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Kuwait Emir HH Sheikh Nawaf Al-Ahmad Al-Jaber Al-Sabah and Crown prince HH Sheikh Meshal Al-Ahmad Al-Jaber Al-Sabah

Late Emir HH Sheikh Sabah Al-Ahmad Al-Jaber Al-Sabah headed a meeting for Kuwait Foundation for the Advancement of Sciences (KFAS)

R.I.P. SHEIKH SABAH AL-AHMAD AL-JABER AL-SABAH

THE EMIR OF KUWAIT

1929-2020

Late Emir HH Sheikh Sabah Al-Ahmad Al-Jaber Al-Sabah.
Late Dr. Abdulrahman Abdullah Al-Awadi, Dr. Rasheed Hamad Al-Hamad and Dr. Khaled Ahmed Al-Saleh

Late Emir His Highness welcomes the Minister of Health and members of the Gulf Federation for Cancer Control (GFFCC)
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Cancer Risk Factors Among Omanis: A Review

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Abstract

Background: Studying risk factors for cancer is the way for prevention and control. This study aims to review analytic studies reporting the identified risk factors of cancer in Oman.

Methods: A comprehensive literature search was conducted on “PubMed database, Scopus database, and Google Scholar”, using appropriate key terms/words. No date limits were defined until March 2019. Both; keyword and MeSH term strategies were used to retrieve studies.

Results: This review yielded 10 analytic studies related to cancer risk factors in Oman, all of which utilized the case control design. Seven studies were related to various genetic factors, two were related to dietary factors and obesity, and one was related to diabetes as a risk factor. There was insufficient evidence available on essential modifiable risk factors such as smoking, use of alcohol, environmental factors and infectious agents.

Conclusion: The scanty local literature is focused on genetic, non-modifiable factors, and very little is related to modifiable factors which should be given more attention to allow prevention and control. Locally, this is challenged by training needs for health professionals, and availability of financial resources, emphasizing the need for multi-sectorial work.

Keywords: Cancer, malignancy, neoplasm, risk, risk factors, predictors, gastric, stomach, prostate, colorectal, lymphoma, leukemia, breast, thyroid, Oman, Royal Hospital, Sultan Qaboos University Hospital.

Introduction

Cancer is considered as one of the leading cause of death across the globe nowadays. Globally, around 9.6 million deaths were attributed to cancer in the year 2018(1). According to the World Health Organization (WHO) estimates in 2015, cancer is the first or second leading cause of death before the age of 70 years in 91 countries worldwide (1). Globally, lung cancer is the commonest cancer, followed by female breast cancer, prostate cancer, and colorectal cancer (1). Among males, lung, prostate, colorectal, stomach, and liver cancers constituted 16.7%, 15.0%, 10.0%, 8.5% and 7.55 respectively. Among females, the most common incident sites of cancer were the breast (25.2% of the total), colorectal (9.2%), lung (8.7%), cervix (7.9%), and stomach (4.8%) (2).

Cancer risk factors

World Health Organization has reported tobacco use as one of the most common risk factors for cancer. Globally, cancer related deaths caused by tobacco represents 22% (3). Apart from tobacco use, the following risk factors are reported to be risk factors for cancer; overweight or obesity, low fruit and vegetable intake, lack of physical activity, alcohol use, ionizing and ultraviolet radiation, urban air pollution, and indoor smoke from household use of solid fuels (3).

Specific risk factors

In addition to the common risk factors, there are other factors identified to be linked to specific types of cancers. For example, early menarche and parity status were identified to be significantly related to an increased risk of breast cancer (4,5). In addition, oral contraceptive pills were observed to be linked to breast

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cancer as well (9). In the same contexts, breast cancer was linked to genetic factors such as BRCA genes (8). On the other hand, increased salt and red meat consumption, as well as certain genetic factors are one of the associated risk factor for stomach cancer (7,8). With regard to diabetes as a risk factor, studies revealed that diabetes might play a role in the development of colon, liver and pancreatic cancer (6,9). However the longer the duration usage of metformin showed an inverse trend, suggesting a protective effect of this anti–diabetic agent (10). Furthermore, radon gas, which is a radioactive, colorless, odorless noble gas, occurring naturally, has been reported to be associated with lung cancer (11). On the other hand, asbestos was also identified to have a role in developing lung cancer and mesothelioma (12). Certain viral infections have also been blamed for certain neoplasms. In this regard, human papilloma virus has been linked to cervical cancer among females, and hepatitis B & C infections have been linked to hepatocellular carcinoma (5).

Cancer incidence in the Gulf countries and Oman

In the Eastern Mediterranean Region, cancer is the fourth most common killer and is increasingly recognized as a major health problem in this region (13). Three quarters of cancer mortality worldwide were related to developing countries. This number is projected to be around 11.5 million in 2030 (14). Particularly for the Arabian Gulf region, the rapid socio–economic changes occurred in past few decades have substantially modified the local lifestyles towards unhealthy patterns, such as increased tobacco use, decreased physical activity, and increased consumption of unhealthy food, all of which have likely increased the prevalence of cancer in the Gulf countries (15). Due to the young population structure in the Arabian Gulf countries, the cancer age standardized rates (ASR) in this region is almost half the rates reported globally (Oman 103.3 per 100,000, Bahrain 105.2 per 100,000, Qatar 79.3 per 100,000, Saudi Arabia 88.7 per 100,000, Kuwait 121.8 per 100,000, and the UAE 112.5 per 100,000 population) (16).

In Oman, cancer cases are treated mainly in two main tertiary centers, named the National Oncology Center in Royal Hospital and Sultan Qaboos University Hospital. Based on the Ministry of Health (MoH) statistics for 2017, cancer was the fourth leading cause of inpatient mortality (17). According to the latest report from Oman National Cancer Registry, the total number of all tumors registered in 2016 were 2,015. Of these, 1, 780 (88.3%) were among Omani and 215 (10.7%) were Non–Omanis, and only 15 (0.7%) cases were carcinoma in situ (18). Of the total 1780 Omani, male accounted for 826 cases (46.4%) and females’ accounts for 954 cases (53.6%). The male: female ratio was 1:1.15. The median age at diagnosis was 54 years (18).

The crude incidence rates for all cancer among Omani were 67.4 per 100,000 for males and 79.3 per 100,000 for females. The ASR was 105.3 per 100,000 for males and 113.6 per 100,000 for females (19). The five most common cancers among males were prostate (10.3%), colorectal (9.3%), liver (7.8%), leukemia (7.8%) and Non–Hodgkin Lymphoma (7.3%). While among female breast cancer was the commonest (27.4%), followed by thyroid (15.5%), colorectal (7.8%), Non–Hodgkin Lymphoma (4.5%) and leukemia (3.9%) (19).

Up–to–date, risk factors associated with various types of cancer in Oman have not been reviewed. This review aims to summarize the risk factors identified to be associated with cancer among Omani patients. This is particularly important to establish a database and to plan preventive measures. In addition, we aim to highlight gaps in existing knowledge for future research.

Methods

Search strategy

For this review propose, PubMed and Scopus databases were searched. In addition, Google Scholar was also searched for relevant studies. No date limits were defined until March 2019. Both; keyword and MeSH term strategies were used to retrieve studies. Keywords and terms included the following: cancer, risk, risk factors, factors, predictors, gastric, stomach, prostate, colorectal, lymphoma, leukemia, breast, thyroid, Oman, Royal Hospital, Sultan Qaboos University Hospital. Boolean operators and truncation symbols were used to focus and broaden data retrieval.

Inclusion and exclusion Criteria

This review included all analytic original studies that studied the possible associated risk factors of cancer among Omani patients. The review included original peer–reviewed journal articles, written in English and published as full texts until April 2019. We searched for all types of studies including retrospective, prospective, case control, cohort, cross-sectional, cross over design, and randomized controlled trials if any. Related dissertations and thesis were also searched.

Selection Criteria and data extraction

The selected studies were the ones mainly focused on examining risk factors of cancer among Omani population only. Titles and abstracts were skimmed initially for inclusion/exclusion. Full texts were reviewed where needed. Duplicates were removed prior to analysis. Finally, included articles were analyzed qualitatively.
Results

In general, very scanty analytic literature is available addressing the associated risk factors for various types of cancer among the Omani population. Table 1 summarizes the available analytical studies that addressed some risk factors for different types of cancer among Omanis.

A total of 10 retrospective studies of case–control design were identified. Eight of them applied the classical case–control design and two were matched case–control studies. The oldest study was conducted in 2006 and the most recent was conducted in 2017. Most of the studies (n=6) were related to gastric cancer, and the remaining four were related to breast cancer, leukemia, non–Hodgkin lymphoma (NHL) and colorectal cancer. The number of cases included ranged between 43 and 192, and the number of controls ranged between 43 and 245. Most (n=7) of the studies are related to genetic

<table>
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<td>• A case control design.</td>
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<tr>
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<td>Jennifer A Rusiecki et. al (23)</td>
<td>2011</td>
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<td>• 43 cases of NHL and 43 controls</td>
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<td>2017</td>
<td>• A case control study</td>
<td>– No association between type 2 diabetic mellitus and risk of colorectal cancer</td>
</tr>
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Table 1: Analytical studies that identified risk factors for various types of cancer among Omanis.
epidemiology, addressing genetic factors associated with gastric cancer (n=6), and breast cancer (n=1). The remaining three addressed socio-demographic, lifestyle and comorbid factors.

In relation to gastric cancer, Mansour S et al. conducted a classical case-control study to assess the association between CDH1 gene polymorphisms (four polymorphisms) and gastric cancer risk among Omani population (14). The studied sample consisted of confirmed gastric cancer cases diagnosed at Sultan Qaboos University Hospital and Royal Hospital. On the other hand, the healthy control group included individuals from the same ethnic and geographical origin as the patients. They observed that CDH1 -160 -AA genotype was associated with an increased risk of gastric cancer. In addition, there was no significant association between the other polymorphisms and gastric cancer risk.

No significant association between N-acetyltransferase 2 (NAT2) genotypes and phenotypes and gastric cancer risk was concluded from a case control study conducted by Mansour S et al. (15). The study population consisted of a series of consecutive unrelated gastric cancer patients diagnosed in three main hospitals in Oman (Sultan Qaboos University Hospital, Royal Hospital, and Sohar Hospital). The control group included apparently healthy population-based subjects of the same ethnic and geographical origin as the patients. Moreover, NAT2 phenotypes had no clinic-pathological associations or prognostic significance.

A case-control study among Omani Arab population was carried out to examine the association between Interleukin-1b gene (IL-1B) and interleukin 1 receptor antagonist gene (IL-1RN) polymorphisms and gastric cancer risk (16). The target population consisted of a series of consecutive unrelated gastric cancer patients diagnosed in the period between January 2002 and May 2005, in three main hospitals in Oman (Sultan Qaboos University Hospital, Royal Hospital, and Sohar Hospital). The control group composed of subjects of the same ethnic and geographical origin as the patients. The study concluded that interleukin 1 receptor antagonist gene (IL-1RN) polymorphism increased the risk of gastric cancer among Omani Arab population. However, the Interleukin-1b gene (IL-1B -31) polymorphism was not associated with an increased gastric cancer risk.

Jennifer A Rusieckiet al. conducted a case-control study to investigate the association between gastric cancer and peripheral blood leukocyte DNA methylation in LINE-1 and in the tumor suppressor genes CDH1, p16, TP53 and RUNX3 among Omani Arab population (17). They found that age was a significant effect modifier, however there was no differences by tumor grade, stage or histology. They concluded that Global DNA hypomethylation in LINE-1 and promoter region hypomethylation for TP53 and p16 are associated with gastric cancer.

A classical case control study was carried out to analyze genetic polymorphisms GSTM1/G1 and IL-1B/ IL-1RN genes in gastric adenocarcinoma (18). Samples of genomic DNA were extracted from peripheral blood of 107 control subjects and 107 gastric cancer patients. They concluded that there was a statistically significant association between the presence of the IL-1RN*2 allele and gastric cancer. In addition, the null GSTM1 genotype was significantly correlated with gastric cancer and carriers of IL-1RN*2. Moreover, the study concluded that the individual differences in both the cellular inflammatory modulator IL-1RN and the anti-oxidative property of GSTM1 may increase risk of gastric cancer.

No significant association between the Vascular Endothelial Growth Factor (VEGF) polymorphisms and gastric cancer was concluded from the case-control study carried out by Mansour S et al. (19). The study sample included 130 gastric cancer cases and 130 controls. In addition, no association was observed between the six common haplotypes identified and both gastric cancer risk predisposition and survival.

With regard to breast cancer, a case control study was carried out among Omani women aimed at assessing the role of Insulin-like growth factor 1 (IGF1) cytosine adenine (CA) repeats gene polymorphisms in the risk of developing breast cancer (20). The target sample included 147 breast cancer cases and 134 controls. They analyzed CA repeats gene polymorphisms of IGF1 by extracting genomic DNA from the peripheral blood and performed genotyping using DNA sequencing. The result showed no association between the IGF1 CA repeat polymorphisms and breast cancer among Omani females.

Regarding leukemia and lymphoma studies, Mostafa Walyet al. compared 70 leukemic cases to 70 controls taken from family relatives or from the neighbors of family siblings, using a matched case-control design, and observed no association between breastfeeding in general and the risk of childhood leukemia (21). In addition, they concluded that breastfeeding duration has no protective effect against childhood leukemia. Moreover, there was no significant association between dietary carbohydrate/protein consumption and risk of leukemia. On the other hand, Amanat Ali et al. reported in a study conducted to explore the association between NHL and body mass index (BMI) that there was a weak association. Moreover, they added that there was a significant decreased risk of NHL with a higher educational level and higher vegetable intake (22).
However, there was an increased risk in NHL with the higher intake of carbohydrate but not for protein or energy intake.

In relation to the risk of colorectal cancer among Omani, Mafiana R et al. studied the role of type 2 diabetes mellitus in developing colorectal cancer in a case control study (39). They have compared 114 cases to 170 controls taken from a tertiary care institution. After having adjusted for potential confounding variables, there was no association between type 2 diabetes and developing colorectal cancer.

**Discussion**

This is the first review summarizing the available literature related to analytic studies addressing cancer risk factors among Omani population until April, 2019. The review was based on ten case–control studies, mostly addressing genetic factors related to gastric cancer.

This review demonstrated that the available analytic literature addressing associated risk factors for various types of cancer among the Omani population is very limited. This can be thought as a part from the low research output in the country (30). This may be partially due to the modest growing research culture in developing countries and limited available resources (31). In this regard, research is not a core focus for clinicians and staff working in related health institutions in Oman, and until now there is no local center specialized in cancer research. Research knowledge and skills among related staff may represent another explanation for the low research output. In addition, limitation of available funding sources and personal resources are other issues limiting research perspectives in cancer area and other chronic diseases in the country.

Genetic factor studies related to gastric cancer dominated the limited local analytic literature. However, lifestyle related factors including tobacco use, obesity, unhealthy diet, physical inactivity, breastfeeding and alcohol use were not or rarely studied. In addition, carcinogenic infections (including human papilloma virus (HPV) infection and hepatitis viral infections), and environmental factors (including ionizing and ultraviolet radiation, urban air pollution, indoor smoke solid fuels and radioactive radon) have not been studied. This reflects the lack of public health research in this area, which may be explained by the lack of resources including the lack of experts working on this are, and lack of financial support.

Gastric carcinogenesis is a complex process and results from interaction between genetic and environmental factors (22). Few studies in the literature explored the genetic susceptibility of Omani population to various types of cancer. Based on the reviewed studies, the first six studies have analyzed the genetic susceptibility of gastric cancer and one study on breast cancer. A meta–analysis by Gao, showed a reverse link of L CDH1 –160C>A with gastric cancer among Asians and a positive association among Caucasians (33). The local study conducted by Mansour MS et al. is consistent with the finding in Caucasians population and thus confirmed the ethnic variations between CDH1 –160 –AA genotype and increased risk of gastric cancer. In addition, NAT2 seems to have no role in gastric cancer risk among Omani population (39), which is in agreement with the previous published study conducted by Lan Q et al. (34), showing no significant association between N–acetylttransferase 2 (NAT2) genotypes and phenotypes and gastric cancer risk. However, literature evidence showed that the effect of NAT2 genotype depends on its types. In this regard, a study among Taiwanese suggests that NAT2 slow acetylators have a higher risk of gastric cancer than intermediate and rapid acetylators (39). A higher–level evidence suggested that the effect of this genetic factor is ethnic dependent. A meta–analysis data suggest that the NAT2 acetylation status has an effect on the risk of gastric cancer among East Asian populations (38), explaining the variation in association results.

Interleukin–1b gene (IL–1B) and interleukin1 receptor antagonist gene (IL–1RN) polymorphisms have shown different association results with the risk of gastric cancer in different populations (37). In keeping with this controversy, two local studies conducted by Al–Moundhri et. al. (22,24) illustrated that IL–1RN polymorphism contributes significantly to the risk of gastric cancer. The presence of IL–1RN*2 allele independently increases the risk of gastric cancer, with an odds ratio (OR) of 2.2 in the Omani population. However, no significant association was found between IL–1B –31/-511 polymorphism and gastric cancer in these local studies. On the other hand, global DNA hypomethylation was identified as a biomarker for gastric cancer (38,39). Consistent with this, the local case control study conducted by Jennifer A. et al showed that Global DNA hypomethylation in LINE–1, and promoter region hypomethylation for TP53 and p16 were associated with gastric cancer among Omani population. In fact, DNA hypomethylation was observed to be a marker for different types of cancer including Head & Neck, and bladder cancer (40,41).

A recent meta–analysis showed that vascular endothelial growth factor (VEGF) plays a role in the pathogenesis of human cancer including gastric cancer (32). In contrary, a local case control study conducted by Al–Moundhri et. found no significant associations between the VEGF polymorphisms and gastric cancer risk. However,
this is consistent with some studies reviewed by the same meta-analysis. Furthermore, one local study investigated the role of Insulin-like growth factor 1 polymorphisms (IGF1 CA repeats genotypes) and the risk of developing breast cancer among Omani women. This case control study showed no association between the two entities among Omani women. However, a previous study among Chinese women illustrated a positive association between the (CA)19 and the risk of developing breast cancer (43).

In general, the reason behind the conflicting findings between the genetics studies worldwide could be explained by the variation in the ethnic composition of the study populations and the interaction component between the genetic factors and environmental and lifestyle factors which vary in their prevalence in different populations. In addition, the risk of bias due to small sample sizes and other study quality measures, and the effect of confounding, could play a role in result variation in different studies.

In this review, two of the included studies addressed the impact of dietary factors in the pathogenesis of NHL and childhood leukemia in Oman. Mostafa Walyet investigated the relationship between duration of breastfeeding and risk of childhood leukemia among Omani children (21). The result showed that the duration of breast feeding did not have any protective effect against the risk of childhood acute lymphoblastic leukemia, contradicting with the world literature. In this context, a meta-analysis concluded that 14% to 20% of all childhood leukemia cases may be prevented by breastfeeding for 6 months or more (44). This conflicting result may be attributed to the small sample size used in the local study. In addition, a local case control study, conducted to identify dietary factors associated with the risk of developing NHL in Omani population (15), revealed that higher consumption of carbohydrate and protein are associated with increased risk of NHL, whereas higher intake of vegetables is associated with a significantly reduced risk of NHL. A similar finding were found among Iranian population in a study conducted by Zahra Mozaheb (45). A large case control study has suggested that high consumption of meat products may increase the lymphoma risk (34). However, another study showed no effect for meat intake (46). On the other hand, some literature suggest that dietary patterns might have ethnic- and subgroup-specific effects on NHL, explaining variation in results across different population (47).

**Conclusion**

This is the first review attempting to gather evidence related to risk factors associated with cancer among Omanis. We revealed that the available literature is scanty and there is crucial need for further efforts. The scant local literature is more focused on genetic, non-modifiable factors, and very little is related to modifiable factors including dietary factors, breastfeeding and obesity. This emphasizes the necessity for studying modifiable risk factors that allow prevention and control. Locally, this is challenged by training needs for health professionals, and availability of financial resources. However, the responsibility of such work should be extended to multi-sectorial collaboration.

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