratinizing and is usually caused by genetic alterations; whereas, HPV-associated HNSCC is non-keratinizing and is triggered by inactivation of tumor suppressor genes (*e.g.* TP53 and RB) by viral oncogenes E6 and E7<sup>[116]</sup>. However, a subset of patients with HPV related HNSCC develop metastasis similar to non-HPV related HNSCC<sup>[117]</sup>.

Furthermore, transcriptionally active HPV has been detected in metastatic lymph nodes in these cancers<sup>[118,119]</sup>. Takes *et al*<sup>[120]</sup> proposed that hr-HPV positive DNA in metastatic cervical lymph nodes, could identify the primary origin of head and neck cancers. 70% of OSCC patients were diagnosed with LNM at early stages and 20-30% have occult metastases. Cancer free lymph nodes with high viral load could indicate occult metastasis<sup>[42]</sup>.

HPV driven head and neck cancer especially in oropharyngeal and tonsillar regions have an increased overall survival. Schwartz *et al*<sup>[121]</sup> and Nicolas *et al*<sup>[122]</sup> found that patients with HPV-positive tumors have an increased disease free, overall survival and reduced disease specific mortality rates compared to viral negative head and neck cancers. Fujita *et al*<sup>[121]</sup> concluded that LNM was more prevalent in HPV linked HNSCC and HPV negative tumors were associated with disease recurrence.

### Gastric cancer

Gastric cancers (GC) have been caused by various microbial infections. Major pathogens linked to GC are *Helicobacter pylori* (*H. pylori*) and Epstein Barr virus (EBV)<sup>[122-124]</sup>. EBV infection raises the risk of gastric cancer. It is present in 9% of gastric carcinomas<sup>[125]</sup>. Very few studies have been reported on the prevalence of EBV in lymph nodes in GC. These studies found that EBV positive gastric cancer was negatively associated with lymph node metastasis, resulting in better prognosis<sup>[126-128]</sup>.

The association of HPV and gastric cancers is still poorly understood. de Souza *et*

*al*<sup>[128]</sup> and Fakhraei *et al*<sup>[129]</sup> observed only 3% and 5% of samples infected with HPV. Although, hr-HPV 16 and 18 were found in some tumors, E6 and E7 expression was negative implying the absence of biologically active virus. These studies therefore concluded that HPV had no role in initiation or progression of GC. Where some studies reported higher frequencies (37.5%-52%), other publications documented complete absence of the virus in GC tumor samples<sup>[130-135]</sup>. This discrepancy can be attributed to DNA detection and tumor samples processing methods. In a meta-analysis of 1917 patients, Zeng *et al*<sup>[136]</sup> reported that the HPV positivity was greater in the Chinese population (31%) than in non-Chinese regions (9%). Also, higher rates of HPV infection were obtained using the ISH (36%) method than PCR technique (26%).

## CONCLUSION

HPV associated LNM has been well established as a major prognostic factor in oropharyngeal, head and neck squamous cell carcinoma and other anogenital cancers. Studies have demonstrated an association of transcriptionally active HPV with esophageal adenocarcinoma. The viral involvement in LNM in EAC is still unexplored and unidentified. Through this review, we propose that HPV detection should be undertaken in LNM of EAC tissue samples which test positive for HPV infection in the primary tumor, using PCR, DNA ISH, RT-PCR, E6-E7 mRNA ISH and p16<sup>INK4A</sup>. We shall correlate HPV status of the primary tumor and lymph nodes with clinical outcomes including overall survival, disease-free survival micro-metastasis and diseases-specific death. The results of these studies we hope, shall be keenly anticipated in the coming years.

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