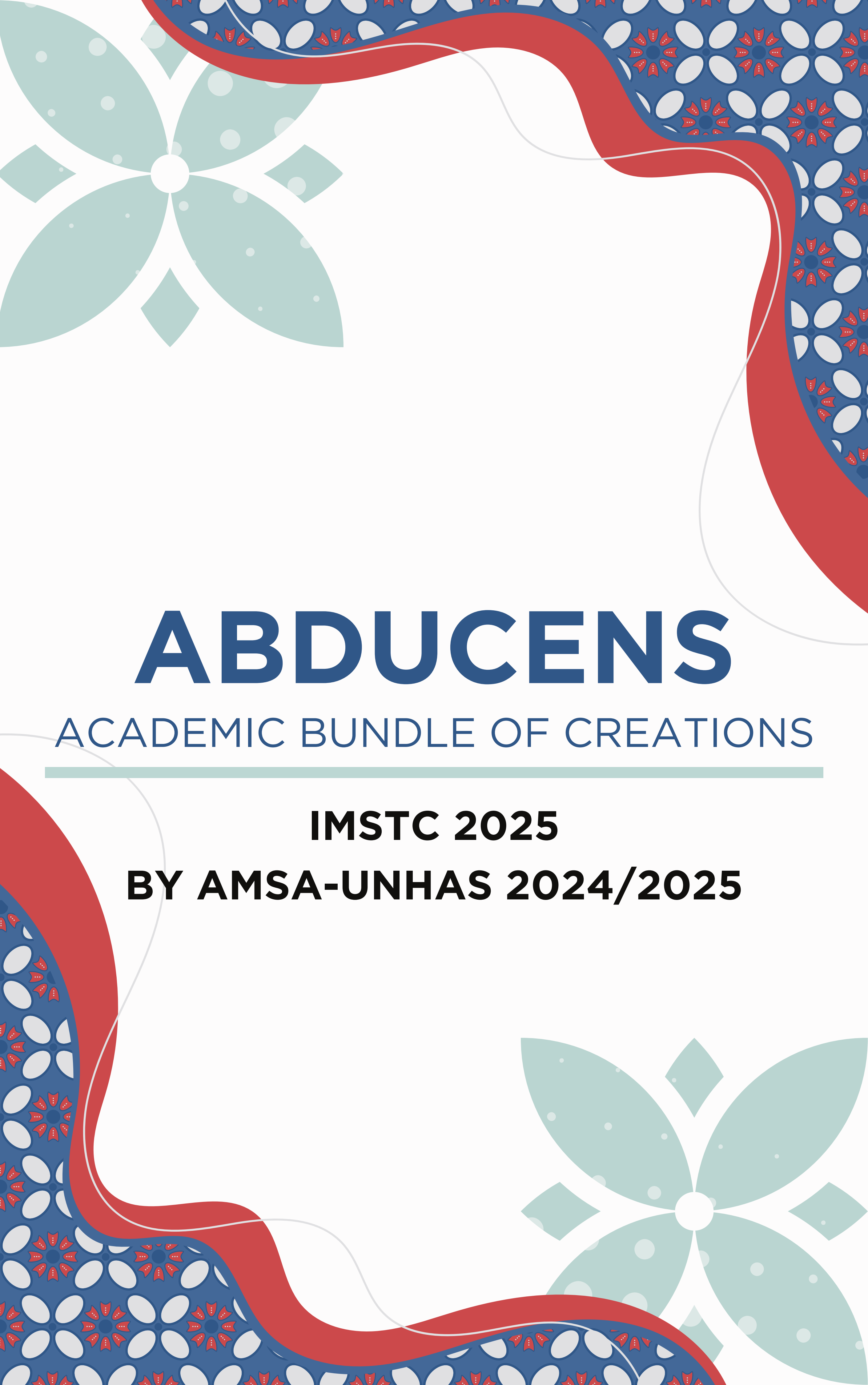




ABDUCENS

ACADEMIC BUNDLE OF CREATIONS

IMSTC 2025

BY AMSA-UNHAS 2024/2025



VIDEOGRAPHY





UNVEILING CONSEQUENCES: CERVICAL CANCER RISKS FACTOR AND AWARENESS



**YAYANG JUNITA SARI
AQILA SHAKIRA PATUNRU
IBRAHIM BAYUWINDRA BAHJURI
PURNA HIDAYAT FEBRIANTO**



Unveiling Consequences: Cervical Cancer Risks Factor and Awareness

Background

Globally, cervical cancer is the fourth most common cancer in women, with around 660 000 new cases in 2022. In the same year, about 94% of the 350 000 deaths caused by cervical cancer occurred in low- and middle-income countries. Regional differences in the cervical cancer burden are related to inequalities in access to vaccination, screening and treatment services, risk factors including HIV prevalence, and social and economic determinants such as sex, gender biases and poverty. Women living with HIV are 6 times more likely to develop cervical cancer compared to the general population, and an estimated 5% of all cervical cancer cases are attributable to HIV (1). Cervical cancer disproportionately affects younger women, and as a result, 20% of children who lose their mother to cancer do so due to cervical cancer (2).

Human papillomavirus (HPV) is a common sexually transmitted infection which can affect the skin, genital area and throat. Almost all sexually active people will be infected at some point in their lives, usually without symptoms. In most cases the immune system clears HPV from the body. Persistent infection with high-risk HPV can cause abnormal cells to develop, which go on to become cancer. Persistent HPV infection of the cervix (the lower part of the uterus or womb, which opens into the vagina – also called the birth canal) if left untreated, causes 95% of cervical cancers.

Objectives

Edukasi masyarakat tentang pencegahan infeksi HPV dan perilaku seksual yang aman sangat penting untuk mengurangi insiden kanker serviks di populasi wanita. Beberapa faktor risiko dalam video dapat dihindari dan dicegah, seperti:

1. Hubungan Seksual

Usia Pertama Berhubungan Seksual: Melakukan hubungan seksual pada usia dini (kurang dari 20 tahun) dapat meningkatkan risiko kanker serviks. Penelitian menunjukkan bahwa wanita yang mulai berhubungan seksual sebelum usia 16 tahun memiliki risiko kanker serviks yang

lebih tinggi, dengan odds ratio (OR) mencapai 3,4 kali lebih besar dibandingkan mereka yang mulai berhubungan seksual setelah usia 20 tahun. Ini disebabkan oleh peningkatan durasi paparan terhadap HPV, yang biasanya ditularkan melalui hubungan seksual.

Frekuensi Hubungan Seksual: Wanita yang memiliki banyak pasangan seksual juga berisiko lebih tinggi terkena kanker serviks. Infeksi HPV dapat terjadi lebih sering pada individu dengan perilaku seksual berisiko, seperti berganti-ganti pasangan

2. Merokok

Dampak Merokok: Merokok telah terbukti menjadi faktor risiko independen untuk kanker serviks. Zat-zat karsinogenik dalam rokok dapat mempengaruhi sel-sel serviks dan memperburuk efek dari infeksi HPV. Wanita perokok memiliki risiko yang lebih tinggi untuk mengembangkan kanker serviks dibandingkan non-perokok. Bahan karsinogenik spesifik dari tembakau dapat dijumpai dalam lendir dari mulut rahim pada wanita perokok. Bahan karsinogenik ini dapat merusak DNA sel epitel skuamosa dan bersama infeksi HPV dapat mencetuskan transformasi keganasan.

3. Berganti-ganti Pasangan

Risiko Infeksi HPV: Berganti-ganti pasangan seksual meningkatkan kemungkinan terpapar berbagai jenis HPV, terutama tipe-tipe berisiko tinggi seperti HPV 16 dan 18, yang bertanggung jawab atas sebagian besar kasus kanker serviks. Penelitian menunjukkan bahwa perilaku ini dapat memperpanjang durasi infeksi HPV dan meningkatkan risiko transformasi sel menjadi kanker

4. Human Papillomavirus (HPV)

Penyebab Utama Kanker Serviks: HPV adalah penyebab utama kanker serviks, dengan tipe-tipe tertentu yang memiliki potensi tinggi untuk menyebabkan kanker. Sekitar 70% kasus kanker serviks disebabkan oleh infeksi HPV tipe 16 dan 18. Virus ini ditularkan melalui hubungan seksual, dan infeksi yang berlangsung lama tanpa diobati dapat menyebabkan perubahan sel abnormal pada serviks.

World Health Organization (n.d.) *Cervical cancer*. Available at: <https://www.who.int/news-room/fact-sheets/detail/cervical-cancer>

Putri, R.D.K., Jannah, F., Rahayu, D. and Anggraini, D. (2018) 'Analisis faktor risiko kejadian kanker serviks di RSUP Dr. Sardjito Yogyakarta', *Indonesian Journal of Cancer*, 12(4), pp. 150–156. Available at: <https://www.indonesianjournalofcancer.or.id/e-journal/index.php/ijoc/article/view/123/84>

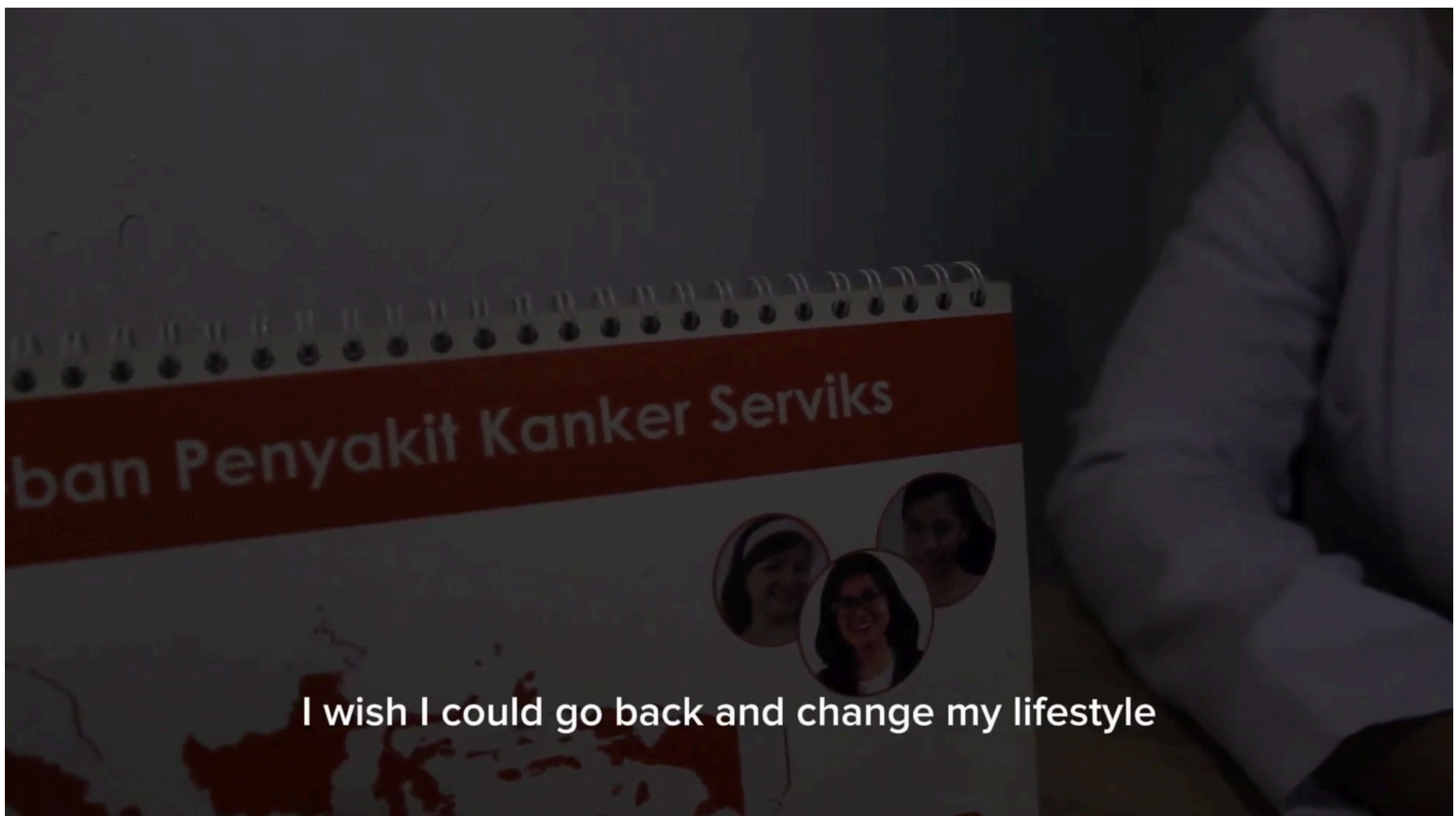
Perkumpulan Obstetri dan Ginekologi Indonesia (POGI) (2021) *Pedoman Praktik Klinis Kanker Serviks*. Available at: <https://www.poijaya.org/wp-content/uploads/2021/03/PPKServiks.pdf>

Link Gdrive Video:

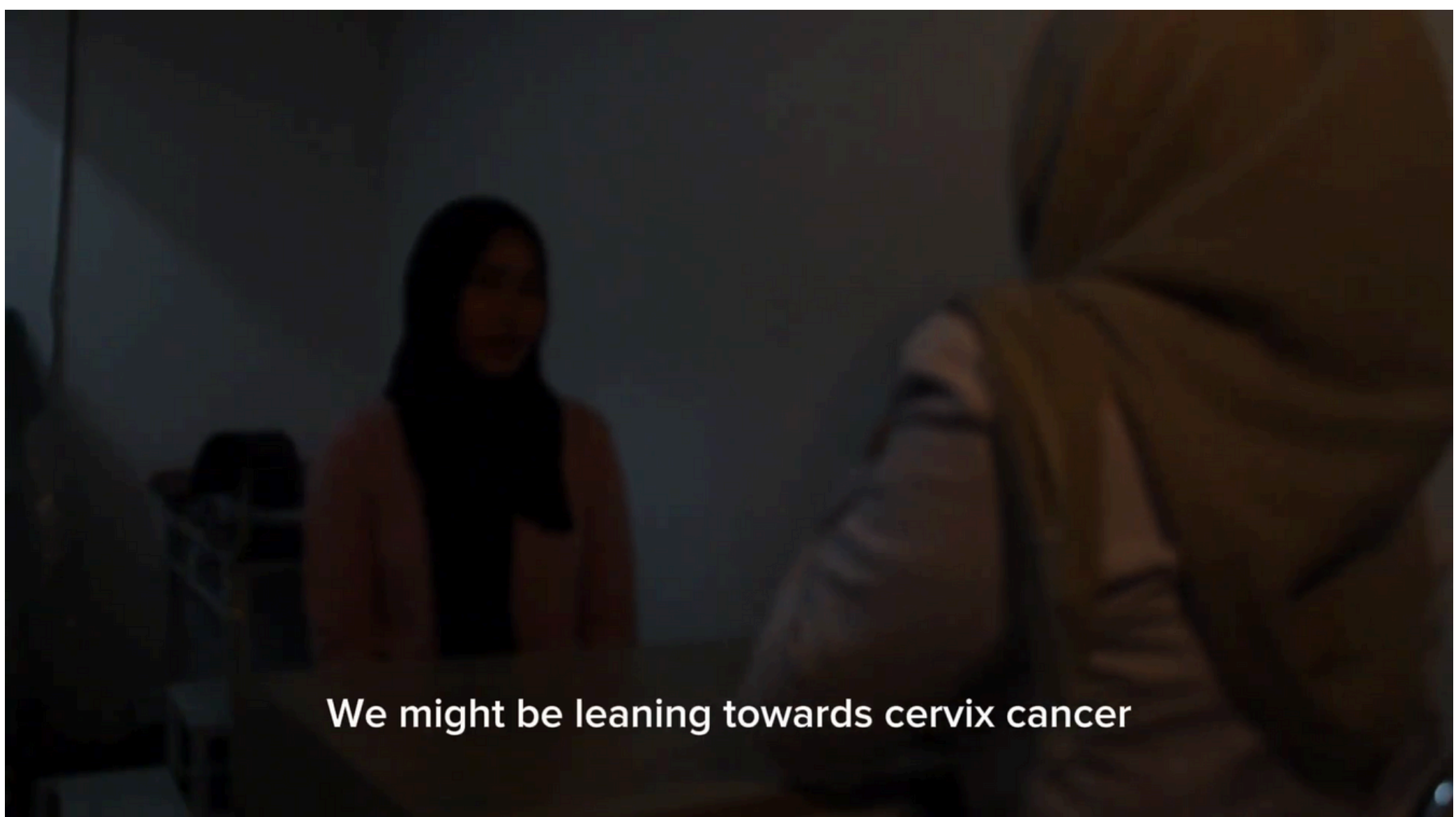
<https://drive.google.com/file/d/1-3YsTVdTbgRrzdS0IJiVR6s4xG7vbkg3/view?usp=drivesdk>



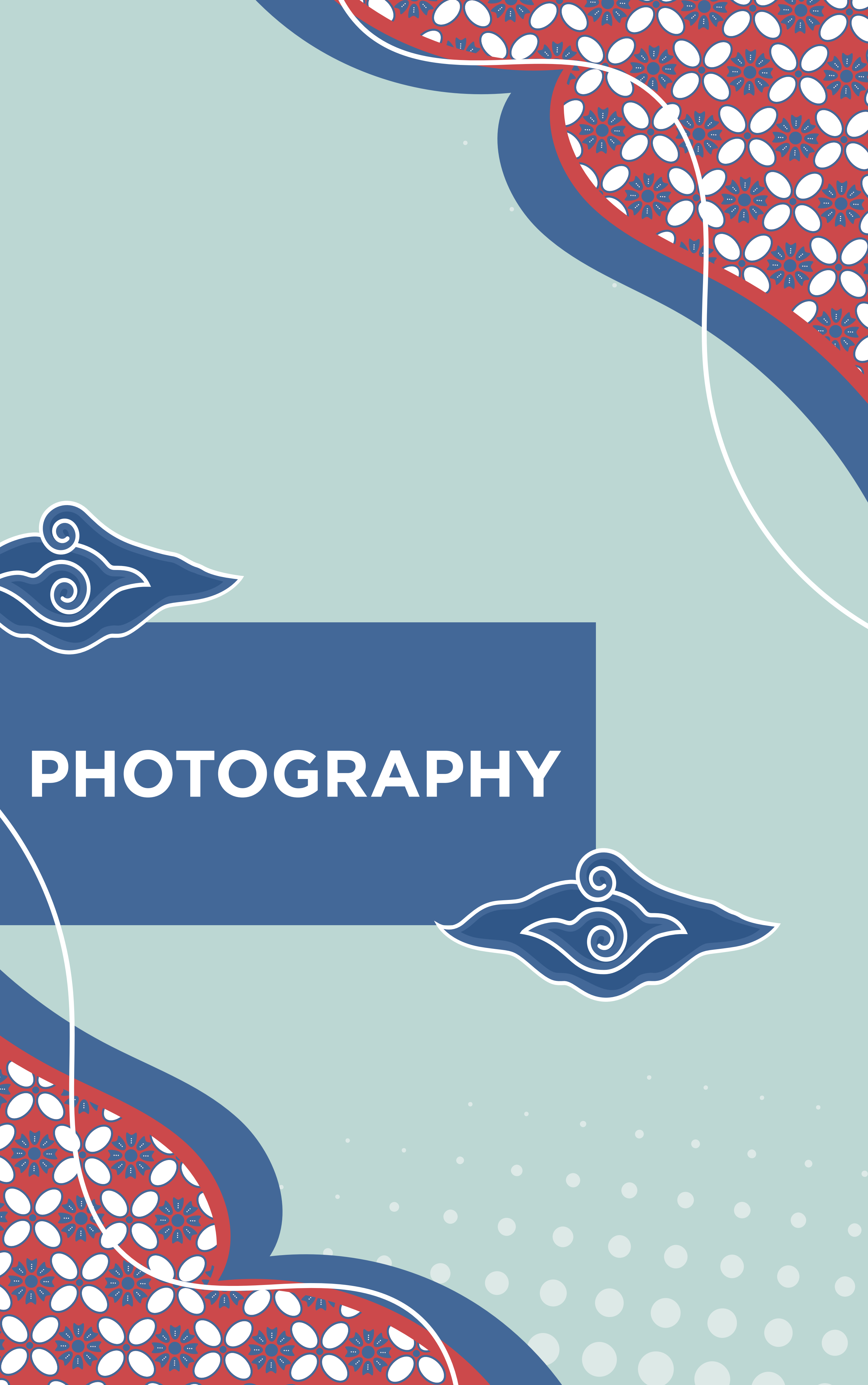
my boyfriend always takes me to the club



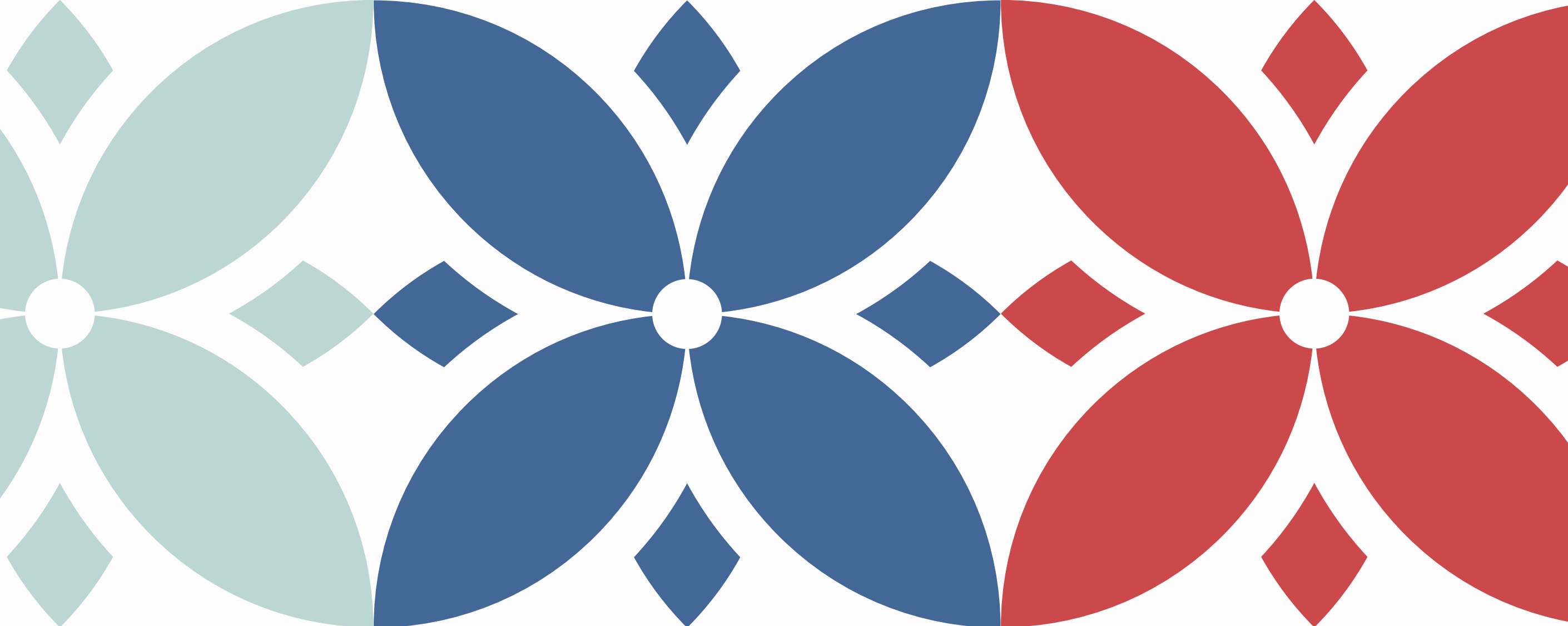
I wish I could go back and change my lifestyle



We might be leaning towards cervix cancer



PHOTOGRAPHY



3RD PLACE

PRECISION IN MOTION

SURYA LEONARD LIESWAN



Precision in Motion

Surya Leonard Lieswan

Suryaleonard2003@gmail.com

Introduction

Childbirth is a transformative experience, and the Caesarean section reflects significant advancements in ensuring safe deliveries. What was once a life-saving procedure has now evolved into a precise and collaborative surgery. Modern C-sections rely on the combination of skilled medical professionals, advanced technology, and compassionate care to manage complex births and ensure the safety of both mother and child.

Objectives

To highlight the critical role of Caesarean sections in ensuring mother and baby safety, especially in complex cases and also to emphasize teamwork among obstetricians, anesthesiologists, nurses, and assistants, and the importance of advanced technology in modern obstetrics.

Description & Philosophy

The photograph illustrates the synergy of human skill and technology in Caesarean deliveries. The vibrant surgical lights symbolize clarity and focus, while the team's unity reflects the philosophy of shared responsibility in patient care. This image is a tribute to the compassion and professionalism inherent in modern obstetrics.

Impact & Conclusion

This photo serves as a reminder of the intricate balance between science and humanity in medicine. By celebrating teamwork, innovation, and compassion, it inspires appreciation for the dedication of healthcare professionals and underscores the significance of safe childbirth practices.

Keywords: *Caesarian Delivery, Childbirth, Modern Medicine*





PUBLIC POSTER

**BEWARE OF
CERVICAL CANCER:
PROTECT YOURSELF
WITH A VACCINE**



**ANDI MUHAMMAD FARRYL
DIVANYA ALEA RAZIL
FIRYAL FADHILAH
SYIFANIA NURHALIZA**



BEWARE of Cervical Cancer: Protect Yourself with a VACCINE

Introduction/Background

Cervical cancer is a preventable disease caused primarily by persistent infection with high-risk human papillomavirus (HPV), a virus transmitted through sexual contact. Globally, cervical cancer ranks as the fourth most common cancer among women, with higher prevalence in low- and middle-income countries. In Indonesia, it is the second leading cause of cancer-related deaths among women, emphasizing the urgent need for effective prevention and education. Symptoms such as abnormal bleeding, persistent pelvic pain, and foul-smelling discharge often go unnoticed, leading to late-stage diagnosis.

Objectives

This poster aims to educate the public on the importance of early detection, vaccination, and lifestyle modifications to prevent cervical cancer. The campaign highlights the symptoms using the acronym “BEWARE” and promotes prevention strategies summarized as “VACCINE.” Key prevention steps include:

- Vaccination against HPV to protect against high-risk strains.
- Regular screenings with Pap smears and HPV testing to detect early changes.
- Healthy lifestyle choices, including avoiding smoking and practicing safe sex.

By increasing awareness, encouraging HPV vaccination, and advocating for regular screening, this campaign seeks to reduce the burden of cervical cancer and empower individuals to take proactive steps toward prevention.

Keywords: *Cervical Cancer, HPV, Vaccine, Prevention*

BEWARE OF CERVICAL CANCER

PROTECT YOURSELF WITH VACCINE

WHAT IS CERVICAL CANCER?

Cervical cancer is a condition where **abnormal cells grow in the cervix**, usually due to persistent infection with high-risk **human papillomavirus (HPV)**, a sexually transmitted virus.



DID YOU KNOW?

Cervical cancer is **Indonesia's 2nd DEADLIEST CANCER**

KNOW THE SYMPTOMS

Bleeding unusually (between periods, after menopause, or intercourse) **E**xcess and foul-smelling vaginal discharge **W**eight loss, fatigue, and loss of appetite **A**che (persistent pain in back, legs, or pelvis) **R**aised discomfort in the vagina **E**xtrême leg swelling

WHAT ARE THE RISK FACTORS

Chlamydia infection **A**ge (young age at first full-term pregnancy) **N**icotine (Smoking) **C**ontraceptives (long-term use of oral contraceptives) **E**conomic status (low) **R**ecurrent HPV infection

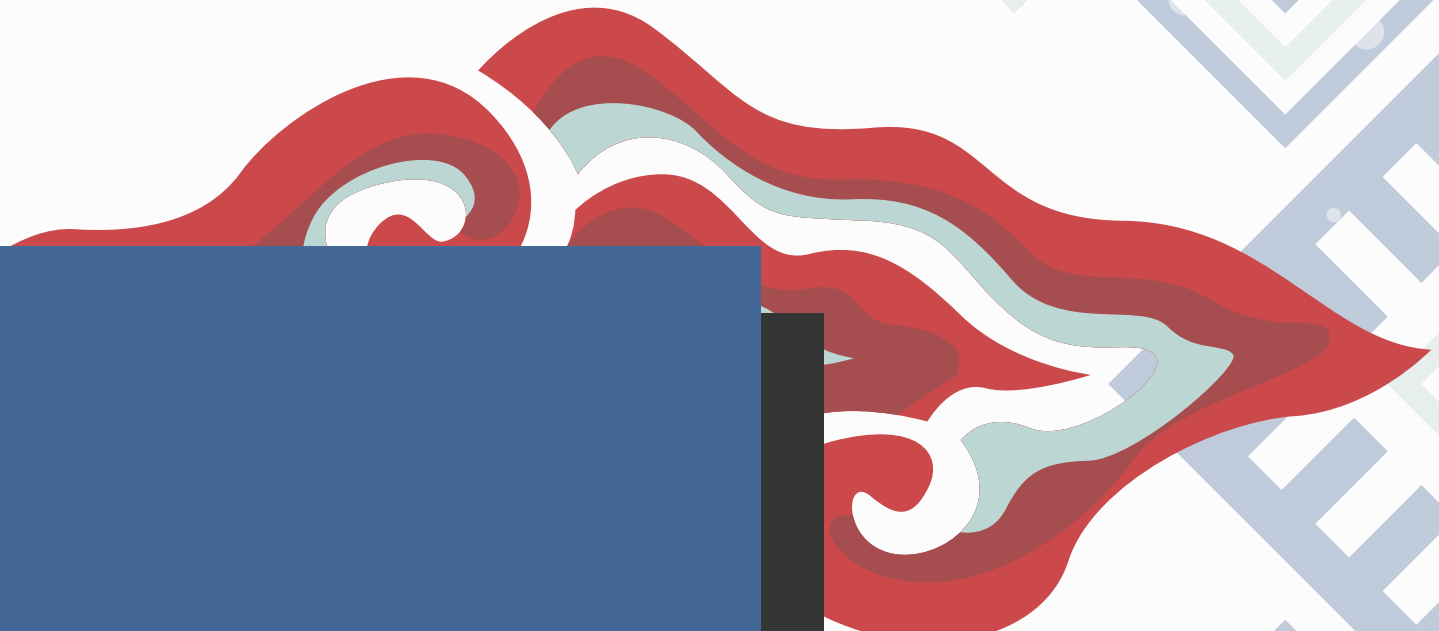
LET'S PREVENT IT WITH



SCAN THIS TO
VIEW OUR
WEBSITE!!

[BIT.LY/CANCERVIXAWARE](https://bit.ly/cancervixaware)

Vaccinate against HPV **A**void Smoking **C**heck regularly with Pap smears and HPV tests **C**ondom use during sexual intercourse **I**nteract with your doctor about cervical cancer risks **N**otify doctor if you have any symptoms **E**mbbrace a healthy lifestyle



DEFLECT THE HPV WITH THE SHIELD



**ANDINI PUTRI ASHAARIA
AHMAD RIZQI MAULANA MIHIDIN MADUBUN
SAMANTHA ALMIRA AZIS
SURYA LEONARD LIESWAN**



Deflect The HPV With The SHIELD

A. Background

Human Papillomavirus (HPV) is the most common sexually transmitted infection globally, spread primarily through skin-to-skin contact during sexual activity. While most infections clear on their own, high-risk strains can lead to genital warts and cancers such as cervical, anal, and throat cancer. In 2018, 42 million people in the U.S. were infected, with 13 million new cases that year. Globally, HPV-related cancers caused over 690,000 cases in 2019. Early detection through Pap smears and vaccination is key to preventing serious health issues.

B. Objectives

This poster aims to raise awareness about HPV, its health risks, and prevention strategies, highlighting its link to severe conditions like cervical cancer.

C. Description of poster

The poster visually communicates the health impact of HPV, with a medieval-inspired shield symbolizing protection. It introduces the “SHIELD” approach to prevention:

- S:** Stop HPV transmission with safe practices.
- H:** Healthy lifestyle choices.
- I:** Initiate Pap smears and testing.
- E:** Early marriage avoidance.
- L:** Limit contraceptive pill use.
- D:** Doctor visits for vaccination and check-ups.

D. Impact

The poster inspires action by encouraging vaccination, regular screenings, and healthy practices to reduce HPV-related risks.

E. Conclusion

Through this poster, we emphasize the importance of education, vaccination, and regular check-ups to combat HPV effectively and ensure a healthier future for all.

Keyword : *Cancer, Human Papilloma virus, Sexual Transmission, Warts*

References

1. de Martel, C., Plummer, M., Vignat, J., & Franceschi, S. (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. *International journal of cancer*, 141(4), 664–670. <https://doi.org/10.1002/ijc.30716>
2. Goldstone, S., Palefsky, J. M., Giuliano, A. R., Moreira, E. D., Jr, Aranda, C., Jessen, H., Hillman, R. J., Ferris, D. G., Coutlee, F., Liaw, K. L., Marshall, J. B., Zhang, X., Vuocolo, S., Barr, E., Haupt, R. M., Guris, D., & Garner, E. I. (2011). Prevalence of and risk factors for human papillomavirus (HPV) infection among HIV-seronegative men who have sex with men. *The Journal of infectious diseases*, 203(1), 66–74. <https://doi.org/10.1093/infdis/jiq016>
3. Guida, F., Kidman, R., Ferlay, J. et al. (2022). Global and regional estimates of orphans attributed to maternal cancer mortality in 2020. *Nat Med* 28, 2563–2572. <https://doi.org/10.1038/s41591-022-02109-2>
4. Human papillomavirus and cancer, World Health Organization. Available at: <https://www.who.int/news-room/fact-sheets/detail/human-papilloma-virus-and-cancer> (Accessed: 27 December 2024).
5. Kombe Kombe, A. J., Li, B., Zahid, A., Mengist, H. M., Bounda, G. A., Zhou, Y., & Jin, T. (2021). Epidemiology and Burden of Human Papillomavirus and Related Diseases, Molecular Pathogenesis, and Vaccine Evaluation. *Frontiers in public health*, 8, 552028. <https://doi.org/10.3389/fpubh.2020.552028>
6. Lewis, R. M., Laprise, J. F., Gargano, J. W., Unger, E. R., Querec, T. D., Chesson, H. W., Brisson, M., & Markowitz, L. E. (2021). Estimated Prevalence and Incidence of Disease-Associated Human Papillomavirus Types Among 15- to 59-Year-Olds in the United States. *Sexually transmitted diseases*, 48(4), 273–277. <https://doi.org/10.1097/OLQ.0000000000001356>
7. Luvían-Morales, J., Gutiérrez-Enríquez, S. O., Granados-García, V., & Torres-Poveda, K. (2024). Risk factors for the development of cervical cancer: analysis of the evidence. *Frontiers in oncology*, 14, 1378549. <https://doi.org/10.3389/fonc.2024.1378549>
8. PDQ Screening and Prevention Editorial Board. (2021). Cervical Cancer Prevention (PDQ®): Patient Version. In: *PDQ Cancer Information Summaries* [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-. Available from: <https://ncbi.nlm.nih.gov/books/NBK65901.8/>
9. Stelze, Dominik et al. (2020). Estimates of the global burden of cervical cancer associated with HIV. *The Lancet*. [https://doi.org/10.1016/S2214-109X\(20\)30459-9](https://doi.org/10.1016/S2214-109X(20)30459-9)
10. Tsige, A. W., & Beyene, D. A. (2024). Cervical cancer: Challenges and prevention strategies: A narrative review. *Health Sci Rep*, 7(6):e2149. <https://doi.org/10.1002/hsr2.2149>

DEFLECT THE HPV WITH THE SHIELD

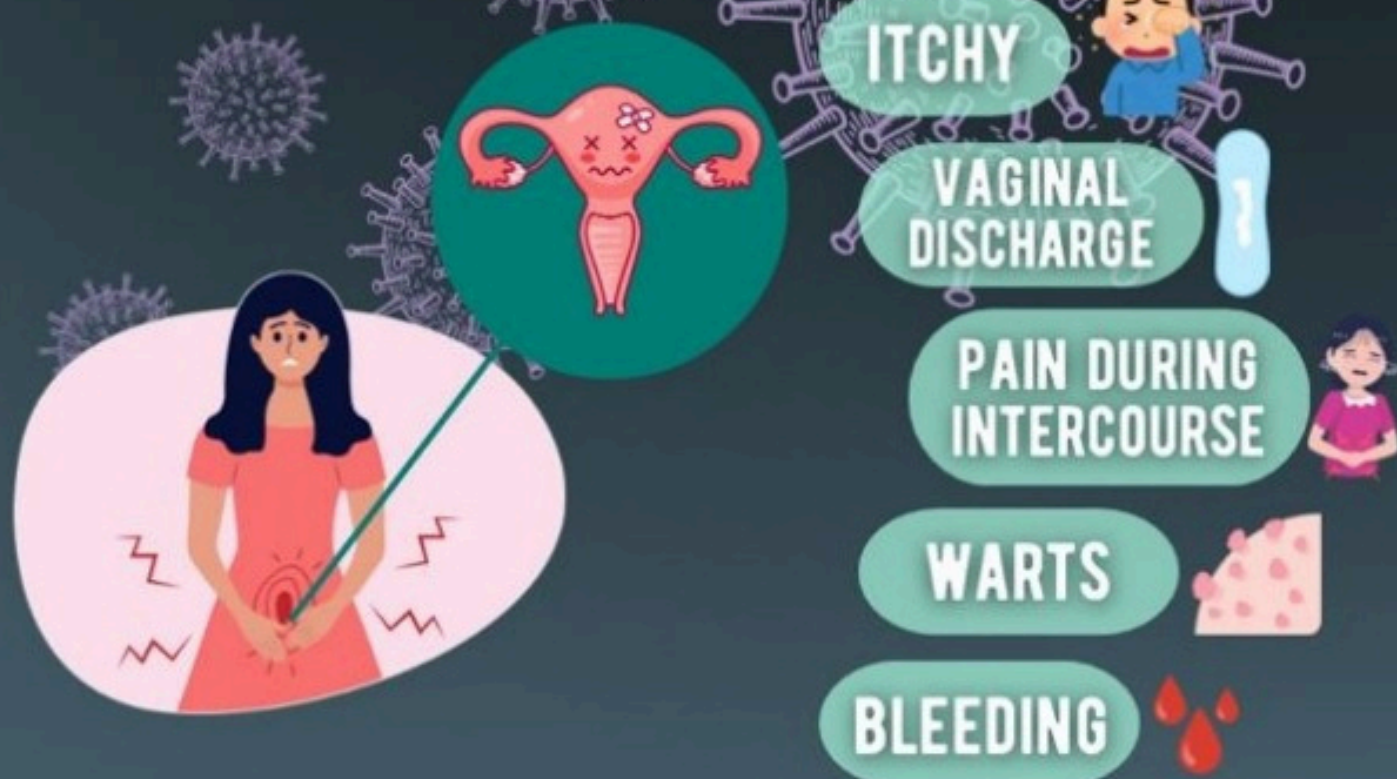
WHAT IS HPV?

Human Papillomavirus (HPV) is a group of over 100 different viruses, some of which can cause genital warts and others that are linked to cancers.

PREVALENCE

The global pooled prevalence of any HPV infection is approximately 31%, with 21% of individuals infected with high-risk HPV types. Among men, nearly **one in three** are infected with at least one genital HPV type

SYMPTOMS



RISK FACTORS



WAYS TO PREVENT!

S H I E L D

Stop HPV transmission through safe practices

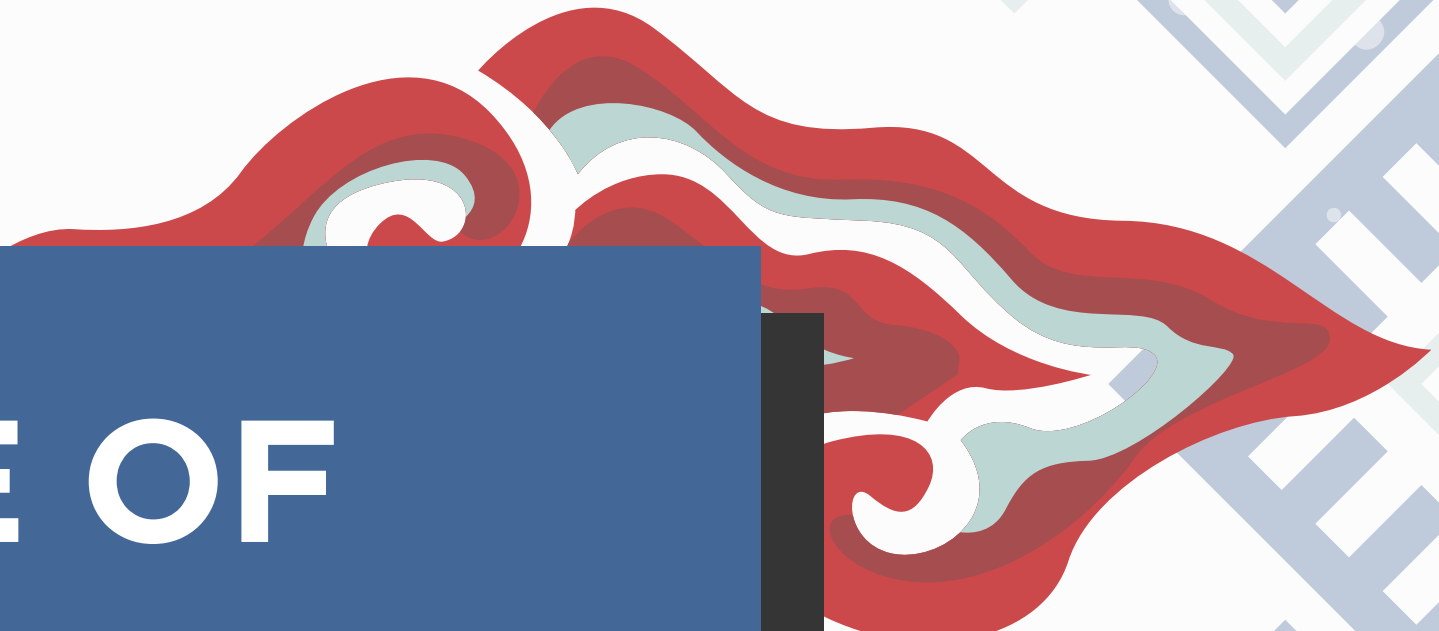
Healthy lifestyle choices to boost immunity

Initiate regular pap smears and HPV testing

Early marriage avoidance

Limiting the use of contraceptive pills,

Doctor visits for regular check-ups and vaccination



**BEWARE OF
CERVICAL CANCER,
LET HPV VACCINE
BE OUR GUARDIAN**



**HEYTIANA JULIANI ARISKA
FAJAR SHODIQLUL YAQIN
ATHIFAH FATIN
ADINDA FAKIHAN LAHFANI**



BEWARE of Cervical Cancer, Let HPV Vaccine Be Our GUARDIAN!

Heytiana Juliani Ariska, Athifah Fatin, Adinda Fakhah Lahfani, Fajar Shodiqul Yaqin

Cervical cancer is a cancer that begins in the cervix—the lower part of the uterus—and often develops due to long-term infection with high-risk types of human papillomavirus (HPV). These infections cause cellular changes that, if untreated, can progress to cancer. Cervical cancer is the 4th most common cancer in women worldwide. In Indonesia, it ranks as the 2nd most frequent cancer in women, with 36,633 new cases annually.

The risk factors for this disease, according to various studies are

- HPV Infection: Primary cause of most cervical cancers.
- Smoking: Increases the risk of cancer.
- Weak Immunity: Reduces the body's ability to fight HPV infections.
- Multiple Sexual Partners: Higher likelihood of HPV exposure.
- Early Sexual Activity: Increased risk of HPV infection.
- Family History: Close relatives with cervical cancer increases risk.

With such high prevalence, raising awareness is crucial to reduce its burden. This poster aims to educate and empower the public to take action about cervical cancer.

BEWARE (Signs and Symptoms):

- Bleeding irregularly
- Excessive discharge (vaginal)
- Weight loss unexpectedly
- Abdominal pain or discomfort
- Rectal bleeding
- Experience fatigue

GUARDIAN (Steps to Prevention):

- Get vaccinated early
- Undergo regular screenings
- Avoid smoking
- Reduce risky sexual behavior
- Detect symptoms early
- Initiate healthy lifestyle
- Access timely treatment
- Nurture awareness in others

Keywords: *cancer, cervix, HPV, prevent, vaccine*

Source:

1. National Cancer Institute. Cervical Cancer [Internet]. 2024 [cited 2024 Dec 27]. Available from: <https://www.cancer.gov/types/cervical>
2. American Cancer Society. Cervical cancer leads cancer deaths in 37 countries [Internet]. 2024 [cited 2024 Dec 27]. Available from: <https://www.cancer.org/research/acs-research-news/cervical-cancer-leads-cancer-deaths-37-countries.html>
3. World Health Organization. Cervical cancer [Internet]. 2024 [cited 2024 Dec 27]. Available from: <https://www.who.int/news-room/fact-sheets/detail/cervical-cancer>

BEWARE OF CERVICAL CANCER, LET HPV VACCINE BE OUR GUARDIAN

What is Cervical Cancer?

Cervical cancer begins in the cervix—the lower part of the uterus—and often develops due to long-term infection with high-risk types of human papillomavirus (HPV). These infections cause cellular changes that, if untreated, can progress to cancer.

Did you know?

4th most common cancer in women worldwide

2nd most frequent cancers in Indonesia

BEWARE of the Signs

- B**leeding irregularly
- E**xcessive discharge (Vaginal)
- W**eight loss unexpectedly
- A**bdominal pain or discomfort
- R**ectal bleeding
- E**xperience fatigue

Know the Risk Factors

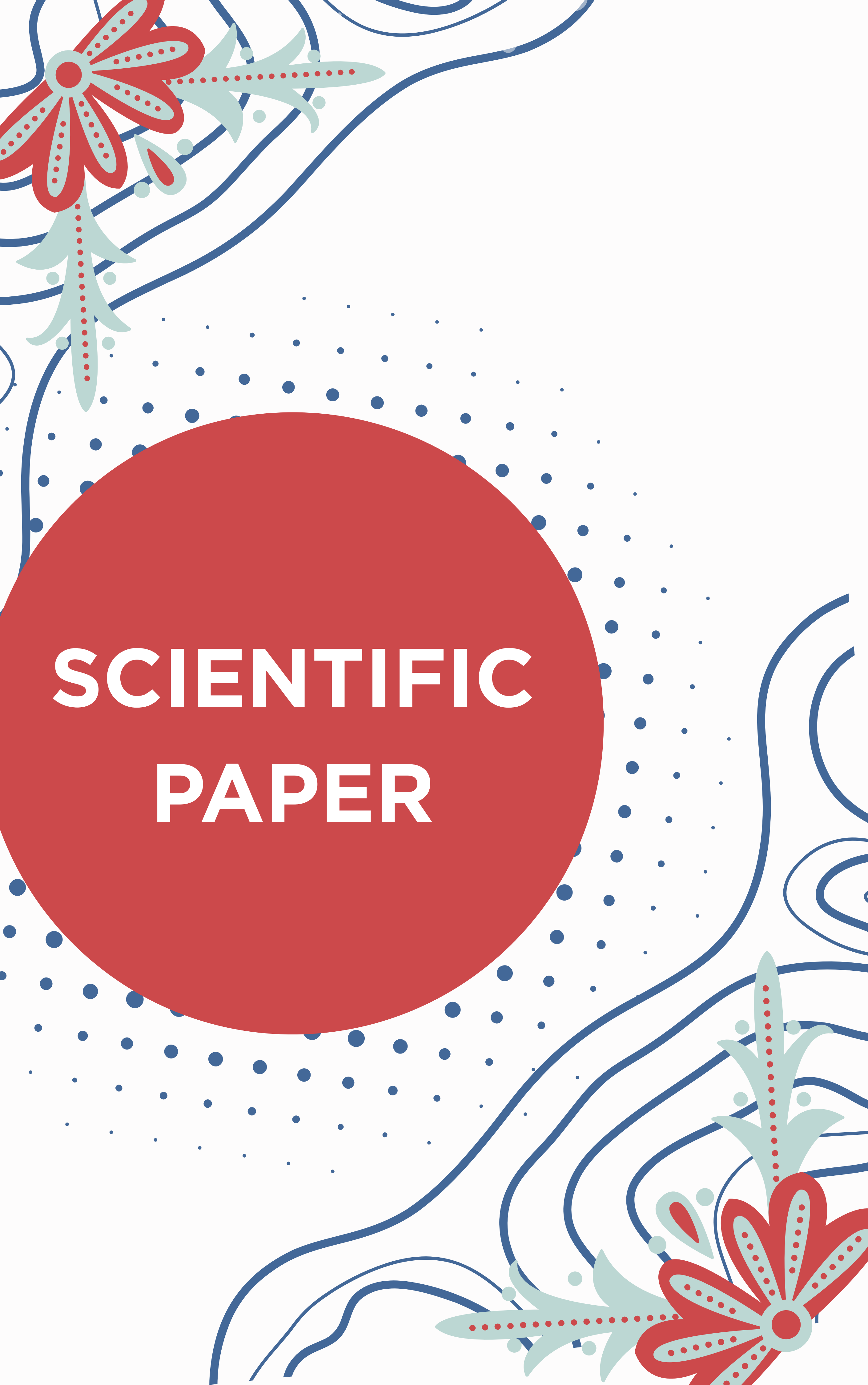
- HPV Infections
- Smoking
- Weak Immunity
- Multiple Sexual Partners
- Early Sexual Activity
- Family History



SCAN ME

Let HPV Vaccine Be Our GUARDIAN

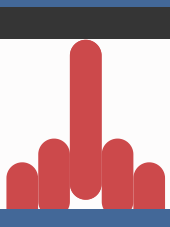
- G** Get vaccinated early
- U** Undergo regular screening
- A** Avoid smoking
- R** Reduce risky sexual behavior
- D** Detect symptoms early
- I** Initiate healthy lifestyle
- A** Access timely treatment
- N** Nurture awareness in others



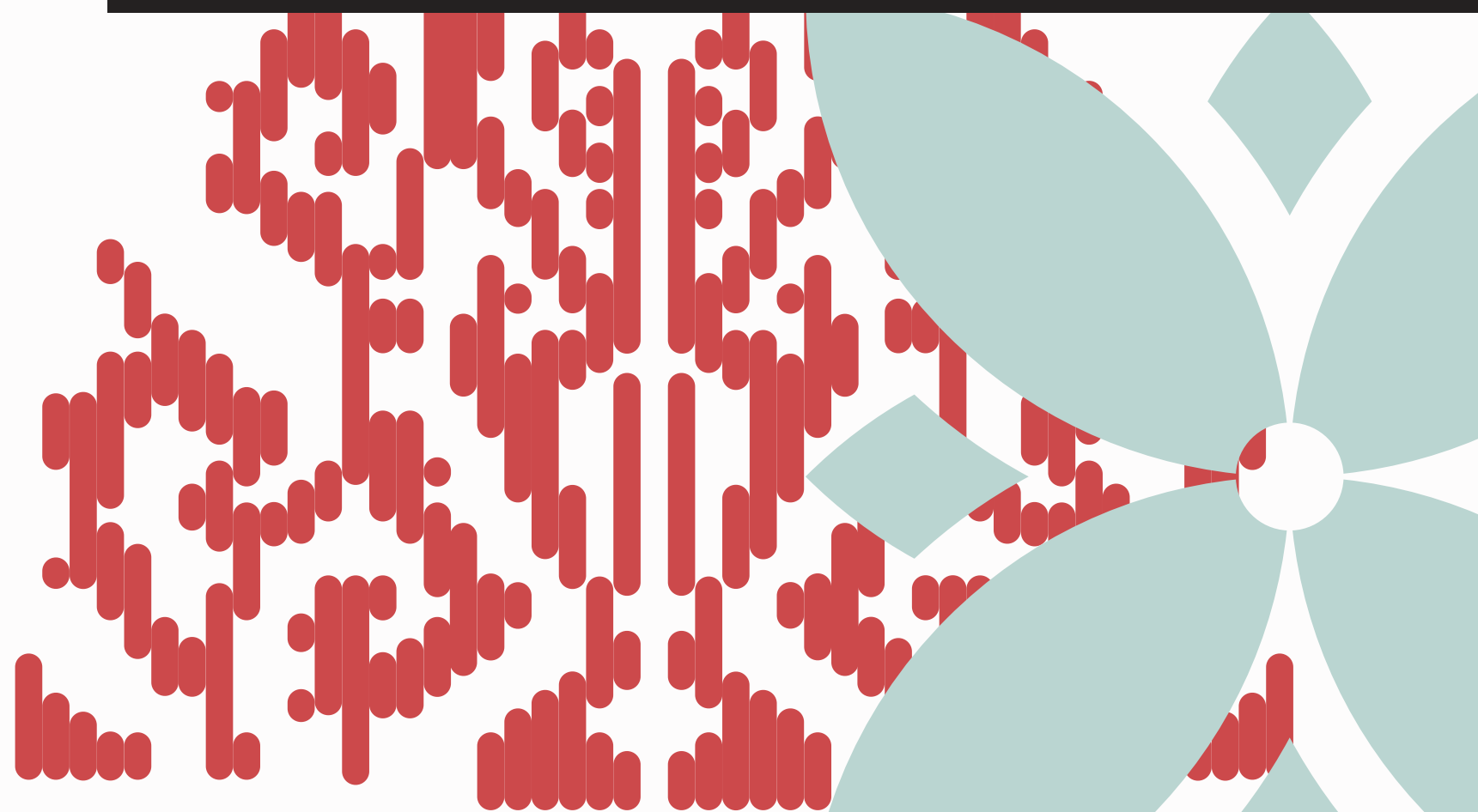
SCIENTIFIC PAPER



Evaluating Cold Tumor Treatment: Synergistic Approach and Combination of Chimeric Antigen Receptor T-Cell Linked Tumor-Associated Antigen in Prostate Cancer



**ANGELA VALESKA HARIJONO
FELICIA VIRGINIA THIOS
MUHAMMAD RIZA ILYASA
REX JEREMY SANTOSO**



**Evaluating Cold Tumor Treatment: Synergistic Approach and
Combination of Chimeric Antigen Receptor T-Cell Linked
Tumor-Associated Antigen in Prostate Cancer
Indonesian Medical Student's Training and Competition 2025**



Abstract

Introduction: Prostate cancer (PCa) is a prevalent malignancy with a rising global burden, characterized by its immunologically "cold" tumor microenvironment (TME) that hinders effective immune responses. Conventional therapies such as surgery, radiotherapy, and chemotherapy often fall short due to the challenges posed by PCa's TME and its limited tumor-specific antigens. This highlights the urgent need for innovative treatment strategies.

Methodology: A comprehensive literature review was conducted using databases like PubMed and ScienceDirect, focusing on studies from 2014 to 2024. The review examined the efficacy of chimeric antigen receptor (CAR) T-cell therapy targeting tumor-associated antigens in PCa, alongside combination therapies. Inclusion criteria emphasized studies exploring CAR T-cell therapy innovations, tumor-associated antigen targeting, and combinatorial approaches.

Results and Discussion: Tumor-associated antigens such as Prostate-Specific Membrane Antigen (PSMA) and Prostate Stem Cell Antigen (PSCA) have shown potential as targets for CAR T-cell therapy. Advances in CAR T-cell engineering, including the use of dominant-negative TGF- β receptors and gamma-enriched CAR T-cells, offer enhanced efficacy. Combination strategies—such as pairing CAR T-cells with radiotherapy, chemotherapy, immune checkpoint inhibitors, oncolytic viruses, or nanotherapy—demonstrate promising synergies in overcoming TME-induced immunosuppression and improving therapeutic outcomes. However, the limited success in clinical translation emphasizes the need for further research.

Conclusion: CAR T-cell therapy targeting tumor-associated antigens, when combined with complementary treatment modalities, represents a promising frontier in PCa management. Continued advancements in CAR T-cell design and integrative strategies are crucial to addressing the immunosuppressive challenges posed by PCa's TME and achieving clinical efficacy.

Keywords: *CAR T-cell Therapy, Combination Therapy, Prostate Cancer, Tumor-Associated Antigens, Tumor Microenvironment*

Introduction

Cancer is a genetic disorder defined by genomic instability, which results in the accumulation of numerous point mutations and structural alterations as the tumor progresses. Although the immune system plays a crucial role in suppressing tumor cells through direct cytotoxicity, Numerous cancer cells have evolved sophisticated mechanisms to evade immune surveillance^[1]. Among the various malignancies, prostate cancer (PCa) stands out as a significant health concern for males, holding the second highest incidence rate of cancer in men. This cancer is most prevalent among older individuals, with six out of ten PCa cases occurring in men over the age of 65, establishing it as the second most prevalent solid organ malignancy among males^[2]. The global incidence of PCa has shown a consistent upward trend, establishing it as the fourth leading cause of cancer-related mortality in men, with more than 1.46 million cases and 396.000 deaths in 2022^[3, 4]. Projections indicate that by 2040, the global incidence will rise further, reaching approximately 2.4 million cases and 712.000 deaths, largely due to the aging and growing global population^[4]. Meanwhile, in Indonesia, the latest data from the World Health Organization (WHO) indicates an alarming increase in PCa prevalence. In 2022, there were an estimated 13.130 new cases of PCa diagnosed in Indonesia, with a mortality rate of approximately 4.860 deaths^[4]. The rising incidence and mortality rates of PCa establish it as one of the most significant global health concerns.

Over the past century, the standard treatments for cancer have included surgical resection, radiotherapy, and chemotherapy. Although complete surgical removal of the tumor theoretically offers a cure, the propensity of cancer cells to metastasize often renders this approach inadequate. Other treatments also work in some patients, but they often cause significant side effects that harm the patient^[4]. In order to address these limitations, a number of therapeutic strategies have been developed, among which immunotherapy has emerged as a groundbreaking approach to overcoming cancer metastasis^[5, 6]. Immunotherapy represents a significant advancement in oncology, aiming to enhance and restore the immune system's ability to recognize and eliminate cancer cells, which often weaken immune responses^[7]. Current immunotherapy modalities, such as immune checkpoint inhibitors and adoptive transfer of manipulated immune cells, have shown promise in improving antitumor immune responses. With this promising advancement, cancer immunotherapy is regarded as a new stronger and creative treatment compared with other conventional therapy.

Despite its promise, immunotherapy faces critical challenges in PCa, which is categorized as a cold tumor. Cold tumors are characterized by a lack of immune cell infiltration and low immunogenicity, making them less responsive to immunotherapy compared to hot tumors that exhibit high immune activity. The immunologically cold phenotype of PCa is driven by its tumor microenvironment (TME), which harbors immunosuppressive cells and cytokines, creating a barrier to effective immune responses, including those triggered by immunotherapies^[8].

Among immunotherapy modalities, chimeric antigen receptor (CAR) T-cell therapy has emerged as a transformative approach, offering a solution to some of the challenges posed by the cold tumor nature of PCa. Unlike conventional immunotherapy, CAR T-cells are engineered to bypass the need for natural immune cell activation, directly targeting tumor antigens^[9]. However, the application of CAR T-cell therapy in PCa presents significant challenges due to the lack of tumor-specific antigens, as PCa primarily expresses tumor-associated antigens, which are also found at low levels in normal tissues. This similarity increases the risk of off-target effects and toxicity, making precise targeting more difficult. Moreover, the effectiveness of CAR T-cell therapy depends on its ability to reach tumor sites, but abnormal vasculature and dense fibrosis in solid tumors hinder their penetration and limit therapeutic outcomes.^[10]

To address the challenges of CAR T-cell therapy in PCa, innovative strategies focus on enhancing its specificity and functionality. One promising approach involves engineering CAR T-cells to target tumor-associated antigens, thereby improving the precision of immune responses while minimizing off-target effects^[10]. Furthermore, combining CAR T-cell therapy with complementary immunotherapeutic modalities aims to overcome the immunosuppressive TME, optimize CAR T-cell activity, and boost therapeutic efficacy. These integrative strategies hold potential to refine tumor targeting and enhance CAR T-cell performance within the hostile environment of PCa.

This literature review aims to evaluate the potential of combining CAR T-cell therapy linked with tumor-associated antigens and other immunotherapy modalities to overcome the challenges of PCa treatment. By examining current evidence, it aims to provide insights into how these strategies could revolutionize the management of PCa.

Methods

This literature review employs a comprehensive approach to exploring scientific evidence from various databases, including PubMed and ScienceDirect, with the objective of acquiring information on the combinatorial strategies involving CAR T-cell therapy linked to tumor-associated antigens and other therapeutic modalities in treating PCa patients. The keywords used were *Prostate Cancer*, *CAR T-cell Therapy*, *Tumor-Associated Antigens*, *Tumor Microenvironment*, *Combination Therapy*. After obtaining relevant articles and journals, the full texts were examined to determine the eligibility of the studies according to the inclusion criteria. We included primary and secondary studies as our main sources of articles in this review. We strived to evaluate how combining CAR T-cells targeting specific tumor-associated antigen with additional treatments address the unique challenges of PCa to enhance therapeutic efficacy. Studies published in languages other than English or Indonesian, or lacked full-text access were excluded from this review. Those literatures which met the inclusion criteria are qualitatively analyzed, discussed, summarized, and presented in the discussion section. The eligibility criteria are studies published from 2014 to 2024.

Result and Discussion

Tumor Microenvironment (TME) of Prostate Cancer

Fibroblast, immunological cells, and endothelial cells are among the various non-epithelial types of cells which make up TME. In primary PCa TME, cancer associated fibroblast (CAF) constitutes the most prevalent component, in numerous studies which have been conducted, the PCa-promoting characteristic of CAF shown to favour the metastatic process^[11]. The development and progression of different tumors depend on the heterogeneity of CAFs, which also promotes angiogenesis, immunosuppression, extracellular matrix (ECM) remodeling, and cancer cell proliferation^[12]. The PCa is also regarded as an immunologically "cold" tumor form that is immune treatment unresponsive, it is due to the numerous mechanisms of the immune related process, including the TGF- β pathway, regulatory T-cells, and myeloid-derived suppressor cells which protect PCa from being eliminated by the immune system^{[13][14]}. Another explanation for the poor responsiveness of immunotherapy in PCa is due to its environment which normally includes only a few immune cells^[15].

Tumor-Associated Antigens in Prostate Cancer

One of the most significant challenges in treating PCa with immunotherapy is the fact that it is a solid tumor. As previously noted, the immunosuppressive TME is a crucial aspect

of a solid tumor that affects T-cell function, limits T-cell proliferation, and impairs T-cell recognition and killing of tumor cells. In solid tumors, its major impediment to using CAR T-cell as an immunotherapy is that it interferes with the ability of immunotherapy target specificity because no tumor-specific antigen has been found in the tumor. On the other hand, major target antigens for solid tumors are tumor-associated antigens that influence the off-target effects and even promote bad prognosis^[10]. The example of these tumor-associated antigens are Prostate Specific Membrane Antigen (PSMA), Prostate Specific Antigen (PSA), and Prostate Stem Cell Antigen (PSCA).

Prostate Specific Membrane Antigen (PSMA) or also known as glutamate carboxypeptidase II is a type II membrane glycoprotein that is highly expressed on PCa cells^{[16][17]}. High expression of PSMA leading to an independent biomarker of poor prognosis of PCa and associated with reduced survival. This biomarker is positively found in metastatic lesions in most patients with metastatic castration-resistant PCa^[17]. Although initial studies indicated a high tissue-specificity of expression, PSMA was also discovered in other normal tissues such as the salivary gland, brain, small intestine, renal tubular epithelium, and breast epithelium. However, expression levels that were 100- to 1000-fold were found to be lower with absolute measurement in non-prostatic tissues^[18]. Many approaches use PSMA, either for positron emission tomography (PET) imaging or antibody-targeted treatments^[16]. This is shown according to its surface expression on PCa cells making it a viable target molecule for antibody treatment^[18]. Since 2010, anti-PSMA CAR T-cells with a CD28 costimulatory and CD3 ζ activation domain have been used in trials. This trial proved to have limited persistence of the CAR T-cells and no identifiable responses, suggesting a need for a more potent PSMA-specific CAR T-cell^[16].

Aside from PSMA, Prostate Specific Antigen (PSA) is a commonly used tumor-associated antigen for screening, aiming to detect PCa at an early, intervenable stage allowing for curative therapy and lowering overall and disease-specific mortality^[19]. It is a kallikrein-like serine-protease making it exclusively expressed by prostate epithelial cells, can be found in the majority of PCa tissues, and is the most extensively used blood marker for diagnosis and monitoring of PCa^[18]. In addition, PSA screening appears to increase the finding of PCa at any stage, especially increases the detection of stage I and II and modestly reduces the detection of stage III and IV PCa^[19]. Although it is widely utilized to identify patients in need of a diagnostic test, many studies implied that PSA has high sensitivity and

low specificity for diagnosing patients in symptomatic state. There are a number of biases being worried in the published studies which leads to a probability of overestimating the accuracy of PSA^[20]. Therefore, this indicates a need for urgent study of the utility of PSA in diagnosing clinically significant PCa and its combinatorial setting with CAR T-cells.

Another tumor-associated antigen specifically for PCa is Prostate Stem Cell Antigen (PSCA). PSCA, a glycosylphosphatidylinositol-anchored cell surface glycoprotein, is found in the prostate basal and secretory epithelial cells. It was first identified by its overexpression in a human PCa xenograft model. At the transcript level, it is largely expressed in the prostate. PSCA expression is detected in more than 80% of primary PCa samples and bone metastases. It is higher in both androgen-dependent and androgen-independent prostate tumors than in normal prostate tissues, particularly in advanced stages^[18]. Along with PSMA, PSCA is one of the unique tumor-associated antigens in metastatic castration-resistant prostate cancer (mCRPC) that are often and highly expressed, which could be leveraged as targets for effective cellular immunotherapy modalities. It is validated in published study that PSCA is a viable CAR T-cell therapeutic target and provides promising early clinical data to support future studies aimed at extending CAR T-cell persistence, which, with the use of new dosing and/or combinatorial settings, is expected to result in improved patients condition^[21].

CAR T-Cell in Prostate Cancer

CAR T-cells are T-cells that have undergone genetic engineering and express a distinct fusion receptor. CAR T-cell antigen recognition is not a major histocompatibility complex. In contrast with the normal T-cells antigen recognition, CAR T-cell activation and activity is dependent on its capability in reaching the appropriate tumor antigen. In order to further improve the effectiveness of CAR T-cell against cancer cells, five generations of structural and functional modifications have been made. The success of CAR T-cell therapy in hematologic malignancies is regarded as a new revolutionized therapy against cancer and promotes the new beginning of immunotherapy. However, the same therapy which is used in solid tumors such as PCa has not reached the same result, it is found that CAR T-cells were just 9% effective overall in solid tumors. The relatively restricted advancements in CAR T-cell treatments for solid tumor malignancies may be explained by the complexity of the PCa environment^{[10][22][23]}. Furthermore, the immunosuppressive signal owned by the PCa such as TGF- β should be overcome by the CAR T-cell in order to achieve therapeutic success^[16]. Nowadays, the development of CAR T-cell is focusing more on the identifying

particular target in cancer cells, the most widely utilized diagnostic antigen for PCa is Prostate Specific Antigen (PSA), however this antigen is not suitable as the target of CAR T-cell therapy. Today, the Prostate Specific Membrane Antigen (PSMA) and prostate stem cell antigen (PSCA) are the primary targets of CAR T-cell in PCa research^[10].

Prostate Specific Membrane Antigen (PSMA) is weakly expressed or even absent in normal prostate tissue. However, the fact that during the presence of PCa such as prostate adenocarcinoma, its presence can increase up to one thousand times, PSMA has the potential to become a therapeutic target especially in PCa, the continuous success between PSMA and radioligand therapy has been one of the reasons that PSMA is believed as a promising target ligand for both diagnosis and also treatment. An early preclinical finding has proven that the first and second generation of CAR T design elicited a strong immune response and a promising in vitro effectiveness in a variety of PSMA cell lines. A study comparing the efficacy of both generations of CAR T targeting the PSMA showed that only 12.5% of the first generation of CAR T group experienced a total remission. In contrast with the second generation CAR T group who achieved the efficacy of 75% in total remission. However, there was still insufficient evidence of these CAR T innovations which have the ability to overcome the immunosuppressive element inside the TME to support further clinical research. One significant advancement of CAR T design is the inclusion of a dominant-negative transforming growth factor (TGF)- β RII (dnTGF- β RII) domain in PSMA-targeting CAR T, a study has shown that the coexpressing dnTGF- β RII in PCa models using PSMA-specific CAR T-cells. In mouse models, this TGF- β CAR design has successfully boosted the T-Cell proliferation and cytokine production resulting in a long term elimination of the tumor cells expressing PSMA^{[10][22]}.

Prostate stem cell antigen (PSCA) is an antigen which is expressed highly in PCa early stages and increases in advanced stages^[21]. Although it is a promising targeting property in PCa, PSCA is also expressed at a lesser level in noncancerous tissue^[24]. This ideal targeting property has been tested with CAR T therapy, a finding from a study showing that a third generation CAR T targeting PSCA has proven to treat PCa in mice. According to this in vitro test, CAR T-cells produced a lot of IL-2 and interferon γ when they attached precisely to the target cell PSCA which efficiently eliminated tumors and encouraged CTL proliferation. Another study verified the benefit of PSCA as a potential targeting properties, when compared to CD28 as a costimulatory molecule, PSCA-CARs have a greater capacity

to control disease and to demonstrate superior T-cell persistence in PCa and bone metastasis of PCa^[10]. Another significant improvement of the CAR T design is the gamma-enriched CAR T-Cell targeting PSCA, when combined with gamma-enriched T-cell, the CAR generated a strong release of cytokines and antigen-specific cytotoxicity. In a in vivo test, this anti PSCA gamma-enriched CAR T-cell caused an existing tumor to recede and in certain mice, it can even be eradicated^[25].

CAR T-Cell and Radiotherapy or Chemotherapy

Radiotherapy is well-known as one of the most often utilized local therapies for tumors, thus it can directly kill cancer cells via apoptosis and necrosis^[26]. Radiotherapy induces the release of tumor-related antigens and pressure signals, resulting in tumor regression at non-radiotherapy sites. More crucially, radiation enhances the local TME, allowing CAR T-cells to penetrate the tumor^[10]. Weiss et al. found that combining low-dose radiation with NKG2D-CAR T-cells promoted CAR T-cell penetration, IFN- γ release, therapeutic efficacy, and mouse survival^[27]. Another study by DeSelm et al. found that tumors were more susceptible to CAR T-cells after low dose radiation therapy^[28]. These results showed that radiation is a significant approach for reshaping the TME, and it can generate a new immunological homeostasis, making CAR T-cell therapy with radiotherapy exerts an excellent synergistic method for PCa^{[10][26]}.

Chemotherapy has been known to be a widely used aid for cancer. Chemotherapy helps to release IL-2, IL-7, and IL-15, which generate an initial burst of cell growth when CAR T-cells are infused. This indicates that heightened cytokine release may increase CAR T-cell activity in the TME^[29]. Chemotherapy plays an immunomodulatory role when administered at low doses, such as promoting dendritic cell activation and tumor antigen presentation to CAR T-cells, and limiting suppressive immune cells. Some studies have indicated that immunosuppressive cells are more responsive to specific chemotherapeutic medications than T-cells^{[26][29]}. In addition, those immunomodulatory roles result in improved persistence of CAR T-cells and stimulate tumor cells to CAR T-cell activity by promoting granzyme B penetration to the tumor cells^[26]. In conclusion, low-dose chemotherapy may not be harmful for infused CAR T-cells meaning that chemotherapeutic doses that do not directly impair CAR T-cells have the potential to promote CAR T-cell function of tumor trafficking through increased cytokine release in the TME. This causes more apparent tumoricidal responses and enhances the rate of tumor rejection, leading to greater survival rates ^{[26][29]}.

CAR T-Cell and Immune Checkpoint Inhibitor

CAR T-cell activities can be inhibited by the expression of PDL-1 and PDL-2 in the tumor surface, particularly following prolonged antigen stimulation, a recent in vivo activity show that CAR T-cell with the combination of pembrolizumab, an immune checkpoint inhibitor which target PD-1 protein, it can improve the CAR T-cell function and survivability, another study also shown that the administration of immune checkpoint inhibitor also influence the efficacy of the combination, in a mice model of PCa, the PDL-1 oncolytic approach show better efficacy than systemic injection of PDL-1 antibodies^[30]. More promising outcomes are shown by these two combinations, it is interesting that CAR T-cell secreted PD-1 blocking antibodies which can bind to PD-1 competitively hence increasing the cytotoxicity and proliferation of CAR T-cell. Furthermore, a recent study demonstrated that the anti tumor activity against PCa is increased when both anti-PD-L1 monoclonal antibodies and anti-PSMA CAR-NK-92 cells are combined^[26]. To further analyze these two combinations, a trial was conducted, with the result that PCa can be treated using PD-1 antibodies and PSMA targeted second generation CAR T-cells, although it was only for a brief duration, the efficacy of CAR T was improved^[10]. However, the clinical evidence regarding the combination of CAR T-cell and immune checkpoint inhibitor is still low, as the CAR T-cell is still a new and promising future approach especially in treating PCa patients^[31].

CAR T-Cell with Oncolytic Virus

With the finding that some types of tumor have low susceptibility to immunotherapy, there is a new innovation to transform a “cold” tumor like PCa into a “hot” tumor. This innovation found a great promise with oncolytic viruses (OVs) as tools to overcome some of the limitations and improve the efficiency of CAR T-Cell treatment in solid tumors like PCa^[32]. Oncolytic viruses (OVs) are viruses that are naturally selected or manufactured to multiply preferentially in cancer cells while remaining restricted in healthy cells. OVs set up targeted infection and lysis of tumor beds while also producing therapeutic transgenes such as cytokines, tumor antigens, checkpoint inhibitors, or T-cell engagers in the tumor milieu to improve anti-tumor immunity^[33]. Although they can not selectively infect and lyse tumor cells, their combined therapy with CAR T-cells can significantly induce CAR T-cells to infiltrate TME and enhance therapeutic effect in solid tumors^[10]. A study conducted by Ponterio E. et al., OVs are administered for cancer treatment prior to CAR T-cell therapy,

resulting in tumor debulking, immunogenic cell death, and reversal of tumor immunosuppression. In a combined effort, manufactured OV's may change an immunologically "cold" tumor into a "hot" tumor (**Fig 1**). In conclusion, first, therapeutic transgenes can be introduced into OV's to increase CAR T activation. Second, OV's may be able to survive and sustain cytotoxicity functions in an immunosuppressive TME. This may give warning signs that can reverse tumor immunosuppression. Third, OV's direct lytic action on cancer cells causes tumor cell death, resulting in the production of tumor-associated antigens^[32]. Thus, the concept of "all-in-one" therapy introduces a novel idea for immunotherapy of PCa^[10].

On the other hand, another study provides a contradiction statement according to the combination therapy of OV's and immunotherapy, specifically CAR T-cells. Their findings indicate that the immunological heat induced by tumor infection by an OV's is a complex multifactorial process that is not always favorable for immunotherapy. There is a link between type I IFN response to viral infection from OV's, which can act negatively on a pre-existing effector T-cell response in the form of adoptively transplanted CAR T-cells. Although numerous preclinical and clinical papers have revealed enhanced tumor-infiltrating lymphocytes (TIL) density following viral treatment, they believe that several elements are necessary to explain how an OV and its accompanying inflammation may dynamically enhance the number of T-cells^[33].

CAR T-Cell with Nanotherapy

Nanotherapy has been considered as a new promising advancement in combination with CAR T-Cell against the PCa, a recent study conducted by Hassani et al., shows that using camelid nanobody (VHH), to build the CAR T-cell and when co-cultured with LNCaP, a cell line of human prostate adenocarcinoma, the VHH CAR T-Cell multiplied by about 60% in comparison to the PSMA-negative PCa cells, from here, it is proven that the PCa can be inhibited with CAR T-cell and nano antibodies combination^[10]. Another nano antibodies therapy which is made from a llama inoculated with four human-derived PCa, this nanobody is called JVS-007 and made up by CD28 transmembrane, co-stimulatory domain and CD3 ζ signaling domain which reacted to PSMA tumor cells and LNCaP by boosting the CD69 expression and the triggering of release IL-2 and IFN- γ which supported CAR T-cells immunotherapy targeting PSMA^[34].

Conclusion and Further Recommendation

In conclusion, the TME in PCa is a critical driver of its progression and metastasis, dominated by immunosuppressive elements such as cancer-associated fibroblasts (CAFs), regulatory T-cells, and myeloid-derived suppressor cells. Compounding this challenge, PCa's inherently "cold" immune profile diminishes the effectiveness of immunotherapies. Nevertheless, tumor-associated antigens like Prostate Specific Membrane Antigen (PSMA), Prostate Specific Antigen (PSA), and Prostate Stem Cell Antigen (PSCA) have emerged as promising targets, particularly for CAR T-cell therapy. While advancements in CAR T-cell engineering, including iterations targeting PSMA and PSCA, have shown promise, their impact remains constrained by the TME's robust immunosuppressive mechanisms. Innovative combination approaches, such as integrating CAR T-cell therapy with radiotherapy, chemotherapy, immune checkpoint inhibitors, oncolytic viruses, or nanotherapy, have demonstrated potential to counteract TME barriers. These strategies aim to boost tumor antigen recognition, improve CAR T-cell persistence, and modulate the immune landscape. However, most remain in exploratory stages, with inconsistent results necessitating further rigorous validation.

Moving forward, research must prioritize refining CAR T-cell technologies to counteract the immunosuppressive challenges of PCa. Innovations such as dominant-negative TGF- β receptors, gamma-enriched CAR T-cells, and nanobody-based designs are promising avenues to enhance therapeutic potency. Additionally, combining CAR T-cells with therapies like radiotherapy, chemotherapy, immune checkpoint inhibitors, and OV's should be explored more comprehensively. Large-scale clinical trials will be pivotal in verifying these approaches' safety, efficacy, and durability. As CAR T-cell therapy evolves, the integration of cutting-edge immunotherapy, molecular biology, and precision medicine is essential to revolutionize PCa treatment and achieve transformative outcomes.

Conflict of Interest

The authors confirm that there are no conflicts of interest or financial interests, connections, or other circumstances that may give rise to concerns about bias in our writing or affect the conclusions we have reached.

Reference

1. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cell Mol Immunol*. 2020 Aug;17(8):807-821. Available from: <https://doi.org/10.1038/s41423-020-0488-6>.
2. Wasim, S., Lee, S. Y., & Kim, J. Complexities of Prostate Cancer. *International journal of molecular sciences*, 2022, 23(22), 14257. Available from: <https://doi.org/10.3390/ijms232214257>.
3. International Agency for Research on Cancer. Global cancer observatory: Data visualization. World Health Organization. Available from: https://gco.iarc.fr/today/en/dataviz/pie?mode=cancer&group_populations=1&sexes=1&types=1. Accessed December 18, 2024.
4. Elizabeth J. Schafer, Mathieu Laversanne, Hyuna Sung, Isabelle Soerjomataram, Alberto Briganti, William Dahut, Freddie Bray, Ahmedin Jemal, Recent Patterns and Trends in Global Prostate Cancer Incidence and Mortality: An Update, *European Urology*, 2024, ISSN 0302-2838. Available from: <https://doi.org/10.1016/j.eururo.2024.11.013>.
5. Rui, R., Zhou, L., & He, S. Cancer immunotherapies: advances and bottlenecks. *Frontiers in immunology*, 2023, 14, 1212476. Available from: <https://doi.org/10.3389/fimmu.2023.1212476>
6. Cha, J. H., Chan, L. C., Song, M. S., & Hung, M. C. New Approaches on Cancer Immunotherapy. *Cold Spring Harbor perspectives in medicine*, 2020, 10(8), a036863. Available from: <https://doi.org/10.1101/cshperspect.a036863>
7. Sridaran D, Bradshaw E, DeSelm C, Pachynski R, Mahajan K, Mahajan NP. Prostate cancer immunotherapy: Improving clinical outcomes with a multi-pronged approach. *Cell Rep Med*. 2023;4(10):101199. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10591038/#ack0010>
8. von Amsberg, G.; Alsdorf, W.; Karagiannis, P.; Coym, A.; Kaune, M.; Werner, S.; Graefen, M.; Bokemeyer, C.; Merkens, L.; Dyshlovoy, S.A. Immunotherapy in Advanced Prostate Cancer—Light at the End of the Tunnel? *Int. J. Mol. Sci*. 2022, 23, 2569. Available from: <https://doi.org/10.3390/ijms23052569>

9. Zhang Z, Li D, Yun H, Liu W, Chai K, Tong J, Zeng T, Gao Z and Xie Y. CAR-T Cells in the Treatment of Urologic Neoplasms: Present and Future. *Front. Oncol.* 2022, 12:915171. Available from: <https://doi:10.3389/fonc.2022.915171>
10. Jiang, Y.; Wen, W.; Yang, F.; Han, D.; Zhang, W.; Qin, W. Prospect of Prostate Cancer Treatment: Armed CAR-T or Combination Therapy. *Cancers* 2022, 14, 967. Available from: <https://doi.org/10.3390/cancers14040967>
11. Kang J, La Manna F, Bonollo F, et al. Tumor microenvironment mechanisms and bone metastatic disease progression of prostate cancer. *Cancer Lett.* 2022;530:156-169. Available from: <https://pubmed.ncbi.nlm.nih.gov/35051532/>
12. Yu X, Liu R, Gao W, Wang X, Zhang Y. Single-cell omics traces the heterogeneity of prostate cancer cells and the tumor microenvironment. *Cell Mol Biol Lett.* 2023;28(1):38. Published 2023 May 9. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10170780/>
13. Zanvit P, van Dyk D, Fazenbaker C, et al. Antitumor activity of AZD0754, a dnTGF β RII-armored, STEAP2-targeted CAR-T cell therapy, in prostate cancer. *J Clin Invest.* 2023;133(22):e169655. Published 2023 Nov 15. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10645390/>
14. Wu W, Wang X, Le W, et al. Immune microenvironment infiltration landscape and immune-related subtypes in prostate cancer. *Front Immunol.* 2023;13:1001297. Published 2023 Jan 9. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9868452/>
15. Hirz T, Mei S, Sarkar H, et al. Dissecting the immune suppressive human prostate tumor microenvironment via integrated single-cell and spatial transcriptomic analyses. *Nat Commun.* 2023;14(1):663. Published 2023 Feb 7. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9905093/>
16. Kloss CC, Lee J, Zhang A, et al. Dominant-Negative TGF- β Receptor Enhances PSMA-Targeted Human CAR T Cell Proliferation And Augments Prostate Cancer Eradication. *Mol Ther.* 2018;26(7):1855-1866. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6037129/>
17. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med.* 2021;385(12):1091-1103. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8446332/>

18. Kiessling A, Wehner R, Füßel S, Bachmann M, Wirth MP, Schmitz M. Tumor-Associated Antigens for Specific Immunotherapy of Prostate Cancer. *Cancers*. 2012 Feb 22;4(1):193–217. Available from: <https://doi:10.3390/cancers4010193>
19. Ilic D, Djulbegovic M, Jung JH, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. *BMJ*. 2018;362:k3519. Published 2018 Sep 5. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6283370/>
20. Merriel SWD, Pocock L, Gilbert E, et al. Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients. *BMC Med*. 2022;20(1):54. Published 2022 Feb 7. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8819971/#Sec23>
21. Dorff TB, Blanchard MS, Adkins LN, et al. PSCA-CAR T-cell therapy in metastatic castration-resistant prostate cancer: a phase 1 trial. *Nat Med*. 2024;30(6):1636-1644. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11186768/#Abs1>
22. Zarrabi KK, Narayan V, Mille PJ, et al. Bispecific PSMA antibodies and CAR-T in metastatic castration-resistant prostate cancer. *Ther Adv Urol*. 2023;15:17562872231182219. Published 2023 Jun 15. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10285603/>
23. Minn I, Huss DJ, Ahn HH, et al. Imaging CAR T-cell therapy with PSMA-targeted positron emission tomography. *Sci Adv*. 2019;5(7):eaaw5096. Published 2019 Jul 3. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6609218/>
24. Priceman SJ, Gerds EA, Tilakawardane D, et al. Co-stimulatory signaling determines tumor antigen sensitivity and persistence of CAR T-cells targeting PSCA+ metastatic prostate cancer. *Oncoimmunology*. 2017;7(2):e1380764. Published 2017 Oct 16. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5749625>
25. Frieling JS, Tordesillas L, Bustos XE, et al. $\gamma\delta$ -Enriched CAR-T cell therapy for bone metastatic castrate-resistant prostate cancer. *Sci Adv*. 2023;9(18):eadf0108. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10156127>
26. Maalej KM, Merhi M, Inchakalody VP, et al. CAR-cell therapy in the era of solid tumor treatment: current challenges and emerging therapeutic advances. *Mol Cancer*. 2023;22(1):20. Published 2023 Jan 30. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9885707/#Sec38>

27. Weiss, T.; Weller, M.; Guckenberger, M.; Sentman, C.L.; Roth, P. NKG2D-Based CAR T Cells and Radiotherapy Exert Synergistic Efficacy in Glioblastoma. *Cancer Res.* 2018, 78, 1031–1043.
28. DeSelm, C.; Palomba, M.L.; Yahalom, J.; Hamieh, M.; Eyquem, J.; Rajasekhar, V.K.; Sadelain, M. Low-Dose Radiation Conditioning Enables CAR T Cells to Mitigate Antigen Escape. *Mol. Ther.* 2018, 26, 2542–2552.
29. Mukherjee AG, Wanjari UR, Prabakaran DS, et al. The Cellular and Molecular Immunotherapy in Prostate Cancer. *Vaccines (Basel)*. 2022;10(8):1370. Published 2022 Aug 22. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9416492/#sec7-vaccines-10-01370>
30. Grosser R, Cherkassky L, Chintala N, Adusumilli PS. Combination Immunotherapy with CAR T Cells and Checkpoint Blockade for the Treatment of Solid Tumors. *Cancer Cell.* 2019;36(5):471-482. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7171534/>
31. Rathi N, McFarland TR, Nussenzveig R, Agarwal N, Swami U. Evolving Role of Immunotherapy in Metastatic Castration Refractory Prostate Cancer. *Drugs.* 2021;81(2):191-206. Available from: <https://pubmed.ncbi.nlm.nih.gov/33369720/>
32. Ponterio E, Haas TL, De Maria R. Oncolytic virus and CAR-T cell therapy in solid tumors. *Front Immunol.* 2024;15:1455163. Published 2024 Oct 30. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11557337/#s4>
33. Evgin L, Huff AL, Wongthida P, et al. Oncolytic virus-derived type I interferon restricts CAR T cell therapy. *Nat Commun.* 2020;11(1):3187. Published 2020 Jun 24. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7314766/#Sec1>
34. Bao, C.; Gao, Q.; Li, L.-L.; Han, L.; Zhang, B.; Ding, Y.; Song, Z.; Zhang, R.; Zhang, J.; Wu, X.-H. The Application of Nanobody in CAR-T Therapy. *Biomolecules* 2021, 11, 238. Available from: <https://doi.org/10.3390/biom11020238>

Appendix

Figure 1. Synergistic Combination of CAR T-cells and OV

