JURNAL KEPERAWATAN DAN FISIOTERAPI (JKF)
E-ISSN: 2655-0830
https://ejournal.medistra.ac.id/index.php/JKF

DNMT1 Level as Biomarker for Early Detection of Nasopharyngeal Carcinoma

Raudah Putri Syari[1*], Zulham Yamamoto[2], Farhat[3], Sry Suryani Widjaja[4], Ririe Fachrina Malisie[5]

[1]*Biomedical Science Study Program, Faculty of Medicine, Universitas Sumatera Utara, 20155, Indonesia, syahriraudahputri@gmail.com*
[2]*Department of Histology, Faculty of Medicine, Universitas Sumatera Utara, 20155, Indonesia, zulham@usu.ac.id*
[3]*Department of Ear, Nose, and Throat, Faculty of Medicine, Universitas Sumatera Utara, 20155, Indonesia, farhat@usu.ac.id*
[4]*Department of Biochemistry, Faculty of Medicine, Universitas Sumatera Utara, 20155, Indonesia, srysuryani@gmail.com*
[5]*Department of Pediatrics, Faculty of Medicine, Universitas Sumatera Utara, 20155, Indonesia, ririe.fachrina.malisie@usu.ac.id*

Abstract
Introduction: Nasopharyngeal carcinoma (NPC) is a malignant disease often diagnosed at an advanced stage. Early detection of NPC is necessary to reduce morbidity and mortality of this disease. To date, early detection methods for NPC still have limitations, especially in terms of positive predictive value. Identification of DNA methylation abnormalities has been studied for its role as a marker for early detection of NPC. Objective: This review describes the potential of DNMT1, an enzyme involved in DNA methylation, as a biomarker for early detection of NPC. Methods: We conducted a literature search using PubMed and Google Scholar databases. The keywords used were "nasopharyngeal carcinoma AND DNMT1", nasopharyngeal carcinoma AND early detection, "nasopharyngeal carcinoma AND screening", nasopharyngeal carcinoma OR DNMT1, "DNMT1 OR Carcinoma", nasopharyngeal carcinoma OR screening, and nasopharyngeal carcinoma OR early detection. Results: Increased DNMT1 expression is associated with global hypermethylation which is part of the early pathogenesis of NPC. LMP1, as an oncoprotein released by EBV, increases DNMT1 expression and activity. Conclusion: High DNMT1 expression in NPC indicates its potential as an early detection method for NPC.

***Keywords*:** *Biomarker; DNMT1; Early Detection; Methylation; Nasopharyngeal Carcinoma*

1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant disease that is found to have a high incidence in Asia, which were 100,298 (83.3%) cases out of a total of 120,434 cases worldwide. In Indonesia, NPC is ranked 6th for the highest incidence of cancer and the highest mortality due to cancer[1]. The cause of high mortality is that patients are generally treated at an advanced stage. Furthermore, clinicians also often fail to identify and diagnose NPC during the early stage[2], [3]. Early detection is important to overcome the high incidence and mortality of NPC, which allows a survival rate of more than 95%[4], [5], [6], [7]. With early detection of the disease, treatment can be carried out immediately to prevent cancer progression, better prognosis, reduce the risk of mortality, and reduce the psychological and economic burden caused by the disease[8].

Compared with other cancers, hypermethylation is more common in NPC[9]. Therefore, efforts are directed to the early detection of NPC through the detection of hypermethylation of tumor suppressor genes (TSG) in the host[10]. DNA hypermethylation causes inactivation of TSG, which supports carcinogenesis. Changes in DNA methylation patterns are associated with carcinogenesis through stimulation of cell proliferation[11], [12]. DNA methyltransferase (DNMT1) is an enzyme that plays a role in DNA methylation. Increased expression of DNMT1 results in hypermethylation involved in carcinogenesis[13]. EBV infection associated with NPC pathogenesis causes hypermethylation of various genes involved in oncogenesis through increased expression of DNMT1. The effect of hypermethylation occurs at the pre-invasive lesion stage of NPC[14]. This article is written to explain the potential of DNMT1 as a marker for early detection of nasopharyngeal carcinoma.

[*]Corresponding author: Raudah Putri Syari Universitas Sumatera Utara, Medan, Indonesia.
E-mail : syahriraudahputri@gmail.com
Doi : 10.35451/qwakjv41
Received : July 9, 2025. Accepted: October 13, 2025. Published: October 31, 2025

2. METHOD

We conducted a literature search using PubMed and Google Scholar. PubMed is a database containing articles related to medicine and medical sciences, while Google Scholar contains a wider range of articles, including those not found in PubMed. Because research on DNMT1 in cancer is still limited, these two databases were sufficient to meet the search needs for related articles. Furthermore, we did not limit the publication year. The keywords used were "nasopharyngeal carcinoma AND DNMT1," nasopharyngeal carcinoma AND early detection," "nasopharyngeal carcinoma AND screening," nasopharyngeal carcinoma OR DNMT1, "DNMT1 OR Carcinoma," nasopharyngeal carcinoma OR screening, and nasopharyngeal carcinoma OR early detection. Original articles, literature reviews, meta-analyses, or systematic reviews in English were included. We selected a total of 11 articles discussing DNMT1 expression in NPC or other types of cancer.

3. RESULTS

DNA Methyltransferase1 (DNMT1) and Nasopharyngeal Carcinoma

The DNA methyltransferase (DNMT1) gene is located on chromosome 19 with a total protein-coding area of 4851 bp. DNMT1 plays a role in DNA methylation and maintaining genome integrity. DNMT1 ensures that specific methylation patterns in parental DNA are also passed on to offspring DNA during the replication process. In addition to its role in the methylation process, DNMT1 also affects gene expression through its involvement in the cell cycle, DNA damage repair, and stem cell function. Disruption of DNMT1 affects changes in gene expression by DNA methylation. Subsequently, it is related to the disruption of gene expression suppression, chromosome inactivation, and genome stability. Maintaining optimal DNMT1 levels is important for normal growth and health[15], [16], [17].

Abnormalities of DNMT1 are associated with tumor formation. For example, DNMT1 deletion is associated with lymphoma and breast cancer. In addition, DNMT1 overexpression is found in leukemia, breast cancer, colon cancer, liver cancer, melanoma, pancreatic cancer, esophageal cancer, lung cancer, thyroid cancer, gastric cancer, and pituitary adenoma[16], [17]. A study using NPC cell lines showed DNMT1 expression in 31 of 32 samples[18]. DNMT1 overexpression causes increased DNA methylation[19]. DNA methylation can cause changes in gene expression that trigger cancer formation, such as increased genome instability, decreased expression of tumor suppressor genes, and increased expression of oncogenes. Studies in lung cancer have found that DNMT1 overexpression disrupts p53/Sp1 pathway regulation and hypermethylation of tumor suppressor genes such as p16 and RASSF1A, which are associated with poor prognosis[16]. In NPC, DNMT1 expression is found to be associated with invasion and metastasis. These findings point to targeted epigenetic therapy in NPC[19].

In NPC, EBV infection is an epigenetic trigger for cancer development. EBV causes changes in the regulation of epigenetic mechanisms in host cells by affecting DNMT1. LMP1 associated with EBV is an oncoprotein that can cause increased expression and activity of the DNMT1 enzyme[20]. LMP-1 causes activation of the JNK signaling pathway, resulting in phosphorylation of the transcription factor c-jun. The AP-1 complex containing phosphorylated c-jun binds and activates the DNMT1 promoter[18], [21]. Furthermore, methylation changes occur in both viral and cellular genes, especially in tumor suppressor genes. Increased DNMT1 expression is associated with global hypermethylation in NPC[22], [23], [24]. Tumor suppressor genes such as RASSF1A are frequently methylated in primary NPC tissues. Methylation leading to p16 inactivation is also the most frequent and earliest epigenetic event in cancer development[11]. Genetic and epigenetic abnormalities complement each other in cancer initiation and progression, especially in the early stages of NPC development. DNA methylation abnormalities have also been found in gastric carcinoma associated with EBV infection[25].

DNMT1 Expression as A Biomarker and for Early Detection of Cancer

Early detection of cancer has led to the analysis of epigenetic abnormalities, such as DNA methylation. This is because DNA methylation changes are found in precancerous lesions and are proposed to be triggered by inflammation, smoking, or viral infections. The gene expression abnormalities that occur can continue and are associated with cancer[25]. A study comparing cancers from 5 different organs, namely the lung, stomach, kidney, breast, and liver, showed that there was the same pattern of DNA methylation changes between the five organs.

The result raised the suspicion that the same carcinogenesis process occurs in all organs and that this process is DNA methylation that occurs in the early stages of carcinogenesis. In addition, the same DNA hypermethylation that occurs in many of these organs occurs in genes that play a role in cell development and/or differentiation[26]. DNA methylation changes mediated by DNMT1 activity during tumor development and abnormal DNMT1 activity that precedes symptoms of malignancy make it possible for DNMT1 level tests to be used for early detection and diagnosis of cancer[27].

The role of DNMT1 as a cancer biomarker for early detection is explained in several studies that have been conducted on several cancer cases. A study by Yoshimasa Saito et al. found that DNMT1 mRNA levels were higher in chronic hepatitis or cirrhosis tissue compared to normal liver tissue but lower when compared to hepatocellular carcinoma. DNMT1 overexpression was also found to be significantly associated with the accumulation of DNA hypermethylation in CpG islands and the clinicopathology of HCC. The same results were also found in cases of gastric carcinoma. In addition, DNMT1 mRNA expression also increased in non-cancerous urothelium from urothelial cancer patients. This shows the relationship between DNMT1 overexpression and pre-cancerous conditions. Increased DNMT1 expression in various organs causes the accumulation of abnormalities in DNA methylation, for example, the accumulation of DNA hypermethylation in tumor suppressor genes such as p16. In addition to causing changes in DNA methylation, DNMT1 also works to maintain the changes that occur. Because it appears at the precancerous level, DNA methylation profiles can be used as a risk marker for carcinogenesis[25], [28], [29], [30], [31].

DNMT1 as a biomarker can be in the form of mRNA expression, protein, or analysis of DNMT1 activity. There have been studies to examine DNMT1 mRNA and protein levels in cancer. Detection of mRNA using quantitative reverse transcriptase-PCR is found to be more sensitive so that it can be detected in pre-cancerous conditions. This is different from protein detection using the immunohistochemical method, which can be detected if it is already in a malignant condition[29]. Several methods used for DNMT1 activity analysis are isotope labeling, electrochemical test, calorimetry, chemiluminescence methods, and fluorescence testing. Fluorescence testing is a simpler method, can be combined with other methods, is easy to operate, and is not easily influenced. The test has the potential to analyze DNMT1 activity so it can be considered for clinical diagnosis related to DNMT1[27].

4. DISCUSSION

Common methods for early detection of NPC are anti-EBV serology tests, plasma EBV DNA levels, and nasopharyngeal cytology examination. Several of these methods were found to have high sensitivity and specificity, but with low positive predictive value[8]. Liu et al. in their study found that several anti-EBV serological markers, namely VCA-IgA, EA-IgA, EBNA1-IgA, EBNA1-IgG, Zta-IgA, and Rta-IgG, the combination of VCA-IgA and EBNA1-IgA was the method with the best sensitivity and specificity, but with a positive predictive value of 4% [32]. Plasma EBV DNA test was found to have high sensitivity and specificity, as well as a higher positive predictive value than serology test. Chan et al.'s study found that the sensitivity and specificity of plasma EBV DNA for NPC screening were 97.1% and 98.6%, respectively, and the PPV value was 10%[33]. Studies have shown that a dominant hypermethylation pattern is a typical characteristic of NPC. However, studies related to epigenetics, including biomarkers associated with DNA methylation in NPC, are still few. Published studies are generally related to genes that experience DNA methylation in NPC [22], [23], [24], [34]. Methylation identification of genes that play a role in NPC from both cell-free DNA and nasopharyngeal swabs showed fairly good sensitivity and specificity values but required a combination with EBV biomarker tests to increase the specificity value. Moreover, the PPV value of this test was quite satisfactory. This is a consideration that the combination of EBV biomarker tests and DNA methylation analysis can be a better screening option for NPC[8], [11], [35].

Research related to DNMT1 expression in NPC is still at the cellular and histopathological tissue levels. A study by Tsai et al. found that there were 31 of 32 histopathological tissues of NPC with methylation expression High DNMT1. This study also found that in adjacent non-tumor tissues that were negative for EBV and LMP1, there was little or no DNMT1 expression. This indicates that DNMT1 expression is closely related to EBV and clearly distinguishes tumors from non-tumors. The DNMT1 level test may be applicable in areas with a high incidence of NPC (endemic areas) because of its close relationship with EBV infection[18], [36].

5. CONCLUSION

Biomarkers for early detection of NPC to date are generally centered on biomarkers of EBV infection. Although it has good sensitivity and specificity, the performance of the methods is still lacking due to the low positive predictive value. The high hypermethylation pattern in NPC, compared to other cancers, directs the study of DNA methylation for early detection of NPC and also to the methylation of genes involved in NPC. As is known, EBV infection induces DNMT1 expression, which is related to global hypermethylation, and DNMT1 regulation in NPC affects a large set of genes. It is interesting to analyze whether high DNMT1 expression in NPC is associated with all gene methylation ever found in NPC and, thus, whether DNMT1 level can be used as an early detection method for NPC.

REFERENCES

[1] Ferlay J *et al.*, "Global Cancer Observatory: Cancer Today," *Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed [6 2 2024]*. Jan. 2024.

[2] A. Balasubramanian and N. Mat Lazim, "Nasopharyngeal carcinoma screening and prevention programs," in *An Evidence-Based Approach to the Management of Nasopharyngeal Cancer: From Basic Science to Clinical Presentation and Treatment*, 2020. doi: 10.1016/B978-0-12-814403-9.00012-4.

[3] E. Waliyanti, F. S. T. Dewi, S. Supriyati, and R. Fles, "Treatment-seeking behaviour of nasopharyngeal cancer patients in Yogyakarta, Indonesia," *Pan African Medical Journal*, vol. 29, 2018, doi: 10.11604/pamj.2018.29.98.12817.

[4] R. W. Januarti, "Pendekatan deteksi dini non invasif karsinoma nasofaring," *Wellness And Healthy Magazine*, vol. 2, no. 1, 2020, doi: 10.30604/well.57212020.

[5] K. M. O. Kumar and R. B. S. M. N. Mydin, "Nasopharyngeal cancer: Geographic variation and risk factors," *Malaysian Journal of Medicine and Health Sciences*, vol. 15, 2019.

[6] S. M. Sekarutami, S. Gondhowiardjo, R. Yuliasti, L. Syarifah, and M. Adham, "Survival of nasopharyngeal cancer in national referral hospital of Indonesia: A study on radiotherapy patients," *Oral Oncol*, vol. 106, 2020, doi: 10.1016/j.oraloncology.2020.104707.

[7] J. K. Tay *et al.*, "A comparison of EBV serology and serum cell-free DNA as screening tools for nasopharyngeal cancer: Results of the Singapore NPC screening cohort," *Int J Cancer*, vol. 146, no. 10, 2020, doi: 10.1002/ijc.32774.

[8] Y. Yuan, F. Ye, J. H. Wu, X. Y. Fu, Z. X. Huang, and T. Zhang, "Early screening of nasopharyngeal carcinoma," 2023. doi: 10.1002/hed.27466.

[9] W. Dai, H. Zheng, A. K. L. Cheung, and M. L. Lung, "Genetic and epigenetic landscape of nasopharyngeal carcinoma," 2016. doi: 10.21037/cco.2016.03.06.

[10] R. Tan *et al.*, "Clinical utility of Epstein-Barr virus DNA and other liquid biopsy markers in nasopharyngeal carcinoma," 2020. doi: 10.1002/cac2.12100.

[11] L. Li, J. Xie, B. Ma, A. T. C. Chan, and Q. Tao, "CpG methylation as epigenetic biomarkers for nasopharyngeal carcinoma diagnostics," *Annals of Nasopharynx Cancer*, vol. 6, 2022, doi: 10.21037/anpc-21-9.

[12] A. Nishiyama and M. Nakanishi, "Navigating the DNA methylation landscape of cancer," 2021. doi: 10.1016/j.tig.2021.05.002.

[13] T. Ma, H. Li, M. Sun, Y. Yuan, and L. P. Sun, "DNMT1 overexpression predicting gastric carcinogenesis, subsequent progression and prognosis: A meta and bioinformatic analysis," *Oncotarget*, vol. 8, no. 56, 2017, doi: 10.18632/oncotarget.21480.

[14] C. M. Tsang, V. W. Y. Lui, J. P. Bruce, T. J. Pugh, and K. W. Lo, "Translational genomics of nasopharyngeal cancer," 2020. doi: 10.1016/j.semcancer.2019.09.006.

[15] S. Dhe-Paganon, F. Syeda, and L. Park, "DNA methyl transferase 1: Regulatory mechanisms and implications in health and disease," 2011.

[16] J. Zhang, C. Yang, C. Wu, W. Cui, and L. Wang, "DNA methyltransferases in cancer: Biology, paradox, aberrations, and targeted therapy," 2020. doi: 10.3390/cancers12082123.

[17] W. Zhang and J. Xu, "DNA methyltransferases and their roles in tumorigenesis," 2017. doi: 10.1186/s40364-017-0081-z.

[18] C. L. Tsai *et al.*, "Activation of DNA methyltransferase 1 by EBV LMP1 involves c-Jun NH 2-terminal kinase signaling," *Cancer Res*, vol. 66, no. 24, 2006, doi: 10.1158/0008-5472.CAN-06-2194.

[19] Z. W. Lu *et al.*, "MiR-152 functioning as a tumor suppressor that interacts with DNMT1 in nasopharyngeal carcinoma," *Onco Targets Ther*, vol. 11, 2018, doi: 10.2147/OTT.S154464.

[20] M. Ahmadi Hedayati, A. Ahmadi, and Z. Khatooni, "DNMT1 Gene Expression in Patients with Helicobacter pylori Infection," *Scientific World Journal*, vol. 2022, 2022, doi: 10.1155/2022/2386891.

[21] C. N. Tsai, C. L. Tsai, K. P. Tse, H. Y. Chang, and Y. S. Chang, "The Epstein-Barr virus oncogene product,

latent membrane protein 1, induces the down-regulation of E-cadherin gene expression via activation of DNA methyltransferases," *Proc Natl Acad Sci U S A*, vol. 99, no. 15, 2002, doi: 10.1073/pnas.152059399.

[22] L. Ka-Yue Chow *et al.*, "Epigenomic landscape study reveals molecular subtypes and EBV-associated regulatory epigenome reprogramming in nasopharyngeal carcinoma," *EBioMedicine*, vol. 86, 2022, doi: 10.1016/j.ebiom.2022.104357.

[23] D. H. Heiland *et al.*, "C-Jun-N-terminal phosphorylation regulates DNMT1 expression and genome wide methylation in gliomas," *Oncotarget*, vol. 8, no. 4, 2017, doi: 10.18632/oncotarget.14330.

[24] Y. Jiang *et al.*, "Multi-omic analyses reveal aberrant DNA methylation patterns and the associated biomarkers of nasopharyngeal carcinoma and its cancer stem cells," *Sci Rep*, vol. 15, no. 1, p. 9733, Mar. 2025, doi: 10.1038/s41598-025-87038-z.

[25] Y. Kanai, "Molecular pathological approach to cancer epigenomics and its clinical application," 2024. doi: 10.1111/pin.13418.

[26] K. Ohara *et al.*, "Genes involved in development and differentiation are commonly methylated in cancers derived from multiple organs: A single-institutional methylome analysis using 1007 tissue specimens," *Carcinogenesis*, vol. 38, no. 3, 2017, doi: 10.1093/carcin/bgw209.

[27] L. Song *et al.*, "A high sensitivity strategy of DNMT1 activity detection based on self-assembled nucleic acid probe signal amplification technique," *Sens Actuators B Chem*, vol. 385, 2023, doi: 10.1016/j.snb.2023.133610.

[28] Y. Saito, Y. Kanai, M. Sakamoto, H. Saito, H. Ishii, and S. Hirohashi, "Expression of mRNA for DNA methyltransferases and methyl-CpG-binding proteins and DNA methylation status on CpG islands and pericentromeric satellite regions during human hepatocarcinogenesis," *Hepatology*, vol. 33, no. 3, 2001, doi: 10.1053/jhep.2001.22507.

[29] T. Etoh *et al.*, "Increased DNA Methyltransferase 1 (DNMT1) Protein Expression Correlates Significantly with Poorer Tumor Differentiation and Frequent DNA Hypermethylation of Multiple CpG Islands in Gastric Cancers," *American Journal of Pathology*, vol. 164, no. 2, 2004, doi: 10.1016/S0002-9440(10)63156-2.

[30] T. Nakagawa, Y. Kanai, Y. Saito, T. Kitamura, T. Kakizoe, and S. Hirohashi, "Increased DNA methyltransferase 1 protein expression in human transitional cell carcinoma of the bladder," *Journal of Urology*, vol. 170, no. 6 I, 2003, doi: 10.1097/01.ju.0000095919.50869.c9.

[31] T. Nakagawa, Y. Kanai, S. Ushijima, T. Kitamura, T. Kakizoe, and S. Hirohashi, "DNA hypermethylation on multiple CpG islands associated with increased DNA methyltransferase DNMT1 protein expression during multistage urothelial carcinogenesis," *Journal of Urology*, vol. 173, no. 5, 2005, doi: 10.1097/01.ju.0000154632.11824.4d.

[32] Y. Liu *et al.*, "Establishment of VCA and EBNA1 IgA-based combination by enzyme-linked immunosorbent assay as preferred screening method for nasopharyngeal carcinoma: A two-stage design with a preliminary performance study and a mass screening in southern China," *Int J Cancer*, vol. 131, no. 2, 2012, doi: 10.1002/ijc.26380.

[33] K. C. A. Chan *et al.*, "Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer," *New England Journal of Medicine*, vol. 377, no. 6, 2017, doi: 10.1056/nejmoa1701717.

[34] W. Jiang, R. Cai, and Q. Q. Chen, "DNA methylation biomarkers for nasopharyngeal carcinoma: Diagnostic and prognostic tools," 2016. doi: 10.7314/APJCP.2015.16.18.8059.

[35] T. Qian, Z. Zhou, Q. Zhang, Y. L. Liou, and H. Zhou, "SEPT9, H4C6, and RASSF1A methylation in nasopharyngeal swabs: A reflection of potential minimally invasive biomarkers for early screening of nasopharyngeal cancer," *Medicine (United States)*, vol. 102, no. 50, 2023, doi: 10.1097/MD.0000000000036583.

[36] Z. Y. Su, P. Y. Siak, C. O. Leong, and S. C. Cheah, "The role of Epstein–Barr virus in nasopharyngeal carcinoma," 2023.