Oncogenes and their Role in Oral Oncogenesis - A Survey

P. Kalyani\textsuperscript{1}, Dhanraj Ganapathy\textsuperscript{2}\textsuperscript{*}, Revathi Duraiswamy\textsuperscript{2} and M. P. Santhosh Kumar\textsuperscript{3}

\textsuperscript{1}Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-600077, India.
\textsuperscript{2}Department of Prosthodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-600077, India.
\textsuperscript{3}Department of Oral Surgery, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-600077, India.

Authors' contributions

This work was carried out in collaboration among all authors. Authors PK, DG and RD performed the search, interpretation and wrote the manuscript. Author MPSK contributed to analysis and critically revised the manuscript. All authors read and approved the final manuscript.

ABSTRACT

Background: Oral squamous cell carcinoma [OSCC] is the most common malignancy of the oral cavity. The etiological agents for OSCC are tobacco, betel quid, smoking, and alcohol. Oral cancer also has a genetic basis that is mediated by oncogenes.

Aim: The aim of the survey was to evaluate the knowledge about the role of oncogenes in oral oncogenesis among undergraduate dental students.

Materials and Methods: The study was a questionnaire-based survey and the respondents were to fourth year or interns of an undergraduate dental school. The sample size of the study was 100 and simple random sampling was used for choosing the sample population. The collected data was validated, tabulated, and analyzed with Statistical Package for Social Sciences for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA), and results were obtained.

Results and Conclusion: 25% of the respondents were fourth-year students and 75% were interns. About 98% of respondents were aware of the genetic basis of oral cancer. However, their

*Corresponding author: E-mail: dhanraj@saveetha.com;
knowledge about the role of oncogenes in oral cancer was very limited. A statistically significant association \( P < 0.05 \) was seen between the year of study and knowledge about oncogenes. Hence, measures have to be taken to impart knowledge about oncogenes for better diagnosis and targeted therapy.

Keywords: Fourth-year; interns; knowledge; oncogenes; oral cancer; oral squamous cell carcinoma.

1. INTRODUCTION

A neoplasm can be defined as an abnormal mass of tissue the growth of which is uncoordinated with that of normal tissues and proceeds in the same excessive manner even after the cessation of stimulus that evoked the change. Neoplasm can be of different origins and can involve the epithelial or mesenchymal components. It can be benign or malignant in nature. The malignant neoplasm of epithelial origin is termed a carcinoma and that of non-epithelial or mesenchymal origin is called a sarcoma. Oral squamous cell carcinoma (OSCC) is the most common malignant neoplasm of the oral cavity. According to Murugan et al. [1], OSCC represents about 90% of malignancies arising in the head and neck region.

The most commonly identified etiological agent for Oral squamous cell carcinoma is tobacco in all forms - smoke or smokeless. In the western population prostate cancer is the most common malignancy in males. But in the Indian population Oral Squamous Cell Carcinoma is the most common malignancy in males. This can be attributed to the high usage of tobacco products in India. The occurrence of Oral Squamous Cell Carcinoma is also reported in females because of use of smokeless/chewable forms of tobacco such as chutta, mawa, misher, khaini, betel quid placement, etc. The habit of alcohol consumption is found to have a synergistic effect on tobacco in causing oral cancer. Apart from the stated habits, the Human Papilloma Virus (HPV) types 16 and 18 also have a predominant role in the etiopathogenesis of oral cancer. They lead to the functional downregulation of the tumor suppressor genes p53 and the retinoblastoma gene, resulting in uncontrolled DNA proliferation [2].

A strong genetic basis exists for the pathogenesis of Oral Squamous Cell Carcinoma. The body is composed of normal cellular genes called Proto-oncogenes that control normal cell cycle and replication. Mutation of proto-oncogene results in an oncogene that propagates the process of oncogenesis. The activation of oncogenes occurs through a series of events: translocations and mutations occur as initiating events whereas amplification occurs as a tumor progression event [3]. According to Irish et al. [4], the expression of oncogenes is sometimes linked to various clinical parameters such as tumor aggressiveness, tumor metastasis and tumor radioresistance. These mutations do not occur de novo but are associated with exposure to genetic mutagens and carcinogens in tobacco, alcohol and betel quid. The activated oncogenes code for many of the signal transmitting proteins such as ras, c-myc, EGFr, etc. This makes the cells sensitive to external growth signals, leading to uncontrolled proliferation.

There are thousands of oncogenes that have been identified and implicated in the pathogenesis of oral cancer. It is quite impossible for a dental student at the undergraduate level to have knowledge about all the oncogenes in oral cancer. However, there are certain common oncogenes that have to be known and understood for proper diagnosis and treatment of Oral cancer.

Previously our department has published extensive research on various aspects of prosthetic dentistry [5–15], this vast research experience has inspired us to research about the knowledge among undergraduate dental students regarding oncogenes and their role in oncogenesis.

Thus, the aim of the study is to determine the level of knowledge among the undergraduate dental students regarding the various oncogenes implicated in oral cancer and their role in oncogenesis and to create awareness based on the study results.

2. MATERIALS AND METHODS

2.1 Study Design and Study Setting

This survey was conducted in Saveetha Dental College and Hospital, Saveetha University, Chennai, from December 1st to December 31st, 2019, to determine the knowledge about oncogenes and their role in oral oncogenesis among undergraduate dental students.
2.2 Study Population and Sampling

The survey included the fourth year undergraduate dental students and undergraduate interns. The sample size of the study was set at 100 and a simple random sampling was followed for selecting the respondents.

2.3 Data Collection and Tabulation

The survey was conducted through distribution of questionnaires to the respondents. All the questions were of the multiple-choice type and only a single best answer was allowed. The responses were collected and tabulated.

2.4 Statistical Analysis

The collected data was validated, tabulated and analyzed with Statistical Package for Social Sciences for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA) and results were obtained. Categorical variables were expressed in frequency and percentage; and continuous variables in mean and standard deviation. Chi-square test was used to test associations between categorical variables. P-value < 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

The sample size of the study was 100. Among these respondents, 25.0% [n=25] were fourth year undergraduate dental students and 75.0% [n=75] were undergraduate interns (Fig. 1). Gender based distribution shows that 32.0% [n=32] were males and 68.0% [n=68] were females [Fig. 2].

75.0% of the participants who were interns and 23.0% who were final year students were all aware that a genetic basis existed behind the pathogenesis of oral cancer [Fig. 3]. Chi-square test, P-value 0.017<0.05, statistically significant. Fig. 4 shows the distribution of knowledge about the various products of oncogenes with 10.0% interns and 5.0% final year students having knowledge about transcription factors, 18.0% interns and 10.0% final years about growth factors 20.0% interns on growth factor receptors, 9.0% interns and 1.0% final years students about signal transducers, 11.0% [n=11] about chromatin remodelers and only 8.0% [n=8] had known about all the above factors and all of them were interns. Chi-square test, P-value 0.086>0.05, statistically not significant.

Fig. 1. Pie Figure depicting the year wise distribution of respondents with higher prevalence of interns [75.0%]
Fig. 2. Pie Figure depicting the gender distribution of respondents with higher prevalence of females [68.0%] than males [32.0%]

Fig. 3. Bar graph depicting the association between year of study and knowledge about genetic basis of oral cancer. X-axis - year of study; Y-axis - Number of respondents. Higher knowledge among interns than final years. Chi-square test, P-value 0.017<0.05, statistically significant
Fig. 4. Bar graph depicting the association between year of study and knowledge about products of oncogenes. X-axis - year of study; Y-axis - Number of respondents. Only interns (8.0%) were aware of all the products of oncogenes. Chi-square test, P-value 0.086>0.05, statistically not significant.

Fig. 5. Bar graph depicting the association between year of study and knowledge about methods of oncogene activation. X-axis - year of study; Y-axis - Number of respondents. Only 2.0% final years and 5.0% interns were aware about all the methods of oncogene activation. Chi-square test, P-value 0.647>0.05, statistically significant.
Fig. 6. Bar graph depicting the association between year of study and knowledge about oncogenes for oral cancer. X-axis - year of study; Y-axis - Number of respondents. All interns [75.0%] were aware about all the oncogenes for oral cancer. Chi-square test, P-value 0.000<0.05, statistically significant.

Fig. 7. Bar graph depicting the association between year of study and knowledge about ErbB-2 overexpression in oral cancer. X-axis - year of study; Y-axis - Number of respondents. Only 23.0% [n=23], all interns, were aware of the fact that ErbB-2 overexpression was more frequent in oral cancer than other head and neck cancers. Chi-square test, P-value 0.002<0.05, statistically significant.
The knowledge about different methods of oncogene activation is depicted in Fig. 5. About 13.0% of final years and 29.0% interns were aware of chromosomal rearrangements, and only 2.0% final years and 5.0% interns were aware of all the methods of oncogene activation [Fig. 5]. Chi-square test, P-value 0.647>0.05, statistically not significant.

The knowledge about the various oncogenes for oral cancer was as follows: 2.0% [n=2] were aware of only RAS, 3.0% [n=3] on only Bcl-2, 2.0% [n=2] about only Bcl-x, 1.0% [n=1] each for only Pax-3 and only ErbB-2 and all of them were final year students. About 16.0% final years and all interns [75.0%] had knowledge about the role of all the above genes in oral cancer [Fig. 6]. Chi-square test, P-value 0.000<0.05, high statistical significance.

Only 23.0% [n=23], all interns, were aware of the fact that ErbB-2 overexpression was more frequent in oral cancer than other head and neck cancers, while 73.0% [n=73] had no knowledge about the same [Fig. 7]. Chi-square test; P-value 0.002<0.05; statistically significant.

Only interns 10.0% and final year students 1.0% were aware of the fact that ErbB-2 expression was associated with the worst prognosis of oral cancer [Fig. 8]. Chi-square test; P-value 0.157>0.05; statistically not significant.

The ras protooncogene family includes three genes. But only 12.0% [11.0% interns and 1.0% final years] had knowledge about this. Highest response was for the incorrect option of two genes [7% final year students and 30% interns]. Chi-square test; P-value 0.000<0.05; statistically significant [Fig. 9]. The microRNA regulation of ras oncogenes plays a role in therapeutic determination of oral cancer. Only 9.0% [all interns] had knowledge on this, while 91.0% [n=91] were totally unaware of this [Fig. 10]. Chi-square test; P-value 0.019<0.05; statistically significant.

Fig. 8. Bar graph depicting the association between year of study and knowledge about ErbB-2 associated with the worst prognosis of oral cancer. X-axis - year of study; Y-axis- Number of respondents. Only interns 10.0% and final year students 1.0% were aware of the fact that ErbB-2 expression was associated with the worst prognosis of oral cancer. Chi-square test, P-value 0.157>0.05, statistically not significant.
Fig. 9. Bar graph depicting the association between year of study and knowledge about number of oncogenes in ras family. X-axis - year of study; Y-axis- Number of respondents. Only 12.0% [11.0% interns and 1.0% final years] had knowledge about this. Chi-square test, P-value 0.000<0.05, statistically significant

Fig. 10. Bar graph depicting the association between year of study and knowledge about microRNA as a therapeutic target. X-axis - year of study; Y-axis- Number of respondents. Only 9.0% [all interns] had knowledge on this, while 91.0% [n=91] were totally unaware of this fact. Chi-square test, P-value 0.019<0.05, statistically significant
Oral squamous cell carcinoma is of particular interest to surgeons not just because of its incidence and prevalence proportions but also due to the rate of mortality. It also leads to a considerable amount of disfiguration and dysfunction that persists even after treatment. OSCC also shows extensive metastasis to both local and distant lymph nodes. According to Sugerman et al. [16], for OSCC with cervical lymph node metastasis, the five-year survival rate is less than 50 percent. Hence, before treating OSCC one must have thorough knowledge about the genetic basis of oral cancer. According to Mendes et al. [17], oral carcinogenesis is a multistep process at the molecular level that involves the exaltation of many oncogenes and suppression of tumor suppressor genes, leading to the loss of cell cycle checkpoints. When tumor tissues are examined, alterations in several genes that regulate growth and proliferation of epithelial cells are seen [18]. These are called the oncogenes and lead to uncontrolled division of cells. Out of all other oncogenes, those related to epidermal growth factor, transforming growth factor-alpha and beta have been studied extensively for their association with oral carcinomas [19]. There are no studies reporting the awareness of oncogenes among students.

The activation of oncogenes alters the structure and increases its expression. Activation of oncogenes occurs through the following three pathways: 1. Chromosomal rearrangements: Inversion and translocations are the most common chromosomal abnormalities in cancer cells. 2. Mutations: ras oncogene family is activated by exposure to environmental carcinogens leading to mutations. This changes the structure of the encoded protein and enhances its transforming activity. 3. Gene amplification: MYC, cyclin D1, EGFR and RAS are the commonly amplified genes [20]. The chromosomal rearrangements and mutations serve as initiating events whereas amplifications occur as an event of progression. After this, the action of oncogenesis carried out by its products which are as follows: Transcription factors, chromatin remodelers, growth factors - EGF, TGF alpha and beta in OSCC, growth factor receptors - EGFR, TGFR [21], signal transducers, and apoptosis regulators such as the anti-apoptotic genes- Bcl-2, Bcl-x.

Vairaktaris et al. [22], have listed the oncogenes implicated in the oral oncogenesis, based on their study. According to the study, tyrosine kinase receptors such as EGFR, erbB2,3, FGFR-2,3; cytoplasmic proteins such as the ras family, apoptosis-related proteins [Bcl-2, Bcl-x] and nuclear transcriptional factors (p53,c-myc, c-fos, c-jun) were the identified oral oncogenes [22].

The growth factor receptors that are produced by activated oncogenes play a vital role in oral cancer. The ErbB family of receptors has received attention due to their inherent capacity to stimulate epithelial cell proliferation. The amplification of ErbB2 also known as Her-2 or Neu has been proved in oral cancer specimens, non dysplastic leukoplakia, and patient sera [23]. The study by Tsantoulis et al., also quotes that ErbB-2 overexpression was more frequent in oral cancer than in head and neck cancer, and high levels of ErbB-2 was associated with a worse prognosis.

Another important family of oncogenes associated with oral cancer is the ras family. According to J K Field, overexpression of ras p21 has been reported by many in a high percentage of head and neck cancers [24]. The ras oncogene family consists of three isoforms - Hras, Kras and Nras. The mutations of Hras are found to be more prevalent in OSCC than Kras and Nras. Further, the role of Hras is not just limited to the initiation of tumorigenesis but also extends with an important role in maintaining tumor [25]. Das et al., in their study of OSCC specimens of the Eastern Indian population have reported that Hras and Kras mutations were observed at a frequency of 28% and 33% respectively, while no Nras mutations were observed [26,27]. MicroRNAs [miR-21] have the capacity to down-regulate the expression of ras and c-myc oncogenes at a translational level. Hence, this can be used as a novel therapeutic target for treatment of oral carcinomas.

4. CONCLUSION

Oncogenes play an important role in oral oncogenesis and particularly the family of ras, ErbB-2, Bcl-2, and Bcl-x. There is a statistically significant difference between final year students and interns in the knowledge about oncogenes of oral cancer (P<0.05). Many are aware about the genetic basis of oral cancer and the basic oncogenes. However, most lack knowledge about the action of oncogenes, their products, and therapeutic targets (77%). Hence, it is important to impart knowledge in these aspects for better diagnosis and management of oral cancer.
CONSENT AND ETHICAL APPROVAL
The study was approved by the Institutional Ethical Committee. Basic demographic details were collected after the prior consent of the respondents.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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