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Review Article

Primary Care for Cancers: Epidemiology, Causes, Prevention and Classification- A Narrative Review

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Abstract

This paper is meant as an overview and updates of fundamental information on cancers. It contains many cancer-related aspects that primary care providers and professionals (PCPP) need to be reminded of and aware in their quest for convincing reason and purpose in dealing with cancer patients. Cancer incidence and prevalence have been alarming in the world. There were about 25 new cancers and 16 cancer deaths every minute in the world in 2008. The causes of cancers are multi-factorial; right from the family history, pathogens, environmental elements, personaldietary choices to exercise. Preventive measures are effective in managing the modifiable factors such as staying away from carcinogenic agents and practising healthy life-styles. There was evidence that lacking confidence in knowledge of cancer and risk assessment were common barriers among the PCPPs for effective cancer care. Many patients with cancer desired more information about life after cancerfrom their PCPPs. Being in the front-line of health systems and functioning as gate-keepers in primary care, essential cancer-related knowledge is important for PCPPs. Thus, this paper aims to provide some update on cancerepidemiology, causes, preventive measures and classification of cancers to PCPPs.

ABBREVIATIONS

PCPP: Primary Care Providers and Professionals; **USPSTF:** United States Preventive Services Task Force; **HPV:** Human Papillomavirus; **LDCT:** Low Dose Computerized Tomography; **PSA:** Prostate-Specific Antigen; **DRE:** Digital Rectal Examination; **ASR:** Age-Standardised Incidence Rates; **Cumr:** Cumulative Risk; **NCR:** National Cancer Registry; **IARC:** The International Agency for Research On Cancer; **WHO:** World Health Organization; **CIN:** Cervical Intraepithelial Neoplasia; **OCs:** Oral Contraceptives; **DNA:** Deoxyribonucleic Acid; **EPIC Study:** European Prospective Investigation into Cancer and Nutrition; **OR:** Odd Ratio; **VO_{2max}:** Maximal Oxygen Uptake; **CDC:** Centre for Disease Control; **ICD:** International Classification of Disease; **ICPC-2-R:** International Classification of Primary Care-2-Revised; **IDLE:** Indolent Lesions of Epithelial Origin

INTRODUCTION

It is widely recognized that up to half of the cancer deaths could be prevented should there be more awareness of healthy life-styles, better uptake of screening services and more effective treatments [1]. It is also widely accepted that one third of cancers can be cured only if they were detected and treated early [2]. Mortality is related to the cancer stage at diagnosis, with the best prognosis being in early stage. There was evidence that lacking confidence in knowledge of cancer risk and risk assessment were common barriers among the primary care providers and professionals (PCPP) [3]. Furthermore, the relationship between perceived cancer risk and exposure to established risk factors differs in important ways from what health campaigns have communicated with the public [4].

Up to 43% of patients with cancers surveyed had expressed their need for more information on diet and exercise, side-effects of treatment and indicators of recurrent [5]. Since prevention and patient education are the primary scopes of PPCPs' duty and service, this paper was written for the purpose of educating and strengthening the essential cancer-related knowledge that are thought to be important for the PCPPs. PCPPsas used in this paper refers to allied health professionals such as nurses, physician assistants, nutritionists, pharmacists, physiotherapists as well as the primary care physicians. Primary care is defined as the health system which patients experience first contact of health care and it is mainly provided at the community-based health

clinics and hospital-based emergency departments. Systematic searches with terms comprised "cancer", "malignancy", "primary care", "general practice", "cancer AND causes" and "cancer AND prevention" were done in the major databases such as Pubmed, ScienceDirect and Ovid. We employed selective searches with the above terms and their combination in some of the major journal such as The Lancet Oncology, The Lancet, New England Journal of Medicine etc. We snowballed relevant references from some of the key papers identified from the above. Cancers screening is not included in this review as it is a distinctive topic by itself and has been well collated elsewhere [6]. However, owing to the importance of cancer screening for early detection of cancers at primary care, we have presented the recommendations for screening of some of the common cancers from United States Preventive Services Task Force (USPSTF) (http://www.uspreventiveservicestaskforce.org/uspstopics.htm) in Table 1 [6].

CANCER BURDEN IN THE WORLD

There was a worldwide estimation of cancer burden in 2008: an estimated of 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008, with 56% of new cancer cases and 63% of the cancer deaths occurring in the less developed regions of the world [7]. In the same year, there were about 700,000 new cancer cases and half a million cancer deaths in ASEAN region [8]. The cancer rate in the world was projected to increase to 15 million and more than 25 million new cases by 2020 and 2030 respectively [1,9]. The most commonly diagnosed cancers worldwide were lung (1.61 million, 12.7% of the total), breast (1.38 million, 10.9%) and colorectal cancers (1.23 million, 9.7%). The most common causes of cancer death were from lung cancer (1.38 million, 18.2% of the total), stomach cancer (738,000 deaths, 9.7%) and liver cancer (696,000 deaths, 9.2%). It was noted that striking differences in the patterns of cancer were observed between regions [7].

Cancer incidence and prevalence have been alarming in Malaysia. Cancer occurs at all ages and increases with age. A total of 18,219 new cancer cases were reported in 2007, consisted of 8,123 (44.6%) males and 10,096 (55.4%) females [10]. The most frequent cancers in children (0-14 years old) were leukaemia and lymphoma. This was followed by cancers in the brain/nervous system and bone [10]. In 2007, cancer was the third common cause of death in Malaysian hospitals after cardiopulmonary diseases and septicaemia. The ten leading cancers among population of Malaysia in 2007 were breast (18%), colorectal (12%), lung (10%), nasopharynx (5%), cervix (5%), lymphoma (4%), leukaemia (4%), ovary (4%), stomach (4%) and liver (3%). The five most frequent cancers among Malaysian males were lung, colorectal, nasopharynx, prostate and lymphoma, while the five most common cancers in females were breast, colorectal, cervix, ovary and lung [10]. This local cancer data is believed to be under-reporting and better quality data is expected in a later registry database.

The age-standardized cancer incidence rates (ASR) in Malaysia were 85.1/100,000 in males and 94.4/100,000 in females. The cumulative risk (CumR) was 9.6 for males and 9.9 for females, representing the risks of males and females in Malaysia who developed cancers before the age of 75, in the absence of other causes of death. The incidence rate in males exceeded the incidence rate in females after the age of 60 years. Similar with previous National Cancer Registry (NCR) reports, cancer seems to be predominantly among the Chinese as compared to the Malay and Indian.[10]National Cancer Control Program with its many policies and initiatives emphasize on health promotion via public campaigns, cancer prevention via healthy life-style and screening, early diagnosis, effective treatment and rehabilitation [11]. However, late presentation of many cancers were still prevalent especially cancers of the breast and cervix. The causes were said to be related to the ethnic background or cultural beliefs [12]. Of the 8,869 (48.7%) new cases reported and registered in NCR, 17.0% were reported as stage I, 25.3% as stage II, 25.0% as stage III and 32.7% as stage IV [10]. One of the possible reasons for more late cancer presentation in Scotland as compared to other European countries was said to be restricted family physician direct access to hospital investigations [13,14]. In developing countries such as Malaysia and India, this could be related to patient's factors such as unmarried and low education, poor symptoms recognition, inadequate disease knowledge, wider beliefs in and usage of traditional therapies, fearful of modern medicine therapies, family coping mechanism and affect etc. [15,16]. The other possible causes for delay had been attributed to primary health care workers and doctors especially in cancers diagnosis of the head and neck region [17,18].

WHAT IS CANCER?

Traditional models of tumorigenesis have largely focused on identifying cancer-causing genetic changes present in the neoplastic cells. Weinberg and colleagues experimentally defined a series of six hallmark changes necessary for the progression from cancer initiation to tissue invasion and metastasis. These include growth signal self-sufficiency, antigrowth signal insensitivity, apoptosis evasion, limitless replicative potential, angiogenesis, and tissue invasion and metastasis [19].

Metastasis is the major cause of morbidity and mortality in patients with cancer. The molecular mechanisms that control metastasis are related to alterations in various oncogenes, tumor suppressor genes, metastasis suppressor genes, and growth factors and their receptors. These abnormalities affect the downstream signal transduction pathways involved in the control of cell growth and other malignant properties. One of the most recognized signal transduction pathways involves the signal transducer and activator of transcription 3 (STAT3) protein [20]. Advances in this aspect have led to the discovery of molecular targeting drugs (MTC) that could offer a more effective chemotherapy in many cancers treatment.

CAUSES OF CANCERS

In 2001, a study published in Lancet reported that smoking, alcohol use, low fruit and vegetable intake, overweight/obesity and sexual transmission of human papilloma virus were the leading risk factors for cancer death [21]. The International Agency for Research on Cancer (IARC) under the auspice of World Health Organization (WHO) (http://monographs.iarc.fr/index.php) is regularly reviewing published studies and weighing the evidence of any human-related environmental factors (these include chemicals, complex mixtures, occupational exposures,

physical agents, biological agents, and lifestyle factors) that can increase the risk of cancer. Since 1971, IARC have evaluated more than 900 agents, of which more than 400 have been identified as carcinogenic, probably carcinogenic, or possibly carcinogenic to humans. IARC Monographs are highly regarded by many national health agencies in guiding actions to prevent human exposure to potential carcinogens. Each Monograph is complete with descriptions of the carcinogenic agent and how people are being exposed (eg. occupation), critical overviews of the epidemiological studies, a concise review of the agent's toxico kinetics, plausible mechanisms of carcinogenesis, susceptible populations and of the most susceptible human life-stages. The IARC latest announcement was on the outdoor air pollution as a leading environmental cause of cancer deaths. The principal sources of this pollution were reported to come from transportation, power plants, and industrial and agricultural emissions. Table 2 shows the IARC classification of the overall evidence on cancers and Table 3 provides an example of the descriptions and carcinogens according to the IARC cancer classification.

Some of the pathogens have been found to be carcinogenic. In developing countries, up to 23% (compared to about 8% in developed countries) of malignancies are caused by infectious agents. These include hepatitis B and C viruses (liver cancer), human papillomaviruses (cervical and ano-genital cancers), and Helicobacter pylori (stomach cancer) [1]. High-risk human papillomaviruses (HPV stypes 16, and 18) are involved in the aetiopathogenesis of cervical intraepithelial neoplasia (CIN) and cervical cancer [22,23]. Epstein-Barr virus was found to be associated with B-cell lymphomas [24]. Therefore, vaccinations have been advocated to be instrumental in preventing these cancers.

A systematic review of 28 studies found that oral contraceptives (OCs) users when compared with never pill users had the relative risk of cervical cancer increased with increasing duration of OCs use. However, there was no correlation reported between hormone replacement therapy and cervical cancer [22]. Dietary supplementation with vitamin E (400 IU/d of all rac-α-tocopheryl acetate) on the other hand was shown to significantly increase the risk of prostate cancer among the healthy men; the absolute increase in risk of prostate cancer per 1000 person-years was 1.6. [25].

Both exogenous and endogenous agents are potential threats to deoxyribonucleic acid (DNA) integrity. Exogenous environmental agents such as the ultraviolet, ionizing radiation, genotoxic chemicals and endogenous by-products of metabolism including reactive oxygen species can cause DNA damage. This unrepaired DNA damage has been linked to a variety of human disorders including cancer [26,27]. Many genotoxic chemicals are found in the pesticides, herbicides, synthetic dyes and colorants of the related industries. Much of the work in relating these agents as carcinogens in humans was done by the IARC.

Ever smokers in Europe were reported to have an increased risk of colon cancer, which appeared to be more pronounced in the proximal than the distal colon location [28]. In this same study, smokers who had stopped smoking for at least 20 years still had the same risk of developing colon cancer compared to the never smokers [28]. Smoking was noted to be the only significant risk factor (OR = 15.53, 95% CI 5.36–44.99) in a multivariate analysis of socioeconomic circumstances (education, occupational social class, unemployment, smoking and alcohol consumption) for head and neck cancer in Scotland [29]. Smoking habit appeared to be the most significant environmental risk factor for cervical cancer even after taking HPV into account, and this cancer risk correlated significantly with intensity and duration of smoking [22].

European Prospective Investigation into Cancer and Nutrition (EPIC) study in eight countries (France, Italy, Spain, United Kingdom, the Netherlands, Greece, Germany, Denmark) reported that 3 to 10% of total cancer incidence was attributable to alcohol consumption. For selected cancers the figures were 44% (31 to 56%) and 25% (5 to 46%) for upper aero digestive tract, 33% (11 to 54%) and 18% (−3 to 38%) for liver, 17% (10 to 25%) and 4% (−1 to 10%) for colorectal cancer for men and women, respectively, and 5.0% (2 to 8%) for female breast cancer. This substantial part of the alcohol-attributable fraction was associated with alcohol consumption that was higher than the recommended upper limit (two drinks a day for men with about 24 g alcohol, one for women with about 12 g alcohols) [30].

Magnetic field exposure around power grid lines and electrical appliances, especially the former, was reported to have consistent but limited evidence of relationship with childhood leukaemias (relative risk of 1.5 to 2.0). There was no such observation among the adult. Cell phones radiofrequency exposure and cancer study, the INTERPHONE Study Group which was published in May 2010 reported negative association between cell phone use and brain tumours namely glioma, meningioma, and acoustic neuroma [31]. In another update of Danish cohort study, the investigators also concluded there was absence of causal relationship between mobile phone use and cancers of the central nervous system [32]. Although there were inadequate studies in the paediatric age groups, it is cautioned that children might be at significant risk of cancers from the radiofrequency based on physiological points of view.

Some diseases predispose to cancer occurrence. Diabetes mellitus and its major risk factor of obesity were frequently found to co-exist with malignant tumours in many epidemiologic studies and meta-analyses [33,34]. A meta-analysis of the all-cancer risk in both Japanese men and women showed an increased cancer risk in subjects with diabetes, compared with non-diabetic subjects (OR 1.70, 95% CI 1.38–2.10). The increase in the risk ratio adjusted for possible confounders was significant in men and borderline in women with diabetes mellitus (adjusted RR 1.25, 95% CI 1.06–1.46 in men; adjusted RR 1.23, 95% CI 0.97–1.56 in women). An analysis of site-specific cancers also revealed increased risks for incident hepatocellular cancer (OR 3.64, 95% CI 2.61–5.07) and endometrial cancer (OR 3.43, 95% CI 1.53–7.72) in people with diabetes mellitus [35]. A consensus report [36] by the American Cancer Society stated that type 2 diabetes mellitus is associated with increased risk of some cancers in the liver, pancreas, endometrium, colorectal, breast and bladder; but with reduced risk of prostate cancer. The report went into further details on the anti-hyperglycaemic agents, the possible mechanisms of carcinogenesis and evidence gap for future research. In another study in Taiwan, adults patients with

depressive disorders (ICD-9-CM codes 296.2, 296.3, 300.4, and 311) on hospital admission was independently associated with an overall 1.62-fold (95% CI: 1.12, 2.34) increased risk of subsequent malignant neoplasm during the next five years of follow-up [37]. It was postulated that depressed person had altered immune response and this could be compounded by unhealthy lifestyles predisposing them to more cancers occurrence.

Consanguinity, which increases the chances of homozygosity, is linked to an increased overall risk of cancer and elevated risk of breast cancer, all leukemias, and acute lymphocytic leukemia in children [38, 39]. However, it was otherwise in a local Arab population in the United Arab Emirates, inbreeding was associated with reduced overall risk of cancer in the studied population. Reduction of cancer risk was greater in men than women, and in women it was restricted to those older than 30 years [40]. This apparent contradiction needs confirmation from further studies with better sample size and study design.

PREVENTION OF CANCERS

Many preventive measures are dietary and life-styles related. The greatest impact would be from the control of tobacco smoking [9]. Nevertheless, not all cancer causes or mortality rates could be explained by the regional variations in the consumption of nutrients [41]. In fact, there are many non-modifiable familial factors, exogenous unidentified potential confounders and endogenous unexplained biochemical metabolism that are carcinogenic. IARC has published a series of cancer prevention handbooks with titles range from tobacco control, fruits and vegetables; weight control and physical activity; carotenoids to sunscreen (http://www.iarc.fr/en/publications/list/handbooks/index.php).

A high intake of fruits and vegetables is associated with a lower risk of cancer, especially of the gastrointestinal tract, namely the oesophagus, stomach and colorectum [42]. Reduction in salt, salt-preserved food and fat intake with simultaneous increased intake of fresh fruits and vegetables could prevent about 10% fraction of cancer incidence [43]. Men may benefit from the intake of isoflavones with regard to reducing the risk of prostate cancer [44]. Epidemiological evidence consistently suggested that milk intake was protective against colorectal cancer; calcium supplements reduced risk for recurrence of adenomatous polyps [45]. However, high calcium intake from both food and supplements was associated with increased risk for advanced or fatal prostate cancer. Dietary guidelines for cancer prevention encourage meeting recommended levels of calcium intake primarily through food choices rather than supplements, and choosing low-fat or nonfat dairy foods [45]. Some epidemiologic studies had observed an association between increased intake of dietary antioxidants and decreased risk of cancers in the lung, esophagus, and gastrointestinal tract [46]. Although antioxidants are substances that counteract free radicals and prevent them from causing tissue and organ damage,evidence supporting antioxidants in preventing cancers were limited. Therefore, there is no recommendation for any of these agents to be used in chemo prevention of cancer in healthy and well-nourished adults [9].

Experimental studies have consistently shown the inhibitory activities of tea extracts on tumorigenesis in multiple model systems [47]. Epidemiologic studies, however, have produced inconclusive results in humans. In general, consumption of black tea was not associated with lower risk of cancer but high intake of green tea was associated with reduced risk of upper gastrointestinal tract cancers. Green tea might exert beneficial effects against mammary carcinogenesis in premenopausal women and recurrence of breast cancer [47]. However, there is limited data to support the protective effect of green tea on the development of cancers of the lung, liver, colorectum, pancreas, urinary tract, glioma, lymphoma, and leukemia. Although observational studies did not support a beneficial role of tea intake on prostate cancer risk, phase II clinical trials had demonstrated an inhibitory effect of green tea extract against the progression of prostate pre-malignant lesions. Future prospective observational studies with biomarkers of exposure and phase III clinical trials are proposed [47].

Cardio respiratory fitness has been shown to be protective of cancer in men. After adjustment for age, examination year, alcohol, smoking, socioeconomic status, waist-to-hip ratio and energy, fibre and fat intake, men with maximal oxygen uptake (VO_{2max}) of more than 33.2 mL/kg/min (highest tertile) had 27% (95% confidence interval (CI) 0.56–0.97) decreased cancer incidence and 37% (95% CI 0.40–0.97) reduced cancer mortality than men with VO_{2max} of less than 26.9 mL/kg/min (lowest tertile). The adjusted risk of cancer was 0.73 (95% CI 0.55–0.98) among fit ($VO_{2max} \geq 26.9$ mL/kg/min) men with the total energy expenditure of physical activity over 2500 kcal/week.[48] Fit men in this 16.7-years population-based cohort study had the greatest risk reduction in lung cancer.

Some literature reported that it might be appropriate to routinely vaccinate both males and females to prevent the spread of Human Papilloma virus (HPV) types 6, 11, 16, and 18 [49,50]. The CDC's Advisory Committee on Immunization Practices had voted unanimously to recommend the quadrivalent human papilloma virus vaccine (marketed as Gardasil) for boys aged 11 and 12 years, for protection against genital warts and HPV-related cancer. The vaccines had been demonstrated to be highly effective in preventing cervical dysplasia, vulvar cancer, and genital warts related to HPV types 6, 11, 16, and 18; they are most effective, however, in vaccines who have never been infected with HPV [49]. Contrary to the usual three doses HPV vaccination schedule, one or two doses of HPV-16/18 vaccine were reported to be as effective for preventing persistent infection among the Costa Ricans women [51].

Topical use of sunscreen protects against squamous cell carcinoma. Its use didnot cause vitamin D deficiency/insufficiency and had not been demonstrated to adversely affect the health of humans [52]. In penile cancer prevention, studies had shown that circumcision, prevention ofsexuallytransmitteddiseases and adequate penile hygiene were beneficial [53]. Interestingly, religiosity within religions wasassociated with reduced risks for certain cancers and this said to be due to improved healthy life-styles among the more religious [54,55].

There was extensive evidence on the effect of regular aspirin use and reduced colorectal cancer [56,57]. This incidental finding of chemoprevention property of aspirin might extend to other gastrointestinal and non-gastrointestinal cancers [58]. Better

evidence is needed to confirm this and its therapeutic dose, duration of use and the best age to begin treatment. Previous reports of the association of lowered blood cholesterol (by statin) and cancer [59] was recently refuted by a large study of about 20000 high-risk subjects who were treated with simvastatin to lower blood cholesterol for five years and follow-upped for 11 years [60].

CLASSIFICATION AND STAGING OF CANCERS

Cancers are broadly divided into benign and malignant. There are many ways of classifying cancers. Amongst them are by the type of tissue the cancer originates (histopathological), the primary site or body organ (anatomical) and by gene expression (molecular) [61,62]. Lately, there was a suggestion of an integrated model of cancer classification which all the attributes of a cancer such as the morphology, stem cell contributions, genetic expression and functional attributes were captured [63]. Similarly, there are many staging systems according to the cancer types. The main purpose and use of staging is in treatment decision and prognostication. Generally, they comprise the clinical (including radiologic) staging, histo-pathological staging and surgical (including laparoscopic) staging. With advancement in diagnostic imaging tests, the role of surgical staging has decreased and the vast majority of patients can be classified by less- or non-invasive staging modalities.

WHO classifies tumours according to ICD-10 version 2007 into Malignant neoplasms (C00-C97), In situ neoplasms (D00-D09), Benign neoplasms (D10-D36) and Neoplasms of uncertain or unknown behaviour (D37-D48). Sarcomas are non epithelial, non hematopoietic malignant tumors that arise from the embryonic mesoderm. Despite their rarity (less than 10% of all cancers) sarcomas are accountable for relatively high morbidity and mortality especially in children and adolescents [64]. International Classification of Primary Care-2-Revised (ICPC-2-R), which is another set of classification good in capturing reason for encounter in primary care, allocates a label (or known as rubric) for of fear of cancer as A26 [65].

National Cancer Institute in the United States had suggested a re-classification of the low grades or pre-malignant stage cancers as IDLE (indolent lesions of epithelial origin) conditions [66]. This was following observation over the past 30-40 years that improved screening programs had resulted in significant increases in early-stage diseases, without a proportional decline in later-stage diseases and mortality. For example, expanded screening for thyroid cancers and melanoma had resulted in increased detection of indolent diseases in these organs; other examples such as Barrett esophagus and ductal carcinoma of the breast for which the detection and removal of precancerous lesions have not led to lower incidence of invasive cancers. The indolent diseases are believed to cause no harm during the patient's lifetime. It is hoped that this new classification would curb over-diagnosis of cancers leading to overtreatment and burden of healthcare utility and on patients. Use of the term "cancer" should then be reserved for describing lesions with a reasonable likelihood of lethal progression if left untreated.

CONCLUSION

There were about 25 new cancers and 16 cancer deaths every minute in the world in 2008. Cancer was the third common cause of death in Malaysian public hospitals in 2007. The causes of cancers are often multi-factorial; family history or genomic make-up, pathogens, environmental elements, life-styles such as dietary choices and exercise. Preventive measures are effective against the modifiable factors aforementioned, staying away from carcinogenic elements and agents and practicing healthy life-style. We recognize that the evidence presented here is far from exhaustive and having observed all the "rules and regulations" does not ensure life without cancer. Failing this primary prevention, screening for cancers does have significant effect on reducing the mortality rates [9]. We believe health should be defined as "the ability to adapt and self manage in the face of social, physical, and emotional challenges"[67]. Henceforth, PCPP should be equipped and ready to support every men and women in facing life challenges even in face of cancer diagnosis, treatment, survival and death [68].

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