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Cancer Genetics in the Arab World

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Abstract

Cancer remains a major global health burden, with incidence rates rising globally. The Arab world, which is often regarded as an underrepresented population in literature, shows distinct patterns in cancer incidences, genetics, and outcomes in comparison with Western populations. This review aims to highlight key genomic studies conducted in the Arab world. We describe the epidemiological and genetic landscape of cancer in the Arab populations, focusing on lung, breast, and colorectal cancers, given their prominence and distinctive patterns in the region. We utilised data from GLOBOCAN 2022 and published genomic studies to assess subregional incidence trends, identify significant mutations, and explore hereditary and early-onset cancers profiles. Breast, lung, and colorectal cancers dominate the cancer profile in the region, with disparities in genetic alterations when compared to global trends. Variation in *EGFR* mutation frequencies in lung cancer across diverse ethnicities in the MENA region is representative of the extreme heterogeneity in the Arab region. Variations in *BRCA1/2* mutation frequency, and unique founder mutations highlight breast cancer's particular regional genetic traits. Similarly, colorectal cancer studies show variations in mutational profiles, such as a low incidence of *BRAF* mutations and distinct epigenetic characteristics that represent region-specific disease pathways. Early-onset cancers, particularly breast and colorectal cancers, occur at higher rates than in Western populations and often diverge from the typical germline mutation patterns reported globally. The review emphasises the importance of conducting localised genetic studies in improving personalised medicine and public health strategies. Despite these efforts, significant gaps remain, particularly in understanding early-onset cancers and hereditary cancer genetic disorders, which are overrepresented in the region. Further research on the genetic basis of cancer in Arab populations is essential for advancing personalised treatment and improving cancer outcomes in these under-researched groups.

Keywords

cancer genetics, the Arab world, cancer in underrepresented populations, cancer genomics, cancers in Arab world

Introduction

Cancer remains a global burden, being the second most common cause of death worldwide with approximately 10 million deaths in 2020.[1] The aetiology of cancer is complicated, but our knowledge of the causes of malignancies has advanced substantially over the past 50 years.[2,3] It is now widely accepted that malignancies result from mutation-driven evolutionary processes driving genetic variation and natural selection, which favour expansion of cells with carcinogenic variants.[4] This genetic diversity contributes to the observed heterogeneity in cancer incidence and death, both within and between population subgroups.[5,6]

Variations in cancer incidence and mortality are well documented, with studies showing that they are driven by disparities in age, sex, ethnicity, and geographical location.[7,8] For instance, African Americans have the greatest death rate and the shortest survival for most cancer types among all racial/ethnic groups in the United States.[9]

Recent studies have consistently demonstrated the impact of racial and ethnic differences on cancer incidence, survival, medication response, and on basic cancer biology in terms of

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activities of molecular pathways and epigenetics.[8] However, inclusiveness with respect to race/ethnicity has not been a priority within the literature, and most large-scale studies aimed at examining the impact of race/ethnicity on cancer incidence have mostly concentrated on individuals with European ancestry.[10]

Among nations that lack of representation of underlying genetic causes of cancer and the genomic changes associated with it is the Arab population. Cancer in the Arab world has witnessed the same overall increase in incidence as seen globally, although it exhibits distinct pattern in cancer types. Long-term projections show that by 2030 there would be a 1.8-fold increase in cancer incidence from 2002.[11]

The genomic diversity of the Arab population is shaped by historical, geographical, and cultural factors, resulting in distinct genetic profiles and varying susceptibility to cancers across the region. This can be illustrated in terms of unique cancer incidence between indigenous and admixed populations within the region.[12,13] A study in Qatar assessed genetic susceptibility to common cancers, including breast, prostate, and colorectal cancers, by analysing the DNA of 6142 native Qataris with different ancestry groups (Arab, Persian, Arabian Peninsula, Admixture Arab, African, and South Asian). The study found significant genetic variation in cancer risk, with individuals of Arabian Peninsula ancestry showing lower susceptibility to colorectal cancer, while those of African ancestry had higher risk scores for prostate cancer.[14] These findings highlight the importance of understanding genetic differences to identify at-risk groups and develop personalized prevention and treatment strategies.

There has been an increasing effort to define the tumour genomic profiles for the most prevalent cancers in this region such as lung, breast, and colorectal cancers. Improved knowledge of cancer genetics among underrepresented populations will enhance cancer prevention, diagnosis and treatment. Even though current data indicates that cancer disparities persist among race/ethnic groups, Arab population genomic data should be added to fill this gap.[15,16]

In this review paper we aim to highlight key genetic research in cancer in the Arab world. Despite limited studies, the existing research has made significant impacts. We explore unique aspects in the region such as the prevalence of Early-Onset Cancers (EOCs) and hereditary cancers. Genomic studies in this region and beyond are essential for personalised medicine progress. Variations between Western and Arab populations' genomic data, particularly in cancer treatments, emphasize the need for localised research. These studies are pivotal for shaping prevention strategies, enhancing therapeutic efficacy, and ensuring the applicability of clinical trial results from Western populations.

Cancer Epidemiology in Arab World

In Arab populations, cancers incidences and trends exhibit different patterns from global trends, which merit further exploration. The 18 Arab countries in the Middle East and North Africa (MENA) region can be divided into subregions, including the Levant (Jordan, Lebanon, Syria, Palestine), the Gulf Council Countries (GCC) (Saudi Arabia, UAE, Qatar, Kuwait, Bahrain, Oman), North Africa (Algeria, Libya, Tunisia, Morocco, Egypt, Sudan), Iraq, and Yemen[17] . These subregions share similar cultural and environmental factors that influence cancer trends, but each area can exhibit distinct patterns in cancer incidence and mortality rates, reflecting both shared and unique risk factors across the region (Figure 1). We analysed age-standardized cancer incidence of the Arab countries in the MENA region and compared it with the world and Europe, using data obtained from Global Cancer Observatory 2022 (GLOBOCAN 2022: https://gco.iarc.fr/en). The data from GLOBOCAN include comprehensive global cancer statistics such as the age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) for various regions, including the MENA region. The mortality-to-incidence ratio (MIR) was calculated based on the extracted data from this platform and reflects the likelihood of death following a cancer diagnosis.

Cancer-Specific Subregional Trends in Males

Globally, lung cancer is the most common cancer, followed by prostate and colorectal cancers. The GCC present a unique pattern, with colorectal cancer topping the list, surpassing prostate and lung cancers (Figure 2). This deviation may be attributed to changing dietary habits and lifestyle factors in the region.[18–20] North Africa shows lung cancer dominating, followed by liver and bladder cancers. The high incidence of liver cancer in this region could be linked to the prevalence of hepatitis B and C infections.[21] Iraq's trend is similar to North Africa's, with lung cancer leading, but prostate cancer ranks second. The Levant region closely follows the global trend with lung cancer at the top. Yemen shows a markedly different pattern, with colorectal cancer leading, followed by stomach and liver cancers, which might be related to specific dietary patterns and environmental exposures.

Notably, bladder cancer ranks consistently highly in North Africa and Iraq (Figure 2), potentially due to the prevalence of schistosomiasis in these regions.[22] Non-Hodgkin lymphoma (NHL) and leukaemia appear among the top cancers across most regions, indicating a consistent burden of haematological malignancies. This might be due to the high prevalence of infectious agents such as Epstein-Barr Virus (EBV) and Helicobacter Pylori which have been directly linked to specific NHL subtypes, including Burkitt lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma.[23,24] Hepatitis C Virus (HCV), more prevalent in the region compared to Europe, is also associated with an increased risk of NHL, particularly diffuse large B-cell lymphoma (DLBCL).[25,26] Additionally, environmental exposures such as pesticide use and occupational hazards in agricultural communities are significant contributors, uniquely impacting NHL incidence in the Middle East.[27,28]

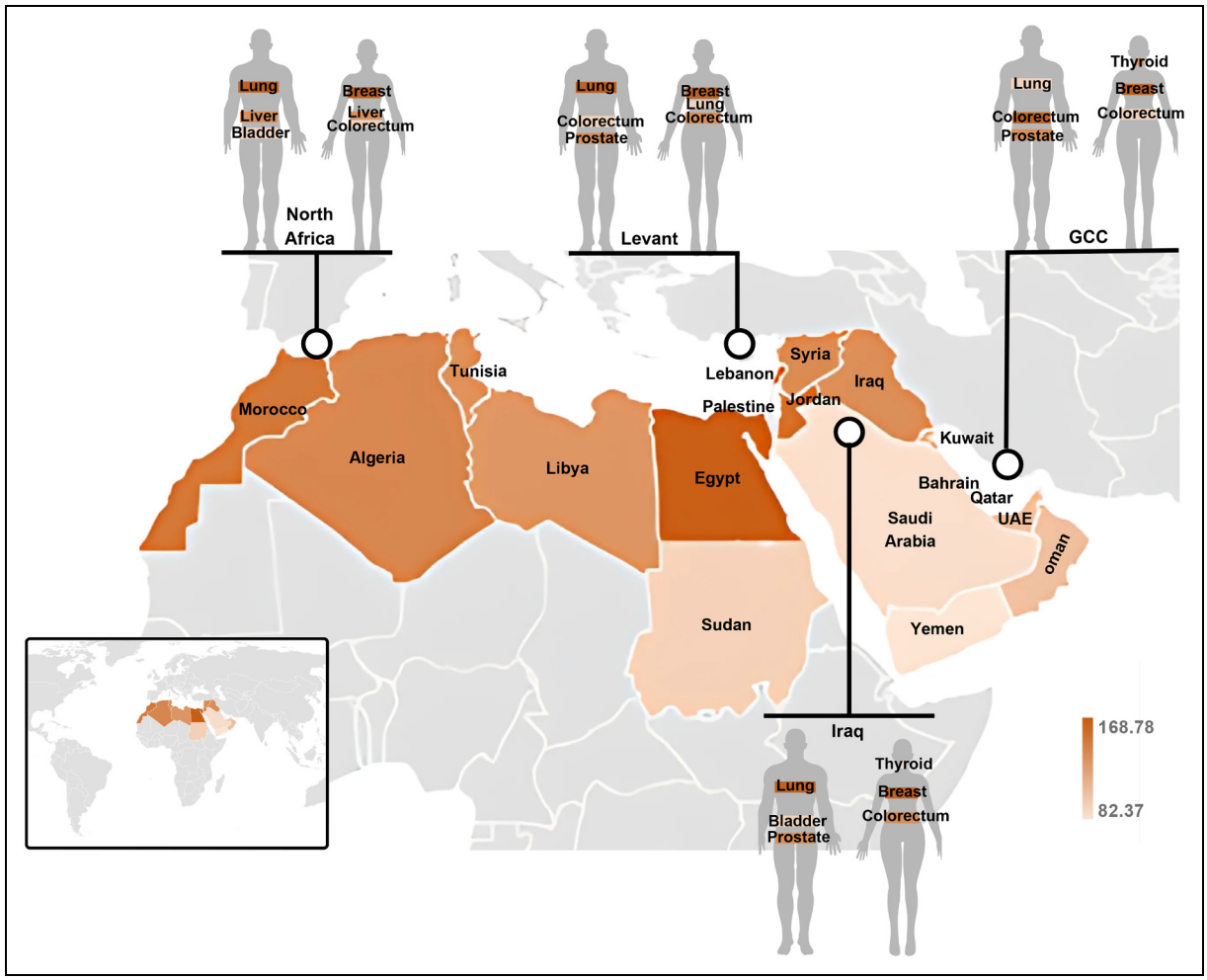

Figure 1. Age-Standardized Incidence Rate (ASIR) Across the Middle East and North Africa (MENA) Region by Gender. Darker Shades Represent Higher ASIR Values.

Cancer-Specific Subregional Trends in Females

Breast cancer consistently ranks as the most common cancer among females across all regions (Figure 3). Globally, breast cancer is followed by lung and colorectal cancers. This pattern is consistent with epidemiological studies that have identified various risk factors for breast cancer, including genetic traits, increased alcohol consumption, physical inactivity, and female reproductive factors.[29–32]

The GCC countries show a similar pattern to the global picture, but with thyroid cancer ranking second (Figure 3). While studies specifically addressing the reasons behind the thyroid cancer pattern in the GCC are limited, global studies suggest that the increasing incidence may be attributed to environmental exposure to carcinogens, including ionizing radiation and alterations in dietary iodine intake, combined with improved detection techniques such as fine needle aspiration Cytology (FNAC) and advanced imaging.[33,34] Notably, breast cancer in the GCC countries often manifests with distinctive characteristics, including early onset (typically before age 50), advanced stage at presentation, and more aggressive features such as HER2 positivity or triple-negative attributes, particularly among younger patients.[35,36]

North Africa presents a unique trend with liver cancer following breast cancer (Figure 3). This high incidence of liver cancer, observed in both men and women, could be associated with the prevalence of hepatitis C virus (HCV), a recognized risk factor for hepatocellular carcinoma.[37] Iraq's pattern closely resembles the global trend, with colorectal cancer ranking second. The Levant region mirrors the global trend. Yemen presents a distinct pattern with colorectal and oesophageal cancers ranking high after breast cancer, which could be associated with specific dietary habits and environmental factors.[38]

Genetic Landscape of Cancer in Arab World

The MENA region has a heterogeneous genetic background, which contributes to differences in cancer risk and treatment responses. Genetic predispositions in specific groups can result in different cancer profiles, emphasizing the importance of conducting localised studies to better understand these genetic

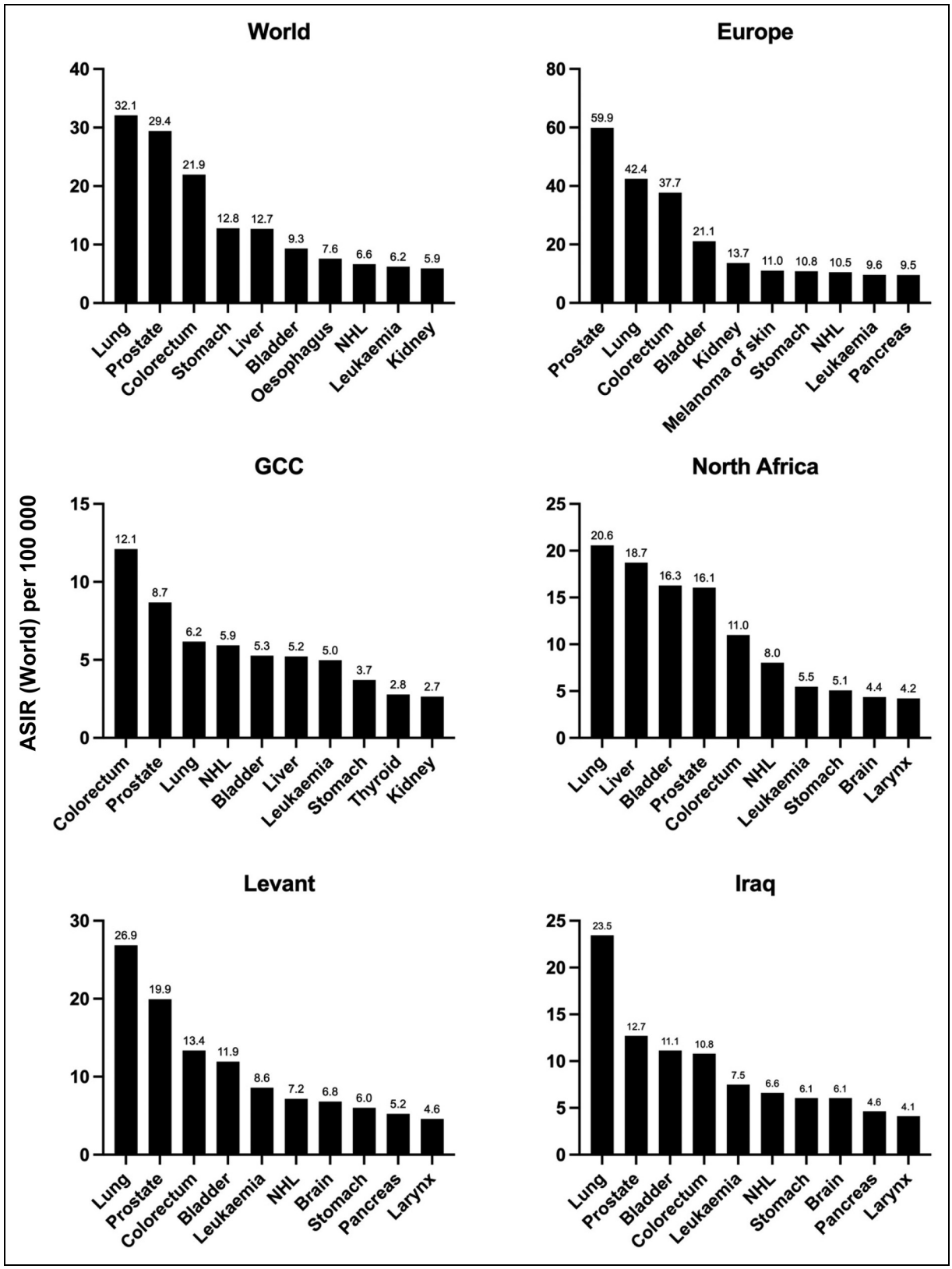

Figure 2. Cancer-Specific Subregional Trends in Males in World, Europe, and Middle East & North Africa (MENA).

differences.[14,39] Cancer incidence in the MENA region, like in other parts of the world, is increasing, which has been attributed to increased life expectancy and the adoption of Western lifestyle practices.[40] The MENA region is expected to see the

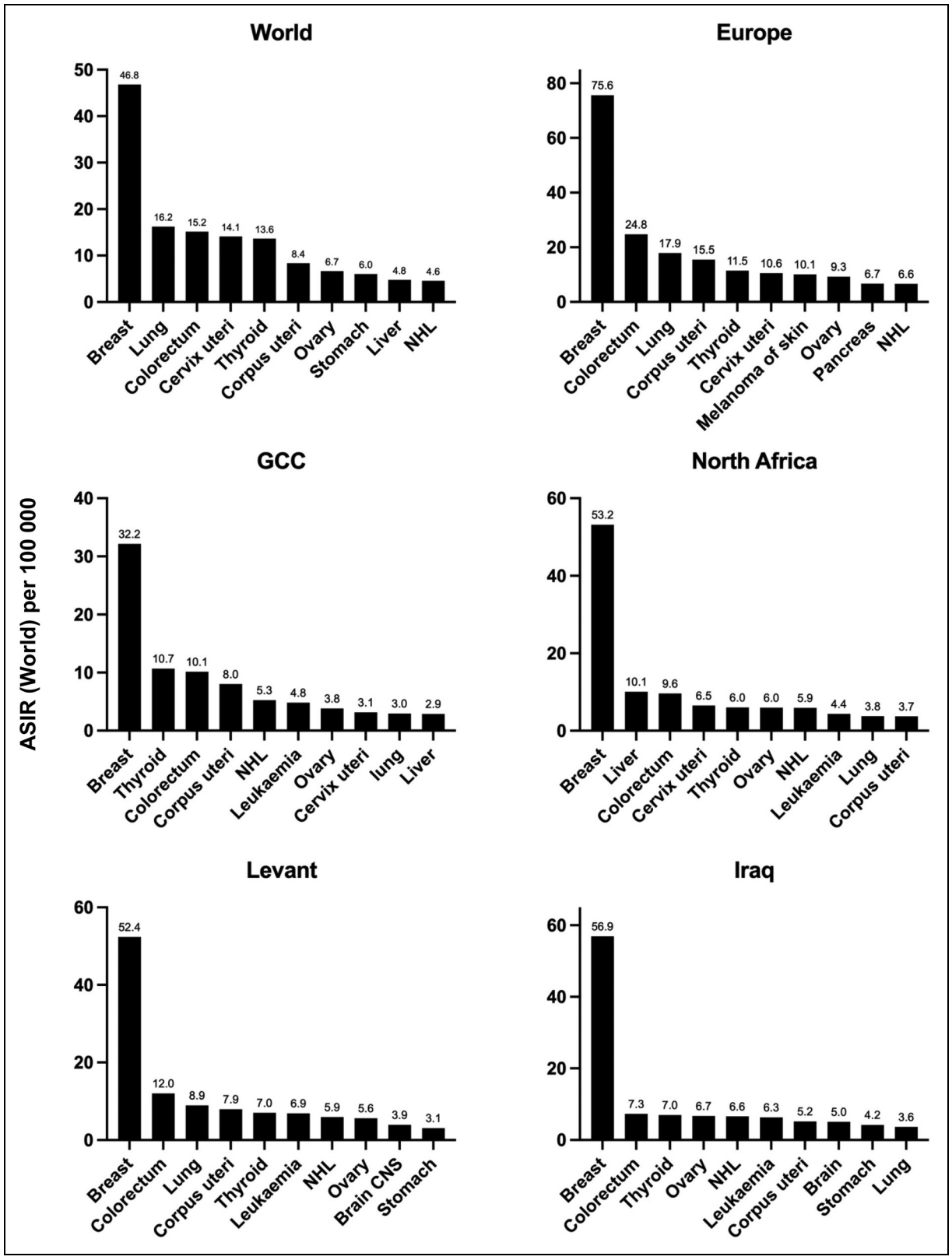

Figure 3. Cancer-Specific Subregional Trends in Females in World, Europe, and Middle East & North Africa (MENA).

highest increase in cancer burden globally due to a multitude of factors, including increases in smoking rate, insufficient physical activity due to shifting towards white collar jobs, poor diets in form of fast food and processed meat consumption, infections from repeated endemics, and increasing environmental contamination.[41] Recently, several governments in the MENA

region have launched projects to better understand the genetic basis of cancer in local populations, with the goal of identifying specific cancer mutations that are more common in their local populations, as well as pathways and biomarkers relevant to cancer in diverse ethnic groups.[42,43]

The 1000 Arab genome project in Emirates, the Egyptian genome project, the Saudi genome project, genome Tunisia project, the Qatar genome program, and the Oman genome project (in preparation stage), are the most well-known genomic projects in the MENA region which have integrated cancers as part of their investigations. The findings of these studies so far highlighted differences in incidence rates and genetic changes between the MENA area and other countries.[44–49] However, more efforts are needed to characterise the genetic landscape of cancers in MENA region due to its distinctive populations with a long history that exhibit distinctive genetic and ethnic variety.[50]

Lung Cancer in Arab World

Lung cancer is the leading cause of cancer-related death worldwide and most common cancer among male in many Mddle Eastern countries.[51] Epidermal Growth Factor Receptor (*EGFR*) is one of most studied mutated genes in lung cancer, due to its successful implication in targeted therapies in a form of *EGFR* inhibitors such as osimertinib (Tagrisso), and erlotinib (Tarceva).[52] The frequency of *EGFR* somatic mutation was assessed in Iraqi patients with non-small cell lung cancer (NSCLC), which revealed 27.53%, which is a higher than prevalence rate in some Arab countries such as Sauid Arabia (15.3%) and Lebanese population (8.5%) but lower than in Western countries such as Italy and Germany (up to 39%).[53] By contrast a systematic review conducted by Benbrahim et al showed that the *EGFR* mutation frequency in MENA patients was higher than that shown in white populations, but still lower than the frequency reported in Asian populations.[54] This demonstrates the variation of prevalence of *EGFR* mutation in NSCLC across diverse ethnicities in the MENA region and hence, local studies are needed to address the EGFR mutations frequency across MENA subregions. Another systemic review, performed by Nasser et al, showed that 15.7% of Arab patients with NSCLC had *EGFR* mutations and 56% of the mutated patients were female and 66% of them non-smokers, which broadly agrees with global data.[55] *EGFR* mutational status has become a key biomarker for lung cancer management, however there is a need to explore genetic targets for lung cancer beyond EGFR in the Arab world, since the majority of patients have cancers that are not suitable for the *EGFR* mutation-targeting *EGFR* inhibitors, and in any event resistance to these *EGFR* inhibitors is frequently reported.[56,57]

Breast Cancer in Arab World

Breast cancer (BC) is the most common cancer in women worldwide, and the Arab world is no exception. It is estimated around 30 cases averagely are reported per 100 000 women annually among MENA countries, with incidence has been increasing consistently with global trend.[58] Because of its relatively high frequency, BC is one of the most extensively studied cancers in range of different Arab countries.

Germline variants in the *BRCA1* or *BRCA2* genes and their prevalence in BC are fairly well-studied in Arab populations. Studies have been performed in a variety of cancer groups from most of the main Middle Eastern regions (Table 1). Considerable variation in rates of *BRCA1* or *BRCA2* mutations have been found in these studies, ranging from 3.1%-22% in *BRCA1*, and 0.4%-19% in *BRCA2*. A common theme is the identification of mutations that are potentially unique to the region, underlining the genetic differences between the Middle East and the rest of the world.

Also, a study from Libya investigated the characteristics and distribution of *BRCA1* variants in exons 5, 11, and 20 in Libyan families with BC. Out of 18 unrelated families, 10 tested positive for *BRCA1* gene mutations (55.6%). The identified variants included a frameshift pathogenetic variant, and one other novel variant.[65] Similarly, a study conducted in Central Sudan showed a high prevalence of germline *BRCA1/2* mutations. 33 out of 35 BC patients (34 females, 1 male) were found to carry 60 variants (32 in *BRCA1*, 28 in *BRCA2*) including 17 (28%) variants classified as novel.[66] These indicates a relatively high prevalence of *BRCA* gene mutations among Arabs in the north African populations.

In addition, a review study gathered 14 relevant papers from Arab nations to thoroughly examine the prevalence of *BRCA1/BRCA2* within Arab populations. They reported that the prevalence of *BRCA1/2* genes mutations differs in the Arab population compared to the rest of the world. The prevalence of *BRCA1/2* gene mutations in BC patients was much greater in India, Japan, Hispanics in the USA, and Spain, whereas it was significantly lower in Iran, Mexico, Sweden, Germany, Australia, and Turkey.[67] These studies showed different *BRCA1/2* genes mutations frequency and founder mutations across the Arab populations. This extreme variability in *BRCA1/2* genes illustrate that the Arab population possess distinct cancer genetic landscape which warrant further exploration.

Very few studies have examined the population-level genetic profile of the Arab groups, as opposed to testing only cancer cases, therefore little is known about cancer risk. One pioneering study from the region was reported by the Qatar genome program investigating genetic risk of cancer across 6 different ancestry group within the Qatari population namely: Admixture Arab, African, South Asian, Arabian Peninsula, Persian, and Arab. The study was conducted on 6142 samples to examine the genetic diversity of cancer-susceptibility genes including BC genes. The study showed that pathogenic variants in *BRCA1/2* genes were significantly overrepresented in Qataris of Persian, while they were completely absent in the people of Arab Peninsula descent. This reflects extreme variability in cancer predisposition risk within a certain population in the Arab world and hence it was suggested a cancer-risk stratification system should be implemented within Arab populations.[14]

Beyond the *BRCA1/2* genes in Arab populations. A study from Saudi Arabia investigated variants in the Ataxia-telangiectasia

Table 1. Summary of BRCA1/2 Genes Studies Conducted in Middle Eastern Cancer Populations. BC: Breast Cancer, OC: Ovarian Cancer, FH: Family History.

Ethnic group	Cohort type	Cohort size	%BRCA1 %BRCA2	Identified founder/Unique mutations	Ref.
Saudi Arabian	BC with FH	310	11% in *BRCA1* 2% in *BRCA2*	c.4136_4137delCT, c.5530delC and c.4524G > A in *BRCA1*	[59]
Arab descent mainly from Saudi Arabia	BC and OC	108 BC 65 OC	8.3% in *BRCA1* 0.9% in *BRCA2*	c.1140dupG, c.4136_4137delCT, c.5095C > T, and c.5530delC in *BRCA1*	[60]
Lebanese	Individuals with BC or OC or family members known to carry mutation	281	6% in *BRCA1* 1.4% in *BRCA2*	c.131G > T in *BRCA1*	[61]
Mixed ethnicity with dominant Arabs from United Arab Emirates	BC	309	17% in *BRCA1* 19% in *BRCA2*	Not identified	[62]
Arabs decent from Oman	BC	262	4.6% in *BRCA1* 11.6% in *BRCA2*	Whole exon 3 deletion, C.9382C > T, C.9018C > A, C.2588dupA in *BRCA2*	[36]
North African	BC	388 familial and 159 young sporadic cases	22% in *BRCA1*	C.798_799delTT in *BRCA1*	[63]
Middle Eastern mainly from Saudi Arabia	BC	818	3.1% in *BRCA1* 0.4% in *BRCA2*	c.1140 dupG and c.4136_4137delCT in *BRCA1*	[64]

mutated gene (*ATM*), which has previously been identified as a moderate susceptibility factor for BC. They screened 715 BC patients who did not have *BRCA1/2* variants, revealing approximately a 0.8% prevalence of *ATM* germline pathogenic or likely pathogenic mutations. The findings appear to be in alignment with reported frequency of mutated *ATM* in other populations (range: 0.5%-4%), which affirms *ATM* gene as a moderate-risk BC gene globally.[68] In an effort to explore the prevalence of other BC genes in the Arab population, a study conducted in Jordanian population revealed 3 Single Nucleotide Polymorphisms (SNPs) in *MMP9, TOX3, and DAPK1* genes were significantly associated with an increased risk of breast cancer.[69]

Also, another study found a SNP in the tumour suppressor *TP53* and its negative regulator *MDM2* increased the risk of BC in the Saudi population.[70] In addition. Karakas et al found SNP mutations in *PIK3CA* to be prevalent among Arab BC population (SNP, rs17849079) compared with disease-free individuals.[71]

The relationship between some SNPs and BC risk has also been studied in the Arab populations, although study sizes are relatively small on a global scale. In one example, 4 of the most common *TP53* gene polymorphisms (Pro47Ser, Arg72Pro, intron 3 Ins16 bp and intron 6 [G > C]) were evaluated in 288 women with BC and in 188 controls. The study provided valuable insights about associated risks of these polymorphisms and suggested that proline homozygosity at *p53* codon 72 is associated with decreased BC risk in Arab women[72] . Also, a small-scale study (26 patients) which aimed to investigate SNPs for their possible association with BC patients among Arab Ancestries, revealed a highly significant 4 associated SNPs [SNRK and SNRK-AS1-rs202018563G; BRCA2-rs2227943C; ZNF484-rs199826847C; and DCPS-rs1695739G] among women with BC versus the healthy controls even after Bonferroni corrections (*P* value $<2{:}05 \times 10^{-07}$). The study underscores the importance of specific ethnicity genetic studies to explore candidate biomarkers and possible targets of BC among Arab ancestries.[73]

Preliminary studies have also been made into the role of somatic mutations in BC genes. Shamsi et al investigated somatic mutation frequencies in *TP53, ATM, IDH1, IDH2, PTEN, PIK3Ca, APC, NPM1, MPL, JAK2, KIT, KRAS*, and *NRAS* among of 78 Arab women with BC. The cohort comprised a majority of patients with estrogen receptor positive disease (54 patients; 69.2%), while 15 (19.2%) were *HER2-neu* positive, and 21 (26.9%) had the triple-negative subtype. They revealed variation in their occurrences compared with an American population, asserting unique genetic characteristics in Arab women BC patients.[74]

Colorectal Cancer in Arab World

Colorectal cancer (CRC) is the third most common cancer and is the second leading cause of cancer death globally.[75] CRC is

ranked as the most common cancer in men in many Middle Eastern countries, and the incidence has been increasing especially among younger people.[76,77]

Somatic mutations in *KRAS, BRAF, PIK3CA and EGFR* are considered as biological markers for personalised medicine and prognosis prediction in CRC. According to reports, the prevalence of *KRAS* mutations in CRC patients in the Arab population is between 30% and 50%, which is comparable to data from seven European countries.[78–80] Also, *KRAS* mutant tumours are linked to more advanced stages of CRC in Western population, however, such a relationship was not found in the Arab studies involving individuals at various stages of CRC.[81] In a study conducted to assess *KRAS* mutations in 100 Jordanian CRC patients who developed metastatic disease, it was found that 44% had mutated *KRAS*, with pGly12Asp being the most detected mutation (54.5%). The findings are similar to the European countries and the United States.[82] Also, another study to assess the prevalence of *KRAS* mutations among Saudi Arabian CRC patients found these in 56% of tested patients.[83]

The frequency of *BRAF* somatic mutations has also been assessed in 779 Middle Eastern CRC patients utilising DNA sequencing. The incidence was found to be very low, at 2.5%, which were overwhelmingly *BRAFV600E* mutations (90%); this contrasts with the global frequency of *BRAF* mutation in CRC, which is usually reported within the range of 5%-20%. Also, the study showed a significant association between *BRAF* mutation and MSI-H status and CpG island methylator phenotype (CIMP). The authors suggested the low incidence of *BRAF* mutations and CIMP in CRC from Saudi Arabia could be attributed to ethnic differences and hence further investigations are needed to unravel the epidemiological and genetic factors contribute to this variation among Middle Eastern CRC patients.[84] *PIK3CA* somatic mutations were identified in 12.2% of 410 Middle Eastern CRC cases along with 13 colon cell lines, and these were especially prevalent in the MSI CRC cases; this frequency is somewhat similar to the reported frequency in Caucasian European populations.[85]

Al-Shamsi et al carried out a direct comparison of the prevalence of hotspot mutations in CRC genes between an Arab population from the Gulf region (99 cases) and matched Western patients who were treated in the United States at the MD Anderson Cancer Centre (99 cases), utilising high-depth sequencing. While the frequency of *KRAS, NRAS, BRAF, TP53, APC,* and *PIK3CA* mutations were similar between Arab and Western populations, interestingly, *SMAD4* and *FBXW7* showed respectively lower and higher mutation frequencies compared with the Western population.[86] Similarly, in a Saudi Arabian population, the somatic mutation frequency of most common CRC druggable genes were observed in *BRCA2* (79%), *CHEK1* (78%), *ATM* (76%), *PMS2* (76%), *ATR* (74%), and *MYCL* (73%), based on 107 CRC patients without family history of the disease. The results showed that 98% of cancers had molecular targetable gene alteration, which provided valuable insights about genomic landscape and potentially enabled personalised medicine implementation of CRC patients in Saudi Arabia.[46] In addition, a review study, the authors suggested genetic variants in *ABCB1, ADIPOQ, CTNNB1, SFRP3, LRP6, CYP19A1, PARP-1, TDG* genes exhibited significant protection against CRC development in Saudi population. Whereas, other gene mutations in *ABCB1, ABCC1, CASR, IL-17F, NOTCH1, NOTCH4, PRNCR1, TDG, TLR2, TLR4, TLR-9, TSLP, TSLPR* and *TNF-α* showed no correlation with CRC risk in Saudi Arabia population.[87] This shows that Saudi CRC patients may possess different genetic landscape from global CRC patients, which emphasizes the importance of conducting localised genomic studies.

In a biomarkers discovery study, Almuzzaini et al performed AmpliSeq comprehensive cancer panel sequencing to identify novel somatic variants in 99 archived CRC samples from Saudi Arabia. In addition to 466 novel variants identified, the analyses established the *APC, RET*, and *EGFR* genes to be the most frequently mutated. Also, occurrence of variants in *ERBB2* was significantly correlated with those of *EGFR and ATR* genes. The study identified driver gene mutations for local population of Saudi Arabia.[88]

Epigenetic changes frequently occur in CRC in forms of changes in DNA methylation status and histone modification.[89,90] Two attempts have been made to characterise CRC in Middle Eastern patients including epigenetic features. Firstly, a cohort of 770 CRC from Middle Eastern patients was thoroughly classified based on their genetic and epigenetic factors using PCR for MSI, *BRAF* and *KRAS* mutational assessment, and MethyLight technology for *CpG* island methylator phenotype (CIMP). The pathways analyses included traditional, alternate, and serrated pathways and were hypothesised to stratify CRC based on prognosis. The following criteria were used to define these pathways: the traditional pathway, characterised by early adenomatous polyposis coli (*APC*) mutation and chromosomal instability, resulting in low or stable MSI (MSS), and CIMP-negative, *BRAF* mutation-negative, and *KRAS* mutation-negative tumours; the alternate pathway, in which either *KRAS* or *APC* mutation precedes the development of MSI-low or MSS and CIMP-low tumours; and the serrated pathway, in which *BRAF* mutation can lead to CRCs with CIMP-high, MSI-low, or MSS phenotype.[91,92] While, cases that did not conform to either of the pathways were assigned to a non-specific group.[91,93] The authors believed these pathways had not previously been assessed in an Arab population. The study showed that the majority of CRC cases (54.2%) were unassigned group, while a subset of CRC cases were distributed as 33.4%, 11.6%, and 0.8% assigned as traditional pathway, alternate pathway, and serrated molecular pathway, respectively. This indicates the pathways analysis implemented in global populations is not necessarily applicable for the Middle Eastern CRC patients, and hence there is a need for further discovery of the molecular genetic basis in the Arab CRC patients to sub-categorise them.[91] Similarly, a separate study reported DNA methylation status and gene mutation frequencies of CRC carcinomas across 3 Middle Eastern countries; Egypt, Jordan, & Turkey; it was found that Turkish colorectal carcinoma was most similar to those reported for Western cases,

while variable gene methylation patterns and mutation frequencies across Middle Eastern countries. For example; methylation involving the *p16* tumour suppressor and *MINT31* locus was more frequently noted in Jordanian colorectal carcinomas, while *KRAS* oncogene was more frequently mutated in colorectal carcinoma from Turkey. Egyptian carcinomas had the least frequency of methylation in comparison with Jordanian and Turkish colorectal carcinomas. The authors concluded that more inclusivity of population from the Arab world is required in the oncology research particularly in CRC, since this has implications on prevention strategies, therapeutic efficacy, and transferability of clinical trial results from Western populations.[94]

There has been an increase popularity of Microsatellite instability (MSI) testing in CRC due to its significant prognostic and therapeutic implications. While, the presence of MSI predicts a good outcome in CRC, according to National Comprehensive Cancer Network (NCCN) guideline, chemotherapy is not recommended for patients with MSI high, because of their good prognosis.[95] It is estimated that 15%-20% test positive for MSI.[96] A study conducted in Egyptian CRC patients showed unique findings that are different from Western patients from America, Canada, and New Zealand. A relatively high frequencies of MSI (36%) and over-expression of *p53* gene products (50%) were found in Egyptian CRC patients. Also, they reported schistosomiasis contributed to the molecular pathogenesis of some colorectal tumours.[97] Such findings warrant for further assessment of MSI across populations in the Arab world.

Early-onset Cancers in Arab World

Over the past years, there has been an increase in incidence of early-onset cancers (EOCs) globally and particularly in the developing countries. Data from all population-based cancer registries worldwide indicate a higher frequency of EOCs has been observed in low/middle income countries, such as Arab or Asian countries, than in high income countries. For example, in breast cancer (BC) the observed median age for diagnoses in high income countries is about a decade higher than in low/middle income countries.[98] The cut off age to define an EOC can be confused in the wider literature by using of different cut off ages (40, 45 or 50 are all used), although the US Centre for Disease Control and Prevention has suggested a standardized definition of younger than 45; we have followed this definition unless we state otherwise.

Various factors may play roles in defining the high rates of EOCs in Arab countries. Younger people can make up a relatively high proportion of the overall population, as compared to many Western countries, and this can lead to raising rates of EOCs incidence.[58]

Also, psychosocial and cultural factors may also contribute to under-reporting of the incidences[99] particularly in older patient groups,,[100,101] thereby potentially rising the reported EOCs proportion. In addition, the rapid development in the Arab world and dramatic change in the lifestyle and adapted more Western culture such as diet in forms of fast processed food, physical inactivity, obesity, and environmental pollution exposure at early age have contributed this phenomenon. Despite of all these aetiological factors, genuine increases in EOCs incidence are observed and the differential role of genetic factors in the Middle East merit further investigations.

Some genetic risk factors are known to increase lifetime risk of developing EOCs. For example, in BC *BRCA1/2* genes with pathogenic mutations are the most common, representing more than 50% of the genetic risk of early-onset BC.[96,102] In our recent published study, we excluded *BRCA1* and *BRCA2* genes mutations as causative genetic factors for early-onset BC in one of the largest Middle Eastern patients' cohorts conducted in Oman.[36] We showed germline BRCA1/2 mutations were not over-represented in early-onset BC cases, which contradicts global data for *BRCA1* or *BRCA2* genes mutations being most commonly associated with under ≤40 years of age, representing 12% of such cases.[103] Thus, further data are needed on the role of other autosomal dominant BC genes, including *ATM, CHEK2,* and *TP53*, in young BC patients in the region.[36] The only other similar study available reported that mutated *ATM* was not significantly associated with age of onset in BC in a Saudi Arabian population.[68]

Despite colorectal cancer (CRC) being the most common cancer in males in many Arab countries, and increasing incidence of the cancer particularly at early-age, there are few studies that have attempted to examine potential genetic causes. In a study by Al Zaabi et al, 253 CRC Arab patients in Oman were investigated and *MSH6* loss of function variants were found to be significantly over-represented among early-onset CRC patients in comparison with later-onset CRC.[104] In addition, the study showed comparable findings in term of clinical, pathological, and survival outcomes among early- versus later-onset CRC patients, which differs from most of global data.[105–107] Similarly, mutational analysis of *MLH1, MSH2*, and *MSH6* in Algerian families with suspected Lynch syndrome, revealed that *MSH6* alterations were associated with CRC onset at younger than 30 years of age.[108] In addition, Egyptian CRC patients under the age of 40 showed significantly fewer *KRAS* mutations and MSI-H was under-represented in comparison with older patients, further highlighting the differences in EOCs.[97]

However, large-scale cancer studies in Arab population studies revealed no correlations of age of cancer onset and family history of cancers, which suggests that inherited germline mutations are not always necessarily a leading cause of EOCs and consideration should be given to sequencing tumour cells for somatic mutations in these genes that are associated EOCs.[103,109] Since EOCs are common in the Arab populations, specific genetic variations whether in forms of germline or somatic mutations are predicted to be involved. Hence, further studies are needed to reveal the underlining genetic cause for EOCs in Arab world. This should enable to inform polices and strategies for early detection of cancer among young population using genetic testing alongside the standard screening methods such as a mammograph in case of BC. Also, this enable recommendations to be put forward for detection EOCs with particular genetic mutations

similarly with Ashkenazi Jews populations screening of *BRCA1/2* genes mutations.[110]

Hereditary Cancers in Arab World

Hereditary cancer syndrome can be defined as an increased risk of cancer which can be passed to offspring. Hereditary cancer makes around 10% of new cancer diagnoses due to inherited germline mutations.[111,112] In the Arab world, a region well-known for its high consanguineous rates, it is reported to be among nations with high rate of hereditary cancers, for example; 40% of children with cancers are related to hereditary causes in Saudi Arabia.[113]

Ovarian cancer (OC) is well known to be associated with germline mutations in the *BRCA1/2* genes, which were already discussed in the context of BC. According to a review study which investigated 802 OC patients across 22 Arab countries, 53 patients and 5 families harbored 22 mutations in *BRCA1/2* genes, indicating the correlation between *BRCA1/2* genes mutations and the high prevalence of OC observed across the Arab world.[114] In another study, the prevalence and effect of *BRCA1/2* mutations in Middle Eastern OC patients showed 50 out of 407 (12.3%) unselected OC patients had a pathogenic variant representing a high prevalence of *BRAC1/2* genes mutations across Middle Eastern population. Also, the haplotype analysis of these variants enabled identification of founder mutations that are unique to the Middle Eastern populations and potentially can be utilised for a development of a rapid and cost-effective screening program for Arab population.[115]

Hereditary non-polyposis colorectal cancer (HNPCC), also known Lynch syndrome is a well-established form of hereditary CRC and is responsible for 1% to 3% of all CRC cases.[116] In the Arab world, a study showed the prevalence of Lynch syndrome is around 1% of all CRC of Middle Eastern cases and demonstrated the efficacy of screening for the syndrome among CRC patients with high microsatellite instability (MSI) in cases that lack *BRAF* mutations.[117] Also, a study investigated mutational landscape of Mismatch Repair (MMR) genes, *MLH1, MSH2,* and *MSH6* which are associated with Lynch syndrome in 21 unrelated Algerian families using whole exome sequencing and multiplex ligand-dependent probe amplification (MLPA) methods. The study revealed 2 novel variants in *MLH1*, c.881_884delTCAGinsCATTCCT and a large deletion in *MSH6* which are described for the first time in Algerian families. Also, the study confirmed the contribution of *MSH2, MLH1,* and *MSH6* to CRC susceptibility consistently with global population which also represents the implementation of a diagnostic algorithm for the identification of Lynch syndrome patients in Algerian families.[108]

Two prominent studies both conducted in Saudi Arabia have revealed important findings relating to cancer susceptibility genes; Alharbi et al used a 30-gene targeted NGS panel to investigate a cohort of 310 participants composed of 57 non-cancer patients, 110 cancer patients, and 143 of cancer patients' family members. The findings showed 119/310 (38.4%) carried pathogenetic or likely pathogenic variants affecting 18 most commonly genes associated with inherited cancer namely; *TP53, ATM, CHEK2, CDH1, CDKN2A, BRCA1, BRCA2, PALB2, BRIP1, RAD51D, APC, MLH1, MSH2, MSH6, PMS2, PTEN, NBN/NBS1* and *MUTYH*. This representing relatively higher prevalence of genetic variants linked to familial cancers compared with other populations. Also, the study revealed specific variants in Saudi Arabian populations that are significantly associated with occurrence of CRC/Lynch syndrome and multiple colon polyposis.[118] Similarly, Siraj et al designed a panel of most known genes to be associated with cancers and tested it on a large cohort (1300 samples) mainly taken from patients with breast, ovarian, colorectal, and thyroid cancers. The designed panel [hereditary oncogenesis predisposition evaluation (HOPE)] enabled the authors to identify pathogenic or likely pathogenic variants in high and intermediate risk genes with variable levels. Remarkably, pathogenic or likely pathogenic alleles in DNA repair/genomic instability genes (other than *BRCA2, ATM and PALB2*) accounted for at least 16.8, 11.1, 50 and 45.5% of mutation-positive breast, ovarian, thyroid and colorectal cancer patients, respectively. The authors concluded that inherited mutations in form of germline mutations are widely distributed among Middle Eastern cancer patients and beyond commonly known designed hereditary cancer genes panels.[109]

Conclusion

Despite considerable advances in cancer genomics studies in the Arab world, there is a need to investigate the genetic landscape of cancers in Arab populations at a wider scale using sequencing technology such as whole genome or exome sequencing. Also, the scope of investigations should expand into transcriptomic, epigenomic, proteomic and metabolomic since current studies suggest cancer is a multifactorial disease. This would enable to discover new genetic targets, beyond classical molecular targets, and potentially discover new biomarkers for unique populations of Arab world. Prior to incorporating these studies, the Arab world should address a number of social, legal and ethical issues such as regional collaborations, institutional data access, infrastructure, and the integration of genomic results into clinical practice. Initiating cancer projects in partnership with other nations that already have well-established cancer registries may aid in the molecular characterization of a wide range of human cancers across all populations. This will subsequently improve our understanding of genetic variation across all human groups, resulting in more opportunities for discovery and improvement in precision medicine across diverse populations.

This narrative review carries some limitations; we were not able to include all the studies from all the Arab countries in the MENA region, but we included the most relevant to the topic. Since narrative reviews induce selections bias of studies, we aimed to overcome this by selecting a variety of studies conducted in different Arab countries. We aimed to provide an overview of current state of cancer genetic research in the Arab world and highlight the gaps in this area, hence this review

does not inform practice or policy, nor endorse guidelines. Therefore, we recommend a comprehensive systematic review for suitable evidence-based decision-making as more studies in cancer genetics are being emerged in the MENA region. There are many challenges associated with comparing cancer genetic studies across different populations; for example, availability of studies, lack of consistency of study designs, quality, and cohorts' types and sizes. These challenges are being addressed through international organisations such as Global Alliance for Genomics & Health (GA4GH) by setting standards and framing policies for international community searching on genomic and other related health data.

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References

1. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. Cancer as a complex phenotype: Pattern of cancer distribution within and beyond the nuclear family. *PLoS Med*. 2004;1(3):e65.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin*. 2021; 71(3):209–249.
3. Wu S, Zhu W, Thompson P, Hannun YA. Evaluating intrinsic and non-intrinsic cancer risk factors. *Nat Commun*. 2018;9(1):3490.
4. Ewald PW, Swain Ewald HA. Toward a general evolutionary theory of oncogenesis. *Evol Appl*. 2013;6(1):70–81.
5. Haiman CA, Stram DO. Exploring genetic susceptibility to cancer in diverse populations. *Curr Opin Genet Dev*. 2010;20(3): 330–335.
6. Safri F, Nguyen R, Zerehpooshnesfchi S, George J, Qiao L. Heterogeneity of hepatocellular carcinoma: From mechanisms to clinical implications. *Cancer Gene Ther*. 2024;31(8):1105–1112.
7. Minas TZ, Kiely M, Ajao A, Ambs S. An overview of cancer health disparities: New approaches and insights and why they matter. *Carcinogenesis*. 2021;42(1):2–13.
8. Zavala VA, Bracci PM, Carethers JM, et al. Cancer health disparities in racial/ethnic minorities in the United States. *Br J Cancer*. 2021;124(2):315–332.
9. Heath EI, Lynce F, Xiu J, et al. Racial disparities in the molecular landscape of cancer. *Anticancer Res*. 2018;38(4):2235–2240.
10. Mitchell E, Alese OB, Yates C, et al. Cancer healthcare disparities among African Americans in the United States. *J Natl Med Assoc*. 2022;114(3):236–250.
11. Arafa MA, Rabah DM, Farhat KH. Rising cancer rates in the Arab World: Now is the time for action. *East Mediterr Health J*. 2020;26(6):638–640.
12. Teebi AS (ed.). *Genetic Disorders among Arab Populations*. Springer Science & Business Media; 2010.
13. Almarri MA, Haber M, Lootah RA, et al. The genomic history of the Middle East. *Cell*. 2021;184(18):4612–25.e14.
14. Saad M, Mokrab Y, Halabi N, et al. Genetic predisposition to cancer across people of different ancestries in Qatar: A population-based, cohort study. *Lancet Oncol*. 2022;23(3): 341–352.
15. Rotimi SO, Rotimi OA, Salhia B. A review of cancer genetics and genomics studies in Africa. *Front Oncol*. 2021;10:606400.
16. Bhattacharya R, Chen N, Shim I, et al. Massive underrepresentation of Arabs in genomic studies of common disease. *Genome Med*. 2023;15(1):99.
17. Congress Lo. Libaray of Congress; [9 March 2025]. https://guides.loc.gov/arab-world-newspapers/country.
18. Alsanea N, Abduljabbar AS, Alhomoud S, Ashari LH, Hibbert D, Bazarbashi S. Colorectal cancer in Saudi Arabia: Incidence, survival, demographics and implications for national policies. *Ann Saudi Med*. 2015;35(3):196–202.
19. Rashed Adam T, Bakhamees BH, Abdulla Ali Ahmed Ali M, et al. A systematic review of the impact of dietary and lifestyle factors on colorectal cancer prevention in gulf cooperation council countries. *Cureus*. 2024;16(9):e69439.
20. Al-Ahwal MS, Shafik YH, Al-Ahwal HM. First national survival data for colorectal cancer among Saudis between 1994 and 2004: What's next? *BMC Public Health*. 2013;13:1–6.
21. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012;142(6):1264–73.e1.
22. Salem S, Mitchell RE, El-Alim El-Dorey A, Smith JA, Barocas DA. Successful control of schistosomiasis and the changing epidemiology of bladder cancer in Egypt. *BJU Int*. 2011;107(2): 206–211.
23. Wong Y, Meehan MT, Burrows SR, Doolan DL, Miles JJ. Estimating the global burden of Epstein-Barr virus-related cancers. *J Cancer Res Clin Oncol*. 2022;148(1):31–46.
24. Alsulaimany FAS, Awan ZA, Almohamady AM, et al. Prevalence of helicobacter pylori infection and diagnostic methods in the Middle East and North Africa region. *Medicina (Kaunas)*. 2020;56(4):169.
25. Chaabna K, Mohamoud YA, Chemaitelly H, Mumtaz GR, Abu-Raddad LJ. Protocol for a systematic review and meta-analysis of hepatitis C virus (HCV) prevalence and incidence in the Horn of Africa sub-region of the Middle East and North Africa. *Syst Rev*. 2014;3:1–5.
26. Cowgill KD, Loffredo CA, Eissa SA, et al. Case-control study of non-Hodgkin's lymphoma and hepatitis C virus infection in Egypt. *Int J Epidemiol*. 2004;33(5):1034–1039.
27. Alavanja MC, Bonner MR. Occupational pesticide exposures and cancer risk: A review. *J Toxicol Environ Health B Crit Rev*. 2012;15(4):238–263.

28. Sherif M, Makame KR, Östlundh L, et al. Genotoxicity of occupational pesticide exposures among agricultural workers in Arab countries: A systematic review and meta-analysis. *Toxics*. 2023; 11(8):663.
29. Coughlin SS. Epidemiology of breast cancer in women. In: *Breast Cancer Metastasis and Drug Resistance: Challenges and Progress*. 2019;9:9–29.
30. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol*. 2001;2(3):133–140.
31. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. *Nat Rev Dis Primers*. 2019;5(1):66.
32. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: Data from the nurses' health study. *Am J Epidemiol*. 2000;152(10):950–964.
33. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: Update on epidemiology and risk factors. *J Cancer Epidemiol*. 2013; 2013(1):965212.
34. Vigneri R, Malandrino P, Vigneri P. The changing epidemiology of thyroid cancer: Why is incidence increasing? *Curr Opin Oncol*. 2015;27(1):1–7.
35. Al-Shamsi HO, Abdelwahed N, Abyad A, et al. Breast cancer in the Arabian Gulf countries. *Cancers (Basel)*. 2023;15(22): 5398.
36. Al Amri WS, Al Amri AH, Al Abri A, Hughes TA, Al Lawati F. BRCA1/2 mutations and outcomes among Middle Eastern patients with early-onset breast cancer in Oman. *Oncologist*. 2024;29(12):e1714–e1722.
37. Baecker A, Liu X, La Vecchia C, Zhang ZF. Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. *Eur J Cancer Prev*. 2018;27(3):205–212.
38. Ibrahim A, El Baldi M, Mohammed S, El Rhazi K, Benazzouz B. Cancer statistics in Yemen: Incidence and mortality, in 2020. *BMC Public Health*. 2024;24(1):962.
39. Abdul-Sater Z, Shamseddine A, Taher A, et al. Cancer registration in the Middle East, North Africa, and Turkey: Scope and challenges. *JCO Global Oncology*. 2021;7:1101–1109.
40. Mansour R, Al-Ani A, Al-Hussaini M, Abdel-Razeq H, Al-Ibraheem A, Mansour AH. Modifiable risk factors for cancer in the Middle East and North Africa: A scoping review. *BMC Public Health*. 2024;24(1):223.
41. Laguna JC, García-Pardo M, Alessi J, et al. Geographic differences in lung cancer: Focus on carcinogens, genetic predisposition, and molecular epidemiology. *Ther Adv Med Oncol*. 2024;16:17588359241231260.
42. Guerrero S, Lopez-Cortes A, Indacochea A, Garcia-Cardenas J, Zambrano A, Cabrera-Andrade A. Analysis of racial/ethnic representation in select basic and applied cancer research studies. *Sci Rep*. 2018;8(1):13978.
43. Ateia H, Ogrodzki P, Wilson HV, et al. Population genome programs across the Middle East and north Africa: Successes, challenges, and future directions. *Biomedicine hub*. 2023;8(1):60.
44. Al-Ali M, Osman W, Tay GK, AlSafar HS. A 1000 Arab genome project to study the Emirati population. *J Hum Genet*. 2018;63(4):533–536.
45. El-Attar EA, Helmy Elkaffas RM, Aglan SA, Naga IS, Nabil A, Abdallah HY. Genomics in Egypt: Current status and future aspects. *Front Genet*. 2022;13:797465.
46. Alsolme E, Alqahtani S, Fageeh M, et al. The genomic landscape of colorectal cancer in the Saudi Arabian population using a comprehensive genomic panel. *Diagnostics*. 2023; 13(18):2993.
47. Hamdi Y, Trabelsi M, Ghedira K, et al. Genome Tunisia project: Paving the way for precision medicine in North Africa. *Genome Med*. 2024;16(1):104.
48. Mbarek H, Devadoss Gandhi G, Selvaraj S, et al. Qatar Genome: Insights on genomics from the Middle East. *Hum Mutat*. 2022; 43(4):499–510.
49. Al-Maawali A. Oman Genome project is the future of using genomics as the determinant of health and disease in the society. *Oman Med J*. 2022;37(6):e440.
50. Dawood S, Sandhir N, Akasheh M, et al. Genomic landscape of advanced solid tumors in Middle East and North Africa using circulating tumor DNA (ctDNA) in routine clinical practice. *Oncology*. 2024:1–24.
51. Jazieh AR, Algwaiz G, Errihani H, et al. Lung cancer in the Middle East and North Africa region. *J Thorac Oncol*. 2019; 14(11):1884–1891.
52. Bethune G, Bethune D, Ridgway N, Xu Z. Epidermal growth factor receptor (EGFR) in lung cancer: An overview and update. *J Thorac Dis*. 2010;2(1):48.
53. Ramadhan HH, Taaban DF, Hassan JK. The frequency of epidermal growth factor receptor (EGFR) mutations in Iraqi patients with non-small cell lung cancer (NSCLC). *Asian Pac J Cancer Prev: APJCP*. 2021;22(2):591.
54. Benbrahim Z, Antonia T, Mellas N. EGFR Mutation frequency in Middle East and African non-small cell lung cancer patients: A systematic review and meta-analysis. *BMC Cancer*. 2018;18:1–6.
55. Nassar D, Chidiac C, Ibrahim E, Abou Zeid K, Haddad F, Kourie H. EGFR Mutation in non-squamous non-small-cell lung carcinoma (NS-NSCLC) in the Arab world: A systematic review. *Gulf J Oncolog*. 2023;1(41):54–61.
56. Song X, Cao L, Ni B, et al. Challenges of EGFR-TKIs in NSCLC and the potential role of herbs and active compounds: From mechanism to clinical practice. *Front Pharmacol*. 2023; 14:1090500.
57. Doebele RC, Oton AB, Peled N, Camidge DR, Bunn PA Jr. New strategies to overcome limitations of reversible EGFR tyrosine kinase inhibitor therapy in non-small cell lung cancer. *Lung Cancer*. 2010;69(1):1–12.
58. Chouchane L, Boussen H, Sastry KS. Breast cancer in Arab populations: Molecular characteristics and disease management implications. *Lancet Oncol*. 2013;14(10):e417–e424.
59. Abulkhair O, Al Balwi M, Makram O, et al. Prevalence of BRCA1 and BRCA2 mutations among high-risk Saudi patients with breast cancer. *J Glob Oncol*. 2018;4:JGO.18.00066.
60. Alhuqail A-J, Alzahrani A, Almubarak H, et al. High prevalence of deleterious BRCA1 and BRCA2 germline mutations in arab breast and ovarian cancer patients. *Breast Cancer Res Treat*. 2018;168:695–702.

61. Farra C, Dagher C, Badra R, et al. BRCA Mutation screening and patterns among high-risk Lebanese subjects. *Hered Cancer Clin Pract*. 2019;17(1):4.
62. Altinoz A, Al Ameri M, Qureshi W, Boush N, Nair SC, Abdel-Aziz A. Clinicopathological characteristics of gene-positive breast cancer in the United Arab Emirates. *The Breast*. 2020;53:119–124.
63. Laraqui A, Uhrhammer N, El Rhaffouli H, et al. BRCA Genetic screening in Middle Eastern and North African: Mutational spectrum and founder BRCA1 mutation (c. 798_799delTT) in North African. *Dis Markers*. 2015;2015(1):194293.
64. Bu R, Siraj AK, Al-Obaisi KA, et al. Identification of novel BRCA founder mutations in Middle Eastern breast cancer patients using capture and Sanger sequencing analysis. *Int J Cancer*. 2016;139(5):1091–1097.
65. Elmaihub ES, Alhudiri I, Ramadan AM, et al. Analysis of BRCA1 germline variants (exons 5, 11 and 20) in breast cancer families from Libya. *Libyan J Med*. 2024;19(1):2356906.
66. Awadelkarim KD, Aceto G, Veschi S, et al. BRCA1 And BRCA2 status in a central Sudanese series of breast cancer patients: Interactions with genetic, ethnic and reproductive factors. *Breast Cancer Res Treat*. 2007;102:189–199.
67. Abdulrashid K, AlHussaini N, Ahmed W, Thalib L. Prevalence of BRCA mutations among hereditary breast and/or ovarian cancer patients in Arab countries: Systematic review and meta-analysis. *BMC Cancer*. 2019;19:1–12.
68. Bu R, Siraj AK, Al-Rasheed M, et al. Identification and characterization of ATM founder mutation in BRCA-negative breast cancer patients of Arab ethnicity. *Sci Rep*. 2023;13(1):20924.
69. Al-Eitan LN, Jamous RI, Khasawneh RH. Candidate gene analysis of breast cancer in the Jordanian population of Arab descent: A case-control study. *Cancer Investig*. 2017;35(4):256–270.
70. Alshatwi AA, Hasan TN, Shafi G, Alsaif MA, Al-Hazzani AA, Alsaif AA. A single-nucleotide polymorphism in the TP53 and MDM-2 gene modifies breast cancer risk in an ethnic Arab population. *Fundam Clin Pharmacol*. 2012;26(3):438–443.
71. Karakas B, Colak D, Kaya N, et al. Prevalence of PIK3CA mutations and the SNP rs17849079 in Arab breast cancer patients. *Cancer Biol Ther*. 2013;14(10):888–896.
72. Alawadi S, Ghabreau L, Alsaleh M, et al. P53 gene polymorphisms and breast cancer risk in Arab women. *Med Oncol*. 2011; 28:709–715.
73. Osman Y, Elsharkawy T, Hashim TM, et al. Study of single nucleotide polymorphisms associated with breast cancer patients among Arab ancestries. *Int J Breast Cancer*. 2022;2022(1):2442109.
74. Al-Shamsi HO, Abu-Gheida I, Abdulsamad AS, et al. Molecular spectra and frequency patterns of somatic mutations in Arab women with breast cancer. *Oncologist*. 2021;26(11):e2086–e2089.
75. Makhlouf NA, Abdel-Gawad M, Mahros AM, et al. Colorectal cancer in arab world: A systematic review. *World J Gastrointest Oncol*. 2021;13(11):1791.
76. Shamseddine A, Chehade L, Al Mahmasani L, Charafeddine M. Colorectal cancer screening in the Middle East: What, why, who, when, and how? *Am Soc Clin Oncol Educ Bk*. 2023;43:e390520.
77. Al-Shamsi HO, Iqbal F, Kourie HR, Zaabi AA, Abyad AM, Abdelwahed N. Colorectal cancer in the UAE. In: Al-Shamsi HO (ed.) *Cancer Care in the United Arab Emirates*. Springer; 2024:435–450.
78. Phua LC, Ng HW, Yeo AHL, et al. Prevalence of KRAS, BRAF, PI3K and EGFR mutations among Asian patients with metastatic colorectal cancer. *Oncol Lett*. 2015;10(4):2519–2526.
79. Alghamdi M, Alabdullatif N, Al-Rashoud A, et al. KRAS mutations in colorectal cancer: relationship with clinicopathological characteristics and impact on clinical outcomes in Saudi Arabia. *Cureus*. 2022;14(3).
80. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: A retrospective consortium analysis. *Lancet Oncol*. 2010;11(8):753–762.
81. Li W, Qiu T, Zhi W, et al. Colorectal carcinomas with KRAS codon 12 mutation are associated with more advanced tumor stages. *BMC Cancer*. 2015;15:1–9.
82. Elbjeirami WM, Sughayer MA. KRAS Mutations and subtyping in colorectal cancer in Jordanian patients. *Oncol Lett*. 2012;4(4): 705–710.
83. Zahrani A, Kandil M, Badar T, Abdelsalam M, Al-Faiar A, Ismail A. Clinico-pathological study of K-ras mutations in colorectal tumors in Saudi Arabia. *Tumori Journal*. 2014;100(1):75–79.
84. Siraj AK, Bu R, Prabhakaran S, et al. A very low incidence of BRAF mutations in Middle Eastern colorectal carcinoma. *Mol Cancer*. 2014;13:1–9.
85. Abubaker J, Bavi P, Al-Harbi S, et al. Clinicopathological analysis of colorectal cancers with PIK3CA mutations in Middle Eastern population. *Oncogene*. 2008;27(25):3539–3545.
86. Al-Shamsi HO, Jones J, Fahmawi Y, et al. Molecular spectrum of KRAS, NRAS, BRAF, PIK3CA, TP53, and APC somatic gene mutations in Arab patients with colorectal cancer: Determination of frequency and distribution pattern. *J Gastrointest Oncol*. 2016;7(6):882.
87. Younis N, AlMasoud E, Al Khawajah F, et al. Potential genetic biomarker of Saudi Arabian patients with colorectal cancer. *Eur Rev Med Pharmacol Sci*. 2022;26(9).
88. Almuzzaini B, Alghamdi J, Alomani A, et al. Identification of novel mutations in colorectal cancer patients using AmpliSeq comprehensive cancer panel. *J Pers Med*. 2021;11(6):535.
89. Danese E, Montagnana M. Epigenetics of colorectal cancer: Emerging circulating diagnostic and prognostic biomarkers. *Ann Transl Med*. 2017;5(13):279.
90. Jung G, Hernández-Illán E, Moreira L, Balaguer F, Goel A. Epigenetics of colorectal cancer: Biomarker and therapeutic potential. *Nat Rev Gastroenterol Hepatol*. 2020;17(2):111–130.
91. Beg S, Siraj AK, Prabhakaran S, et al. Molecular markers and pathway analysis of colorectal carcinoma in the Middle East. *Cancer*. 2015;121(21):3799–3808.
92. Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. The serrated pathway to colorectal carcinoma: Current concepts and challenges. *Histopathology*. 2013;62(3):367–386.
93. Samadder NJ, Vierkant RA, Tillmans LS, et al. Associations between colorectal cancer molecular markers and pathways with clinicopathologic features in older women. *Gastroenterology*. 2013;145(2):348–56.e2.

94. Chan AO, Soliman AS, Zhang Q, et al. Differing DNA methylation patterns and gene mutation frequencies in colorectal carcinomas from Middle Eastern countries. *Clin Cancer Res*. 2005;11(23):8281–8287.
95. Kang S, Na Y, Joung SY, Lee SI, Oh SC, Min BW. The significance of microsatellite instability in colorectal cancer after controlling for clinicopathological factors. *Medicine (Baltimore)*. 2018;97(9):e0019.
96. Shaikh R, Bhattacharya S, Prajapati BG. Microsatellite instability: A potential game-changer in colorectal cancer diagnosis and treatment. *Results Chem*. 2024:101461.
97. Soliman A, Bondy M, El-Badawy S, et al. Contrasting molecular pathology of colorectal carcinoma in Egyptian and Western patients. *Br J Cancer*. 2001;85(7):1037–1046.
98. Bidoli E, Virdone S, Hamdi-Cherif M, et al. Worldwide age at onset of female breast cancer: A 25-year population-based cancer registry study. *Sci Rep*. 2019;9(1):14111.
99. Salem H, Daher-Nashif S. Psychosocial aspects of female breast cancer in the Middle East and North Africa. *Int J Environ Res Public Health*. 2020;17(18):6802.
100. Saadeh S, Abdel-Razeq H. Breast cancer in the Arab world. *Cancer Arab World*. 2022:353–362.
101. Khalil RB. Attitudes, beliefs and perceptions regarding truth disclosure of cancer-related information in the Middle East: A review. *Palliat Support Care*. 2013;11(1):69–78.
102. Chelmow D, Pearlman MD, Young A, et al. Executive summary of the early-onset breast cancer evidence review conference. *Obstet Gynecol*. 2020;135(6):1457–1478.
103. Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): A prospective cohort study. *Lancet Oncol*. 2018;19(2):169–180.
104. Al Zaabi A, Al Shehhi A, Sayed S, et al. Early onset colorectal cancer in arabs, are we dealing with a distinct disease? *Cancers (Basel)*. 2023;15(3):889.
105. Archambault AN, Su Y-R, Jeon J, et al. Cumulative burden of colorectal cancer–associated genetic variants is more strongly associated with early-onset vs late-onset cancer. *Gastroenterology*. 2020;158(5):1274–86.e12.
106. Stoffel EM, Koeppe E, Everett J, et al. Germline genetic features of young individuals with colorectal cancer. *Gastroenterology*. 2018;154(4):897–905.e1.
107. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. *JAMA Oncol*. 2017;3(4):464–471.
108. Ziada-Bouchaar H, Sifi K, Filali T, Hammada T, Satta D, Abadi N. First description of mutational analysis of MLH1, MSH2 and MSH6 in Algerian families with suspected Lynch syndrome. *Fam Cancer*. 2017;16(1):57–66.
109. Siraj AK, Masoodi T, Bu R, et al. Expanding the spectrum of germline variants in cancer. *Hum Genet*. 2017;136:1431–1444.
110. Warner E, Foulkes W, Goodwin P, et al. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst*. 1999;91(14):1241–1247.
111. AlHarthi FS, Qari A, Edress A, Abedalthagafi M. Familial/inherited cancer syndrome: A focus on the highly consanguineous Arab population. *NPJ Genom Med*. 2020;5(1):3.
112. Saletta F, Dalla Pozza L, Byrne JA. Genetic causes of cancer predisposition in children and adolescents. *Transl Pediatr*. 2015;4(2):67.
113. Jastaniah W, Aljefri A, Ayas M, et al. Prevalence of hereditary cancer susceptibility syndromes in children with cancer in a highly consanguineous population. *Cancer Epidemiol*. 2018;55:88–95.
114. Younes N, Zayed H. Genetic epidemiology of ovarian cancer in the 22 Arab countries: A systematic review. *Gene*. 2019;684:154–164.
115. Siraj AK, Bu R, Iqbal K, et al. Prevalence, spectrum, and founder effect of BRCA1 and BRCA2 mutations in epithelial ovarian cancer from the Middle East. *Hum Mutat*. 2019;40(6):729–733.
116. Ghorbanoghli Z, Jabari C, Sweidan W, et al. A new hereditary colorectal cancer network in the Middle East and eastern Mediterranean countries to improve care for high-risk families. *Fam Cancer*. 2018;17:209–212.
117. Siraj AK, Prabhakaran S, Bavi P, et al. Prevalence of Lynch syndrome in a Middle Eastern population with colorectal cancer. *Cancer*. 2015;121(11):1762–1771.
118. AlHarbi M, Mobark NA, AlJabarat WAR, et al. Investigating the prevalence of pathogenic variants in Saudi Arabian patients with familial cancer using a multigene next generation sequencing panel. *Oncotarget*. 2023;14:580.