

Exercise as a method to reduce the risk of oral cancer: A narrative review

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ABSTRACT

Background: Cancer is a major cause of death worldwide. One of the most common forms of cancer is oral cancer, which can occur due to exposure to carcinogenic factors, such as tobacco cigarettes, alcohol, betel-nut chewing, ultraviolet rays or human papillomavirus infection. Physical exercise is known to have many benefits and can contribute to reducing the risk of cancer, minimising the side-effects of treatment and increasing the curative effect of cancer treatment. **Purpose:** This study aimed to explain the role of exercise as a method to reduce oral cancer risk. **Reviews:** Studies examining the impact of exercise on reducing oral cancer risk are currently limited due to a lack of research on this subject. However, according to several laboratory experimental research studies on *Mus musculus* test subjects, moderate-intensity exercise contributes to suppressing the proliferation and development of oral squamous epithelial cells, which can subsequently become cancer cells. Exercise can also increase intracellular proteins that can induce apoptosis in cells (e.g. wild protein p53, the ratio of Bax/Bcl-2, and caspase-3), and can also decrease p53 mutant expression and transformed cells that can trigger cancer. Exercise must be optimally performed to prevent or control cancer symptoms, although the exact duration and intensity of exercise required to reduce cancer risk in humans have not been established. **Conclusion:** Exercise plays a role in reducing oral cancer risk by inducing apoptosis and preventing the development of transformed cells that can lead to developing cancer.

Keywords: apoptosis; exercise; oral cancer; oral squamous cell carcinoma; physical activity; moderate-intensity exercise; transform cells; wild p53

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INTRODUCTION

Cancer is a major cause of death worldwide. According to the Global Cancer Observatory, 19.3 million new cases of cancer and roughly 10 million deaths are estimated to have occurred worldwide in 2020.¹ In 2018, Riset Kesehatan Dasar reported that Indonesia had a cancer prevalence of 1.79 per 1000 people, an increase compared with 2013 at 1.4 per 1000 people. As a result, Indonesia has risen to the eighth position in the list of countries in Southeast Asia with the most cancer cases.²

Head and neck cancer cases include approximately 60%–70% of cases occurring in the oral cavity and larynx.³ In 2020, oral and lip cancers included 377,713 new cases and 177,757 deaths.¹ In Indonesia, the five-year prevalence

for oral and lip cancer cases is 5.19 per 100,000 population.⁴ Squamous cell carcinoma accounts for more than 90 malignancies that occur in the oral cavity.⁵

Most malignancies arise from a complex and multifactorial aetiology that includes genetic, environmental and lifestyle factors, as well as the interconnections between them.⁶ The excessive use of tobacco, alcohol and betel nut chewing are among the primary causes of oral cancer.⁷ If the body's cells are exposed to these substances, cell mutations will occur. The mutated cells will grow abnormally and develop uncontrollably, forming tumours and giving rise to cancer.

Many studies have discussed exercise as an effective treatment and rehabilitation option for oral cancer. In addition to the various existing medical treatments,

discussing prevention measures is also essential. Ample evidence suggests that exercise provides many health benefits; hence, exercise is a common method that is used in health promotion settings because it is not cost-prohibitive and is safe and feasible.⁸

Exercise has been proven to improve both physical and mental health. In addition to improving cardiovascular function and supporting weight loss, as well as strengthening skeletal muscles, regular exercise also inhibits the formation of transformed cells commonly found in the presence of cancer.⁹ Transformed cells are normal cells that undergo behavioural changes due to DNA mutations; as a result, these transformed cells cannot die and proliferate abnormally, subsequently forming tumour tissue.^{10,11} Exercise has been found to lower the risk of breast, colorectal, endometrial, bladder, oesophageal, and kidney cancers. Moderate evidence is associated with lung cancer risk, with relative risk rates decreasing by 10%–20%. Due to a lack of research on head and neck malignancies, the evidence supporting a reduced risk of cancer remains limited.⁶ This paper aims to explain the role of exercise as a method for reducing oral cancer risk.

Oral Cancer

Oral cancer is a malignancy that occurs in the lips, oral cavity, tongue, gingiva, oropharynx, hypopharynx and other oral mucosa but does not include the nasopharynx or the major salivary glands.¹² Men are much more likely than women to develop oral cancer, as represented by a 5.5–2.5 ratio for every 10,000 people worldwide in 2020.¹³ The incidence of oral cancer increases with age. According to the American Cancer Society (2021), the average age of patients diagnosed with oral cancer is 63. However, this type of cancer can also develop among young people, with 1 in 5 cases (20%) occurring in patients younger than 55.¹⁴

Oral cancer is a disease with multifactorial causes. Some of the risk factors for oral cancer include smoking, consuming alcohol, viral infections, e.g. the human papillomavirus or hepatitis B, betel-nut chewing, ultraviolet radiation, the presence of pre-cancerous lesions, including leukoplakia, erythroplakia and lichen planus,

immunosuppressed conditions, and a genetic predisposition. Tobacco cigarettes contain benzopyrene and nitrosamines, which are carcinogenic and result in DNA mutations when exposed to human cells.^{13,15,16}

Oral cancer, also known as oral squamous cell carcinoma (OSCC), is a malignant tumour that develops on the lips and oral cavity. OSCC cancers, which target the epithelial cells of the oral cavity and oropharynx, contribute to 90% of all oral cancers.¹⁷ In the early stages, OSCC often presents as very small, painless or asymptomatic. Pain is a typical symptom in people with oral cancer; however, it generally develops only when the tumour has grown to a significant size. Notably, in slower-growing and more widespread lesions on the tongue, symptoms may range from slight discomfort to a severe ache. Ear discomfort, bleeding, tooth movement, difficulty breathing, dysphagia, trismus and numbness are other symptoms.

The clinical features of OSCC vary. In the early stages, lesions are typically leukoplakia, erythroplakia or erythroleukoplakia. Lesions present as slightly rough and coarsely circumscribed, defined red or red and white areas. In advanced OSCC lesions, lesions may be ulcerated, nodular (exophytic) or fixed to the underlying tissue (endophytic) (Figure 1).¹⁸ The ulcer form is the most common type of OSCC.^{17,19,20}

Oral cancer can impact the patient's quality of life by affecting their physical, mental and economic well-being. Oral cancer patients may experience speech and swallowing dysfunction, facial and vocal changes, sensory disturbances, and prolonged pain, leading to poor mental health.²¹

Tumour suppressor gene p53

The p53 gene is a tumour suppressor gene. Cell-cycle arrest, cell ageing and DNA repair are all controlled by the p53 gene. Deoxyribonucleic acid damage will activate ataxia-telangiectasia mutated, which phosphorylates and releases p53 from mouse double minute 2 homolog (MDM2) binding, causing the amount of p53 proteins to increase. Increased p53 proteins will activate the p21 gene, which works as a cyclin-dependent kinase inhibitor to stop the cell cycle in damaged cells. After cell cycle arrest, damaged



Figure 1. An exophytic form with a central depression and widespread keratosis on the left lateral side of the tongue characterises a well-differentiated squamous cell carcinoma lesion.¹⁸

cells can be repaired.^{22,23} If DNA damage is extensive and irreversible, p53 can initiate apoptosis. Additionally, p53 stimulates cytochrome-c from mitochondria by activating apoptotic genes, e.g. Bax, and by inhibiting anti-apoptotic genes, such as Bcl-2. Cytochrome-c triggers caspases, which subsequently activate deoxyribonuclease (DNase), an enzyme which penetrates the cell nuclear membrane and damages DNA, causing cell death.^{22,24} Therefore, cells with mutations in the p53 gene can turn into cancerous cells.

A mutated p53 gene is associated with 50% of cancer cases.²⁵ One study noted that the expression of the p53 gene increased in 63% of OSCC cases.²⁶ The altered p53 gene, also known as mutant p53, caused a reduction or loss of wild p53 gene activity, resulting in the build-up of DNA damage and the cell's inability to repair DNA and undergo apoptosis.²⁷

Apoptosis

Apoptosis is a form of programmed cell death that aims to preserve a balance between living and dead cells, both physiologically and pathologically. Apoptosis can be triggered by DNA damage, uncontrolled cell proliferation, stressful or toxic conditions, and several diseases.²⁸ Where cancer is present, cell division and death are out of balance. Because the p53 gene is downregulated or inactivated, cells that should undergo apoptosis do not receive an apoptotic signal. The cells cannot experience death, and the growth and development of the cells lead to increased tumours.²⁴ Pro-apoptotic and antiapoptotic genes influence the incidence of apoptosis. Pro-apoptotic genes stimulate the release of mitochondrial-derived cytochrome-c enzymes (e.g. Bax and Bak). Antiapoptotic genes, on the other hand, act to prevent the release of cytochrome-c enzymes (e.g. Bcl-2).²⁹

There are several pathways for initiating apoptosis (Figure 2). When a cell recognises harm from within via various intracellular signals, known as the intrinsic pathway, apoptosis can be triggered. In contrast, apoptosis can occur from interactions with immune system cells or other damaged cells, known as the extrinsic pathway.³⁰ The two pathways can meet to activate caspases. There are two groups of caspases, i.e. initiators and executors. If cell damage is detected, and apoptosis is stimulated, initiator caspases (caspases 8 and 9) will be activated by procaspases. Initiator caspases will then activate the executor caspases (caspases 3 and 6). The disintegration of DNA, the destruction of the cell nucleus and the cytoskeleton, protein cross-linking, the production of ligands for phagocytic immune cells and the development of apoptotic bodies, which are eventually phagocytised by macrophages, are all caused by the activation of the executor caspase.^{24,29,31}

Exercise

Exercise is a structured, systematic and persistent physical activity that is engaged in to improve or maintain physical fitness. Exercise should consider the co-called FITT principles, i.e. frequency, intensity, time and type. The frequency is the number of times exercise is completed within a certain period. Intensity is the degree to which the exercise or physical activity is completed. The intensity is determined according to the heart rate (HR) percentage, i.e. the maximum oxygen volume (VO₂max) and the maximum work capacity (MC) of the muscles. Based on HR, VO₂max, and MC, exercise intensity is classified as mild (0%–50%), moderate (50%–70%), submaximal (70%–85%) and maximal (above 85%).³² The time aspect refers to the duration of the exercise. There are

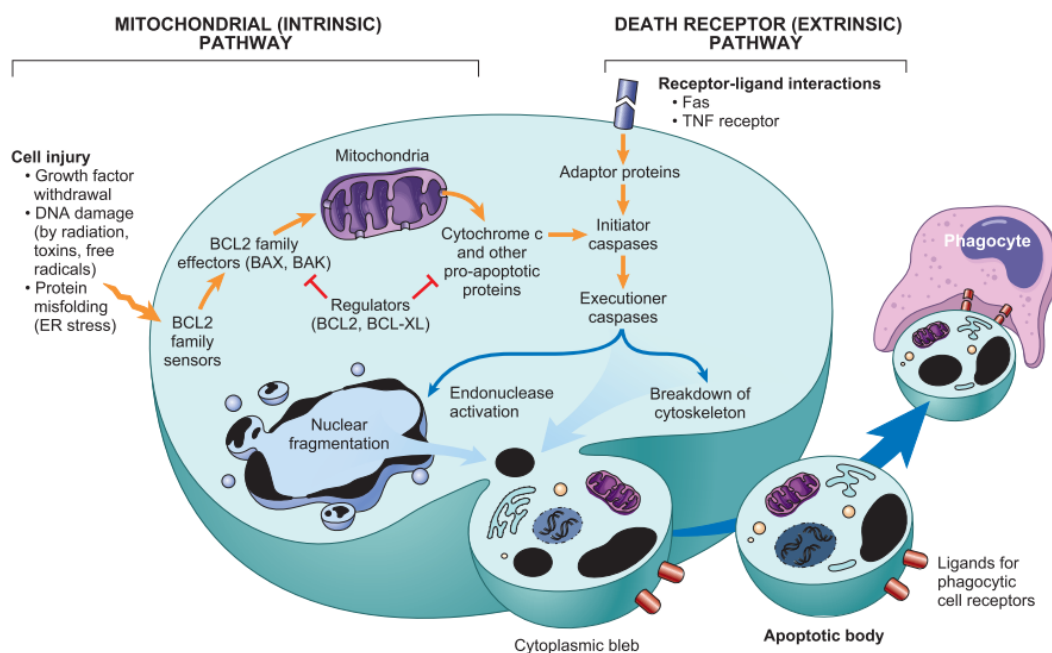


Figure 2. The apoptotic mechanism. Two pathways can initiate apoptosis, i.e. the intrinsic and extrinsic pathways.²⁸

two types of exercise times, i.e. continuous and interval times. Continuous time refers to a period longer than 30 minutes, with mild to moderate intensity, and the interval is performed alternately between activity and rest, with submaximal and maximum intensity. Type refers to the type of exercise that is performed, such as walking, jogging, cycling, swimming and aerobics.^{32,33}

Exercise is divided into aerobic and anaerobic types, based on the amount of oxygen consumption or the dominant energy system used. Aerobic exercise is a type of continuous, mild-to-moderate-intensity exercise, such as walking, jogging, running, swimming and cycling. Conversely, anaerobic exercise is a form of high-intensity exercise that requires energy quickly within a short time and cannot be done continuously for an extended period.³⁴

Regular exercise can help to relieve stress, anxiety and depression, as well as lower blood pressure and the risks of cardiovascular disease, stroke, certain malignancies and diabetes.³⁵ Many studies have underscored the role of exercise in lowering the risk of various malignancies. Exercise has been shown to lower the risk of cancer in the breast, colon, endometrium, and urinary bladder, as well as adenocarcinoma in the oesophagus and kidney.⁶ Exercise activities can open Ca^{2+} channels in cell membranes, then activate mitogen-activated protein kinase (MAPK), which can enter the cell nucleus and act as transcription factors, one of which is wild p53. Increased wild p53 expression activates Bax messenger ribonucleic acid (mRNA) transcription, allowing Bax protein production as a pro-apoptosis factor for increasing and triggering apoptosis in cells.^{32,36,37}

DISCUSSION

Exercise is a physical activity that has been shown to widely affect the quality of life and physical health of people. Programmed exercise can be used as a cancer prevention method, to improve physical fitness and prevent several chronic diseases.³⁸ Exercise helps lower the risk of cancer, reduces treatment-related adverse effects and can improve cancer treatment's curative impact. According to Hojman et al., several systemic factors, such as sympathetic stimulation, increased blood flow, tissue stress and elevated body temperature are experienced during exercise, which can put direct pressure on tumour homeostasis and metabolism.³⁹ By decreasing cancer cell growth, signalling apoptosis, controlling cancer metabolism and modulating immunological conditions, exercise provides benefits for preventing cancer. When followed by long-term exercise, the acute effects on the body during exercise cause adaptations in intratumoral tissue, i.e. increased blood perfusion, immunity and metabolic adjustments that slow tumour progression.³⁹ Exercise has many benefits for people with cancer, such as an improved quality of life, an increased chance of recovering from disease and improved

physical abilities.⁴⁰ However, due to a lack of research on this issue, studies concerning the benefits of exercise for lowering oral cancer risk is currently limited.

Exercise can induce apoptosis in cancer cells because of the increased mobilisation of natural killer cells towards tumour tissue. Natural killer cells are immune cells that are particularly sensitive to exercise and play a role in destroying infected cells or cells that have been converted into cancer cells.^{41,42}

Several studies have discussed the effect of exercise in preventing the transformation of cells in the mucosal cells in the mouth, i.e. squamous epithelial cells. In *Mus musculus* test subjects, moderate-intensity exercise (swimming) significantly increased the ratio of Bax/Bcl-2 ($n = 6$, $p = 0.00$) and caspase-3 expression ($n = 18$, $p = 0.00$) in oral squamous epithelial cells that had been injected with benzopyrene, a carcinogenic substance commonly found in cigarettes.^{43,44} The Bax/Bcl-2 ratio, as well as caspase-3, are components in cells that, when their expression increases, receive a signal to perform apoptosis.

Exercise can open Ca^{2+} channels in cell membranes, thus increasing Ca^{2+} concentration. Increased intracellular Ca^{2+} activates signal transduction Ras-GAP (GTPase activating protein) and Src, thus activating MAPK. Activated MAPK will enter the cell nucleus and initiate the wild p53.^{36,37,45} Wild p53 expression will activate BAX mRNA transcription to increase the BAX expression (Bax/Bcl-2 increases). The permeability of the outer mitochondrial membrane increases when Bax/Bcl-2 levels rise. This causes the release of cytochrome-c, Smac/Diablo, an apoptotic-inducing factor, and HtrA2/Omi, a group of pro-apoptotic proteins from the mitochondria into the cytoplasm. These released proteins will activate caspase-9, thus conforming to the apoptotic pathway and activating caspase-3, which will act as an executor for inducing cells to undergo apoptosis.^{24,31,46}

Another study stated that moderate-intensity exercise could significantly increase the expression of wild p53 ($n = 18$, $p = 0.611$), decrease the expression of the p53 mutant ($n = 18$, $p = 0.00$) and reduce the number of transformed cells ($n = 18$, $p = 0.0874$) in the oral squamous epithelial cells of *Mus musculus* test subjects that had been injected with benzopyrene.^{11,47,48} The p53 mutant is a p53 gene that undergoes mutation; the p53 mutant is capable of causing the loss of function of the wild p53 gene. The absence of the wild p53 gene due to mutant p53 causes genetic instability and stops the apoptotic process from occurring.⁴⁹ If the apoptotic process cannot be activated, cells that have been mutated due to exposure to carcinogenic agents continue to proliferate. The mutated cells will pass on the genetic trait to the successor cell. Transformed cells are normal cells that undergo behavioural changes caused by the transcription of an oncogene. Normal cells that transform into cancer cells result from a disrupted cell cycle or regulatory system, causing cancer cells to multiply uncontrollably.^{11,48} According to the present studies, moderate-intensity exercise inhibits the development of

oral squamous epithelial cells that have the potential to become cancer cells.

Exercise appears to have a role in lowering oral cancer risk, according to the studies described above. Oral cancer risk can be considerably reduced by moderate-intensity exercise, which can potentially cause apoptosis by elevating pro-apoptotic expressions, such as the ratio of Bax/Bcl-2 and caspase-3. In addition, moderate-intensity exercise is beneficial for inhibiting the development of transformed cells that can turn into cancer.

The duration, type and intensity of exercise are essential for cancer prevention. The exact duration and intensity of exercise required to reduce oral cancer risk in humans have not been established. However, experts recommend that to prevent the occurrence of cancer, at least 150–300 minutes of moderate-intensity exercise per week, or the equivalent of 75–150 minutes of vigorous-intensity exercise should be completed; exceeding more than 300 minutes of vigorous-intensity exercise per week is not recommended.⁵⁰

In conclusion, exercise can help to reduce the risk of cancer, treatment-related adverse effects and improve the cancer treatment's curative impact. However, research on exercise's efficacy in reducing the risk of oral cancer remains limited due to a lack of research on the subject. Although many studies have shown the effect of moderate-intensity exercise in inhibiting the development of cells that can lead to cancer and induce apoptosis in *Mus musculus* study subjects, no research has indicated that exercise reduces the incidence of oral cancer in humans. In addition, further research must be conducted regarding the exact amount of exercise required to prevent oral cancer in humans specifically.

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