Research Article

The Efficacy of Chemotherapy in Advanced-Stage Cervical Cancer on Vitamin A Serum

Efektivitas Kemoterapi pada Karsinoma Serviks Stadium Lanjut terhadap Serum Vitamin A

Raissa Nurwany, Rizal Sanif, Amirah Noviliani, Theodorus

Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Sriwijaya
Dr. Mohammad Husein General Hospital
Palembang

Abstract

Objective: To determine the efficacy of neoadjuvant chemotherapy on changes of vitamin A serum in advanced cervical carcinoma patient.

Methods: A randomized clinical trial was performed in the Oncology Gynecology Polyclinic and Ward of Dr. Mohammad Hoesin General Hospital, Palembang from September 2019 to September 2020. There were 30 subjects of advanced cervical carcinoma. Vitamin A levels and tumor volume subjects were assessed before and 1 month after 3 cycles of NAC and analyzed using the Paired T Test and Wilcoxon test. The correlation between vitamin A levels and tumor volume was analyzed by using Spearman's Rho test. Data analysis was using SPSS version 22.0.

Results: This study showed statistically not significant increase on vitamin A levels after 3 cycles of NAC chemotherapy (p=0.515). However, there was a significantly decrease in tumor volume after 3 cycles of NAC (p=0.000). In addition, there was a moderate negative correlation between tumor size and vitamin A (r=-0.475; p=0.008).

Conclusion: It can be concluded that there was significantly decrease in tumor volume after 3 series NAC chemotherapy and the smaller tumor size, the higher level of vitamin A serum.

Keywords: cervical cancer, neoadjuvant chemotherapy, randomized clinical trial, vitamin A.

Abstrak

Tujuan: *Untuk mengetahui efektivitas kemoterapi neoadjuvan terhadap perubahan kadar serum vitamin A pada karsinoma servik stadium lanjut.*

Metode: *Penelitian uji klinik tanpa pembanding telah dilakukan di Poliklinik dan Bangsal Onkologi Ginekologi RSUP Dr. Muhammad Hoesin Palembang sejak September 2019 hingga September 2020. Didapatkan 30 sampel karsinoma serviks stadium lanjut. Kadar vitamin A dan volume tumor dinilai sebelum dan 1 bulan setelah 3 siklus NAC dan dianalsis menggunakan uji Paired T Test dan Wilcoxon. Korelasi antara Kadar vitamin A dan volume tumor sampel dianalisis menggunakan uji Spearman Rho's. Analisa data menggunakan SPSS versi 22.0.*

Hasil: *Pada penelitian ini terdapat peningkatan tidak signifikan kadar vitamin A setelah kemoterapi (p = 0,515). Terdapat penurunan secara signifikan volume tumor sebelum dan sesudah kemoterapi NAC 3 seri (p = 0,000). Selain itu, didapatkan korelasi negatif sedang yang bermakna antara ukuran tumor dan kadar vitamin A (r = -0,475 ; p = 0,008).*

Kesimpulan: *Disimpulkan bahwa terdapat penurunan volume tumor setelah kemoterapi NAC 3 series dan semakin kecil ukuran tumor maka semakin tinggi kadar vitamin A dalam serum.*

Kata kunci: *kanker serviks, kemoterapi neoadjuvan, uji klinik tanpa pembanding, vitamin A.*

Correspondence author. Raissa Nurwany. Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Sriwijaya. Dr. Muhammad Hoesin General Hospital. Palembang.
Email. raissa.nurwany@gmail.com

INTRODUCTION

Cervical cancer ranked the fourth most common cancer in women worldwide after breast, colorectal, and lung cancer, where there were around 604,127 cases with 341,831 cervical cancer deaths in 2020. Deaths from cervical cancer are projected to continue to increase and estimated to reach 481 thousand deaths in 2040 if not treated properly. The incidence of cervical cancer in Indonesia is estimated to have 36,600 new cases in 2020 and the death rate is estimated to reach 75% in the first year. These deaths are mainly associated with the majority of cervical cancer stages (70% of cases) are invasive, advanced, and even terminal at the time of diagnosis.[1-3]

The optimal treatment for the early stages (stages IA1, IA2 and IB1) consists of radical surgery or chemoradiation. In advanced stage cervical cancer (IIB-IVB), where surgery is not possible, primary therapy is generally performed with chemoradiation or in combination with chemotherapy and radiation. Because most cervical cancers are diagnosed at an advanced stage, it creates various obstacles in the availability of facilities and infrastructure. The administration of neoadjuvant chemotherapy (NAC) alone in late advanced cervical carcinoma (LACC) is still a matter of debate and has not been included in therapeutic recommendations by various international oncology organizations. Cancer treatment delay is a worldwide problem. The limitations of radiation facilities in Indonesia cause chemotherapy as the only therapeutic modality, which can be offered. The effectiveness of giving chemotherapy itself is still questionable, whereas at Mohammad Hoesin General Hospital Palembang, the only available radiotherapy facilities are external radiation with Cobal 60 which is problematic so chemotherapy is the main choice.[4-7]

Cisplatin is often used as a single chemotherapy regimen. Carboplatin has effectiveness in cervical cancer with a response rate of up to 20%. While paclitaxel is known to have moderate effectiveness in cervical cancer with a response rate of up to 17%. The success of the paclitaxel-carboplatin combination is higher in squamous cell carcinoma because each of these agents has high cytotoxic activity as a single agent. Neoadjuvant chemotherapy in patients with late advanced cervical cancer has a beneficial effect by increasing the willingness to undergo surgery, reducing the risk of surgery and at a young age, it helps influence the patient's psychology.[7-9]

Retinoic acid (RA), an active metabolite of vitamin A, is an important signaling molecule involved in the differentiation, proliferation, and apoptosis processes of almost all cell types. Regulation by retinol or retinoic acid includes controlling cell proliferation through activities that stimulate resting G1 phase and resting S phase. This mechanism occurs because retinol or retinoic acid has a role in strengthening p53 expression, activating p21, and activating cyclin suppression. A study revealed that improving nutritional status plays a role in the prevention and improvement of cervical dysplasia. Improvement of mild and moderate cervical dysplasia has been seen in patients who received vitamin A supplements within a few months. Therefore, a number of clinical studies have shown that topical application of vitamin A to the cervix results in the improvement of cervical dysplasia in 50% of cases.[9-14]

The main objective of administering chemotherapy or chemoradiation is abnormal cell death which will also affect normal cells, especially proliferating cells such as intestinal cells and hepatocyte cells. They are very important in the absorption and metabolism of vitamin A, so that this will cause serum vitamin A to decrease. Because of the role of vitamin A in the cell cycle, which is very important, it can be predicted that cell death will be disrupted, so that carcinoma treatment will be disrupted. In other words, the response to therapy will be less good.[13,14]

Based on the above reasons, the researchers conducted a study to see how the efficacy of neoadjuvant chemotherapy on changes in vitamin A level in advanced cervical carcinoma at dr. Mohammad Hoesin General Hospital as a successful predictor of chemotherapy.

METHODS

This study was a clinical trial without comparison. The research was conducted at the Oncology Outpatient Clinic and Ward, Department of Obstetrics and Gynecology, Dr. Mohammad Hoesin Palembang. Data collection and observations were carried out from September 2019 to September 2020.

Subjecst were all cervical carcinoma patients who were treated at the Oncology Outpatient Clinic and Ward, Department of Obstetrics and Gynecology, Dr. Mohammad Hoesin Palembang

from September 2019 until September 2020. Patients with advanced-stage cervical carcinoma (stage IIB to IVA according to FIGO classification in 2018), treated with 3 series of neoadjuvant chemotherapy, and willing to participate in the study by signing the consent form were included in this study.

Patients with early-stage cervical carcinoma, advanced-stage with chronic renal failure, an advanced-stage with severe systemic disease, and advanced-stage cervical carcinoma who were on radiation were the exclusion criterias in this study. In addition, the drop out criterias in this study were advanced cervical carcinoma patients who did not complete treatment and advanced-stage cervical carcinoma who died before completing treatment.

Subjects were collected by consecutive sampling. In this study, there were 38 subjects who met the inclusion criterias, 4 people dropped out due to death, 4 people dropped out due to not completing chemotherapy. A total of 30 patients with advanced-stage cervical carcinoma who were treated with 3 series of neoadjuvant chemotherapy were taken as research subjects.

All patients who will be included in this study were asked several questions (name, age, address, parity, last menstrual period, and previous medical history), physical examination (general condition, blood pressure, pulse rate, respiration rate, temperature, body weight, and height). Then, the patient was asked to have fasting (they were not allowed to eat and drink, except drinking water) for 12-14 hours before taking 3 ml of the cubital venous blood sample. The venous blood sample was then immediately taken to the Prodia laboratory and tested for serum vitamin A using the HPLC (High-Performance Liquid Chromatography) method.

The patient is then subjected to an ultrasound examination before chemotherapy treatment to determine the size of the tumor by a consultant oncologist and gynecologist or fetomaternal consultant. The size of the tumor mass was calculated in 3 sections, namely superior-inferior, lateral-lateral, and anterior-posterior by transabdominal ultrasound. Then, chemotherapy was given every cycle until the 3rd cycle. After 1 month post 3 cycles of NAC, another ultrasound examination was performed to assess tumor size after 3 cycles of chemotherapy by a consultant oncologist and gynecologist or fetomaternal consultant in the same way. The patient was then checked for vitamin A levels by the Prodia Laboratory by doing the same examination and an evaluation of the chemotherapy response based on the size of the tumor mass.

After the data were collected, we did a statistical analysis using SPSS, where continuous variables used student t-test using p 0.05 to assess significance. The categorical variables used the Chi-square test to assess differences between treatment groups. Presentation of data used tables to facilitate data reading and analysis of results.

RESULTS

A total of 30 subjects were treated with 3 series of neoadjuvant chemotherapy were sampled. Vitamin A levels and tumor mass size were assessed before and 1 month after 3 NAC cycles.

In this study, the mean age of the patient with advanced cervical carcinoma was 54.23 ± 13.09 years with an age ranged of 35 to 81 years. The majority of the subjects were married (93.3%) and the highest parity was multiparous (60%), and as many as 6 subjects had history of abortion. The largest sample stage in this study was stage IIIB (70%) and the majority of patients had squamous cell carcinoma based on histopathology examination (83.3%) and received Paclitaxel-Carboplatin chemotherapy (93.3%) (Table 1).

Vitamin A levels and sample mass size were assessed before and 1 month after 3 NAC cycles. In this study, the levels of vitamin A before chemotherapy were found to be 450.03 ± 167.18, after chemotherapy the levels of vitamin A increased to 478.37 ± 197.25. With statistical analysis, it was found that there was no change in vitamin A levels before, and after 3 series of NAC chemotherapy, vitamin A levels increased after chemotherapy but it was not statistically significant (p = 0.515). A total of 15 subjects had increased vitamin A and 15 other subjects had decreased vitamin A (Table 2).

Table 1. Demographic Characteristics of the Subject

| Characteristics	Total	%
Age, mean ± SD	54.23 ±13.098	
Occupation		
Housewife	29	96.7
Entrepreneur	1	3.3
Address		
Palembang	11	36.7
Outside Palembang	19	63.3
Marital Status		
Unmarried	2	6.7
Married 1 time	24	80.0
Married 2 times	4	13.3
Parity		
Nulliparity	4	13.3
Primiparity	2	6.7
Multiparity	18	60.0
Grand multiparity	6	20.0
Abortion		
Negative	24	80
Positive	6	20
Stage		
III A	1	3.3
II B	8	26.7
III B	21	70.0
Concomitant Diseases		
Positive	7	23.3
Negative	23	76.7
Chemotherapy regimen		
Paclitaxel-Carboplatin	28	93.3
Paclitaxel-Cisplatin	1	3.3
Cisplatin-Ifosfamid Mesna	1	3.3
Histopathology		
Squamous Cell Carcinoma	25	83.3
Non Squamous Cell Carcinoma	5	16.7
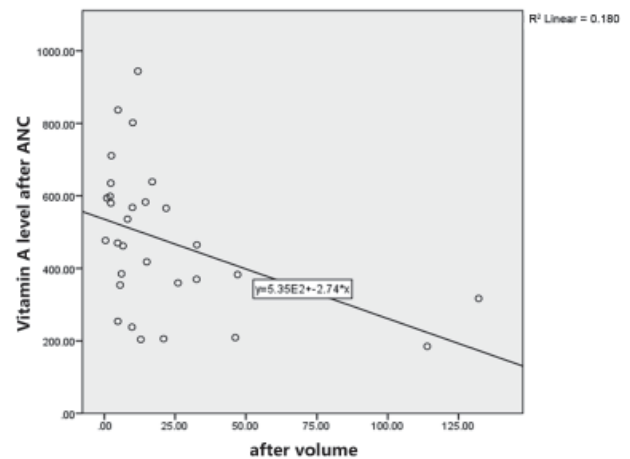
Figure 1. Correlation Graph of Vitamin A Levels And Tumor Volume

In this study, from 29 subjects who had decreased tumor volume, 14 subjects (48.3%) experienced a decrease in vitamin A levels and 15 subjects (51.7%) did not experience a decrease in vitamin A levels. Meanwhile, there was 1 sample who experienced an increase in tumor volume and also decreased levels of vitamin A. With statistical analysis, it was found that a significant negative correlation between tumor size and vitamin A (r = -0.475; p = 0.008), which meant that the smaller the tumor size was, the higher the level of vitamin A was in the serum (Table 3 and Figure 1).

Table 2. Effectiveness of the 3rd Neoadjuvant Chemotherapy

Characteristics	Period		P-value
	before NAC	after NAC	
Vitamin A Level			
Mean ± SD	450.03 ±167.18	478,37 ± 197,25	0.515*
Median (Min-Max)	444.5 (158 - 780)	467,5 (185 – 944)	
Tumor Volume			
Mean ± SD	94.07 ± 114.19	20.84 ± 30.57	0.000**
Median (Min-Max)	57.43 (12.31 – 581.57)	9.97 (0.39 – 132.14)	

In addition, in this study, the tumor volume before chemotherapy was 94.07 ± 114.19, after chemotherapy the tumor volume decreased to 20.84 ± 30.57. With statistical analysis, it was found that there was a change in tumor volume before and after 3 series of NAC, the tumor volume decreased significantly after chemotherapy (p = 0.000).

Table 3. The Relationship between Tumor Size and Vitamin A Levels

Characteristics	Tumor Size	Vitamin A Level	r	P-value
Mean ± SD	20.84 ± 30.57	478.37 ± 197.25		
Median (Min – Max)	9.97 (0.39 – 132.14	467.5 (185 – 944)	-0.475	0.008

Spearman Rho's, p = 0.05

DISCUSSION

The cervix is the lower third of the uterus, is cylindrical in shape, protrudes and connects to the vagina via the external orificium of uterus. Cervical cancer is a malignancy that originates from the cervix. Globally, the average age at diagnosis of cervical cancer was 53 years, ranging from 44 years to 68 years.[1,13] In this study, the average age of patients with advanced cervical cancer was approximately 54 years with a range of 35 to 81 years. The results of this study were not much different from the research which reported the average age of women with CIN III/CIS/cervical cancer was 56.7 years.[14]

The age in this study was slightly greater than the that the mean age of cervical cancer patients was 48.30 ± 9.67 years with a range of 32 to 72 years.[15] The results of this study were similar from the mean age of cervical cancer patients in Canada where the mean age of patients was 45.9 years.[16] This similarity was probably due to the younger age of cervical cancer patients who were included in this study, namely between 15 to 49 years.

Labor contributed to the risk of cervical carcinogenesis in addition to the risks associated with persistent HPV infection. Delivery might increase the risk of direct precursor lesions to cervical cancer, especially in women with persistent high-risk HPV infection.[17] Women with parities greater or equal to three had 2.4 times higher odds of developing cervical cancer.[18] In addition, high parity was associated with the risk of adenocarcinoma or adenosquamous cervical carcinoma which had increased over the past two or three decades.[18,19] In this study the most parity was multiparous. In line with the results of this study, found that the majority of cervical cancer patients were multiparous except 2% nulliparous patients and only 15% had single parity.[19] Previous research in South Sumatera concluded that multiparity (parity of 3 times or more) was associated with 4.55 times greater risk of cervical cancer. Therefore, cervical cancer screening was recommended to focus on high-risk groups, including women with more than three parity.[20]

The optimal treatment for the early stages (stages IA1, IA2, and IB1) consisted of radical surgery or chemoradiation. In advanced-stage disease (IIB-IVB), where surgery was not possible, primary therapy was generally performed with chemoradiation or in combination with chemotherapy and radiation. In this study, 3 series of neoadjuvant chemotherapy were given, the majority of the subjects received Paclitaxel-Carboplatin chemotherapy. The success of the Paclitaxel-Carboplatin combination was higher in squamous cell carcinoma because each of these agents had high cytotoxic activity as a single agent.[21]

The most histopathological type in this study was squamous cell carcinoma (83.3%). These results were in line that the most histopathological types in cervical cancer patients, namely squamous cell carcinoma (75-90%).[22] The histology results of cervical cancer patients as much as 83% was squamous cell carcinoma, 17% of patients had adenocarcinoma and adenosquamous cell carcinoma.[23]

Vitamin A or retinol was a polyisoprenoid compound containing a cyclohexinyl ring.[24] Examination of vitamin A status could be done by examining the relative dose response (RDR). With the RDR method could estimate retinol deposits in the liver and low deposits indicate a long enough deficiency.[25] Retinoic acid (RA) played a role in cancer regulation which can be either promotion or suppression. RA induced protocogene and tumor suppressor.[26-29]

The chemotherapy or chemoradiation was given because abnormal cell death will also affect normal cells, especially proliferating cells such as intestinal cells and hepatocyte cells which are very important in the absorption and metabolism of vitamin A. Thus, this will cause serum vitamin A to decrease. However, in this study, it was found that vitamin A levels after chemotherapy increased compared with before chemotherapy but it was not statistically significant. Thus, the chemotherapy given did not affect the level of vitamin A in the blood of cervical cancer patients. A significant increase in vitamin A levels in cervical cancer patients after 3 months of chemotherapy follow-up, but during and after chemotherapy the levels of vitamin A in cervical cancer patients in all stages were lower than before chemotherapy.[30]

In patients with advanced-stage cervical carcinoma who were given neoadjuvant chemotherapy (NAC) Cisplatin and Paclitaxel with additional vitamin A, after 3 cycles of chemotherapy, there was a change in tumor volume size in the neoadjuvant chemotherapy group plus vitamin A greater than the neoadjuvant chemotherapy group alone. (p = 0.04). This suggested that the addition of vitamin A also affects changes in the mass volume of cervical cancer mass.[31,32]

In this study, there was a decrease in tumor volume after 3 series of neoadjuvant chemotherapy. The change in tumor volume was 73.56 ± 24.69 with the largest change of 99.34% and the smallest was 11.53% and 1 patient experienced an increase in tumor volume by 4.59%. The results of this study were similar which showed that the tumor size decreased significantly in the neoadjuvant chemotherapy group.[33]

In this study, a significant negative correlation was found between tumor volume and vitamin A levels, from 29 subjects with decreased tumor volume by more than 50% experienced an increase in vitamin A levels. The smaller the tumor size after 3 series of neoadjuvant chemotherapy was, the higher the vitamin A levels were. However, the correlation between these two variables was only a moderate correlation possibly because only part of the sample experienced an increase in vitamin A levels. It was found that during the follow-up period after chemotherapy, serum vitamin A levels showed a significant increase. This increase in concentration might be caused by the death of tumor cells due to radiation or cessation of tumor growth by chemotherapy agents. Decreased levels of vitamins played a role in the etiology and development of cervical cancer.[30]

Retinol and vitamin A derivatives affected cell differentiation, proliferation, and apoptosis and played an important physiological roles in various biological processes. Retinoids had many important and diverse functions throughout the body including roles in the regulation of cell proliferation and differentiation, and the activation of tumor suppressor genes. Natural and synthetic retinoids had been used as potential chemotherapeutic or chemopreventive agents due to their differentiating, antiproliferative, proapoptotic, and antioxidant effects. Thus, it could be concluded that increased levels of vitamin A correlated with a decrease in tumor size which indicated the effectiveness of treatment.

There were several limitations in this study, namely the absence of a comparison group that received 3 series of neoadjuvant chemotherapy with additional vitamin A supplementation so that we could see the role of vitamin A in tumor development. In addition, checking vitamin A levels was only done before and after 3 series of chemotherapy, it would be better if vitamin A levels were checked during chemotherapy and was also followed up a few months after chemotherapy.

CONCLUSION

In this study, the average age of patients with advanced cervical cancer was approximately 54 years with 63.3% of the subjects coming from outside Palembang. The most histopathological type in this study was squamous cell carcinoma (83.3%). There was no change in vitamin A levels before and after 3 series of neoadjuvant chemotherapy, vitamin A levels increased after chemotherapy but it was not statistically significant. There was a change in tumor volume before and after 3 series of neoadjuvant chemotherapy, the tumor volume decreased significantly after chemotherapy. There was moderate negative correlation between tumor volume and vitamin A levels. The smaller the tumor size after 3 series of neoadjuvant chemotherapy, the higher the vitamin A levels were.

SUGGESTIONS

Further large-scale studies and longer study time are needed to investigate the effectiveness of 6-series of neoadjuvant chemotherapy by assessing the evaluation of clinical responses to changes in vitamin A levels in advanced stage cervical carcinoma. An analysis is needed by taking into account all the factors that affect serum vitamin A levels in order to obtain more accurate results. Additional vitamin A supplementation can be given in patients with cervical cancer to help increase the success rate and response to therapy.

REFERENCES

1. GLOBOCAN. The Global Cancer Observatory: All Cancer. 2020. https:// gco.iarc.fr/today/data/factsheets/cancers/39-all-cancers-fact-sheet.pdf.
2. GLOBOCAN. The Global Cancer Observatory: Cervix Cancer. 2020. https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf
3. GLOBOCAN. The Global Cancer Observatory : Cancer Today. Estimated number of new cases in 2020, Indonesia, both sexes, all ages. 2020. https://gco.iarc.fr/today/online-analysis-map?v=2020&mode=population&mode_population.
4. Koh W, Abu-Rustum NR, Bean S, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(1):64-84. doi:10.6004/jnccn.2019.0001

5. Hanna T P, King W D, Thibodeau S, Jalink M, Paulin G A, Harvey-Jones E et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087 doi:10.1136/bmj.m4087

6. Jhawar S, Hathout L, Elshaikh MA, Beriwal S, Small W, Mahmoud O. Adjuvant chemoradiation therapy for cervical cancer and effect of timing and duration on treatment outcome. Int J Radiat Oncol Biol Phys.2017;98:1132-41. doi:10.1016/j.ijrobp.2017.03.045

7. Chen C-P, Kung P-T, Wang Y-H, Tsai W-C. Effect of time interval from diagnosis to treatment for cervical cancer on survival: a nationwide cohort study. PLoS One. 2019;14:e0221946. doi:10.1371/journal.pone.0221946

8. Tao W, Yang J, Jiang Y, Chen W, Wang Y. Paclitaxel, Carboplatin, and Bevacizumab in Advanced Cervical Cancer: A Treatment Response and Safety Analysis. Dose-Response. 2020. doi:10.1177/1559325820941351

9. Salihi R, Leunen K, Moerman P, et al. Neoadjuvant Weekly Paclitaxel-Carboplatin Is Effective in Stage I–II Cervical Cancer. Int J Gynecol Cancer. 2017;27:1256-60.

10. Chaninya W, Nasamon W, Jira C, Yong P. Retinoic acid receptor beta promoter methylation and risk of cervical cancer. World J Virol. 2018; 7(1): 1–9.

11. Everts, H.B.; Akuailou, E.-N. Retinoids in Cutaneous Squamous Cell Carcinoma. Nutrients. 202; 13:153. https://doi.org/10.3390/ nu13010153 .

12. Hunsu,V.O,Facey,COB, Fields, JZ, Boman, BM. Retinoids as Chemo-Preventive and Molecular-Targeted Anti-Cancer Therapies. Int. J. Mol. Sci. 2021;22:7731.https:// doi.org/10.3390/ ijms22147731

13. Arbyn, M., Weiderpass, E., Bruni, L., de Sanjosé, S., Saraiya, M., Ferlay, J., & Bray, F. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *The Lancet Global Health.*2020; 8(2), e191–e203.

14. El-Moselhy, E., Salim, S., & Hagrass, S. Prevalence and Risk Factors of Cervical Intraepithelial Neoplasia and Cervical Cancer among Ever Married Adult Females in Egypt : A Survey Study. *J Comprehensive Cancer Research.*2017; 1(1): 1–15.

15. Sanif, R., & Nurwany, R. Prognostic significance of CD4/CD8 ratio in patients with advanced cervical cancer. *J Physics Conference Series.* 2019;1246(1): 0–8.

16. Cusimano, M. C., Baxter, N. N., Gien, L. T., Moineddin, R., Liu, N., Dossa, F., et al. Impact of surgical approach on oncologic outcomes in women undergoing radical hysterectomy for cervical cancer. AJOG. 2019;221(6):619.e1-619.e24. https://doi.org/https://doi.org/10.1016/j.ajog.2019.07.009

17. Baskaran, K., Kumar, P. K., Santha, K., & Sivakamasundari, I. 2019. Cofactors and their association with cancer of the uterine cervix in women infected with high-risk human papillomavirus in south India. *Asian Pacific J Cancer Prev. APJCP.* 2019; 20(11): 3415.

18. Tekalegn, Y., Sahiledengle, B., Woldeyohannes, D., Atlaw, D., Desta, F., Bekele, K., ... & Gezahegn, H. High parity is associated with increased risk of cervical cancer: Systematic review and meta-analysis of case-control studies. 2021. https://assets.researchsquare.com/files/rs-397999/v1/93bf5bfb-33ce-47e3-8f2f-2db0c8158ede.pdf?c=1631880610.

19. Rajeswari, R. An Evaluation of Risk Factors for HPV (Human Papilloma Virus) and its Association with Development of Cervical Carcinoma. Sch Int J Obstet Gynecol. 2021; 4(4): 90-4. doi: 10.36348/sijog.2021.v04i04.002

20. Agustiansyah, P., Sanif, R., & Nurmaini, S. 2021. Epidemiology and Risk Factors for Cervical Cancer. *Bioscientia Medicina. J Biomed Translational Research.* 2021; 5(7): 624-31.

21. Hacker NF. Principles of Cancer Therapy. Essentials of Obstetrics and Gynecology.6th ed. Philadelphia ; Saunders W.B. Company. 2018.

22. Teixeira, J. C., Santos, D. Z., Campos, C. S., Vale, D. B., Bragança, J. F., & Zeferino, L. C. 2021. Cervical cancer in women under 25 years of age and outside the screening age: Diagnosis profile and longçterm outcomes. *Int J Gynecol Obstet.* 2021; 154(1): 150-6.

23. Voinea, S., Herghelegiu, C. G., Sandru, A., Ioan, R. G., Bohilțea, R. E., Bacalbașa, et al. 2021. Impact of histological subtype on the response to chemoradiation in locally advanced cervical cancer and the possible role of surgery. *Experimental Therapeutic Med. 2021; 21*(1): 1-1.

24. Rosmiati H, Wardhini BP. Vitamin A. Farmakologi dan terapi. Edisi 3. FK. Universitas Indonesia.1987:657-60.

25. Sheftel, J., & Tanumihardjo, S. A. 2021. Systematic review and meta-analysis of the relative dose-response tests to assess vitamin A status. *Advances Nutr.* 2021; 12(3): 904-41.

26. Ozgun, G., Senturk, S., & Erek-Ozhan, S. 2021. Retinoic acid signaling and bladder cancer: Epigenetic deregulation, therapy and beyond. *Int J Can.* 2021; 148(10): 2364-74.

27. Wang, C., Zhao, D., Wang, K., Gao, L., He, Y., Wu, H., et al. All-Trans Retinoic Acid Rescues the Tumor Suppressive Role of RAR-β by Inhibiting LncHOXA10 Expression in Gastric Tumorigenesis. *Nutr Can.* 2021; 73(10): 2065-77.

28. Chinapayan, S. M., & Prabhakaran, P. 2019. Anticancer effects of retinoic acid in cervical cancer cells. *Jur Teknol.* 2019; 81(2).

29. Dou, Y., Huang, D., Zeng, X., Zhou, Y., Jiang, X., Yue, C., et al. All-trans retinoic acid enhances the effect of Fra-1 to inhibit cell proliferation and metabolism in cervical cancer. *Biotechnol Letters.* 2020; 42(6): 1051-60.

30. Shrivastava, A., Pradhan, S., Mishra, S. P., Asthana, A. K., Choudhary, S., Zahra, K., et al. Serum vitamin A, E and C status in cervical cancer patients undergoing Concurrent Chemo-Radiotherapy, an institutional study. *J Nutr Intermed Metabol.* 2019; 18: 100107.

31. Sanusi, R. S. 2019. Outcome of combined neoadjuvant chemotherapy and vitamin a in advanced cervical carcinoma: a randomized double-blind clinical trial. APJCP. 2019; 20(7):2213.

32. Ono, A., Koshiyama, M., Nakagawa, M., Watanabe, Y., Ikuta, E., Seki, K., et al. The preventive effect of dietary antioxidants on cervical cancer development. *Medicina.* 2020; 56(11): 604.

33. Huang, Y., Liu, L., Cai, J., Yang, L., Sun, S., Zhao, J., & Wang, Z. The efficacy and response predictors of platinum-based neoadjuvant chemotherapy in locally advanced cervical cancer. *Can Management Research.* 2020;12: 10469.