

Life course models for upper aero-digestive tract cancer

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Upper aero-digestive tract (UADT) cancers are collectively cancers of various human body sites, such as the oral cavity, pharynx, oesophagus and larynx. Worldwide, they are the fourth most frequent cancer type and the fourth most common cause of mortality from cancer. Many studies have shown that several chronic diseases, such as cancer, which occur more commonly in later adulthood, are influenced by social and psychological circumstances during birth, childhood, adolescence and early adult life. It is suggested that the build up of problematic circumstances throughout life is the cause of disease, rather than circumstances that happen at one point in time. UADT cancer is a chronic disease of complex multifactorial origin and most of the underlying exposures/risks cannot be considered as individual factors or in isolation, as they act at different levels, which differ from time to time. Thus, life-course epidemiology, rather than drawing false dichotomies between different risk factors of the underlying disease, attempts to integrate biological and social risk processes that cause the chronic disease. It studies how socially patterned exposures during all stages of life – childhood, adolescence and early adult – influence disease risk in adulthood and socio-economic position and hence may account for social inequalities in adult health and mortality. Furthermore, varying health effects, according to the timing or duration of exposure to socio-economic circumstances, may indicate important traces to the causes of cancer. In this paper, we have attempted to draw a conceptual framework on the relationships between socio-economic inequalities, oral health risk factors along the life-course of an individual and incidence of UADT cancer.

Key words: Life-course, social determinants, cancer of upper aero-digestive tract

INTRODUCTION

Definition of upper aero-digestive tract cancer

Here we define squamous cell carcinomas of the upper aero-digestive tract (UADT) according to the following International Classification of Disease (ICD) cancer diagnostic groups: intra-oral sites (ICD-10 C00-C06); oro-pharynx (ICD-10 C09-C10), and other ill-defined sites of the lip, oral cavity and pharynx (ICD-10 C12-C14)¹; larynx (ICD-10 C32); and oesophagus (ICD-10 C15)². We exclude nasopharynx (C11) and salivary glands (C07-C08) as they have different risk factors and biology from the predominantly squamous cell carcinoma of the foregoing sites³. These cancer sites are often grouped together in epidemiological data⁴, with over 400,000 cases estimated annually⁵.

UADT squamous cell carcinoma is a devastating chronic disease of multifactorial origin and is an

important global health problem^{6,7}. Chronic diseases, such as UADT cancer, often involve diagnosis at the tail end of a long, accumulating pathological process and a stepwise accumulation of genetic alterations^{8,9}. Globally, estimated age-standardised incidence rates per 100,000 for all ages and both sexes for malignant neoplasms of lip plus oral cavity are 3.8, for larynx are 2.2, for other pharynx are 2.0 and for oesophagus are 7.0⁷. Two-thirds of the global burden of these cancer cases occurs in developing countries, with the Indian subcontinent accounting for one-third of the global burden for cancers of lip and oral cavity¹⁰. At the time of diagnosis, most UADT cancers are restricted to the primary site and the regional lymph nodes. At this stage, cancer may be cured with local treatment with surgery and/or radiotherapy¹¹. However, when local control is not achieved within a few years of diagnosis, these cancers usually progress rapidly, resulting in mortality^{12,13}.

Cancer of the UADT, being a chronic disease, has roots years, decades or even generations before the

date of diagnosis, or even of the earliest clinical symptoms¹⁴. Explanation for the social variations in general and oral health are incompletely explored and understood by the traditional aetiological study models that emphasise risk factors at the stage of life when studies are conducted¹⁴.

Therefore, applying the life-course approach (which is explained in the following sections) may further elucidate the relationship between socio-economic, behavioural, psychosocial and dental risk factors and the incidence and mortality of UADT cancer¹⁴⁻¹⁷. Furthermore, social inequalities in cause-specific adult incidence and mortality lie in socially patterned exposures in different stages of the life-course¹⁸.

RISK FACTORS FOR UADT CANCER

The wide variation in worldwide incidence and mortality from cancers of the UADT are mainly attributed to variations in exposure to the major environmental and behavioural risk factors, namely: tobacco and alcohol; low intake of fruits and vegetables; and infection with human papilloma virus (HPV)^{6,8,19-25}. Chronic trauma to the oral mucosa from poor restorations and prostheses, and poor oral hygiene with a consequent heavy bacterial load in the mouth, are re-emerging as significant risk factors²⁶⁻²⁸. Some epidemiological studies²⁹⁻³¹ show that employment in industries with occupational exposure to wood dust, asbestos, acid mists or solvents, and in textiles and leather manufacturing, are associated with an increased risk of UADT cancer^{16,30-32}. Furthermore, a positive relationship between a family history of head and neck cancer and UADT cancer risk have been suggested by a few studies^{33,34}. Low socio-economic status (SES) has been independently linked to an increased incidence of, and poorer survival for those diagnosed with, UADT cancer³⁵⁻³⁷.

Different behavioural/environmental or genetically present exposures/risk factors to health do not occur in solitude¹⁴. The sequence of episodes within the risk factors leading to an adverse health outcome includes both proximal and distal causes – proximal factors act directly or almost directly to cause disease, and distal causes are further back in the causal chain and act via a number of intermediary causes¹⁴. The risk factors that make an individual susceptible to diagnosis of a chronic disease, such as cancer, at early or later stages of life, are likely to have their roots in a complex chain of environmental events that may have begun years previously, which, in turn, were shaped by broader socio-economic determinants¹⁴. Most of the risks are interlinked and cannot be untwined from each other to be considered separately, as they act at different levels and vary over different periods of life¹⁴.

LIFE-COURSE PERSPECTIVE TO UADT CANCER

Socio-economic factors (education, occupation and family income), which are considered as determinants of health, are effective throughout life, across cause, place and time^{14,31}. Their study involves two broad perspectives: one based upon the life-course; and the other emphasising contemporary life circumstances^{31,38}. The life-course approach and health perspectives consider chronic disease epidemiology in terms of social and physical hazards, and the consequent biological, behavioural and psychosocial processes, that act across all stages of the lifespan – gestation, infancy, childhood, adolescence, young adulthood and midlife – to affect the disease risk or health in later adult life³⁹.

The independent interactive and cumulative interconnections between spheres of various biological and psychological pathways and social determinants, such as education, occupation, income and family environment, and the fact that chronic disease development is influenced by participation of individuals in multiple spheres, can be studied under the life-course framework approach^{14,39,40,41}.

Figure 1 illustrates early-life factors, including biological and social factors, which may play a crucial role in causing many later-life conditions in addition to – or in synergy with – those of well-established adult exposures⁴²⁻⁴⁷.

LIFE-COURSE EPIDEMIOLOGY – THEORETICAL MODELS (WITH RELEVANT EXAMPLES)

Life-course epidemiology is not solely a longitudinal study. It basically relies on two models: the first is a theoretical model, whereas the second is a study design^{14,48}. The purpose of life-course epidemiology is to build and test theoretical models that postulate pathways linking exposures across the life-course to later-life health outcomes^{14,48} (Table 1). Considering the wide range of exposures over the life-course and the potential importance of timing and duration, exposures may affect disease risk in a variety of ways. Based on this concept, life-course has been divided into four broad hypothetical models, which are listed here briefly and then are explained in detail in further sections¹⁴:

- *Critical period model*¹⁴ – where an insult during a specific period of growth or development has a lasting, lifelong effect on physical functioning or structure that results in disease later on
- *Critical period influences with later modifiers of their effects*¹⁴ – the later factors modify a risk incurred earlier
- *Accumulation of risk with correlated results*¹⁴ – where risk factors cluster in socially or biologically

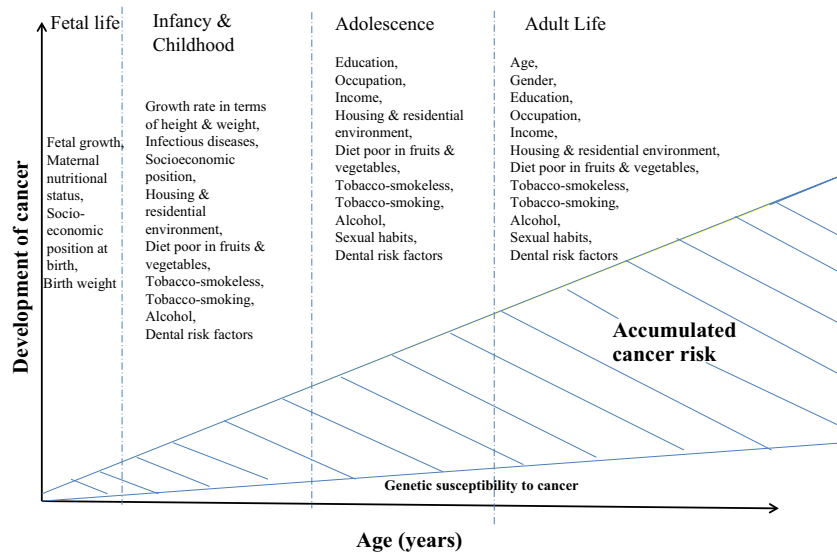


Figure 1. A life-course perspective to upper aero-digestive tract cancer.

Table 1 Structure of life-course epidemiology: concepts

Causal pathway in relation to time
Accumulation
Chain of risk
Trajectory
Timing of casual actions (stages of life)
Birth cohort
Critical period
Sensitive period
Induction and latency period
Different types of mechanisms
Embodiment
Mediating
Modifying factors
Resilience
Susceptibility and vulnerability

Source: Ben-Shlomo and Kuh¹⁴.

patterned ways and hence raise the risk of disease through social and/or biological chains or pathways of risk where one adverse (or protective) experience will tend to lead to another adverse (or protective) experience in a cumulative way

- *Accumulation of risk with independent and uncorrelated results*¹⁴ – where separate and independent risk factors at each stage of life combine to raise disease risk.

These models explicitly require the temporal ordering of exposures and their inter-relationships. The development of these models in life-course epidemiology provides a persuasive rationale for time-related study designs^{39,49,50}. The above-mentioned life-course models occur simultaneously and thereby cannot be segregated from each other. It is hard to distinguish these models empirically, or to develop standardised and acceptable methods of combining cumulative

exposures⁴⁸. Before we understand the four life-course models, we need to understand what the terms ‘critical periods’ and ‘sensitive periods’ mean. Therefore, a brief description of these terms is given in the following section.

CRITICAL PERIOD VERSUS SENSITIVE PERIODS

Qualitatively different exposure-time interactions throughout life describe the ‘critical’ and ‘sensitive’ periods. During both of these periods, exposure to disease risk factors are deterministic, or especially powerful, in predisposing to, or lessening the risk of, disease in later stages of life^{14,39,48}. Early life exposures that must occur in some specified window (s) of time, and often involve exposures that alter normal biological development which may have a long-term effect on body function or disease (protective or an adverse effect), are referred to as the ‘critical period’^{39,48}. A broader class of influences that may have greater impact on later outcomes if they occur in certain periods outside the developmental time window are referred to as the ‘sensitive period’, which is more likely to be seen in behavioural development^{39,48}. The accumulation of risk – chain of risk or pathway model – can have an additive or a trigger effect on the incidence of cancer in later stages of life.

MODEL 1: CRITICAL PERIOD

The critical period model can be with or without effect of later-life risk factors or with later-life effect modifiers¹⁴. Critical period of development refers to a time window when intrinsic changes in the organisa-

tion of living systems or subsystems towards increasing complexity, greater adaptivity and more efficient functioning occurs rapidly and may be most easily modified in a favourable or unfavourable direction⁵¹. This is also known as ‘biological programming’ or as a ‘latency model’³⁸, and is the basis of the ‘fetal origins of adult disease hypothesis’⁵².

The period of *in utero* development is one of the most critical windows during which adverse intrauterine conditions and exposures may influence the growth and development of the fetus as well as its future post-natal health and behaviour, for example: maternal cigarette smoking during pregnancy has been associated with altered DNA methylation and dysregulated expression of microRNA. Another example of ‘biological programming’ can be explained by the following example: the delay in tooth emergence at 12 months of age was associated with those who were shorter at birth and those who were classified as stunted⁵³. Also, the prevalence of not having lower permanent molars at 6 years of age was higher among children who had a chronic malnutrition indicator at 6 months of life⁵³.

During this important period, ‘critical windows’ are narrow and certain disturbances may alter fetal growth and development, leading to health and behavioural consequences that manifest, and possibly persist, across the life-course⁵³ as illustrated in *Figure 2*, Model 1^{54,55}.

MODEL 2: CRITICAL PERIOD MODEL WITH LATER EFFECTS MODIFIERS

This model is an extension of the first model. Active risk factors in later stages of life may interact with exposures in early life either to increase the effects on cancer (‘synergism’) or to diminish them (‘antagonism’)¹⁴. This model includes the possibility that the effect of an exposure during the critical period of development on later disease risk may be suddenly altered by later active stressors – physiological or psychological^{14,56–58} – as illustrated in *Figure 3*, Model 2. An example of this period can be taken from a study

investigating the effect of breastfeeding and non-nutritive sucking habits on the occlusion patterns at 6 years of age, which highlighted that the presence of breastfeeding combined with the non-use of pacifiers ensured a protective effect of the presence of posterior cross-bite in the primary dentition⁵⁹.

MODEL 3: ACCUMULATION OF RISK – INDEPENDENT AND UNCORRELATED INSULTS

In contrast to the first two models⁵⁵, the ‘accumulation of risk model’ assumes that risks to health or factors that promote good health amalgamate gradually over the life-course (through episodes of illness and injury, unfavourable environmental conditions and health-undesirable behaviours) without neglecting factors acting at sensitive developmental periods, which may have a greater impact on health in later life. This idea is complementary to the notion of allostatic load⁵⁹, which means that as the number, duration and severity of exposures increases, there is increasing cumulative damage to biological systems⁵⁹. Risk exposures may be independent and uncorrelated insults, as illustrated in *Figure 4*, Model 3, or clustered, as shown in *Figure 5a*, Model 4^{55,60–62}; the latter is known as an ‘accumulation model with risk clustering’^{14,39}.

MODEL 4: ACCUMULATION OF RISK – CORRELATED INSULTS OR RISK CLUSTERING

A common reason for risk factors clustering is where all exposures relate to an individual’s or family’s socio-economic position in society, as illustrated in *Figure 5a*, Model 4.

MODEL 4: ACCUMULATION OF RISK – CHAIN OF RISK OR PATHWAY MODEL – AN ADDITIVE EFFECT

A ‘chain of risk or pathway model – an additive effect’ refers to a sequence of linked exposures that

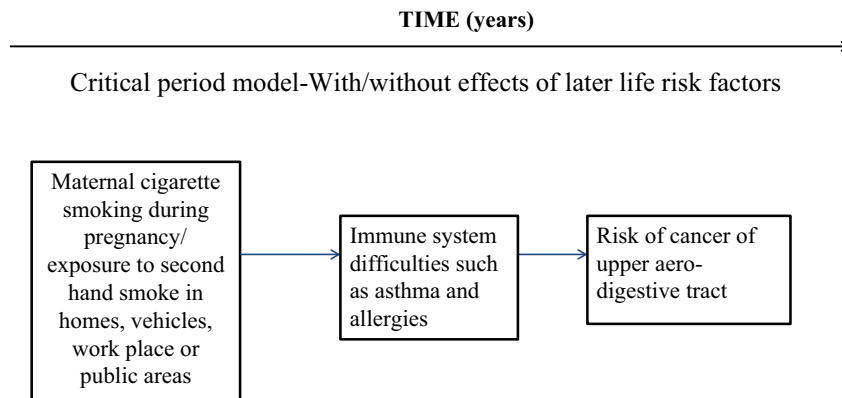


Figure 2. Life-course epidemiology: Model 1 – critical period/sensitive period, with/without effects of later-life risk factors.

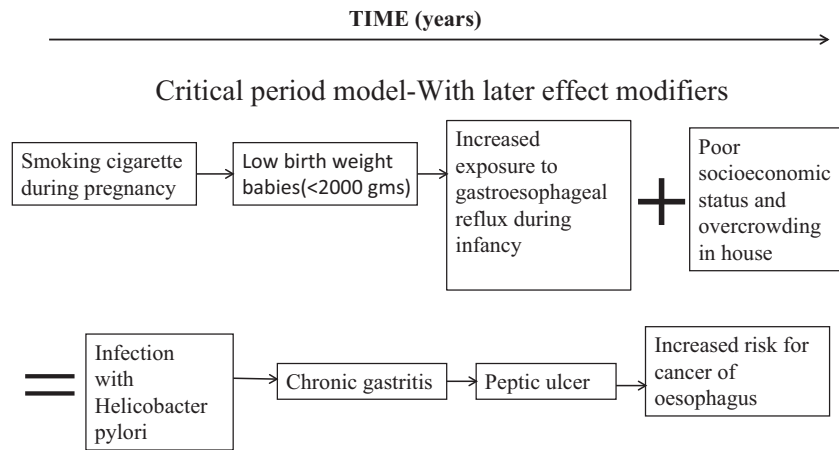


Figure 3. Life-course epidemiology: Model 2 – critical period/sensitive period with later effect modifiers.

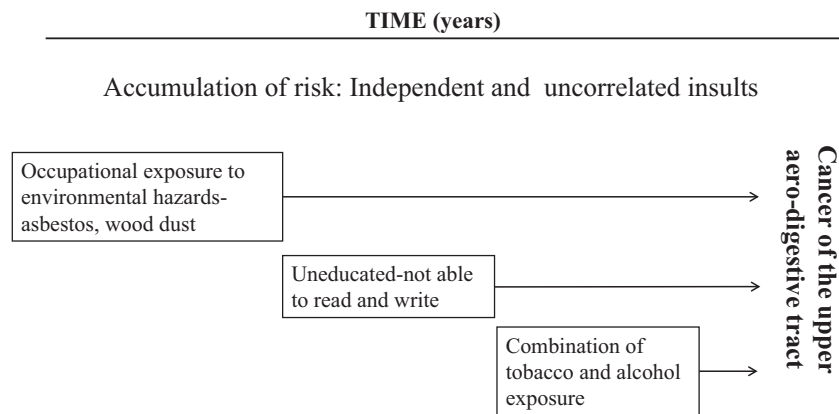


Figure 4. Life-course epidemiology: Model 3: accumulation of risk. Independent and uncorrelated results.

lead to impaired function and an increased likelihood of getting the disease, as one negative experience/exposure/risk leads to another, and so on (in a probabilistic manner)³⁸; it may also have an independent ‘additive effect’ on later function or disease, as shown in *Figure 5b*, Model 4^{60–62}.

Alternatively, a ‘trigger effect’ describes a chain of risk where it is only the final association in the chain that has any considerable influence on the outcome, as shown in *Figure 5c*, Model 4^{61,62}.

The life-course models as explained above are inseparable and may operate concurrently. It may not be easy to distinguish these models empirically or to develop standardised and acceptable methods of combining cumulative exposures¹⁴. Use of the life grid technique has been shown to improve recall and the reliability of past recalled information in life-course model-based studies⁶³.

Few studies have explored the relationship between life-course risk factors and the incidence of UADT cancer. However, the results of a recent European study suggest that a downward life-course social trajectory is an unbiased discrete risk factor for head and

neck cancer among men³¹. Studies in the field of breast, prostate and testicular cancers have obtained similar results⁵⁰. Similarly, a couple of previous studies provide evidence that parental health and their health behaviours have direct and early impacts on their children, placing them at greater risk for subsequent detrimental health outcomes^{64,65}. On the contrary, others have reported loss of effect of social factors when adjusted for smoking and alcohol⁶⁶.

Nonetheless, there are large gaps in knowledge to confirm any definite linkage or influence of socio-economic determinants along the life-course of an individual on incidence of UADT cancer.

CHALLENGES WITH THE LIFE – COURSE MODEL

Understanding the life-course is about understanding lives through time. This requires the researchers to consider the dynamic process and multidimensional nature of health and well-being in adulthood associated with time and place. Another barrier for application of life-course approach to cancer is the lack of intermediate end-points, such as serum lipids and hypertension

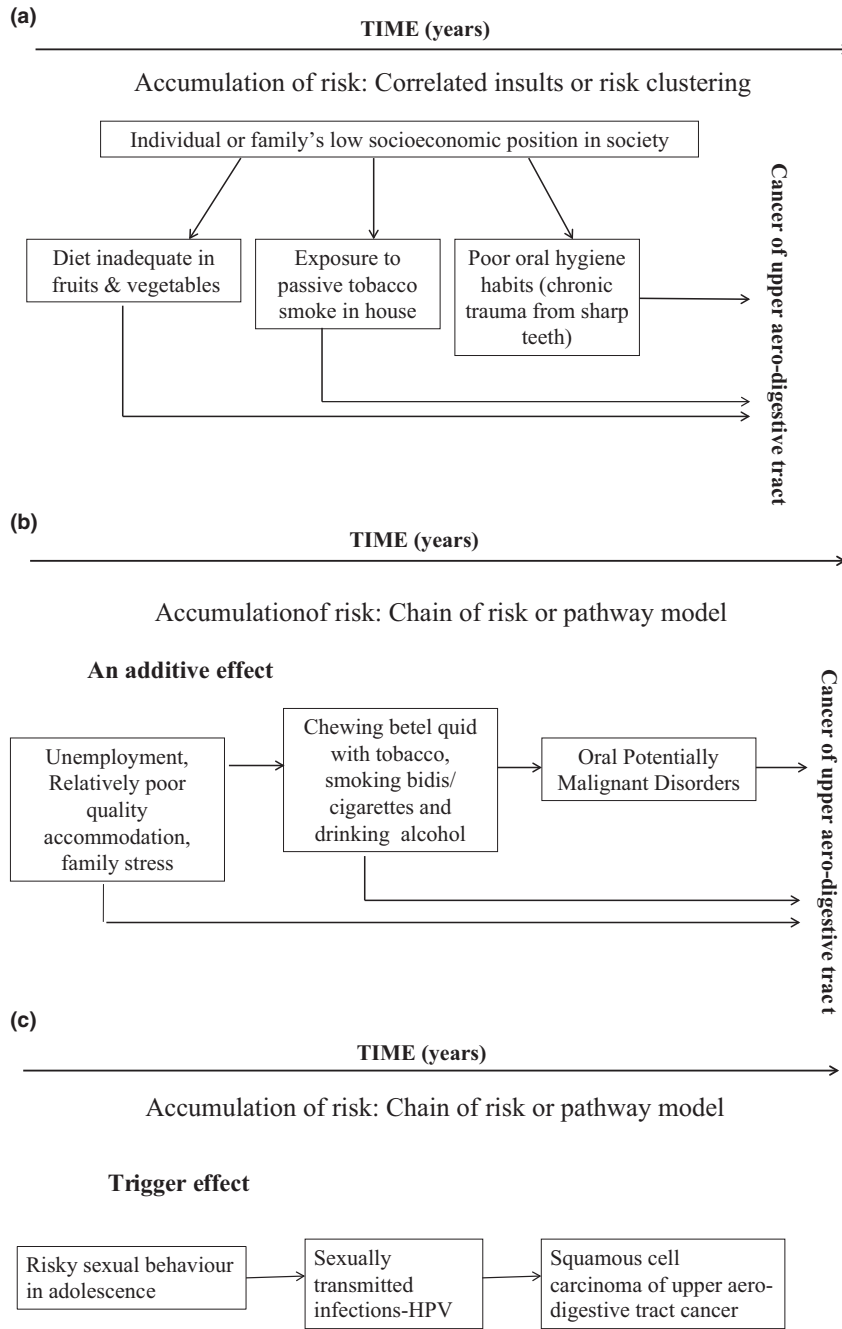


Figure 5. Life-course epidemiology: Model 4: accumulation of risk. (a) Correlated insults or risk clustering. (b) Chain of risk or pathway model (additive effect). (c) Chain of risk or pathway model (trigger effect). HPV, human papillomavirus.

(which exists for cardiovascular diseases), inadequate knowledge of the biological mechanism related to the development of cancer and the relative rarity of specific cancers in populations¹⁴. Case-control studies are limited in types and in accuracy of early life information obtained through recall from adult participants. Missing data as a result of low response rates among participants or surrogates, and the inability to recall exposures in the distant past, presents with other major difficulties¹⁴.

Apart from the initial study design, implementation of life-course models present many methodological challenges. They include the analytical problems associated with modelling repeat observations, hierarchical data, latent exposures or multiple interactive or small effects^{14,67}. When distal exposures operate through different levels of risk factors, their complete impact may not be recorded in traditional regression analysis methods in which both proximal and distal variables are included. More complex multilevel mod-

els and characterisation of causal webs of interactions among risk factors may lead to more appropriate estimates, as well as facilitating estimation of the effect of simultaneous changes in two or more risk factor distributions⁶⁸.

POLICY IMPLICATIONS

Explicit recognition of life-course models can help improve the design and effectiveness of future intervention programmes to promote healthy aging⁶⁹. Based on life-course theories and models, policies targeting health prevention at individual and at social levels should target the health care of infants, children and adults. This would require a major reconfiguration of existing health-delivery systems, with more focus on longitudinal integration of services over time⁴⁹. Investment in child health care would be a key stage for preventing many risk factors that increase the incidence of chronic diseases in adulthood. For example, instructions given to children attending dental clinics, by a dental hygienist/dentist, regarding maintaining good oral hygiene at all stages of life during adolescence, have a positive impact in reduction of tooth loss^{70,71}. Another example could be advocating a message about being a non-smoker, or, for a young adult who smokes, the importance of smoking cessation⁷². The reformed health policies should target the socio-behavioural development, rather than the health outcomes only.

CONCLUSIONS

Chronic diseases, such as cancer, are a major public health problem in both developed and developing countries and there is increasing evidence that life-course exposures during intrauterine growth, postnatal growth and developmental trajectories play a crucial role in the development of these diseases⁷³. Poverty and socio-economic disadvantage are integral in the complex aetio-pathogenesis of many chronic diseases⁷⁴. Most longitudinal studies on the association of life-course exposure with development of cancer have been performed in developed countries and there is a great need to collect data from developing countries so that consistency between exposure and disease associations can be examined in different contexts³⁸. Research has proved that a more holistic approach to cancer is more effective than the medical approach alone.

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Conflict of interests

The authors have no competing interests.

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