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Human Papillomavirus: Cancer, Vaccination, and the Role of the Pharmacist
Written by: Rebecca Powell, Pharm.D. Candidate 2022

Human papillomavirus, or HPV, is the most common sexually transmitted infection around the globe.¹ Papillomaviruses are common across animal species and are specific to their respective host. Though it has more than 200 genotypes, only 85 strains of HPV have been well characterized by researchers. Genotypes differ in the types of tissues which can be infected, the ability to generate topical warts, as well as the associated risk of developing cancer. Human papillomavirus is transmitted via direct skin to skin contact and can be categorized as either cutaneous or mucosal, depending on the type of tissue it infects. Cutaneous viruses target the epidermal tissue of the hands and feet while mucosal viruses target the linings of the mouth, throat, and anogenital areas. Once infected, the virus manifests as either (i) common or genital warts, (ii) an active infection that causes abnormal cell changes which can lead to cancer, or (iii) an inactive and latent infection that can still be transmitted to a sexual partner.²

Approximately 40 genotypes of HPV are associated with genital infections. These genotypes have been categorized as either high or low risk based on their associated link to high-grade lesions and cancer diagnoses.² Nearly 80% of people around the globe will be exposed to HPV in their lifetime, and approximately 35,000 Americans are diagnosed with cancer caused by HPV each year. Infection with human papillomavirus is the most prominent cause of female cervical cancer worldwide.¹

Like all viruses, no cure exists for HPV; however, a preventative vaccine has been FDA approved since 2006. Based on the high-risk genotypes currently covered in the HPV vaccine, immunization could prevent more than 90% of cancers caused by this virus.¹ In 2014, the FDA approved a 9-valent HPV vaccine, covering the nine most common genotypes of human papillomavirus. Prior to this most recently approved Gardasil 9 formulation, the FDA approved both quadrivalent and bivalent compounds, which together have provided over 13 years of efficacy and monitoring data.³ The current HPV vaccination schedule includes a 2-dose series for boys and girls ages 9-14 and a 3-dose series for ages 15-26, or anyone aged 9-26 who may be immunocompromised.¹

Cervical cancer is now one of the most preventable types of cancer in America. Through safe sex education, early detection, mandatory preventative health screening coverage, and timely vaccination we can continue to lower the rates of incidence and mortality of cervical cancer in our country - both of which have already been cut in half since the 1970s. However, the rates of HPV vaccination remain strikingly low. In 2018, only 54% of girls and 49% of boys ages 13-17 were up to date on the HPV vaccine despite a national call to vaccinate between the ages of 11-12.⁴ Interestingly, a recently published study suggests that a single dose of the current HPV vaccine is as effective as multiple doses in preventing invasive cervical disease, which could potentially aid in boosting immunization rates.⁵

Pharmacists play an important role in disease prevention through advocating for and administering immunizations, including the HPV vaccine. However, some limitations exist: two states in the US still do not allow pharmacists to administer the HPV vaccine and several states require a prescription from a prescriber prior to pharmacist administration. Furthermore, the majority of states have an age limitation for pharmacist vaccine administration, meaning that these pharmacists would not be allowed to provide the HPV vaccine within the recommended age window for adolescents.⁶ As the most accessible healthcare providers, it is extremely important to educate the public on the pharmacists’ immunization training and to strive for complete immunization authority around the country. By reducing these barriers to care, we can increase the HPV vaccination
rates and lower the incidence of cancer caused by this virus. By continuing to remain informed, raise the subject, educate our patients, and advocate for our community, pharmacists can continue to pave the way for cervical cancer prevention.

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Breast cancer is the most common invasive cancer and is the leading cause of cancer-related mortality among women worldwide. Nearly half of women with breast cancer report depression and/or anxiety within the first year after diagnosis. Appropriate treatment of depression in these patients is paramount, not only to aid in quality of life but also to ensure optimal long-term outcomes. Higher mortality rates have been found in patients with breast cancer and depression compared to those without depression. Selective serotonin reuptake inhibitors (SSRIs) are indicated to treat depression, sleep disturbance, and vasomotor symptoms while on tamoxifen, a medication used to manage breast cancer. However, debate continues in regard to whether certain antidepressants reduce tamoxifen’s effectiveness in lowering breast cancer recurrence due to drug-drug interactions.

Tamoxifen is a mainstay of managing breast cancer as it is approved for the treatment of breast cancer, as well as risk reduction of breast cancer in adult females at high risk for breast cancer. Tamoxifen is a selective estrogen receptor modulator (SERM) that competitively binds to estrogen receptors on tumors and other tissue targets, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects. As a prodrug, tamoxifen must be metabolized by cytochrome P450 (CYP) 2D6 to the active metabolite, endoxifen. SSRIs antidepressants, particularly paroxetine, are strong inhibitors of CYP2D6. Theoretically, using tamoxifen along with a strong CYP2D6 inhibitor would decrease serum concentrations of the active metabolite, therefore decreasing the efficacy of tamoxifen. In October 2006, a US Food and Drug Administration advisory committee recommended tamoxifen’s label be changed, noting that postmenopausal women with ER-positive breast cancer who are poor CYP2D6 metabolizers by genotype or due to drug interactions may be at increased risk of cancer recurrence. However, evidence is conflicting.

Two large studies have assessed the potential interaction of SSRIs with tamoxifen. A retrospective study of 2430 women aged 66 years or older treated with tamoxifen for breast cancer compared outcomes by receipt of concomitant SSRI (paroxetine (25.9%), sertraline (22.3%), citalopram (19.2%), venlafaxine (15.0%), fluoxetine (10.4%), and fluvoxamine (7.2%)). At the end of follow up, 374/2430 women had breast cancer recorded as the cause of death. Of those deaths, 105/630 (16.7%) received paroxetine and 269/1800 (14.9%) received other SSRIs. Researchers calculated the use of paroxetine during tamoxifen treatment would result in one additional breast cancer death at five years for every 19.7 women treated. Investigators directly related the increased risk of death to the extent of co-prescribing hypothesizing strong CYP2D6 inhibition can reduce the survival advantage of long-term tamoxifen therapy. Of note, this study did not include women who were not taking an SSRI.

Conversely, in a cohort study of 16,887 women with early-stage breast cancer treated with tamoxifen (median duration 2.7 yr) followed for a median of 6 years, researchers did not observe an increased risk of subsequent breast cancer in women who used concomitant antidepressants compared to those not receiving concomitant antidepressants. The antidepressant cohort was divided by the type of antidepressant used, including tricyclics, venlafaxine, other types (i.e., trazodone, bupropion), and multiple types (SSRIs plus other agent). In the total study population, the most commonly used SSRIs were fluoxetine (3361 women or 19.9%) and paroxetine (1784 women or 10.6%). In this analysis, investigators determined that the risk of subsequent breast cancer in patients receiving paroxetine or any other antidepressant was similar to those who
used tamoxifen alone (hazard ratio 1), regardless of duration of tamoxifen therapy. Based on available evidence and FDA guidance, it is recommended to avoid concomitant use of paroxetine with tamoxifen. Pharmacists are advised to recommend alternative antidepressant agents, specifically those with none with weak CYP2D6 activity, such as sertraline, citalopram, escitalopram, and venlafaxine. Pharmacists should provide detailed guidance to providers and patients on how to switch among antidepressants to avoid SSRI withdrawal or adverse effects.

References:
Ovarian cancer is an uncommon but deadly disease that has the highest mortality rate among gynecologic cancers and is the fifth leading cause of cancer-related deaths in women. Approximately 13,940 women will die from ovarian cancer and 21,750 women will receive a new diagnosis of ovarian cancer according to the American Cancer Society estimates for ovarian cancer in the United States for 2020. A woman’s risk of developing ovarian cancer during her lifetime is 1 in 78 and the lifetime chance of dying from ovarian cancer is 1 in 108. However, these statistics do not include low malignant potential ovarian tumors. Although half of the women who are diagnosed with ovarian cancer are 63 years or older, the median age at diagnosis is 59.

Research has led to the discovery of genetic mutations associated with a higher risk for the development of cancers. The prevalence of a specific genetic mutation may be higher in a specific population when a gene or series of genes is conserved among families within a society. Mutations of BRCA1 and BRCA2 are found in women of all races but several distinct mutations, which are not exclusive, are common among Ashkenazi Jews.

Mutations of the genes BRCA1 and BRCA2, located on chromosomes 17q12-21 and 13q12-13 respectively, are related to the development of ovarian cancer. Mutations in BRCA1 are more prevalent than BRCA2 as BRCA1 is associated with 90% of inherited and 10% of sporadic cases of ovarian cancer. Patients with BRCA1 associated ovarian cancers are often younger than patients with BRCA2 mutations with a mean age of 54 years at diagnosis. These patients may also present with an advanced stage at diagnosis and more aggressive tumors of moderate to high-grade serous histology. Highly curable ovarian malignancies that affect primarily young women include germ cell tumors, such as malignant teratoma and dysgerminomas. These histologies comprise 2-3% of all ovarian cancers in Western countries but have an increased incidence in African American and Asian women.

An important risk factor in the development of ovarian cancer is family history. The associated lifetime risk is 9% if one family member has a diagnosis of ovarian cancer. This increases to greater than 50% if two or more 1st degree relatives present with a diagnosis of ovarian cancer or multiple cases of ovarian and breast cancer are present within the same family. Nulliparity, early menarche, or late menopause are conditions associated with an increased risk for epithelial ovarian cancers. Conversely, conditions that limit ovulations may enable a protective effect.

Detection of preclinical disease at an earlier stage would be cost-effective and may improve survival by 10-30%. Cases confined to the ovaries in Stage I disease can be cured in up to 90% of patients. Cases limited to the pelvis are associated with a 5-year survival rate of 70%. Unfortunately, only 20% of ovarian cancers are presently diagnosed in Stages I-II. Cases of stage III and IV ovarian cancer have a long-term survival rate of 20% or less. Therefore, the justification for the early detection of ovarian cancer is indisputable.

Although early studies initially indicated that African American women were significantly less likely than Caucasian women to have BRCA1 and BRCA2 associated mutations, this has since been refuted. Despite the emergence of this new data, African American women undergo BRCA1 and BRCA2 genetic counseling and testing at considerably lower rates than do comparable Caucasian women, even if these women have the same insurance coverage and hold similar attitudes about the risks and benefits of genetic testing. This also includes women with a breast cancer diagnosis and those at risk based only on family history. The disparity is largely powered by inadequate access to testing among African American women, which may be exacerbated by a lack of awareness towards available testing, insufficient screening for risk factors due to
information, inconsistencies in providers recommending genetic testing, and poor support for obtaining genetic counseling in resource-limited settings. Significant evidence in most cancers shows that “equal treatment yields equal outcome and race need not be a factor in outcome,” although a sufficient amount of data shows that race is a factor in the amount and quality of care received.

Most experts recommend that women with mutations in BRCA1 and BRCA2 and women with strong family histories of breast or ovarian cancer should have a screening with CA125, pelvic examinations, and transvaginal ultrasounds performed every 3 months. A macroscopically detectable precursor to ovarian cancer has not yet been identified. Therefore, healthcare providers may encourage women at increased risk to undergo prophylactic removal of ovaries and fallopian tubes when they have completed childbearing or 5 years before the youngest family member was diagnosed with cancer.

Pharmacists play an important role in advocating for early ovarian screening in women found to have mutations in BRCA1 and breast cancer risk assessment can be done online and implemented through mammography at a primary care site. Additional online resources that exist for patients including peer supported chat rooms, message boards, and social media sites which aid in decision-making. There are also websites focused on BRCA1 and BRCA2 assessment, such as https://www.knowBRCA.org or https://www.youngsurvival.org/directory/genes/know-brca, http://www.myriadpro.com/BRCA-risk-calculator/calc.html, and http://www.facingourrisk.org/index.php have been developed. There is the caveat that none of these tools are currently tailored to African American women nor have they been proven to overcome our current barriers to testing. Therefore, pharmacists and healthcare providers can close the gap by creating strategies that utilize culturally appropriate messaging to promote higher rates of appropriate testing among African American women and other minorities so that they are not placed at an increased risk for disease and death from preventable cancers.

References:
Dormancy in cancer cells is a phenomenon that is not fully understood. It was first proposed as a model to explain cancer recurrence in patients whose original tumor had been removed or treated years beforehand. Dormancy is described as a “quiescent state” where cancer cells have arrested growth with no disease progression but remain present, awaiting optimal conditions to proliferate once more. Clinical dormancy has been observed and prevalent in many cancer types, but is particularly noted in breast cancer.

Though there is no single agreed upon mechanism of cancer dormancy development, a few avenues have been deemed the most probable. It is thought that some cancer cells are randomly “selected” to become dormant through complex evolutionary processes that are utilized to adapt to different environments. A tumor cell’s microenvironment can prompt the decision of whether that cell continues growth and metastasizes or halts its own cell cycle and becomes dormant. The latter would likely take place if the microenvironment was unconducive to cell growth involving situations of cellular stress. For example, if a tumor cell could not properly stimulate angiogenesis, the process of creating new vasculature, that cell would not be able to provide itself with nutrients and oxygen to continue growth and thus may “opt” to enter a stagnant state. This state would be called angiogenic dormancy. Other proposed mechanisms include cellular dormancy and immunologic dormancy. Cellular dormancy refers to when the cell cycle is arrested due to down regulation of relevant signaling pathways in response to some sort of catalyst such as stress or a hostile environment. Immunologic dormancy refers to the process in which the immune system keeps the tumor cell in a state of equilibrium, stopping further growth and expansion but not fully eliminating it, promoting latency.

Another proposal is that cancer treatment itself may be a cause of tumor dormancy. The correlation between resistant, dormant cells and chemotherapy exposure has been revealed in many studies thus far, opening up a slew of discussion when it comes to appropriate treatment options for cancer in general. A recent study conducted by Hong et al. (2019) has looked into this puzzling mechanism of dormancy, specifically with how hormonal therapy in breast cancer may cause cancer cells to switch into a dormant state. Hormonal treatment such as tamoxifen is often considered first-line adjuvant therapy for hormone receptor-positive (HR+) breast cancer. In HR+ breast cancer, endocrine therapy interferes with hormonal signaling and stops further growth, potentially leading to dormancy of the cancer cells. While endocrine therapy reduces risk of recurrence, HR+ breast cancer is associated with a high rate of relapse after 5 years, ranging from 10 to 41% at 20 years depending on tumor diameter and nodal status.

Hong et al. (2019) sought to explain these relapse rates through analyzing how adaption and selection leads to dormancy in the context of endocrine therapy. The study utilized a combination of several in vitro techniques ranging from RNA sequencing to live cell imaging to observe estrogen receptor positive breast cancer cells in the lab. Subpopulations of cells were examined for specific phenotypes that showcased characteristics of interest. The transcriptional variability and phenotypic heterogeneity of breast cancer cells were tested and examined under acute hormonal treatment. The authors identified a rare subpopulation of pre-adapted (PA) cells that exhibited early signs of dormancy and suspected survival with short-term endocrine therapy. It was found that PA cells carried a survival advantage during treatment, leading the authors to propose that PA cells may be the initial step of resistance to endocrine therapy, though still requiring
substantial transcriptional reprogramming to reach full resistance. Other characteristics of the PA signature observed included decreased activity of estrogen receptors, hypoxia, and down-regulation signaling of cell cycle components. Some non-PA cells that demonstrated plasticity also seemed to adopt the PA phenotype during hormonal treatment, though PA cells still maintained a distinct survival advantage. The authors propose that the mechanism behind a breast cancer cell's internal switch into dormancy after hormonal treatment survival and consequential delayed relapse could be of a similar process to that of PA cell adaption. Ultimately, this study provided a very preliminary look into the process behind transcriptional and phenotypic variations that result from endocrine therapy. Further research will be needed to expand on this theory in hopes to reveal the truth behind dormancy, relapse, and resistance in breast cancer cells. That knowledge could not only allow us to optimize treatment options for patients but also prevent dormancy and later recurrence of breast cancer.

References:
Recreational use of marijuana is common worldwide despite its illegal federal status in many countries, including the United States. Specifically, over 13.5 million adults in the U.S. confirmed marijuana use in 2014. Substances with tetrahydrocannabinol (THC), such as inhaled marijuana, can be used to alleviate pain, anxiety, and chemotherapy-induced nausea and vomiting (CINV). Some healthcare providers may recommend these products, depending on the legal rules of their state in which they practice. In particular, use of these agents in lieu of opioids is attractive due to the current opioid epidemic and affiliated fatalities. However, which THC product patients choose to utilize may have ramifications on their overall health due to risks associated with certain formulations. In particular, in immunocompromised patients the inhaled marijuana may be associated with serious lung infections that may lead to death.

Several case studies suggesting an association between inhaled marijuana use and fungal lung infections. Invasive aspergillosis (IA) is a serious fungal infection that can lead to pneumonia, allergic reactions, and infections in other organs. Aspergillus is an opportunistic, ubiquitous mold that commonly colonizes immunocompetent people without illness. Unfortunately, for those with weakened immune systems, such as cancer patients undergoing immunosuppressive therapies, aspergillus exposure may increase their risk of developing invasive fungal infections.

The link between fungal infections and marijuana smoke exists due to the direct inhalation of fungal spores, which is a common contaminant on cannabis plants. It is unknown whether the burning process for sterilization is sufficient. Even if burning process sterilizes the product, contact with fungal spores may occur from handling marijuana directly. Storage conditions and aging processes may also contribute to mold presence in marijuana.

Several case studies have recorded fungal infections in cancer patients with marijuana use history. A case example of a 36-year-old man with acute myelogenous leukemia presented to the hospital with neutropenia after chemotherapy. His drug use history was positive for smoking 1 pack per day of cigarettes for 22 years and repeatedly smoking marijuana up until his hospital admission. Nodular patterns were noted on repeat CT scans and were likely associated with his heavy marijuana use (Figure 1). However, there were no significant findings in his review of systems and most of his labs. Serum galactomannan testing was positive, but on a repeat test, was found to be negative. Despite empiric use of posaconazole, the patient died 2 months later from disseminated fungal infection. During a histopathological exam, the fungal infection was discovered on a skin lesion, but...
was unable to grow on culture. A second case example is of a 65-year-old man with limited-stage small cell lung cancer. During chemotherapy, the patient experienced significant CINV and weight loss despite use of traditional antiemetics. He began smoking 3-4 marijuana cigarettes per day for CINV control during his chemotherapy cycles up until 2 months prior to his final hospitalization. Subsequently, the patient presented with fevers. Chest x-rays revealed bilateral interstitial nodules and sputum cultures grew *K. pneumonia*, *S. pneumonia*, and *Candida* species. Although the patient was initiated on multiple antimicrobial and systemic antifungal therapies (specific medications unspecified in report), he died on hospital day 18. Autopsy reports indicated necrotizing aspergillus pneumonia in the left lung. The reports revealed no evidence of carcinoma.

A third case example is of a 65-year-old man with metastatic colorectal cancer who presented with increased dyspnea and fever, despite empiric moxifloxacin for presumed bacterial pneumonia. Although denying cigarette use, he admitted to smoking marijuana for CINV in the past 6 weeks before presentation. CT scans revealed cavitory lesions with ground-glass opacities (Figure 2). CT-guided fine-needle aspirate of the cavity revealed necrosis, inflammation, and masses of hyaline fungal hyphae with dichotomous branching and septations, compatible with *Aspergillus* species (Figure 3A and 3B). The patient was given the standard therapy at the time, which was a 3-month voriconazole regimen, and achieved complete resolution of his infection six months after completion of his antifungal therapy.

Given the prevalence of marijuana use and emerging case reports of fungal pneumonia in cancer patients, more research is needed to examine the association of marijuana inhalation and fungal pneumonia as well as potential methods to mitigate exposure. One strategy that has been explored in a study was the systemic sterilization of marijuana via ethylene oxide gas, plasma, and heat (autoclave). THC activity was variable among the different sterilization techniques, as shown below.

![Figure 2](https://ascopubs.org/doi/abs/10.1200/JCO.2007.15.2777?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rs_dat=cr_pub%3Dpubmed)

![Figure 3A](https://ascopubs.org/doi/abs/10.1200/JCO.2007.15.2777?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rs_dat=cr_pub%3Dpubmed)

![Figure 3B](https://ascopubs.org/doi/abs/10.1200/JCO.2007.15.2777?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rs_dat=cr_pub%3Dpubmed)

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<thead>
<tr>
<th>Sterilization method</th>
<th>Decrease of THC activity (%)</th>
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<tr>
<td>Plasma</td>
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</tr>
<tr>
<td>Autoclave</td>
<td>22.6</td>
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<tr>
<td>Ethylene oxide gas</td>
<td>26.6</td>
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Based on these limited case reports described above, increased efforts are critical to educate cancer patients of the dangers with smoking marijuana. Overall, only approximately 3% of daily marijuana users have their drug use documented in their clinical health records. Because of the potential for serious adverse effects in cancer patients, it is important for healthcare providers working with immunocompromised patients to ask questions about marijuana use.

As trusted healthcare professionals, pharmacists can assist in obtaining patients’ honest drug use history to ensure patients are provided information on risks associated with inhaled marijuana.

References:


