Patient and Diagnostic Intervals in Oral Cancer: Protocol for a Sequential Explanatory Study

Phinse Mappalakayil Philip[1,2], Srinivasan Kannan[2*]

[1]Malabar Cancer Centre, Thalassery, Kerala, India
[2]Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India

ABSTRACT

Background: Oral cancer is an important public health problem in Southeast Asian countries. Generally, cases are reported in advanced stages, resulting in prolonged treatment, high financial burden, and poor prognosis. When diagnosed early, treatment is simple and inexpensive.

Materials and Methods: A sequential explanatory study design, cross-sectional survey followed by in-depth interviews, will be used to assess various factors contributing to the patient and diagnostic intervals in oral cancer. At the outset, Data collection tools will be developed and validated. The study protocol is designed as per the "Aarhus statement" for early diagnosis research. In-depth interviews with selected stakeholders and review of documents related to cancer control will constitute the explanatory component of the study design.

Discussion: Primary prevention helps in reducing cancer incidence whereas secondary prevention helps in reducing morbidity and mortality. Early diagnosis is a key secondary prevention strategy. Research on early diagnosis of cancer in general and oral cancer, in particular, is scarce. In this regard, a comprehensive and thorough evaluation of various factors facilitates or impede early oral cancer symptom presentation will help in designing policies and programs to promote early diagnosis of oral cancer.

Keywords: Early cancer diagnosis, Oral cancer, Patient interval, Diagnostic interval, Aarhus Statement

1. Background

Cancer incidence is increasing in the world with a staggering eighteen million new cancer cases in 2018. Nearly half of these cases were from Asia (Bray et al., 2018). Low middle-income countries account for 72% of worlds cancer deaths (Institute of Medicine, 2007). The cancer pattern also varies across different world regions. Breast cancer is the most common cancer in all six World Health Organization (WHO) regions. If we observe the cancer

* Correspondence to Dr. Srinivasan Kannan, Professor, Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology Trivandrum, Kerala, India 695011, (An Institution of National Importance under Govt. of India) E mail: ksrini@sctimst.ac.in

incidence among men, prostate cancer is the most common cancer in WHO regions of Europe, Africa, lung cancer in western pacific and east Mediterranean regions and lip, oral cavity cancers in South East Asia region (Bray et al., 2018). Oral cancer is the most common type of cancer among men in South Asian Countries like India, Srilanka, Pakistan, and Bangladesh and contributes nearly one-fourth of all new cases of cancer (Bray et al., 2018). Oral cancer is characterized by marked geographical variations in its incidence and prevalence rates (Warnakulasuriya, 2009). Oral cancer is the seventeenth most common cancer in the world with a share of 2.2% in total cancer incidence. India presents an entirely different scenario where oral cancer ranks second with a 10.4% share of total cancer incidence (Bray et al., 2018). WHO predicts a 66% increase in the incidence of oral cancer in India by the year 2040, which is higher than the similar estimate for Asia and the world (Ferlay J et al., 2018). The observed trends in incidence and mortality among men and women are closely correlated with the patterns and trends in tobacco and alcohol use (Sankaranarayanan, Ramadas, Amarasinghe, Subramanian, & Johnson, 2015). The five-year survival rate of early-stage cancer exceeds 80%, while that of patients with advanced stages falls below 20%. Globally, more than half of the oral cancer patients report in late stages (Sankaranarayanan et al., 2015; van der Waal, 2013; Warnakulasuriya, 2009). Oral cancer has a long preclinical phase that consists of well-documented precancerous lesions (Sankaranarayanan et al., 2015). Unlike other cancers, these lesions can be easily recognized (Farah et al., 2014). Early identification and proper management of these lesions will ward off mortality (Messadi, 2013). Health care providers including dentists can detect these precancerous and cancerous lesions through oral visual examination (Sankaranarayanan et al., 2015). Despite all these favorable circumstances for prevention, most of the time, the lesion is reported or diagnosed at an advanced stage (Güneri & Epstein, 2014). Primary prevention through control of risk factors and secondary prevention through early detection are the two strategies for oral cancer control (World Health Organization, 2017). Early detection has two components, namely, screening and early diagnosis. Screening refers to the identification of asymptomatic disease in an apparently healthy population. For a disease to be included in a screening program, it should pass through a detectable pre-clinical phase and early treatment should offer some advantage over late treatment (Isabel dos Santos Silva, 1999).

No national or international guidelines recommend population-based screening for oral cancer except for high-risk population (Brocklehurst et al., 2013; USPSTF, 2013). Early diagnosis is the recognition of symptomatic cancer in its early clinical phase (World Health Organization, 2007). The purpose here is to identify the disease at the earliest possible opportunity (World Health Organization, 2017). Early diagnosis integrated with approachable, affordable and efficacious treatment will lead to furtherance in both the stage of cancer at presentation and mortality from cancer (World Health Organization, 2017). Thus, delay in diagnosis is considered as an impediment for prognosis and survival. Pack and Gallo first introduced the concept of delay in 1938 and they defined it as an interval between the onset of symptoms and the first visit to a physician. The undue delay was arbitrarily defined as three months or more (Pack & Gallo, 1938). The first model to explain the delay in seeking cancer diagnosis was given by Andersen (Andersen, Cacioppo, & Roberts, 1995). The general model of patient delay proposed by Andersen comprised of a series of stages, each characterized by a distinct set of definitions and appraisal processes. The stages include Appraisal delay, Illness delay, Behavioral delay, Scheduling delay, and Treatment delay. Later, Olesen et al proposed a model with various milestones and time intervals to explain the processes leading to diagnosis and treatment of cancer (Olesen, Hansen, & Vedsted, 2009). They include Total delay, Patient delay, Doctor delay, System delay, Primary care delay, Secondary care delay, Diagnostic delay, and Treatment delay (Olesen et al., 2009). Walter et

al refined the Andersen model and proposed the Model pathways to treatment (Walter, Webster, Scott, & Emery, 2012). A recent document by the World Health Organization on early diagnosis of cancer recommends using the term "interval" instead of "delay" as the later amount to blame the patient and provider for the delay (World Health Organization, 2017). The document further refines the time points and intervals described in the above models. The intervals include patient interval, diagnostic interval, and treatment interval (World Health Organization, 2017). The patient interval is the period from the recognition of signs/symptoms suggestive of cancer to the day he/she meet a health care provider to discuss the same. The diagnostic interval is the period from the date of the first visit to a health care provider to discuss a symptom suggestive of cancer to the date of obtaining a definitive histopathological diagnosis (Walter et al., 2012; World Health Organization, 2017). Treatment interval is the duration from definitive diagnosis to initiation of cancer treatment (Walter et al., 2012; World Health Organization, 2017). Several factors including demographical, psychological, social, cultural, disease-related, and system-related factors affect the length of these intervals (Weller et al., 2012; World Health Organization, 2017).

A greater understanding of these intervals is essential for planning and implementing cancer control policies and programs (Coxon et al., 2018). Unfortunately, most of the studies carried out in the field of early diagnosis were marred by methodological incongruities, making it difficult for comparisons and interpretations (Andersen, Vedsted, Olesen, Bro, & Søndergaard, 2009; Weller et al., 2012). As a result of this, a consensus-working group comprising of experts in the field of early diagnosis research had gathered at Aarhus, Denmark in 2011 for evaluating existing research and to produce checklists and guidelines to guide early diagnosis researchers (Weller et al., 2012). The working group found that there is little consistency in the definitions and measurements of key time points and intervals. They also concluded that few studies have used a theoretical framework and there is no transparency in the use or development of study instruments (Weller et al., 2012). The recommendations put forward by the consensus-working group are known as “Aarhus Statement”. It provides recommendations for definitions and methodological approaches and a checklist for designing early diagnosis research studies (Weller et al., 2012). Studies published during the post-Aarhus statement period have also failed to follow Aarhus recommendations. Moreover, there are very few validated instruments to measure these intervals. The only validated tool (Neal et al., 2014) available for measuring the various intervals in the diagnostic journey of cancer did not have provision for measuring those time intervals in oral cancer patients. Knowing more about the magnitude of this late presentation as well as the contributing factors for longer intervals will help in managing this public health problem. The current literature on early diagnosis was largely from western countries. These literature focus much on cancers other than oral cavity cancers as the incidence of oral cancer is very low in those countries. There are very few studies exist in the literature on early diagnosis of oral cancer and within that, the contribution from South East Asia is meager. The scarcity of studies from India on early diagnosis of oral cancer necessitates designing a study for estimating various time intervals in the diagnostic journey of oral cancer and identifying various factors contributing to those intervals in line with the Aarhus statement.

The objectives of the current study are as follows:

1. Estimate the duration of patient interval in the diagnostic journey of oral cancer patients of a tertiary cancer center in northern Kerala.
2. Estimate the duration of diagnostic interval in the diagnostic journey of oral cancer patients of a tertiary cancer center in northern Kerala.

3. Study the various factors associated with the patient interval in the diagnostic journey of oral cancer patients of a tertiary cancer center in northern Kerala.
4. Mapping the structure and function of oral cancer control in the state.
5. To develop and validate instruments for capturing the duration of the patient interval, diagnostic interval and various factors contributing to the patient interval in the diagnostic journey of oral cancer.

2. Methods and Analysis

2.1 Study design

A sequential explanatory study design will be used for conducting this study. Sequential Explanatory Design is characterized by the collection and analysis of quantitative data followed by the collection and analysis of qualitative data. Priority is typically given to the quantitative data. The purpose of the sequential explanatory design is typically to use qualitative results to assist in explaining and interpreting the findings of a primarily quantitative study (Creswell, Plano Clark, Gutmann, & Hanson, 2003). This study has three phases.

Phase 1: Development and validation of tools for a cross-sectional survey
Tools will be developed and validated for conducting the cross-sectional survey. The outcome of phase 1 will be a newly developed and validated interview schedule for measuring patient and diagnostic interval and a questionnaire to identify the various factors related to the patient interval.

Steps for developing the tool:
1. Literature review: A literature review will be conducted to identify the various factors contributing to the patient interval. An inventory will be created from the previous questionnaires identified in the literature review.
2. Expert consultation: The inventory will be discussed with experts individually. The experts include Head and neck oncologists, Oral medicine specialists, ENT specialist, Epidemiologists, Psycho oncologists, Dentists, and General practitioners. These discussions will help in identifying factors unaddressed in other studies as well as factors relevant to our setting.
3. Content validity: Content validity will be objectively measured through a content validity index (CVI). CVI provides a quantitative measurement of content validity. The experts will be provided a copy of the tool individually and will be asked to rate each item based on relevance as relevant or irrelevant. The content validity index will be computed as the number of experts giving a rating of relevant divided by the total number of experts. The items having a CVI score of 0.80 or above only will be retained in the tool.
4. Back translation: Translation-back translation of the draft tool will be carried out to produce a conceptually equivalent version of the tool in the local language.
5. Face validity: The translated version of the questionnaire will be administered to 10 people as cognitive piloting. Cognitive piloting is a method for identifying problems with the question-wording. Besides the participants' overall assessment of the questionnaire, participants will be asked to review each question based on the following checklist:
a) The meaning, clarity, and purpose of the question
b) Difficulty in answering the question
c) Suggestions, if any, to improve the question

6. Reliability: The main outcome variables of the "patient interval" and "diagnostic interval" are time durations obtained from calendar dates. Reliability analysis will not be carried out as the instrument intends to collect only factual, objective information. The Protocol for calculating 'pseudo-exact' dates from estimated dates will be used for calculating the time intervals (Neal et al., 2014).

Phase 2: Hospital-based cross-sectional study

Hospital-based patient interview using the newly developed and validated instrument will constitute the second phase of the study. The patient interview will be done within 3 months from the date of patient registration at the institution to minimize recall bias. The expected outcome of phase 2 study includes the mean duration of the patient interval, mean duration of diagnostic interval and identifying various factors affecting patient interval.

Phase 3: In-Depth Interviews and Mapping the structure and function of oral cancer control

In-Depth Interviews: In-Depth Interviews with patients, health care providers, health care administrators, community leaders, etc. as per the findings of the cross-sectional survey conducted in phase 2 will constitute the explanatory part of this sequential explanatory study. Selection of participants, as well as the preparation of the interview guide, will depend on the outcome of the cross-sectional survey. In-Depth Interviews will help in explaining the findings of the hospital-based cross-sectional survey. The participants for the in-depth interview will be selected purposively. The expected outcome is interview guideline and findings from an in-depth interview.

Mapping the structure and function of oral cancer control: Mapping of the structure and function of the oral cancer control will be done by reviewing Govt documents, institutional documents, and other online resources. The expected outcome is to map existing public health facilities and their role for the prevention, early diagnosis, and treatment for oral cancer. It will also document the referral pattern and other government initiatives for the control of oral cancer.

2.2 Study setting

A tertiary cancer center in northern Kerala will be the study setting for the cross-sectional study. Data on the patient interval, diagnostic interval and factors contributing to these intervals will be collected in a direct patient interview using the newly developed and validated instrument. The principal investigator will inform each participant about the purpose of the research and will obtain signed informed consent from all participants. The participants will be interviewed in a room adjacent to the out-Patient Department or ward or any other place convenient to the patient ensuring privacy for the data collection. Time points like date of biopsy, date of biopsy report, patient registration number, and disease stage information will be collected from the patient case files. The secondary data to study the structure and function of oral cancer control in the state will be collected from published government reports and online government sources. The in-depth interview schedule will be prepared after evaluating the findings of the cross-sectional study. Participants, as determined after evaluating the outcome of phase 2, will be approached by the principal investigator for the interview. They will be interviewed at a place and time convenient to them.

2.3 Participants and sample size

The estimated sample size for the cross-sectional survey is 260. The sample size for the in-depth interview is 15 to 30 participants or until we reach saturation. The sample size was estimated by Epi info version 3.01. According to a study done in Uttar Pradesh, India (Akram, Siddiqui, & Karimi, 2014), the proportion of oral cancer patients with a patient interval of more than 3 months was 60%. Taking 60% as the anticipated prevalence of oral cancer patients with a patient interval of more than 3 months, with a 95% confidence interval between 54% and 66%, the sample size was estimated as 257 rounded off to 260. The latest published hospital-based cancer registry data (2015), from the institution where the study will be conducted, reports 450 new oral cancer patients for that year. Hence, we expect 260 new oral cancer patients within 7 months. All oral cancer patients reporting at the institution during the study period will be invited to participating in the study. All the invited patients consenting to participate in the study will be included in the study if they satisfy the inclusion criteria/exclusion criteria. The subjects for the in-depth interview will be selected purposively based on the findings of the cross-sectional survey conducted in phase 2. We plan to conduct 10 to 20 interviews or until we reach saturation. The inclusion-exclusion criteria for the study are as follows.

Inclusion criteria:

Newly registered Patients with the following malignant neoplasms will be included in the study. They are malignant neoplasm of lip (C00), base of tongue (C01), other and unspecified parts of tongue (C02), gum (C03), the floor of mouth (C04), palate (C05), other and unspecified parts of the mouth (C06).

Exclusion criteria:

- Those known to have, or had, other cancers; patients who were on routine surveillance for cancer and presence detected via that system.
- Those who are not consenting to participate.
- Oral cancer patients who are unable to participate due to health reasons or any other reasons.
- Oral cancer patients with recurrence.
- Patients who have completed treatment or partially treated for oral cancer from elsewhere.

2.4 Variables and data sources

The dependent variables for the study are the patient interval, diagnostic interval, and oral cancer stage at diagnosis. Time points used to calculate these intervals include ‘Date of the first symptom', ‘Date of the first presentation' and ‘Date of diagnosis'. Date of the first symptom is the date on which a patient identifies a bodily change or symptom in the oral cavity. Date of the first presentation is the date on which the patient consults a health care provider to discuss the bodily change or symptom in the oral cavity. Definitions of these time points are based on the ‘phases of clinical pathway' described by Olesen et al (Olesen et al., 2009). These time points are subject to recall bias. Thus, the timing of the patient interview is a determining factor in the accuracy of these measurements. Scheduling an interview date too close to the date of diagnosis may be insensitive and too long will lead to recall bias and participant attrition due to death and terminal illness. In this study, the patient interview will be done within 3 months from the date of diagnosis. Self-reported information on the date of first reporting will be crosschecked with prescription notes, if available. Date of diagnosis will be recorded based on the hierarchical rationale developed by the European Network of

Cancer Registries: Hierarchy for Defining the Date of Diagnosis. The independent variables identified through the preliminary literature review are as follows.

1. Socio-demographic factors:
Age (Allison, Franco, Black, & Feine, 1998; Gullatte, Hardin, Kinney, Powe, & Mooney, 2009; Hafström, Johansson, & Ahlberg, 2011; Jassem et al., 2014; Memon, Shaikh, Rizwan, & Sardar, 2013; Yu, Murugiah, Khan, & Mehmood, 2015).
Sex (Abu-Helalah, Alshraideh, Al-Hanaqtah, Da'na, & Mubaidin, 2016; Allison et al., 1998; Chandra, Mohan, Guleria, Singh, & Yadav, 2009; Gullatte et al., 2009; Hafström et al., 2011; Jassem et al., 2014; Memon et al., 2013; Stuver et al., 2011; Thakur, Humne, & Godale, 2015; Yu et al., 2015).
Marital status (Abu-Helalah et al., 2016; Hafström et al., 2011; Jassem et al., 2014; Memon et al., 2013; Stuver et al., 2011; Thakur et al., 2015; Yu et al., 2015).
Residential status (Chandra et al., 2009; Hafström et al., 2011; Jassem et al., 2014; Thakur et al., 2015).
Religion (Hafström et al., 2011).
Socioeconomic status (Jassem et al., 2014; Marlow, McGregor, Nazroo, & Wardle, 2014).
Knowledge of tobacco causes cancer (Marlow et al., 2014).
Education (Gullatte et al., 2009; Memon et al., 2013; Thakur et al., 2015).
Ethnicity (Jassem et al., 2014; Memon et al., 2013).
Migration status, distance from health facility and occupation (Hafström et al., 2011; Yu et al., 2015).

2. Health behavioral factors:
Cigarette smoking (Hafström et al., 2011; Memon et al., 2013; Thakur et al., 2015; Yu et al., 2015).
Alcohol use (Gullatte et al., 2009; Hafström et al., 2011; Memon et al., 2013; Thakur et al., 2015; Yu et al., 2015).
Betel quid use (Hafström et al., 2011).
Regular medical consultation (Marlow et al., 2014).
Regular dental consultation (Thakur et al., 2015).
Consulting for early detection (Marlow et al., 2014).

3. Psychosocial factors:
Attribution of the symptom as minor (Abu-Helalah et al., 2016).
Absence of fear (Abu-Helalah et al., 2016).
Use of alternate therapy (Abu-Helalah et al., 2016).
Negative thoughts on cancer (Marlow et al., 2014).
Perceptions of being under stress in the period before diagnosis (Jassem et al., 2014).
Severity of life events in the patient delay period (Memon et al., 2013).
Perceived ability to seek help for oral symptoms (Memon et al., 2013).

4. Disease factors:
Dental status (Stuver et al., 2011; Yu et al., 2015).
Tumor site (Hafström et al., 2011; Stuver et al., 2011).
Tumor size (Hafström et al., 2011; Stuver et al., 2011).
Comorbid conditions (Chandra et al., 2009).
TNM stage (Hafström et al., 2011).
Lymph node metastasis (Hafström et al., 2011).

Initial sign or symptom (Hafström et al., 2011; Jassem et al., 2014).
Medical history (Jassem et al., 2014).
Dental history (Jassem et al., 2014).
Experience of symptoms (Thakur et al., 2015).
Initial self-diagnosis (Thakur et al., 2015).

The list of independent variables will be finalized during instrument development.
Data on the patient interval, diagnostic interval and factors contributing to these intervals will be collected in a direct patient interview using the newly developed and validated instruments. Neal et al guideline will be followed for calculating the pseudo exact date from the estimated date provided by the patient (Neal et al., 2014). Time points like date of biopsy, date of biopsy report, patient registration number, and disease stage information will be collected from the patient case files. The secondary data to study the structure and function of oral cancer control in the state will be collected from published government reports and online government sources. The in-depth interview schedule will be prepared after evaluating the findings of the cross-sectional study. Participants for the In-Depth Interview will be identified after evaluating the outcome of phase 2. They will be informed about the purpose of the study and the principal investigator will obtain the consent of those willing to take part. They will be interviewed at a place and time convenient to them.

2.5 Bias

As study requires recollection of past incidences, there is a possibility for recall bias. For reducing recall bias in this study, we will conduct the patient interview within 3 months from the date of diagnosis.

2.5 Limitations

The study participants will be selected from a single institution. This will have implications on the generalizability of results. However, the study setting is the only comprehensive cancer care center in the region and it provides subsidized treatment as per government norms. The early diagnosis research studies were conducted either in hospitals or from cancer registry data. The registry system in our place is in a developmental phase and they cover a less geographical area in comparison to the hospital's catchment area.

2.6 Plan for data analysis

Descriptive statistical methods will be used (frequencies, percentages, means, standard deviations depending on whether the variables are categorical or continuous). Binary logistic and multiple linear regression models will be constructed to identify significant predictors. Early (stage 1 and 2) vs. late (stage 3 and 4) stages of oral cancer will be further explored for differences in duration and factors related to the patient and diagnostic interval. Data will be analyzed to understand gender and class differentials. Thematic analysis will be used for qualitative data. Thematic analysis will be used for qualitative data. Cancer-related documents will be reviewed using a checklist.

2.7 Ethical consideration

The principal investigator (PI) has obtained approval from the Institutional Ethics Committee for conducting the study. The discomforts expected from the study are minimal. Participants have to spend 20-30 minutes for the data collection and they may have difficulty

in recollecting information related to their symptoms. Some of the cancer patients during the initial days of diagnosis may find it difficult to accept it. The study participants will be approached during the physician-waiting period, which is normally, extends to 30 min to 1hr. Thus, the patient will not have to spend extra time on the study. The instrument will have a checklist of all possible symptoms and a calendar that will help the patient to identify the past events. The timing of the data collection will be scheduled in such a way that it will not be too close to the date of diagnosis as the majority of the patients will find it difficult to accept the reality initially. The institution has a dedicated psycho-oncology department that provides psychological support to all newly diagnosed cancer patients. Data collection will be scheduled on a follow-up visit as convenient to them. No invasive procedures are involved in the study and therefore no adverse events are expected. PI will be responsible for safekeeping the data, privacy, and confidentiality of the subjects will be ensured at all levels. The PI before the data collection will obtain an informed signed consent from the participants, after briefing on the study objectives, purpose, benefit, risks and voluntariness to decide participation. The participant will be provided time (not less than 15 minutes) to read and understand the consent form. Ethical approval has been obtained from two Institutional ethics committees (1617/IRB-IEC/13/MCC/13-05-2019/5 and SCT/IEC/1388/JUNE-2019).

3. Discussion

The starting point of any discussion on the patient and the diagnostic interval is the quest for an acceptable duration. From the early study of Pack and Gallo (Pack & Gallo, 1938) to the present day studies (Abu-Helalah et al., 2016; Akram et al., 2014; Chandra et al., 2009; Ibrahim & Oludara, 2012; Mohd Mujar et al., 2017), three months is generally considered as an acceptable patient interval (Andersen et al., 2009; Thakur et al., 2015). Similarly, one month is considered an acceptable diagnostic interval (Abu-Helalah et al., 2016; Morelatto, Herrera, Fernández, Corball, & López de Blanc, 2007). There are other studies, which consider a shorter period for patient interval and a longer period for diagnostic interval as an acceptable period (Allison et al., 1998; Lim et al., 2014; Olesen et al., 2009). Multifarious study designs and summary measures were used for conducting the study and to report the findings in early diagnosis research. Although cross-sectional study design is the preferred one (Abu-Helalah et al., 2016; Bourdeanu et al., 2013; Garcia et al., 2012; Gullatte et al., 2009; Hafström et al., 2011; Ibrahim & Oludara, 2012; Jassem et al., 2014; Memon et al., 2013; Mohd Mujar et al., 2017; Yu et al., 2015), cohort (Stuver et al., 2011; Thakur et al., 2015) and qualitative designs (Marlow et al., 2014) were also used. Very few studies reported measures of dispersion to describe study findings. These observations confirm with expert review findings that lead to the preparation of Aarhus Statement (Andersen et al., 2009; Weller et al., 2012). An oral cancer-specific review of early diagnosis research also reported similar observations (Varela-Centelles et al., 2018). The mean patient interval duration reported from various countries (Kerdpon, Jantharapattana, & Sriplung, 2018) vary considerably necessitating the need for a region-specific estimate of these durations to assess the need and status of early cancer control initiatives.

Several factors influence the patient interval duration. Factors found to be significant in one study may appear as an insignificant one in another study. This poses the biggest challenge to the current research. Studies addressing factors related to this interval were generally focused on socio-demographic factors even though few have attempted to study the psychosocial, health behavioral and equity-related factors. Even though socio-demographic factors are the most frequently studied ones, it is too difficult to generalize the findings from these studies, as contradictory observations exist in the literature. Old age is a risk factor for

oral cancer (Ram et al., 2011) hence researchers also want to know its relationship with patient interval. Out of the eight studies evaluated its significance, only two (Akram et al., 2014; Panzarella et al., 2014) could demonstrate such a relationship. The majority found no such relations(Alahapperuma & Fernando, 2017; Guggenheimer, Verbin, Johnson, Horkowitz, & Myers, 1989; Kerdpon & Sriplung, 2001; Llewellyn, Johnson, & Warnakulasuriya, 2004; Onizawa et al., 2003; Scott, McGurk, & Grunfeld, 2008). Low socioeconomic status is an independent risk factor for developing oral cancer (Conway et al., 2008) and also for a prolonged patient interval (Akram et al., 2014). A study by Sandeep et al from India refutes the presence of such an influence on the patient interval (Sandeep et al., 2000).

Similarly, rural residence and levels of education were also examined in various studies but the current evidence is insufficient to make any inference. Studies from India, Srilanka, and Thailand (Alahapperuma & Fernando, 2017; Baishya et al., 2015; Kerdpon et al., 2018) found education as a significant factor in determining patient interval but those from USA, England, and Italy cannot establish such links (Guggenheimer et al., 1989; Panzarella et al., 2014; Scott et al., 2008). The stark reflection from this observation is the relevance of education in facilitating health care utilization in developing countries. Gender was also assessed for any possible association but none of the studies showed it as significant (Akram et al., 2014; Alahapperuma & Fernando, 2017; Baishya et al., 2015; Guggenheimer et al., 1989; Jovanovic, Kostense, Schulten, Snow, & van der Waal, 1992; Kerdpon & Sriplung, 2001; Llewellyn et al., 2004; Onizawa et al., 2003; Panzarella et al., 2014; Scott et al., 2008). A study based on the data from the Clinical Practice Research Datalink (CPRD) in the UK found gender delays diagnostic interval in some cancers including head and neck cancer (Din et al., 2015). Social support and social networks were minimally (Abu-Helalah et al., 2016; Brocklehurst et al., 2013; Gullatte et al., 2009; Morelatto et al., 2007) investigated in the reviewed studies. Marital status (Akram et al., 2014; Kerdpon & Sriplung, 2001; Panzarella et al., 2014; Scott et al., 2008), number of family members living in the same house (Onizawa et al., 2003), escorted by someone(Sandeep et al., 2000), disclosure to others (Akram et al., 2014) were the few variables that can be related to social support and network but none of them were associated with patient interval as per the study findings. Interestingly, a different study has found partner support and other support as significant factors for shortening patient interval in females (Pedersen, Olesen, Hansen, Zachariae, & Vedsted, 2011). The full spectrum of health behaviors was not investigated in any of these studies. Smoking, alcohol use, the regularity of visiting a dental or medical provider and use of domestic remedies were assessed but could not find any association (Hollows, McAndrew, & Perini, 2000; Onizawa et al., 2003; Panzarella et al., 2014; Sandeep et al., 2000). The lower amount of tobacco smoked is related to the increased patient interval (Llewellyn et al., 2004) as that might lead to underestimation of risk from smoking. Tumor factors, dental factors or comorbid conditions were also found to be insignificant (Jovanovic et al., 1992; Llewellyn et al., 2004; Sandeep et al., 2000). One study from Srilanka identified the impact of travel cost to a health facility as significant(Alahapperuma & Fernando, 2017).

Research in early oral cancer diagnosis done so far has failed to answer the few questions routinely revolve around patient interval duration. The socio-demographic, health-related, cognitive and psychological variables affecting the patient interval were either understudied or when evaluated, had given contradictory results. The methodologies or definitions used in these studies lacked uniformity and hence comparisons were not possible. In these circumstances, we have designed our study in conformity with the "Aarhus statement " which guides the early cancer diagnosis research (Weller et al., 2012) (Table 1). An exhaustive exploration of various factors affecting the reporting of cancer signs and symptoms to a

health care provider is necessary for developing policy measures to contain this public health challenge.

Table 1. Protocol consistency with 'The Aarhus checklist' for early cancer diagnosis research.

No	Item	Yes /No
Definitions Of Time Points And Intervals		
1	For studies requiring the measurement of an interval, are the beginning and endpoints of this interval clearly defined?	Yes. Time points used are the date of the first symptom, date of first presentation and date of diagnosis.
2	For all time points and intervals described, are there precise, transparent and repeatable definitions, and is the complexity of time points such as the date of first symptom and date of the first presentation addressed?	Yes
For studies that require an estimate of the date of the first symptom		
3	Do the researchers refer to a theoretical framework underpinning definition of this time point?	Yes. Phases of the clinical pathway by Olesen et al
4	Is there a discussion of the different biases influencing the measurement of this time point?	Yes
For studies that require measurement of a date of the first presentation to healthcare		
5	Do the researchers discuss the complexity of the date of the first presentation?	Yes
For studies that require measurement of date of referral		
6	Do the researchers discuss the nature of the referral and provide adequate detail – for example, whether it was for investigation or consultation by a colleague in secondary care?	NA
For studies that require measurement of the date of diagnosis		
7	Do the researchers use an existing hierarchical rationale for the date of diagnosis measurement?	Yes. European Network of Cancer Registries: Hierarchy for Defining the Date of Diagnosis
Measurement		
8	Is the healthcare context in which the study is based fully described?	Yes
9	Do the questions on time points and/or intervals clearly derive from stated definitions?	Questions will be developed as per stated definitions
10	Do researchers acknowledge the need for theoretical validation and refer to the theoretical framework(s) underpinning measurement and analysis of the time	Yes

	points?	
For studies using questionnaires and/or interviews with patients and/or health-care providers		
11	Has a validated instrument been used?	A new Instrument will be developed and validated for the study
12	Have the researchers included a copy of their instrument?	The developed instrument will be published in scientific journals
13	Is there some discussion of how reliability and validity (trustworthiness) has been established?	It is described in the steps for tool development
14	Do researchers acknowledge the need for theoretical validation and refer to the theoretical framework(s) underpinning measurement and analysis of the time points?	Yes
15	Is there discussion of the different biases influencing measurement of the time points, such as how and when the question is asked and who is being asked?	Yes
16	Is the timing of the interview about the date of diagnosis provided?	Yes
17	Is there any triangulation of self-reported data with other data sources such as case notes?	Yes
18	Is data analysis described in full including how and why data are categorized, how missing and incomplete data are managed, and how outliers at both ends of the spectrum are accounted for?	Not applicable as protocol paper
For studies using primary case-note audit and database analysis		
19	Case-note analysis: is there a clear and precise description of how case-note data were used to ascertain time points with an acknowledgment of limitations of such data?	Not applicable
20	For database analysis: is there a thorough description of the database chosen including sampling coverage and completeness of information?	Not applicable

Declarations

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interests: The authors declare that they have no conflict of interest.

References

Abu-Helalah, A. M., Alshraideh, H. A., Al-Hanaqtah, M., Da'na, M., & Mubaidin, R. (2016). Review of delay in presentation, diagnosis, and treatment for breast cancer patients in Jordan. *The Breast Journal*, *22*(2), 213–217. https://doi.org/10.1111/tbj.12541

Abu-Helalah, M. A., Alshraideh, H. A., Da'na, M., Al-Hanaqtah, M., Abuseif, A., Arqoob, K., & Ajaj, A. (2016). Delay in presentation, diagnosis and treatment for colorectal cancer patients in Jordan. *Journal of Gastrointestinal Cancer*, *47*(1), 36–46. https://doi.org/10.1007/s12029-015-9783-3

Akram, M., Siddiqui, S. A., & Karimi, A. M. (2014). Patient related factors associated with delayed reporting in oral cavity and oropharyngeal cancer. *International Journal of Preventive Medicine*, *5*(7), 915–919.

Alahapperuma, L. S., & Fernando, E. A. (2017). Patient-linked factors associated with delayed reporting of oral and pharyngeal carcinoma among patients attending National Cancer Institute, Maharagama, Sri Lanka. *Asian Pacific Journal of Cancer Prevention: APJCP*, *18*(2), 321–325. https://doi.org/10.22034/APJCP.2017.18.2.321

Allison, P., Franco, E., Black, M., & Feine, J. (1998). The role of professional diagnostic delays in the prognosis of upper aerodigestive tract carcinoma. *Oral Oncology*, *34*(2), 147–153. https://doi.org/10.1016/S1368-8375(97)00088-2

Andersen, B. L., Cacioppo, J. T., & Roberts, D. C. (1995). Delay in seeking a cancer diagnosis: Delay stages and psychophysiological comparison processes. *British Journal of Social Psychology*, *34*(1), 33–52. doi:10.1111/j.2044-8309.1995.tb01047.x

Andersen, R. S., Vedsted, P., Olesen, F., Bro, F., & Søndergaard, J. (2009). Patient delay in cancer studies: A discussion of methods and measures. *BMC Health Services Research*, *9*, 189. https://doi.org/10.1186/1472-6963-9-189

Baishya, N., Das, A. K., Krishnatreya, M., Das, A., Das, K., Kataki, A. C., & Nandy, P. (2015). A pilot study on factors associated with presentation delay in patients affected with head and neck cancers. *Asian Pacific Journal of Cancer Prevention*, *16*(11), 4715–4718. https://doi.org/10.7314/APJCP.2015.16.11.4715

Bourdeanu, L., Luu, T., Baker, N., Swain-Cabriales, S., Chung, C. T., Mortimer, J., … Somlo, G. (2013). Barriers to treatment in patients with locally advanced breast cancer. *Journal of the National Comprehensive Cancer Network: JNCCN*, *11*(10), 1193–1198. https://doi.org:10.6004/jnccn.2013.0141

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *68*(6), 394–424. https://doi.org/10.3322/caac.21492

Brocklehurst, P., Kujan, O., O'Malley, L. A., Ogden, G., Shepherd, S., & Glenny, A.-M. (2013). Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database of Systematic Reviews*, (11). https://doi.org/10.1002/14651858.CD004150.pub4

Chandra, S., Mohan, A., Guleria, R., Singh, V., & Yadav, P. (2009). Delays during the diagnostic evaluation and treatment of lung cancer. *Asian Pacific Journal of Cancer Prevention: APJCP*, *10*(3), 453–456.

Conway, D. I., Petticrew, M., Marlborough, H., Berthiller, J., Hashibe, M., & Macpherson, L. M. D. (2008). Socioeconomic inequalities and oral cancer risk: A systematic review and meta-analysis of case-control studies. *International Journal of Cancer*, *122*(12), 2811–2819. doi.org/10.1002/ijc.23430

Coxon, D., Campbell, C., Walter, F. M., Scott, S. E., Neal, R. D., Vedsted, P., … Weller, D. (2018). The Aarhus statement on cancer diagnostic research: Turning recommendations into new survey instruments. *BMC Health Services Research*, *18*(1), 677. https://doi.org/10.1186/s12913-018-3476-0

Creswell J. W, Plano Clark V. L, Gutmann M. L, & Hanson W. E. (2003). *Handbook of mixed methods in social and behavioral research*. Sage Publications, Inc.

Din, N. U., Ukoumunne, O. C., Rubin, G., Hamilton, W., Carter, B., Stapley, S., & Neal, R. D. (2015). Age and gender variations in cancer diagnostic intervals in 15 cancers: analysis of data from the UK clinical practice research data link. *PLoS ONE*, *10*(5). https://doi.org/10.1371/journal.pone.0127717

Esmaelbeigi, F., Hadji, M., Harirchi, I., Omranipour, R., vand Rajabpour, M., & Zendehdel, K. (2014). Factors affecting professional delay in diagnosis and treatment of oral cancer in Iran. *Archives of Iranian Medicine*, *17*(4), 253–257. https://doi.org/014174/AIM.007

Farah, C. S., Woo, S., Zain, R. B., Sklavounou, A., McCullough, M. J., & Lingen, M. (2014). Oral cancer and oral potentially malignant disorders. *International Journal of Dentistry*, *2014*. https://doi.org/10.1155/2014/853479

Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, … Bray F. (2018). Cancer tomorrow. Retrieved from Global Cancer Observatory: Cancer Tomorrow website: http://gco.iarc.fr/tomorrow/home

Garcia, R. Z., Carvajal, S. C., Wilkinson, A. V., Thompson, P. A., Nodora, J. N., Komenaka, I. K., … Martínez, M. E. (2012). Factors that influence mammography use and breast cancer detection among Mexican-American and African-American women. *Cancer Causes & Control: CCC*, *23*(1), 165–173. https://doi.org/10.1007/s10552-011-9865-x

Guggenheimer, J., Verbin, R. S., Johnson, J. T., Horkowitz, C. A., & Myers, E. N. (1989). Factors delaying the diagnosis of oral and oropharyngeal carcinomas. *Cancer*, *64*(4), 932–935. https://doi.org/10.1002/1097-0142(19890815)64:4<932::AID-CNCR2820640428>3.0.CO;2-Y

Gullatte, M. M., Hardin, P., Kinney, A., Powe, B., & Mooney, K. (2009). Religious beliefs and delay in breast cancer diagnosis for self-detected breast changes in African-American women. *Journal of National Black Nurses' Association: JNBNA*, *20*(1), 25–35. https://doi.org/ 10.1007/s10943-008-9232-8

Güneri, P., & Epstein, J. B. (2014). Late stage diagnosis of oral cancer: Components and possible solutions. *Oral Oncology*, *50*(12), 1131–1136. https://doi.org/10.1016/j.oraloncology.2014.09.005

Hafström, L., Johansson, H., & Ahlberg, J. (2011). Diagnostic delay of breast cancer—An analysis of claims to Swedish Board of Malpractice (LÖF). *Breast (Edinburgh, Scotland)*, *20*(6), 539–542. https://doi.org/10.1016/j.breast.2011.06.007

Hollows, P., McAndrew, P. G., & Perini, M. G. (2000). Delays in the referral and treatment of oral squamous cell carcinoma. *British Dental Journal*, *188*(5), 262–265. https://doi.org/ 10.1038/sj.bdj.4800449a

Ibrahim, N. A., & Oludara, M. A. (2012). Socio-demographic factors and reasons associated with delay in breast cancer presentation: A study in Nigerian women. *Breast (Edinburgh, Scotland)*, *21*(3), 416–418. https://doi.org/10.1016/j.breast.2012.02.006

Institute of Medicine (2007). *Cancer Control Opportunities in Low- and Middle-Income Countries*. Washington, DC: The National Academies Press. https://doi.org/10.17226/11797

Isabel dos Santos Silva. (1999). *Cancer Epidemiology: Principles and Methods* (1st ed.). Retrieved from http://www.iarc.fr/en/publications/pdfs-online/epi/cancerepi/

Jassem, J., Ozmen, V., Bacanu, F., Drobniene, M., Eglitis, J., Lakshmaiah, K. C., … Zaborek, P. (2014). Delays in diagnosis and treatment of breast cancer: A multinational analysis. *European Journal of Public Health*, *24*(5), 761–767. https://doi.org/10.1093/eurpub/ckt131

Jovanovic, A., Kostense, P. J., Schulten, E. A., Snow, G. B., & van der Waal, I. (1992). Delay in diagnosis of oral squamous cell carcinoma; a report from The Netherlands. *European Journal of Cancer. Part B, Oral Oncology*, *28B*(1), 37–38. /10.1016/0964-1955(92)90009-P.

Kerdpon, D., Jantharapattana, K., & Sriplung, H. (2018). Factors related to diagnostic delay of oral squamous cell carcinoma in southern Thailand: Revisited. *Oral Diseases*, *24*(3), 347–354. https://doi.org/10.1111/odi.12757

Kerdpon, D., & Sriplung, H. (2001). Factors related to delay in diagnosis of oral squamous cell carcinoma in southern Thailand. *Oral Oncology*, *37*(2), 127–131. https://doi.org/10.1016/S1368-8375(00)00072-5

Lim, A. W., Ramirez, A. J., Hamilton, W., Sasieni, P., Patnick, J., & Forbes, L. J. (2014). Delays in diagnosis of young females with symptomatic cervical cancer in England: An interview-based study. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners*, *64*(627), e602-610. https://doi.org/10.3399/bjgp14X681757

Llewellyn, C. D., Johnson, N. W., & Warnakulasuriya, S. (2004). Factors associated with delay in presentation among younger patients with oral cancer. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, *97*(6), 707–713. https://doi.org/10.1016/j.tripleo.2004.01.007

Marlow, L. A. V., McGregor, L. M., Nazroo, J. Y., & Wardle, J. (2014). Facilitators and barriers to help-seeking for breast and cervical cancer symptoms: A qualitative study with an ethnically diverse sample in London. *Psycho-Oncology*, *23*(7), 749–757. https://doi.org/10.1002/pon.3464

Memon, Z. A., Shaikh, A. N., Rizwan, S., & Sardar, M. B. (2013). Reasons for patient's delay in diagnosis of breast carcinoma in Pakistan. *Asian Pacific Journal of Cancer Prevention: APJCP*, *14*(12), 7409–7414. https://doi.org/10.7314/apjcp.2013.14.12.7409

Messadi, D. V. (2013). Diagnostic aids for detection of oral precancerous conditions. *International Journal of Oral Science*, *5*(2), 59–65. https://doi.org/10.1038/ijos.2013.24

Mohd Mujar, N. M., Dahlui, M., Emran, N. A., Abdul Hadi, I., Wai, Y. Y., Arulanantham, S., … Mohd Taib, N. A. (2017). Complementary and alternative medicine (CAM) use and delays in presentation and diagnosis of breast cancer patients in public hospitals in Malaysia. *PloS One*, *12*(4), e0176394. https://doi.org/10.1371/journal.pone.0176394

Morelatto, R. A., Herrera, M. C., Fernández, E. N., Corball, A. G., & López de Blanc, S. A. (2007). Diagnostic delay of oral squamous cell carcinoma in two diagnosis centers in Córdoba Argentina. *Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, *36*(7), 405–408. https://doi.org/10.1111/j.1600-0714.2007.00547.x

Neal, R. D., Nafees, S., Pasterfield, D., Hood, K., Hendry, M., Gollins, S., … Robling, M. (2014). Patient-reported measurement of time to diagnosis in cancer: Development of the Cancer Symptom Interval Measure (C-SIM) and randomised controlled trial of method of delivery. *BMC Health Services Research*, *14*, 3. https://doi.org/10.1186/1472-6963-14-3

Olesen, F., Hansen, R. P., & Vedsted, P. (2009). Delay in diagnosis: The experience in Denmark. *British Journal of Cancer*, *101 Suppl 2*, S5-8. https://doi.org/10.1038/sj.bjc.6605383

Onizawa, K., Nishihara, K., Yamagata, K., Yusa, H., Yanagawa, T., & Yoshida, H. (2003). Factors associated with diagnostic delay of oral squamous cell carcinoma. *Oral Oncology*, *39*(8), 781–788. https://doi.org/10.1016/S1368-8375(03)00075-7

Pack, G. T., & Gallo, J. S. (1938). The culpability for delay in the treatment of cancer. *The American Journal of Cancer*, *33*(3), 443. https://doi.org/10.1158/ajc.1938.443

Panzarella, V., Pizzo, G., Calvino, F., Compilato, D., Colella, G., & Campisi, G. (2014). Diagnostic delay in oral squamous cell carcinoma: The role of cognitive and psychological variables. *International Journal of Oral Science*, *6*(1), 39–45. https://doi.org/10.1038/ijos.2013.88

Pedersen, A. F., Olesen, F., Hansen, R. P., Zachariae, R., & Vedsted, P. (2011). Social support, gender and patient delay. *British Journal of Cancer*, *104*(8), 1249–1255. https://doi.org/10.1038/bjc.2011.87

Ram, H., Sarkar, J., Kumar, H., Konwar, R., Bhatt, M. L. B., & Mohammad, S. (2011). Oral cancer: Risk factors and molecular pathogenesis. *Journal of Maxillofacial & Oral Surgery*, *10*(2), 132–137. https://doi.org/10.1007/s12663-011-0195-z

Sandeep, K., F Heller, R., Pandey, U., Tewari, V., Bala, N., & Khuat, O. (2000). Delay in presentation of oral cancer: A multifactor analytical study. *The National Medical Journal of India,* 14(1),13-7.

Sankaranarayanan, R., Ramadas, K., Amarasinghe, H., Subramanian, S., & Johnson, N. (2015). Oral cancer: Prevention, early detection, and treatment. *Cancer: Disease Control Priorities, (*3rd Ed) (Vols. 3). Washington (DC). https://doi.org/10.1596/978-1-4648-0349-9_ch5

Scott, S., McGurk, M., & Grunfeld, E. (2008). Patient delay for potentially malignant oral symptoms. *European Journal of Oral Sciences*, *116*(2), 141–147. https://doi.org/10.1111/j.1600-0722.2007.00520.x

Stuver, S. O., Zhu, J., Simchowitz, B., Hassett, M. J., Shulman, L. N., & Weingart, S. N. (2011). Identifying women at risk of delayed breast cancer diagnosis. *Joint Commission Journal on Quality and Patient Safety*, *37*(12), 568–575.

Thakur, N. A., Humne, A. Y., & Godale, L. B. (2015). Delay in presentation to the hospital and factors affecting it in breast cancer patients attending tertiary care center in Central India. *Indian Journal of Cancer*, *52*(1), 102–105. https://doi.org/10.4103/0019-509X.175602

USPSTF. (2013). Final recommendation statement: Oral cancer: Screening—US Preventive Services Task Force. Retrieved from https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/oral-cancer-screening

van der Waal, I. (2013). Are we able to reduce the mortality and morbidity of oral cancer; Some considerations. *Medicina Oral, Patología Oral y Cirugía Bucal*, *18*(1), e33–e37. https://doi.org/10.4317/medoral.18486

Varela-Centelles, P., Seoane, J., Lopez-Cedrun, J. L., Fernandez-Sanroman, J., García-Martin, J. M., Takkouche, B., … Seoane-Romero, J. M. (2018). The length of patient and primary care time interval in the pathways to treatment in symptomatic oral cancer. A quantitative systematic review. *Clinical Otolaryngology: Official Journal of ENT-UK ; Official Journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery*, *43*(1), 164–171. https://doi.org/10.1111/coa.12919

Walter, F., Webster, A., Scott, S., & Emery, J. (2012). The Andersen Model of Total Patient Delay: A systematic review of its application in cancer diagnosis. *Journal of Health Services Research & Policy*, *17*(2), 110–118. https://doi.org/10.1258/jhsrp.2011.010113

Warnakulasuriya, S. (2009). Global epidemiology of oral and oropharyngeal cancer. *Oral Oncology*, *45*(4–5), 309–316. https://doi.org/10.1016/j.oraloncology.2008.06.002
Weller, D., Vedsted, P., Rubin, G., Walter, F. M., Emery, J., Scott, S., … Neal, R. D. (2012). The Aarhus statement: Improving design and reporting of studies on early cancer diagnosis. *British Journal of Cancer*, *106*(7), 1262–1267. https://doi.org/10.1038/bjc.2012.68
World Health Organization. (2007). *Early detection*. Retrieved from https://www.who.int/cancer/publications/cancer_control_detection/en/
World Health Organization. (2017). *Guide to early cancer diagnosis.* Retrieved from http://apps.who.int/iris/bitstream/10665/254500/1/9789241511940-eng.pdf
Yu, F. Q., Murugiah, M. K., Khan, A. H., & Mehmood, T. (2015). Meta-synthesis exploring barriers to health seeking behaviour among Malaysian breast cancer patients. *Asian Pacific Journal of Cancer Prevention: APJCP*, *16*(1), 145–152. https://doi.org /10.7314/apjcp.2015.16.1.145