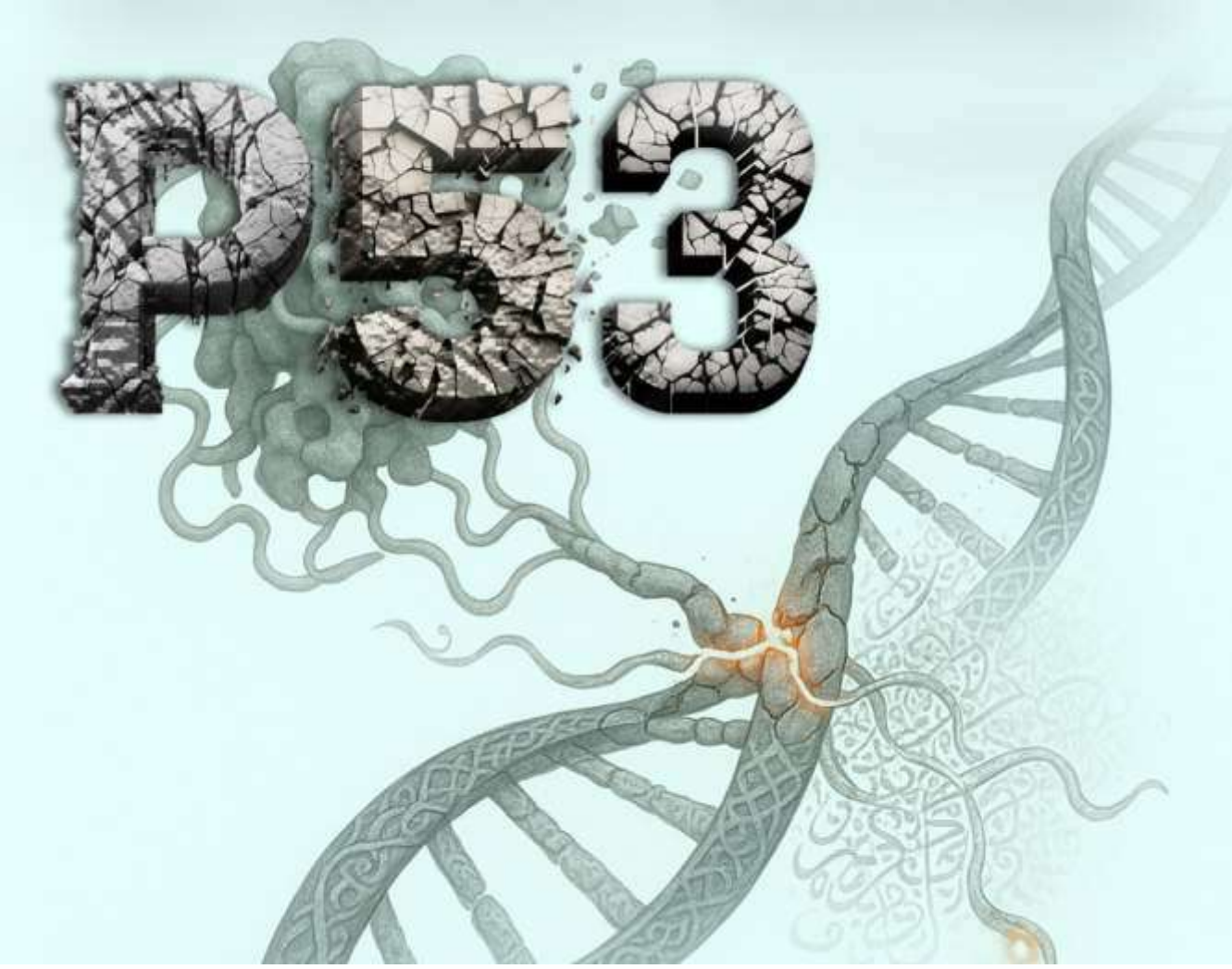

P53 Mutations in Middle Eastern Cancers

Molecular Pathogenesis, Epidemiology, and Clinical Implications

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DeepScience

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Preface

Over recent decades, cancer biology has undergone a significant transformation, but very few molecules have received more attention from scientists than p53, which is commonly referred to as the ‘guardian of the genome’. This fascinating protein represents both the intersection between cellular life and death through its role in protecting the genome from the effects of ongoing extrinsic and intrinsic stressors and is arguably one of the most important proteins to maintain genomic integrity through mediation of cell survival. TP53 is not just an example of molecular regulation; the story of this gene typifies the complex nature of cancer, multifaceted and heavily impacted by genetic, environmental and sociocultural factors.

The objective for writing this book was to combine worldwide understanding regarding the nature of p53 biology with specific emphasis on understanding how p53 relates to the region of the Middle East. Although mutations within TP53 have been widely recognised as the primary contributing factor to tumour formation, recent findings indicate that there are differences in the levels of TP53 mutations and their types and therefore their implications clinically, between populations. The molecular characteristics of the different populations are influenced by the range of genetic variance, patterns of consanguinity, exposure to environment, dietary shifts and the availability of quality health care. This collective effect must be investigated in an independent manner in order to understand the full impact of the molecular characteristics on the Middle Eastern population.

Through the next few chapters, we integrate basic molecular mechanisms with epidemiological data, regional studies and translational concepts. Evaluating TP53 globally and regionally will stimulate specific context-based research, support genomic medicine initiatives, and stimulate efforts among scientists, clinicians and policy-makers to collaborate.

Learning about p53 is more than an intellectual exercise; it elucidates a route to greater accuracy of diagnosis, individualized therapy, and better outcomes for cancer patients. This book seeks to illuminate the involvement of TP53 in the Middle East for the benefit of both regional and global initiatives that advance the field of precision oncology.

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Chapter 1: Foundations of P53 and Regional Context

Regionally Relevant Introduction to P53

TP53, the "guardian of the genome," is a critical regulator of genes responsible for crucial cellular functions including DNA repair, apoptosis, and cell cycle regulation. TP53, one of the most common genetic alterations observed in human cancer, yet plays a key role in tumor initiation and metastasis as well as treatment-induced disease resistance. TP53 mutations are discovered by lifestyle, lifestyle habits and environmental factors. We summarize and review the molecular basis, therapeutic implications, and public health strategies of common TP53 mutants observed in populations across the Middle East.

Data Availability: All relevant data are within the paper and its Supporting Information files. In pursuit of these goals, a review was conducted to study the literature surrounding TP53 gene variations in the Middle East (i.e., epidemiological studies, clinical trials, and public health reports). And even statistical data was analysed and presented in creative graphics that truly made it easier to look at meaningful trends. This review primarily concentrates on the impact of several lifestyle variables, health promotion initiatives, treatment responses, and discrepancies in the quality of healthcare provided to cancer patients across countries from this region.

A strikingly high percentage of Middle Eastern patients with cancer had mutations in the TP53 tumor-suppressing gene than seen in rates in Western nations, particularly those with lung and breast malignancies. These mutations include heterozygous and homozygous mutations, frameshift mutations, and splice site mutations (though heterozygous mutations are the most common). Smoking, for example, is the leading explanation for the estimated toll of mutations in cancer and other well-known environmental and lifestyle risk factors such as obesity, poor dietary practices and smoking all substantially increase mutation rates. Despite great advances in cancer treatment, outcomes remain widely heterogeneous and combination therapy is still a major improvement in response of TP53-mutant tumors.

Cancer services remain underutilized across the region, however, and awareness levels are significantly lower than those found in the western world due to public health interventions that promote elevations in awareness and direct access to early detection programs. But there have been some advancements through purposeful awareness efforts in targeted populations which start to show the call for offsets and increased rate of early detection!

In the Middle East, various methods are being employed to prevent and cure TP53-associated malignances such as customized therapy, lifestyle changes, and public health initiatives. These results underline the importance of location-specific public health policies to increase awareness among those with less access to healthcare and reduce the incidence of these and all cancers overall, as well as the need for exploration of any tumor molecular profiles to tailor therapies — what was found there too to remain highly impactful in decreasing overall burden for cancers. Reducing the burden of cancer and improving survival outcomes is a critical area that requires close collaboration among academics, policymakers, and other healthcare stakeholders.

The TP53 gene encodes the tumor suppressor protein p53, crucial for maintaining genomic integrity. It functions at multiple important cellular check points in response to various types of cellular stresses such as DNA damage, oncogene activation and hypoxia to regulate the cell cycle, initiate DNA repair, trigger senescence and induce apoptosis. This has led to its nickname, the "guardian of the genome" due to its multifaceted function in maintaining genomic stability (Kastenhuber & Lowe, 2017). Under normal physiological situations, p53 is tightly regulated by proteasomal degradation pathways as mediated mainly by MDM2 and remains at low levels. Genotoxic stress also induces stabilizing post-translational modifications, allowing p53 to act as a transcription factor to activate or repress hundreds of downstream target genes.

Mutations in TP53 are the most common genetic alterations across a diverse set of human cancers. According to Donehower et al. (2019), such mutations often result in the loss of wild-type p53 activity or, under specific circumstances, gain-of-function (GOF) properties that enhance malignant transformation and promote disease progression and therapeutic resistance. The impact of these mutations may vary with tissue type, tumor subtype, and patient cohort. TP53 alterations include missense mutations in the DNA-binding domain, deletions, insertions and splice-site changes. More than 50% of human malignancies carry mutations or functional inactivation of TP53, underscoring its universal importance within tumor suppression pathways.

While TP53 mutations and the carcinogenic effects have been extensively studied globally, there are limited data regarding how applicable and consistent these findings are across regions especially in the Middle East.

The frequency, distribution and clinical impacts of TP53 mutations may be markedly different among Middle Eastern populations owing to regional genetic architecture, environmental exposures lifestyle differences, and inequities in healthcare systems. However, because there has been no large-scale population genomics investigation in these settings, little is known about the functional implications of TP53 mutations in such context.

Cancer has become a severe public health problem in the Middle East (ME) with its rapidly increasing incidence over the last couple of decades. The incidence and mortality rates of many diseases, particularly colorectal and breast cancers, are rising in countries across the region. This rise is attributable to multiple interconnected factors including increased longevity, adaptation of Westernized habits and lifestyles, exposure to environmental contaminants, obesity, and cigarette smoking (Al-Madouj et al., 2020). There is also emerging evidence that this growing burden might be largely driven by genetic predisposition, like TP53 mutations.

Numerous studies in the region have indicated that TP53 mutations are common among Middle Eastern cancer patients. For example, breast cancer is the most common cancer diagnosed among women in the region. It appears at an earlier age and tends to be more aggressive than Western groups. Recent studies on breast cancer show that around 40% of breast cancers in Saudi Arabia had TP53 mutations, particularly among women achieving at an early age (less than 50). This genetic alteration is considered significant in the pathophysiology of disease based on a mutation rate of 7.61% for the entire patient cohort (Al-Qasem et al., 2018). These numbers raise important questions about the origins of these mutations, whether they are acquired somatic mutations driven by environmental carcinogens, inherited germline variants or both.

Colorectal cancer ranks second among causes of cancer-related death in the Middle East. Studies utilizing regional molecular profiling of colorectal tumor-derived biospecimens have identified TP53 mutations as frequent anomalies. These mutations often co-exist with defective DNA mismatch repair. Consistent with findings from other parts of the world, a study conducted in Northern Saudi Arabia found a high correlation between TP53 mutations and advanced colorectal cancer (Bazarbashi et al., 2021). Such data highlights the need for regional mutation pattern adjusted next-generation molecular diagnostic techniques followed by region-specific cancer genetic screening.

Interestingly, one of only a handful of mammalian species that are naturally cancer resistant is the blind mole-rat (Nannospalax ehrenbergi), which also resides in the Middle East. This tireless Levantine subterranean horder has an impressive ability to control cancers in its 30-year-long life. Blind mole-rats also display unique changes in certain stress-response pathways, including regulation of TP53 activity (Shams et al., 2022). One way prevents initiation of carcinogenesis altogether by causing coordinated necrotic cell death induced by hyperproliferative signaling. Since its initial discovery, TP53 has been subject to various evolutionary studies examining a large number of human and mole-rat species, drawing novel therapeutic ideas in the field against cancer (Manov et al., 2013)

Notwithstanding these developments, a number of challenges still face the implementation of genomic medicine and precision oncology in Middle Eastern nations. There are various factors that restrict such studies including limited funds, insufficient skilled personnel, inadequate high-throughput sequencing infrastructure and lack of national cancer registers in some countries (Abdel-Rahman, 2018). In addition, most touted genetic research so far has been small in scale, institutional and lacking established methodologies. This fragmentation limits the ability to extrapolate results or apply them in clinical contexts.

Additionally, a number of Middle Eastern populations remain poorly represented in existing international cancer genomic banks such as the ICGC and TCGA. Because of this underrepresentation, it is difficult to assess the applicability of global mutation patterns to Arab populations. It also hinders building region-focused treatment regimens accounting for local genetic diversity and epidemiological patterns.

Investigation of major health concerns in the region falls to Middle Eastern research establishments and healthcare policymakers, who must prioritize large-scale multicenter genomic studies with extensive clinical annotation. These efforts should aim to:

Characterize the range of TP53 mutations in different cancers in that region

Identify population-specific SNPs and haplotypes

Evaluate the association between mutation status and clinical outcomes, including survival, recurrence, or response to therapy

Set up regional biobanks and tumor registries.

Feature molecular data as part of the national cancer control plan

These integrative approaches have the potential to provide locally customized diagnostic, prognostic and therapeutic tools. Alternatively, they would also add an important genetic diversity typically underrepresented to the global dataset of cancer biology.

In order to expedite cancer research, the Middle Eastern countries might leverage existing public health programs, invest more into molecular pathology labs and collaborate with international consortiums. An equally critical component of translating these findings to the clinic will be enhancing medical education and training programs in genomic oncology.

The tale of TP53 in the Middle East is a work in progress. Whether it becomes a major contributor to the regional cancer burden or a springboard for novel therapeutic interventions will depend in large part on the region's dedication to scientific discovery, collaboration, and health system reform.

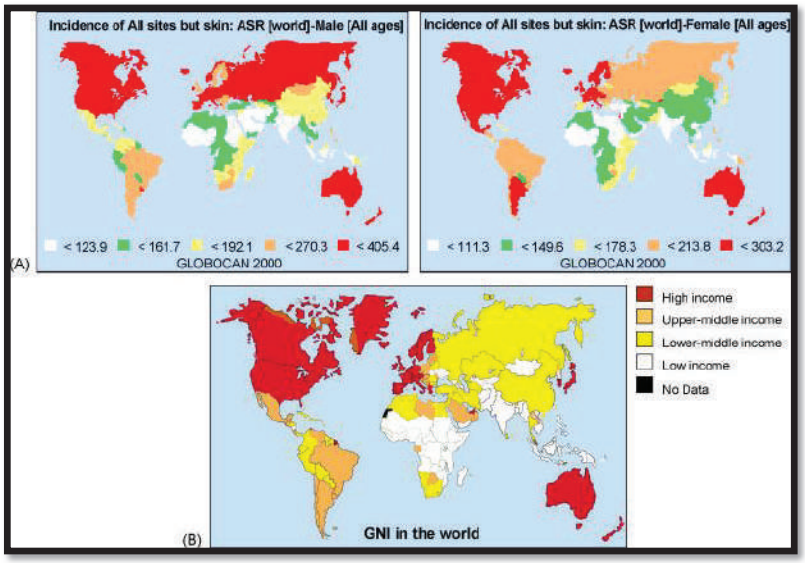


Figure (1) Global Distribution of TP53 Mutations Across the world (Olivier et al., 2010)

Roles of the P53 Gene in Cancer Suppression

The TP53 gene, located on chromosome 17p13 codes for the p53 protein that is crucial in providing cellular protection from genomic instability. 1. This tumor suppressor protein is activated by many cellular stressors including DNA damage, oncogene activation, telomere erosion, oxidative stress and hypoxia. p53 as a transcription factor regulates a network of genes that are critical to maintain the genomic integrity. These genes coordinate are fundamental biological functions such as cell cycle arrest, DNA repair, senescence, apoptosis and metabolic control (Su et al., 2019). By integrating these responses, p53 directly helps to suppress the survival and proliferation of cells that harbor oncogenic mutations.

Under normal conditions, levels of p53 protein are kept low due to constant degradation by its main negative regulator, the E3 ubiquitin ligase MDM2. MDM2 forms a stable complex with p53, allowing for its ubiquitination and proteasomal degradation. Phosphorylation of p53 and MDM2 disrupt their interaction upon the detection of cellular stress. The consequences of this activity are nuclear accumulation and p53 stabilization, which initiate the transcriptional activation of downstream target genes such as BAX, PUMA and NOXA (inducers of programmed cell death) or CDKN1A (p21) to induce cell cycle arrest (Manov et al., 2013).

TP53 mutations are the most frequent genetic alteration found in human cancers, with more than half of all malignant tumors harboring TP53 aberrations. The majority of these mutations are LOF (loss of function) p53 mutants that target the DNA-binding domain. Consequently, cells are unable to induce apoptosis as required or block the cell cycle in response to damage. Many of these mutations are missense and exert dominant-negative effects, making them block any wild-type p53 proteins potentially left. Furthermore, some mutant variants acquire additional gain-of-function (GOF) properties that promote oncogenesis by modifying immune microenvironments, inducing invasiveness, enhancing genomic instability and deregulating transcriptional programs (Gorbunova et al., 2012; Uddin, 2018).

Loss of p53 function disrupts several cell checkpoints. When cells do not properly repair damaged DNA, they escape G1 checkpoint regulation and transit through the cell cycle, leading to mutations, chromosome instability and ultimately tumorigenesis. Standard therapies such as radiation and chemotherapy, which rely on functional apoptotic pathways for the killing of cancer cells, are also less efficacious in TP53-deficient malignancies. In

addition, for multiple cancer types such resistance results in failure of therapy and poor prognosis (Torre et al., 2015).

Beyond its canonical tumor-suppressor function, p53 regulates a plethora of non-oncogenic cellular processes. It helps regulate metabolism and counteracts the Warburg effect, which is a metabolic profile common to cancer cells, by inhibiting glycolysis and promoting mitochondrial respiration. The p53-target genes TIGAR and SCO2 switch cellular metabolism from glycolysis to oxidative phosphorylation. This also diminishes the metabolic adaptability that cancer cells often exploit and helps to restore redox homeostasis (Su et al., 2019).

Another function of p53 is to induce cellular senescence, a permanent cell cycle arrest that acts as a barrier against carcinogenesis (Oren and Saroussel, 2007). P53-regulated senescence can promote tissue dysfunction in aging or chronic stress conditions, but it suppresses the proliferation of damaged or pre-malignant cells. And new research is revealing that p53 and the immune system interact in a much more nuanced way, especially to regulate inflammation. p53 can reduce the immunosuppressive nature of the tumor microenvironment and also inhibit pro-inflammatory gene expression. Conversely, loss of its function could induce immune evasion via upregulated immune checkpoint expression as well as downregulated antigen presentation, facilitating tumor development (IHE Report 2021).

Comparative oncology may yield strong evidence supporting the role of p53 in tumor resistance. One notable example is a Middle Eastern rodent called the blind mole rat (Spalax), which species naturally resists the disease. Studies have shown that these animals, having adapted to hypoxic underground environments by evolving novel TP53 pathway adaptations, can tightly control cellular proliferation and maintain genomic stability (1), two requirements that are highly likely to cause malignant transformations when dysregulated. These alterations in apoptosis (increased susceptibility to) and phenotypes of cellular necrosis are consistent with aspects of hyperplasia with their associated functional changes in gene expression. Due to these properties, the blind mole-rat serves as a model organism for elucidating mechanisms of tumor suppression that may be leveraged into novel therapeutic approaches (Manov et al., 2013).

The translation of p53-related discoveries into the clinic has been a challenge but is ongoing. There are numerous strategies to reactivate p53 function in tumors, including:

Gene therapy with wild-type TP53

Small molecules such as PRIMA-1 and APR-246 which refold mutant p53 into functional conformation

MDM2 inhibitors (e.g. Nutlin-3a) to prevent p53 degradation in wild-type TP53 tumors

Approaches based on synthetic lethality that target vulnerabilities in p53-deficient cells.

These developments have been hampered by tumor heterogeneity, compensation through other mechanisms and risk of toxicity and thus the translation to clinical use has been challenging. Nonetheless, understanding the molecular landscape of TP53 alterations remains critical for developing personalized therapeutic strategies, particularly in understudied populations.

This is particularly important for regions such as the Middle East where cancer epidemiology is shaped by a combination of heterogeneous genetic profiles, variations in environmental exposures and differences in access to and delivery of health care. TP53 mutations are prevalent in colorectal and breast cancers across regions; however, the exact mutation types and functional consequences remain largely unclear due to limited funding and genomic infrastructure. For example, underdiagnosed germline TP53 mutations or unidentified environmental co-factors could link Middle-Eastern breast cancer patients' younger age of onset and higher frequency of aggressive subtypes. Likewise, defects of mismatch repair pathways often coalesce with TP53 mutations within CRCs and can impact treatment availabilities.

However, population specific studies linking genomics data to clinical outcomes are necessary for understanding 1) how TP53 mutation profiles varied regionally and 2) their clinical relevance. There is an urgent need for:

Establishing national cancer genomics registries

Doing large-scale sequencing of common tumors

Molecular oncology training for clinicians and pathologists

Incorporating TP53 status in diagnostic and prognostic pathways

TP53 is more than just a tumor suppressor gene. It's a genomic protector, an arbiter of stress responses and a master regulator of myriad cellular

processes. The mutation of this gene is a critical event in the development and evolution of most human cancers. In other words: information about how p53 works, malfunctions or adapts across diverse biological systems — and at the level of peculiar species such as the blind mole-rat — gives us potent tools for enhancing cancer diagnosis, prognosis and therapy. Geographic regions with differentiated genetic backgrounds e.g. Middle East would also benefit from further investigation into TP53-related pathways. These efforts will not only elucidate the role of this gene in regional cancer burdens, but also contribute on a global scale towards precision oncology.

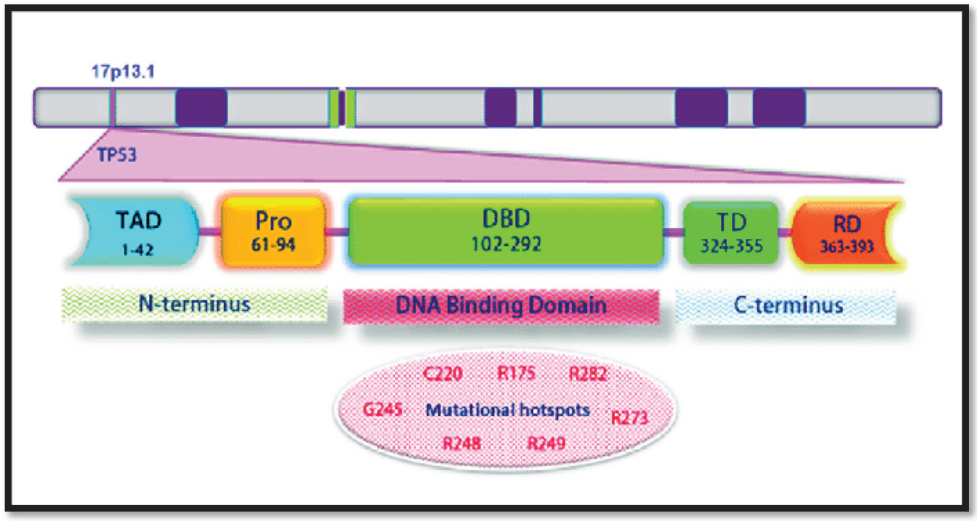


Figure (2) Functional Domains of the p53 Protein and Common TP53 Mutation Hotspots in Human Cancers (Babamohamadi *et al.*, 2022)

P53 Molecular Mechanisms and Tumor Suppression

One of the most thoroughly studied genes in cancer biology is the TP53 gene, a key stone in the molecular architecture of tumor suppression, owin to its high mutation rate and critical role in maintaining genomic stability. p53 is a transcription factor responsible for regulating the expression of genes associated with DNA repair, cell cycle arrest, apoptosis and senescence—all essential processes in clearing oncogenic mutations ^(1)^. Thus, inactivating mutations of TP53 can also disable these defensive processes allowing mutation accumulation, resistance to cell death and excessive proliferation.

Numerous studies over past few years have increasingly reported high frequencies of TP53 mutations in patients diagnosed with cancer in the Middle East, where there is an admixture of genetic ancestries, consanguinity patterns, environmental exposures and lifestyle transitions. These results suggest that TP53 disruption can also serve as a regional signature of carcinogenesis with specific molecular characteristics, and potential clinical consequences, apart from its reaching worldwide importance (Al-Qasem et al., 2011).

Several population-specific studies have demonstrated that the mutation rates and spectrum of Middle Eastern malignancies differ from those reported in Western cohorts. Such diversity encompasses both the spectrum and frequency of mutations, indicating potential etiological factors specific to a region. Several Middle Eastern studies reported unique mutations such as those located in the rarer exon 4 while the majority of Western study reported TP53 mutations mainly localized to exons 5–8.

Breast cancer, which is the most commonly diagnosed cancer among Middle Eastern women, is an evident example of this trend. A landmark study from Saudi Arabia found that TP53 mutations occurred in roughly 40% of breast cancer patients. It is one of the highest rates ever recorded globally (Al-Qasem et al., 2011). That is a higher rate than the global average, which can range between 20% and 30%, depending on the cohort and subtype. Notably, many of these mutations were found in women who were under 50 years old and may suggest an association between TP53 mutation status and early-onset breast cancer in this population.

While a genetic predisposition in early-onset breast cancer is often brought up, the observed spectrum of mutations indicates an environmental carcinogenic contribution as well. In the same Saudi study, G:C→A:T transitions in exon 4 comprised a high percentage of mutations [15]. Those mutational patterns can be caused by exposure to N-nitroso compounds, a class of carcinogens commonly found in processed meats, contaminated water, tobacco smoke and some industrial pollutants. These changes are hallmark of DNA alkylation damage and indicate that genetic susceptibility and environmental risk factors have a joint action.

These data underline the importance of region-specific cancer genomics and confirm novel TP53 mutations in Middle Eastern populations. Some of the mutations detected in these cohorts were not listed previously in published major international TP53 databases, including the IARC TP53 Database,

which could be suggestive that Middle Eastern patients have different traumatic variants. These findings have implications for diagnosis, prognosis and treatment. For instance, Western paradigms of mutation screens may fail to detect some of these unique mutations, and result in either under-diagnosed or misdiagnosing of mutation status in local practice.

TP53 mutations, meanwhile, also represent the most common mutations in colorectal cancer (CRC), another common Middle Eastern cancer besides breast tumors. In CRC cases from the Middle East region, TP53 mutations are frequently identified alongside other well-known driver events such as KRAS and APC, suggesting that a distinctive mutational landscape may influence therapy response. Studies in Iraq [8], Jordan [9], and Egypt [10] reported that >50 % of CRC instances show TP53 mutations, frequently exhibiting atypical mutation patterns when compared to Western cohorts. Unique combinations of frameshift, splice-site, and nonsense mutations have been reported in some individuals; however, many of these mutations remain so far undescribed functionally.

TP53 is another common gene mutation identified in both ovarian and endometrial carcinomas. Research from the Middle East discovered a more diverse spectrum of TP53 mutations between the subtypes, suggesting a potential divergence in molecular sub-classification, while global studies associate TP53 mutations with high-grade serous ovarian cancer. G/SEA TP53 mutations are reported to correlate with an aggressive clinical phenotype, chemoresistance, and poor prognosis in patients originating from the Middle East.

The implications of these results are sizable. Region-specific TP53 mutations may:

• Affect patient response to therapy

Some human tumors associated with mutant p53 can also be resisted classical chemotherapy and radiotherapy by interference of apoptotic pathways.

• Reduce the utility of nongenomic molecular diagnostics

Many currently available commercial assays do not necessarily span region-specific or rarer mutations, particularly in under-sequenced exons.

• Postpone the adoption of precision oncology approaches

Without multi-modality mutation profiling, clinicians may not have the information necessary for risk stratification and targeted therapy.

• Use to identify health intervention needed

If environmental exposures that cause or promote cancer, like N-nitroso compounds, are confirmed to contribute, policy changes in food safety and environmental monitoring and lifestyle education may address a regional cancer burden.

There are several critical steps to make sure we can move forward:

Full-TP53 coverage should be included in all genetic screening programs of cancer clinics throughout the Middle East, which have only previously screened for small TP53-exon panels.

Establish national and regional mutation databases to aggregate data on TP53 variants from populations around the world.

Functional studies of new TP53 mutations for their effects on protein function and tumor behaviour

Conduct pollution-reduction policy efforts for known TP53 mutation-associated carcinogens

Strengthen cancer registries to link molecular data with clinical outcomes, facilitating future epidemiological and therapeutic investigations.

TP53, a powerful cancer biomarker for both initiation and progression. In the Middle East — a region where cancer rates are rising alongside shifting environmental and genetic landscapes — its role is especially relevant. Acknowledging and tailoring healthcare solutions that consider the eclusively regarded distinct characteristics of TP53 mutation in this region will help tap into the breast cancer genomics gap globally and help better disease outcomes through more targeted, culturally or regionally relevant intervention.

Colorectal cancer (CRC) has been the third commonest cancer and the second leading cause of cancer death over the last 20 years and one of the most predominant cancers in the Middle East. This increasing burden is driven by urbanization, changes in dietary habits and sedentary lifestyles, ageing populations and limited access to regular screening programmes. In

colorectal carcinogenesis, TP53 mutations are a crucial molecular event in the progression from adenoma to carcinoma[2]. TP53 is among the most frequently mutated genes in CRC, and it occurs in proportionately significant percentage of patients across all age groups and disease stages based on regional information from Middle Eastern cancer centers and population-based registries.

The TP53 gene encodes the p53 protein, a pivotal component of the DNA damage response machinery. As a barrier against tumor formation in healthy colonic epithelial cells, p53 induces cell cycle arrest or apoptosis upon exposure to DNA damage or oncogenic stress. However, these defense systems are ineffective in the presence of altered TP53. Not only do these mutant p53 proteins lose their ability to suppress tumors, but they may also display pro-oncogenic gain-of-function properties that promote tumor invasion, metastasis and chemoresistance.

TP53 mutations in colorectal cancers from the Middle east show more aggressive clinical behaviour such as deeper invasion, number of involved lymph nodes and higher rates of metastasis at time of diagnosis. Compared with patients presenting with wild-type TP53, these characteristics are associated with poor overall survival and reduced disease-free survival. For example, a study conducted in Northern Saudi Arabia reported TP53 mutations in over 55% of colorectal cancer cases, with the mutation being even more predominant among patients with advanced tumors and poor histological differentiation (Bazarbashi et al., 2021). The authors found that TP53 was associated with increased tumor size, lymphovascular invasion, and diminished response to treatment [10]. These studies provided evidence in support of the potential role for TP53 as a biomarker of poor prognosis.

Similar patterns have also been observed for CRC cohorts in Iraq, Jordan and Egypt, often with mutations concentrated at hot spots located in the DNA-binding domain of p53 protein (exons 5-8). Many missense mutations produce a stable, but dysfunctional protein that disrupts normal transcriptional regulation. For mutation screening of TP53 in resource-limited settings where sequencing is not realistic, immunohistochemistry (IHC) has been a useful proxy method that can also work. IHC can detect the amount of aberrant p53 protein in cancer cells.

Importantly, TP53 mutations in colorectal cancer arise at specific stages of the adenoma–carcinoma sequence rather than randomly. The Vogelstein model posits that APC mutations occur early during adenoma genesis and

that subsequent activation of KRAS, followed by inactivation of TP53, are steps to develop an invasive neoplasm. The progressive accumulation of genetic hits leading to TP53 inactivation emphasizes the role of this gene in late stages of tumorigenesis. In contrast, other studies have shown that in Middle Eastern populations this process is already accelerated with TP53 mutations being detectable even at prune stage lesions. And this brings to the fore whether local genetic or environmental factors alter what we consider normal pattern of progression.

This also seems to apply for the spectrum of TP53 mutations in colorectal cancer in Middle Easterners as well, where environmental exposures may be involved. Among the signatures of mutational fingerprints associated with diets rich in red and processed meat, low in fiber, nitrosamine exposure, and tobacco smoking are G:C→T:A transversions that are commonly attributable to polycyclic aromatic hydrocarbons or alkylating agents. Moreover, these mutated types have commonly been reported in regional CRC studies, suggesting a link between p53 inactivation and lifestyle-associated carcinogens The observation of more TP53 mutant CRC cases in people from regions with greater environmental pollution or heavy metal exposure provides additional support for the notion that carcinogenic environmental stresses determine the landscape of mutation.

These findings hold significant clinical implications for region-specific management of colorectal cancer:

• Screening for TP53 mutations early may assist in selecting individuals at a high risk of aggressive disease phenotypes, particularly in countries without universal CRC screening programs.

• Patient management may be improved by personalized approaches, e.g., TP53 stratification for chemotherapy. For example, p53 mutant tumors are often resistant to 5-fluorouracil-based regimens and may benefit from alternative or intensified treatments.

• The targeted therapies focused on restoring p53 function or exploiting vulnerabilities of TP53-deficient tumors (i.e., synthetic lethality strategies) are in development and may be applicable for Middle Eastern CRC cases upon proper-validation.

• TP53 mutation status may also affect immunotherapy response. The p53 status of tumors may therefore modulate immune response through pathways that positively or negatively affect the efficacy of checkpoint inhibitors:

some evidence indicates that mutant p53–expressing tumors show altered immune cell infiltration and reduced immunogenic phenotypes.

• Family-based genetic counseling has gained a relevance in this region due to high consanguinity rates. Germline mutations (e.g., in the context of Li-Fraumeni syndrome) may be underdiagnosed; although most TP53 mutations in CRC are somatic. Identifying carriers at risk through screening of first-degree relatives of affected individuals with early-onset CRC or multiple primaries.

TP53 mutations in colorectal cancer are highly common and clinically significant events that may lead to a more aggressive disease phenotype, poorer prognosis, and resistance to treatment and they occur with high frequency in Middle Eastern patients. An understanding of regional mutation patterns, their environmental triggers and downstream functional consequences can guide better diagnostic, prognostic and treatment approaches. This will require including population-based cancer research, developing molecular profiling infrastructure and include TP53 testing as a part of routine oncology practice in the Middle Eastern nations. These steps will reduce the rising burden and improve survival for colorectal cancer in this region.

Colorectal cancer, another major concern in the Middle East, has been strongly associated with TP53 mutations. These mutations often occur at early to intermediate stages of tumor development and contribute significantly to the transition from benign adenomas to invasive carcinomas. Several studies from regional cancer centers, such as those in Egypt, Jordan, Saudi Arabia, and Iraq, have documented a high prevalence of TP53 mutations in colorectal cancer samples. These mutations tend to localize within exons 5–8 of the TP53 gene, which encode the DNA-binding domain of the p53 protein—a region critical for its tumor suppressor function. Mutations in this domain often result in loss of function, impaired DNA repair, and failure to induce apoptosis in response to cellular stress.

In Middle Eastern populations, colorectal cancer often presents at a younger age compared to Western countries. This early onset has been partly attributed to a combination of genetic factors, consanguineous marriages, and environmental exposures. Dietary habits, including high red meat consumption, low fiber intake, and increasing adoption of Westernized fast food diets, are also implicated in disease pathogenesis. Inflammatory bowel diseases (IBD), such as ulcerative colitis and Crohn’s disease, which are

known risk factors for colorectal cancer, are increasingly diagnosed in the region and have been shown to promote genomic instability, further increasing TP53 mutation rates. Moreover, exposure to environmental carcinogens such as heavy metals and pesticide residues in agricultural communities has been reported to exacerbate DNA damage, possibly contributing to higher mutation burdens in key tumor suppressor genes including TP53.

From a clinical perspective, TP53 mutations in colorectal cancer are frequently associated with more aggressive tumor behavior, including enhanced invasiveness, lymph node metastasis, and poor histological differentiation. These alterations often correlate with a poorer overall prognosis and reduced disease-free survival. Several studies have also reported a diminished response to standard chemotherapeutic agents, particularly 5-fluorouracil (5-FU)-based regimens, in patients with mutant TP53. This suggests that mutation screening could have significant prognostic value and may help identify patients who would benefit from alternative treatment approaches such as targeted therapies or immune checkpoint inhibitors.

Despite the strong evidence linking TP53 mutations to colorectal cancer progression in the Middle East, routine molecular screening for these mutations remains limited. This is largely due to under-resourced healthcare infrastructure, limited availability of molecular diagnostic tools, and the absence of regionally standardized genetic testing protocols. Most pathology laboratories rely on histopathological evaluation and basic immunohistochemistry, which may miss underlying genetic abnormalities. Furthermore, the cost of next-generation sequencing and the lack of trained personnel further restrict the implementation of comprehensive genetic profiling in routine clinical practice.

There is growing recognition among regional health authorities and academic institutions that incorporating genetic and molecular diagnostics into cancer care is essential. Pilot programs in some Middle Eastern countries have begun integrating TP53 testing into larger cancer genome initiatives. These efforts are crucial not only for advancing personalized medicine but also for establishing mutation databases that reflect the unique genetic architecture of Middle Eastern populations. Such initiatives could help identify population-specific mutation patterns, guide the development of tailored treatment protocols, and improve overall patient outcomes.

Research collaborations between Middle Eastern cancer centers and international genomic research institutions are also beginning to emerge. These partnerships aim to facilitate data sharing, provide training for local clinicians and researchers, and establish biobanks that can support future investigations. In parallel, public awareness campaigns about the importance of early screening, lifestyle modification, and genetic risk assessment are needed to address the growing burden of colorectal cancer and its molecular drivers.

Ultimately, understanding the role of TP53 mutations in colorectal cancer within the Middle East requires a multi-pronged approach involving molecular b Colorectal cancer, another leading type of cancer in the Middle East, is closely linked to TP53 mutations. These mutations typically arise at early to intermediate stages of tumorigenesis, playing a key role in the progression from benign adenomas into malignant carcinomas. A high frequency of TP53 mutations in the colorectal samples has been reported by several studies from regional cancer centers such as Egypt, Jordan, Saudi Arabia and Iraq. These mutations are often clustered between exons 5–8 of the TP53 gene, which encode the p53 protein DNA-binding domain that is essential for its role as a tumor suppressor. This domain is often mutated in a loss of function manner and can lead to defective DNA repair and failure to promote apoptotic cell death under stressful conditions.

Colorectal cancer presents at a younger age in Middle Eastern populations compared to Western countries. Although earlier onset has been partly blamed on a combination of genetic predisposition, consanguineous marriages and environmental exposures. Other aspects of the diet, such as high red meat consumption and low fiber intake, along with increasing adoption of Westernized fast food diets, are implicated in disease pathogenesis. Genomic instability leading to TP53 mutations, often accelerated by inflammatory bowel diseases (IBD) like ulcerative colitis or Crohn's disease—each known risk factors for colorectal cancer—is on the rise in the region. Furthermore, environmental chemicals such as heavy metals and pesticide residues common in agricultural settings have been shown to increase damage to DNA, which may lead to increased burdens of mutation in key tumor suppressor genes including TP53.

Clinically, TP53 mutations are also commonly associated with more aggressive behaviours of colorectal cancer such as invasiveness, lymph node metastasis and poor histological differentiation. Such changes are generally

associated with a worse overall prognosis and decreased disease-free survival. Various studies with patients carrying mutant TP53 have also reported a reduced sensitivity—for standard chemotherapeutic agents mainly for 5-fluorouracil (5-FU) based regimes. It indicates that screening for mutations may be of great prognostic value and allow to identify patients who would benefit from other treatment like targeted therapies or immune checkpoint inhibitors.

Although there is strong evidence supporting TP53 mutations in association with colorectal cancer progression in the Middle East, routine molecular screening for these mutations is limited. This can be blamed on the under-resourced health care infrastructure, limited access to molecular diagnostic tools, and lack of regionally standardized genetic testing protocols. Most pathology laboratories still depend on histopathological evaluation and basic immunohistochemistry that may miss underlying genetic abnormalities. In addition, the cost of next generation sequencing and inadequacy of trained personnel further limits widespread adoption of comprehensive genetic profiling into routine clinical use Adobe Acrobat Document.

Regional health authorities and academic institutions are increasingly aware that cancer care must integrate genetic and molecular diagnostics. In some Middle Eastern countries, pilot programs have incorporated TP53 testing/assessment into broader cancer genomic efforts. Not only will this help advance the field of personalized medicine, but it will also serve to better establish different mutation databases representative of the Middle Eastern genetic architecture. These efforts could identify mutation patterns specific to the population, provide pathways for personalized treatment protocols, and ultimately enhance patient outcomes.

Joint research efforts between Middle Eastern cancer centres and global genomics research bodies are also starting to materialise. The partnerships aim to enable data sharing, training for local clinicians and researchers, and biobanks that can be used in future investigations. Concurrently, it is important that there are public awareness campaigns targeted to the general population about the necessity of early screening, lifestyle modification and genetic risk assessment [3] so we begin to address the increasing burden of colorectal cancer and its molecular drivers.

In conclusion, the impact of TP53 mutations in colorectal cancer in the Middle East can best be analyzed by combining efforts at molecular biology, clinical oncology, public health and international collaboration on all levels.

A regionally tailored strategy that encompasses cultural, environmental and genetic considerations is of paramount importance if we are to minimize the mortality- and morbidity burden of this disease, as well as engage the full potential of precision oncology within Middle Eastern healthcare systems.

iology, clinical oncology, public health policy, and international cooperation. A regionally grounded strategy that accounts for cultural, environmental, and genetic factors is critical to reduce the mortality and morbidity associated with this disease and to harness the full potential of precision oncology in Middle Eastern healthcare systems.

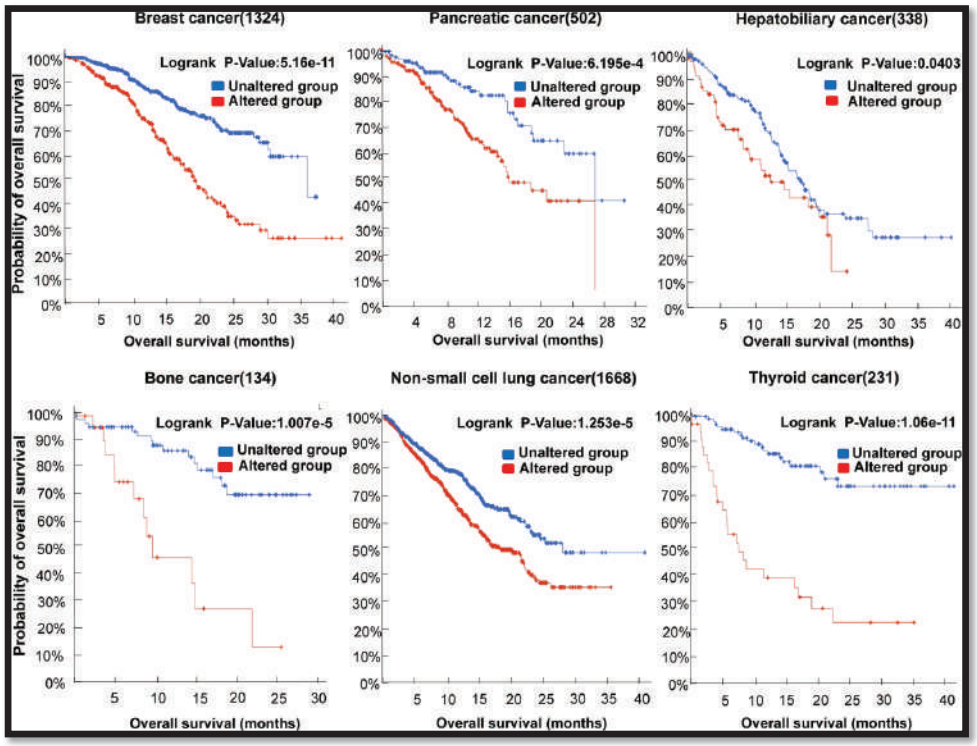


Figure (3) Prevalence and Clinical Impact of TP53 Mutations in Gynecological, Lung, and Gastric Cancers Among Middle Eastern Populations (Chen *et al.*, 2022)

P53-Related Gene Networks and Their Role in Cancer Progression

The TP53 gene encodes the tumor suppressor, p53, a master regulator of cellular integrity. p53 is a transcription factor that is activated by numerous types of cellular stress, such as DNA damage, oncogene activation, hypoxia and oxidative stress. Once activated, p53 interacts with distinct DNA regions and regulates a wide range of downstream genes associated with pivotal cellular functions.

Among the important roles of p53 is its regulation upon cell cycle. It triggers the expression of p21, a cyclin-dependent kinase inhibitor, which arrests the cell cycle at G1/S. His pause gives the cell a chance to fix damaged DNA before proceeding with replication. In the case of irreparable damage, p53 activates apoptotic pathways by transcriptionally activating pro-apoptotic genes including BAX, PUMA and NOXA. This process systematically eradicates cells that suffer major genetic defects, thus preventing malignant transformation.

Additionally, p53 contributes significantly to DNA repair by inducing the expression of genes such as GADD45 and p53R2 involved in nucleotide excision (NER) and base-excision repair (BER) mechanisms. In instances of mild or ephemeral damage, p53 also serves to promote an irreversible state of growth arrest called cellular senescence that can inhibit the replication of damaged cells while maintaining tissue architecture.

In addition to its classical tumor suppressive roles, p53 plays regulatory roles in other important processes including metabolism, autophagy, angiogenesis and immune responses. By modulating glucose transporters as well as glycolytic and oxidative phosphorylation enzymes, it regulates metabolic reprogramming, preventing the typical shift of cancer cells' metabolism. p53 inhibits angiogenesis by inhibiting levels of VEGF and increasing expression of anti-angiogenic factors such as thrombospondin-1.

Loss or mutation of TP53 disrupts these protective mechanisms, allowing deviant cells to escape growth checkpoint control, accumulate further mutations and promote tumor development. This highlights the essential role played by p53 in monitoring genomic stability. TP53 mutations, found in more than 50% of human cancers, provide a loss-of-function or gain of oncogenic properties that promote malignancy.

TP53 is one of the most investigated and therapeutically relevant tumor suppressor genes in cancer biology because of its central role regulating various defence mechanisms.

An important part of p53's tumor-suppressive function is the precise regulation of cell-cycle progression in response to genotoxic stress. In response to DNA damage, p53 stabilizes and becomes transcriptionally active. One of its major transcriptional targets is CDKN1A, which encodes p21^CIP1/WAF1, a potent inhibitor of cyclin-dependent kinases (CDKs). Classical mechanism: In order to progress from G1 to S phase of the cell cycle, p21 binds and inhibits activity CDK2 as well as CDK4/6 so that retinoblastoma protein (Rb) can undergo phosphorylation. A key pause, the p53-dependent cell cycle arrest in G1 phase, which allows DNA repair systems to mend genomic lesions before replication, reduces the likelihood of mutant fixation.

If the DNA damage is excessive and irreparable, p53 changes its behavior from guardian to executioner. It triggers programmed cell death by the intrinsic apoptosis pathway. We show that this is in part achieved by direct transcriptional activation of multiple pro-apoptotic genes. These include:

• BAX (Bcl-2–associated X protein): enhances mitochondrial membrane permeabilization

p53 upregulated modulator of apoptosis (PUMA): promotes BAX activation and opposes anti-apoptotic Bcl-2 proteins

• NOXA: Targits Mcl-1, another anti-apoptotic Bcl-2 family member

Together, their action leads to mitochondrial outer membrane permeabilization (MOMP), release of cytochrome c into the cytoplasm and activation of the caspase cascade that carries out apoptosis.

In addition to cell cycle arrest and apoptosis, p53 promotes long-term control of damaged or abnormal cells by inducing senescence, a state of permanent proliferative arrest. Senescence provides a stable barrier to tumor progression, particularly in cells that have acquired the ability to survive apoptosis.

When these pathways become dysfunctional through TP53 mutation, cells proliferate unchecked (not inherently good for a cell), evades apoptosis, and accumulates RANs to a point of genomic crisis and malignant transformation. When intact, this multi-tiered defense system makes p53 one

of the most powerful antitumor factors in human biology. In particular, when either lost or mutated (as is the case in >50% of human cancers), the results are devastating and fundamental to oncogenesis.

The classic tumor suppressor function of p53 that induces apoptosis and cell cycle arrest is only part of its roles since p53 directly activates DNA repair pathways, which are pivotal for genomic integrity. Upon recognition of DNA damage or genotoxic stress by p53, the transcription of various target genes that impart divergent pathways for DNA repair is activated. This gives the cell the opportunity to fix its damage before these accumulate into chromosomal aberrations or mutations. For example, p53 upregulates GADD45 (Growth Arrest and DNA Damage-inducible 45), which interacts with proliferating cell nuclear antigen (PCNA) and is induced by UV light, oxidative stress, or chemical carcinogens [6].

p53 also induces expression of the XPC gene, which encodes a protein responsible for DNA damage recognition required for initiating global genome NER. XPC attaches to areas of damaged DNA and then brings in other repair factors, paving the way for removal of lesions and the restoration of the native DNA sequence. This repair mechanism activation is crucial in preserving genome fidelity and preventing mutagenesis, especially in the case of cells suffering repeated acute environmental insults or replicative stress.

In addition, p53 helps direct homologous recombination (HR) by activating RAD51 and BRCA1, which are necessary for high-integrity repair of double-strand breaks. This further highlights its wide participation in protecting the genome from many different types of instability.

Hence, through this dynamical orchestration of a network of DNA repair genes, p53 becomes not only a transcriptional master regulator but also acts as a molecular co-regulator that connects the cell cycle checkpoints with repair systems. This enables cells to avoid division with unrepaired lesions, lowering the risk of malignant transformation. Malfuntion or loss of p53, which is observed in many type of human cancers causes impaired repair signalling, increased mutation rates and thus higher tumoral progression.

Moreover, p53 is known to be an essential regulator of cellular senescence, a permanent and irreversible form of growth arrest that acts as a strong barrier to uncontrolled cell division. Whereas temporary cell cycle arrest is reversible, senescence is a long-lasting response that prevents damaged,


senescent or precancerous cells from re-entering the cell cycle. In tissues where prolonged stress results in further hallmarks such as genomic instability, the continual proliferation of cells leads to a greater risk of transformation and tumorigenesis (Häcker et al., 2023).

p53 is activated in response to diverse forms of cellular stress such as telomere shortening, oxidative attack, aberrant activation of oncogenes and replication stress. Under these conditions, p53 promotes the transcriptional activation of CDKN1A and expression of the p21^CIP1 inhibitor for cyclin-CDK complexes, preventing cell cycle progression. Although p21 can stimulate temporary growth arrest, in concert with other pathways—most notably the p16^INK4a/Rb pathway—it can propel cells into a senescent state.

In many cases, the progression from transient arrest to senescence is a cumulative response to chronic stress signals. The CDKN2A gene product p16^INK4a works by blocking CDK4/6-specific activity, preventing the phosphorylation of retinoblastoma protein (Rb) and E2F-dependent transcription involved in S-phase entry. Co-activation of p53/p21 and p16/Rb circuits sets strong checkpoint locking cells in senescence regardless of mitogenic stimulation.

Cellular senescence acts as a tumor-suppressive strategy by removing the proliferative capacity of cells with a risk of malignant transformation. This function is especially crucial in aging tissues, where the accumulation of DNA damage and epigenetic changes raises the risk for oncogenic events. p53 makes sure that these potentially harmful cells are permanently non-dividing, thus maintaining tissue homeostasis.

Senescence is not complication free, however. Senescent cells are still metabolically active and secrete several proinflammatory cytokines, chemokines, growth factors, and proteases—referred to as senescence-associated secretory phenotype (SASP). Collectively, while SASP can enhance immune clearance of senescent cells and leads to tissue remodeling, its sustained presence can drive tumorigenesis by changing the microenvironment in pro-tumorigenic ways, especially when p53 function is deficient. The loss of p53 may enable escape from senescence, and re-entering the cell cycle and accumulating mutations in these senescent cells will only increase cancer risk.

The p53-mediated control of senescence is noteworthy in that it illustrates a role for some of the core molecules upstream (p53, Bcl-2 family proteins, etc.) beyond apoptosis and cell cycle arrest. It serves as a guardian of tissue integrity and regulator of organismal aging. In cancer, loss of p53 function not only diminishes DNA repair and apoptotic responses but also prevents activation of the senescence program, enabling damaged cells to survive and replicate. Restoration of senescence pathways is therefore an emerging approach for cancer therapy, particularly in tumors whereby p53 signaling is defective.

Genome stabilization and cell cycle control are not the only cancer-defensive functions of p53; it also actively modulates metabolism. One of its important regulatory functions is to inhibit the Warburg effect, a metabolic shift frequently associated with tumor cells in which glucose metabolism is directed away from oxidative phosphorylation and toward aerobic glycolysis. p53 opposes this transition by upregulating genes such as TIGAR (TP53-induced glycolysis and apoptosis regulator) that inhibits glycolysis, and SCO2 (synthesis of cytochrome c oxidase 2) promoting mitochondrial respiration (Bensaad et al, 2006; Matoba et al, 2006). These actions maintain normal energy metabolism and prevent the metabolic plasticity of the tumor cell.

Besides energy regulation, p53 also strengthens the antioxidant defense system. It induces the expression of genes like SESN1, SESN2, and GPX1 that prevent the accumulation of reactive oxygen species (ROS), which leads to oxidative DNA damage that drives mutagenesis and cancer progression (Sablina et al., 2005). As a molecular barricade to oxidative stress-induced transformation, p53 tips the balance of redox via fine-tuning.

An additional developing role for p53 relates to tumor immunology. It modulates immune responses by controlling the expression of crucial cytokines and chemokines such as CCL2 and IL-6 that define tumor microenvironment and recruit immunocytes. In addition, p53 regulates immune checkpoint molecules including PD-L1 via indirect pathways and consequently influences tumor immune evasion (Cortez et al., 2016). These actions indicate that p53 plays not only a role as the guardian of the genome, but also that of an immune surveillance mediator linking its tumor-suppressive functions to the host's immune response.

The participation of p53 in cellular metabolism and immune function demonstrates its multifarious contributions to the prevention of tumors and

explains why inactivation of p53 is so common in many human malignancies.

TP53 is one of the most vital tumor suppressor genes in the human genome. It encodes a crucial in maintaining cellular integrity via regulation of key processes including DNA repair, cell cycle arrest, apoptosis and senescence The p53 protein. In its normal capacity, p53 functions as a genome guardian by blocking the growth of cells that possess DNA damage or other oncogenic stresses. As a transcription factor, it binds similar DNA sequences to promote or inhibit the expression of a constellation of genes implicated in these protective pathways.

TP53 is one of the most frequently mutated genes across a broad variety of human cancers, despite its critical tumor-suppressive functions. TP53 covering studies estimate more than 50% of all human tumors to harbor TP53 mutations (Al-Qasem et al., 2011). These mutations are nonrandom and tend to cluster within the p53 DNA binding domain, which covers amino acids 102-292. This domain is thought to be involved in sequence specific binding to DNA and mediates p53 activation of downstream target genes important for its tumor-suppressive activity.

Mutations within the DNA-binding domain impede p53's capacity to effectively bind DNA. Consequently, the protein can no longer transactivate genes implicated in regulating cell cycle such as CDKN1A (p21), DNA repair genes like GADD45, and pro-apoptotic genes including BAX and PUMA. This loss of function shuts down the cellular checkpoints that would ordinarily stop damaged cells from proliferating or kick off programmed cell death. As a result, genetically aberrant cells divide excessively, acquire more mutations and promote tumorigenesis.

In addition to the loss of tumor-suppressive activity, mutations in TP53 are also associated with gain-of-function (GOF) effects, novel oncogenic properties mediated by certain missense variants. These mutant forms of p53 may actively drive the cancer's progression by increasing cell proliferation, invasion, metastasis and therapy resistance [5]. Mutant p53 was already demonstrated to block other tumor suppressor activity, remodel chromatin landscape and regulate signaling pathways such as NF-kB and PI3K/AKT. These GOF mutations are associated with a worse clinical course and more aggressive tumor phenotype.

The importance of this complexity lies in the duality of roles played by TP53 mutations in cancer and emphasizes the need to gain a more profound knowledge of its biological function at the molecular level. Studies of structural changes associated with different mutations have shown that slight differences in the DNA-binding domain can profoundly alter p53's conformational and stability properties. Some mutations destabilize the protein resulting in rapid degradation, whereas others result in stable non-functional or oncogenic forms.

Such insight is crucial for the design of targeted cancer therapies to restore wild-type activities of mutant p53 or mimic its tumor suppressor actions via different routes. Various therapeutic strategies have been explored, such as small molecules able to refold mutant p53 into a functional conformation, gene therapy approaches to substitute mutated TP53 and compounds that activate downstream effectors of p53. Also, therapies that exploit synthetic lethal interactions with p53 dysfunction, for example through inhibitors targeting the DNA damage response pathway are promising.

Overall, TP53 mutations are a critical hurdle in oncology given their high frequency and pleiotropic impact on cancer biology. Delineating molecular functions of mutant p53 at the level of promoting disruption of normal p53 activity, and sometimes gain oncogenic features, is still key to designing future therapeutic approaches. Advances in this area portend a promising future for patients with p53-mutant cancers.

p53 is a master regulator of several key pathways that cooperate to prevent tumorigenesis and preserve cellular integrity. Its potential to elicit cell cycle arrest permits the cell sufficient time to repair its DNA prior to replication, avoiding errors that would result in mutagenic changes in genes responsible for malignant transformation. If damage is extensive and irreparable, p53 induces apoptosis, where the cell actively destroys itself to eliminate potentially damaging cells from the tissue. This reader's balance into repair or disposal is essential in preventing the build-up of genetic defects that drive the development and progression of cancer.

In addition to its roles in cell cycle control and apoptosis, p53 regulates a wide array of genes controlling DNA repair pathways that bolster the ability of the cell to rectify genetic lesions to preserve genome integrity. p53 also regulates pathways connected with oxidative stress and energy metabolism, thereby determining cellular metabolic profile. The top-cellular environment will not be conducive to tumorigenesis is eliminated by metabolic regulation.

p53, for example, is known to inhibit glycolysis and promote oxidative phosphorylation, antagonizing metabolic reprogramming common in cancer cells termed the Warburg effect.

The multifaceted function of p53 emphasizes its critical role in maintaining cellular homeostasis. In fact, the loss of p53 function, whether through mutation or other regulatory mechanisms, abolishes those essential protective barriers that promote cancer. Thus, p53 serves as an important target for therapeutic intervention. Current investigations have emphasized the importance of identifying and developing new strategies to reactivate or mimic p53's tumor-suppressive functions in cancer cells.

These efforts include compounds that can restore the function of mutant p53 proteins, gene therapies directed toward restoring wild-type TP53, and agents that augment the activity of downstream signaling cascades regulated by p53. In addition, several therapies leverage weaknesses introduced by loss of p53 function in cancer cells, from targeting alternative DNA repair pathways to metabolic pathways requisite for tumor growth. reiterating the idea that harnessing the multifaceted tumor-suppressive functions of p53 possesses great potential for cancer therapy.

In a nut shell, p53 is so critical for the cell as it regulates multiple pathways such that impaired p53 can lead to tumorigenesis. Further studies to characterize its complex functions and their manipulation for therapeutic purposes promise considerable potential to improve cancer therapy and patient survival.

Chapter 2
Mutation Patterns and Epidemiology in the Middle East

Prevalence of P53 Mutations in Middle Eastern Cancer Patients

TP53 gene mutation is one of the most common genetic changes in cancer around the world. TP53 mutations in the Middle East: a unique picture? This regional difference is attributed to numerous factors, such as genetic predispositions, environmental exposures, lifestyle habits and sociocultural practices particular to Middle Eastern peoples. This is important in order to ensure the region-specific importance of TP53 is achieved through a better understanding of the prevalence and mutation spectra of TP53 to improve overall treatment strategies, prognosis, and diagnosis.

The TP53 mutations rates associated with breast cancer in Middle Eastern Egyptians are among the highest reported in excess of global averages (Cui et al., 2020).. Breast cancer is the most common malignancy among women in Saudi Arabia, Yemen, Oman, and Gulf Cooperation Council (GCC) countries (Al-Qasem et al., 2018; Al-Sakkaf & Abood, 2022; Al-Madouj, Eldali & Al-Zahrani, 2020). TP53 mutation frequencies exceeding 40% were reported in Saudi Arabian cohorts, much higher than the approximately 20-30% currently observed in Western populations (Bazarbashi et al., Al Eid, & Minguet, 2021; Barakeh et al., 2021). The study also suggest that possible genetic determinants associated with the population's ethnic background, in addition to environmental exposures like dietary habits, carcinogen exposure, and reproductive health trends may play a role in these high mutation rates (Abdel-Rahman, 2018; Amer et al., 2023). In addition, younger median age of breast cancer diagnosis in the Middle East (up to 10 years earlier than in Western countries) has been linked with increased frequency of TP53 mutations and may indicate more aggressive tumor biology (Al-Shamsi et al., 2023).

TP53 mutations are also highly prevalent in colorectal cancers from the Middle East. This is an apparently increasing number of cancers due to slow lifestyle changes such as westernization of diet, less active and increased obesity in the population (Ibrahim et al., 2018; Bishehsari et al., 2014). Similar articles from other countries including Saudi Arabia, Iran and Egypt have reported mutation rates of 35% to 60% for TP53 mutations in colorectal tumors (Al-Shamsi et al., 2016; Jafari et al., 2022; Chan et al., 2005). Importantly, mutations of this type often cluster in canonical hotspots within the DNA-binding domain of p53 that primarily abolish its tumor suppressive activities (Rahman et al., 2019). There are a much different distribution and

types of mutation in the Middle East when compared with Western and East Asian populations (Nieminen et al., 2012; Siraj et al., 2014). These distinctive mutation patterns are thought to be partly driven by environmental factors, such as the higher prevalence of Helicobacter pylori infection and exposure to aflatoxins (Gholipour et al., 2016; Rahman et al., 2019).

Although the incidence of lung cancer in the Middle East is lower than that seen in some Western countries, it appears to be increasing with alarming prevalence, particularly among males with a history of smoking. TP53 mutations are found in around 40-50% of Middle Eastern lung tumors, and the mutation hot spots are typically missense changes in composition that generate non-functional or gain-of-function mutant p53 proteins (Fathi et al., 2018; Khoueiry et al., 2019). These mutations are often associated with different environmental exposures (i.e., tobacco smoke, air pollution, and job-specific hazards endemic to the region) (Lakkis et al., 2023). Furthermore, the interplay between TP53 mutations and alternative oncogenic drivers, such as KRAS and EGFR, varies in Middle Eastern populations highlighting that geographic-specific molecular profiling is required to maximize targeted therapy (Tfayli et al., 2019).

In the Middle East, gastric cancer patients have also been shown to possess a high frequency of TP53 mutations, commonly correlating with poor outcome. Mutational frequencies of 45% to 60% have been indicated in regional studies, and associated with persistent Helicobacter pylori infection or dietary components like high salt intake combined with low fruit and vegetables consumption (Ghojazadeh et al., 2022; Bani-Hani et al., 2005). Lesions-driven mutant p53 proteins in these tumors not only lose tumor suppressive activities but can gain oncogenic functions responsible for invasion, metastasis and therapy resistance (Chen et al., 2022; Uddin, 2018).

Whilst somatically mutated TP53 is prevalent, germline variants at the locus have also been reported in some Middle Eastern populations albeit less frequently. These mutations are integral to heritable cancer predisposing syndromes such as Li-Fraumeni syndrome, presenting with early onset and varied tumor types (Rocca et al 2022; Siraj et al. 2021). Surveillance (Fathallah et al., 2023; Fischer et al., 2023)—due to high consanguinity and large families in some countries of the Middle East, germline TP53 mutation screening becomes more important for early diagnosis and preventive care. Nonetheless, knowledge of genetic counseling and access to it are still

restricted, which poses barriers for its successful implementation (Al-Sukhun et al., 2023).

Variability in TP53 Mutation Prevalence and Types Between Subregions Genetic diversity within the Middle East region results in differences in prevalence and types of TP53 mutations between sub-regions. It is obvious from studies cross comparing Gulf Cooperation Council (GCC) countries, Levant and North African populations the diverse mutational environments. For example, some TP53 hotspots are enriched in Gulf populations while others have the highest prevalence in North Africa, which may be attributed to differences in ancestry and exposure (Al-Madouj, Eldali, & Al-Zahrani, 2020; Jafari et al., 2022). Such findings highlight the importance of regionally adapted molecular diagnostics and therapeutic strategies.

The clinical implications of the high prevalence of TP53 mutations in Middle Eastern cancers are immediately relevant. Mutant p53 status has been associated with aggressive tumor behavior, sensitivity to chemotherapy and radiotherapy, and worse survival outcomes (Monti et al., 2020; Donehower et al., 2019). Thus, we suggest integrating screening of TP53 mutation into routine clinical practice to improve risk stratification and treatment personalization. novel targeted therapies designed to restore wild-type p53 function or inhibit the gain-of-function activities of mutant p53 are being actively researched and hold the potential for better patient outcomes in this area (Joerger & Fersht, 2016; Chen et al., 2022).

Also, analysis of circulating tumor DNA (ctDNA) for TP53 mutations is a non-invasive approach in detecting Middle Eastern patients at early stages, monitoring treatment response and resistance (Parkinson et al., 2016; Dawood et al., 2024). Implementing such powerful molecular tools into cancer care infrastructures in the Middle East could dramatically improve disease management and patient survival rates.

Overall, TP53 mutations are frequently found in many different cancers among Middle Eastern populations. These unique epidemiologic and molecular features found in this region result from genetic, environmental, and sociocultural determinants. It remains essential to continue mapping such mutations with a view to defining their biological significance, so that effective regionally relevant cancer prevention and treatment measures can be designed (Abdel-Rahman, 2018; Bazarbashi et al., 2021; Fathallah et al., 2023). This insight should incentivize countries in the Middle East to expand

both genetic testing and access to personalized medicine as molecular oncology evolves, tackling the cancer burden associated with TP53.

Table (1) Number and percentage of cancer-related publications in Arab countries

Country	Number of publications on cancer	Number of total publications	% cancer of total
Egypt	8917	53,290	16.73
Saudi Arabia	6589	53,898	12.23
Lebanon	2019	12,227	16.51
Tunisia	1811	14,633	12.38
Jordan	1327	10,817	12.27
Morocco	1276	7618	16.75
United Arab Emirates	932	9731	9.58
Qatar	880	8265	10.65
Kuwait	708	5646	12.54
Oman	484	4835	10.01
Iraq	476	4407	10.80
Algeria	314	4062	7.73
Sudan	271	3069	8.83
Syria	175	1356	12.91
Bahrain	170	1460	11.64
Libya	131	997	13.14
Yemen	129	1178	10.95
Palestine	39	1042	3.74
Mauritania	3	108	2.78
Somalia	3	94	3.19
Djibouti	2	97	2.06
Comoros	0	39	0.00
Total	26,656	198,869	13.40
Worldwide	1,750,749	13,995,404	12.509

P53 Mutations in Breast Cancer: Insights from Middle Eastern Studies

Breast cancer is the most prevalent type of cancer among Middle Eastern women (Al-Qasem et al., 2018; Bazarbashi, Al Eid, & Minguet, 2021). Genomic investigations by the authors and colleagues in this e-poster session enable a better understanding of these molecular subtleties, including a highlight of TP53 as one of the most prominent breast cancer drivers in Middle Eastern populations with implications for tumor biology and clinical outcomes. In the regional context, characterized by unique cryo-environmental conditions and genetic diversity, understanding the prevalence, mutation spectrum and functional consequences of TP53 alterations is key to tailor studies aimed at the development of effective diagnostic and therapeutic strategies.

Various investigations conducted in Middle Eastern regions, covering the Gulf Cooperation Council (GCC) states as well as countries such as Saudi Arabia, Oman and Yemen, have reported a notably high frequency of mutations within TP53 among breast cancer patients. In most cohorts, these frequencies are higher than 40%, and in some reach or exceed 50%968-970 — a striking discrepancy compared to the mutation rates of around 20–30% reported in Western populations (Al-Qasem et al., 2011; Barakeh et al., 2021; Al-Shamsi et al., 2023). These high mutation loads might be attributed to a combination of the region-specific factors like unique genetic backgrounds owing to large consanguinity rates, regional environmental exposures and lifestyle. This includes, for example, older age at presentation of breast cancer (in the 40s in Middle Eastern women compared to the 50s and 60s in Western populations), which is associated with significantly higher frequency of TP53 mutations and suggests that underlying biological differences exist between individuals from different geographical regions when it comes to tumorigenesis (Amer et al., 2023; Abdel-Rahman, 2018).

Molecular profiling consistently shows that TP53 mutations in Middle Eastern breast tumors are predominantly missense and clustered to the DNA-binding domain (the key region for p53 function as a transcription factor controlling cell cycle arrest, DNA repair, apoptosis, and senescence) (Al-Qasem et al., 2018; Monti et al., 2020). Such mutations disrupt wild-type p53 functions, which hinder the cell from responding to genomic stress and DNA damage. Additionally, in many cases mutant p53 proteins also gain oncogenic properties which drive enhanced proliferation of tumor cells as

well as invasion, metastasis and therapy resistance (Freed-Pastor & Prives, 2012; Chen et al., 2022). This mechanism of loss of the tumor-suppressive effects of TP53 paired with gain-of-function mechanisms leads to the aggressive clinical outcome seen in Middle-Eastern TP53-mutant breast cancers.

Indeed, clinical correlations underscore the significance of TP53 mutation status in the area. Mutant p53 breast cancers are more often high histological grade, exhibit increased lymphovascular invasion, larger tumor size and hormone receptor-negative status markers (Hatoum et al., 2017; Monti et al., 2020), all of which correlate with poor prognosis and survival. Additionally, TP53 mutations have been implicated in decreased response to conventional chemotherapy and radiation therapies, leading to more challenging prognoses and higher likelihood of recurrence (Bazarbashi et al., 2021). These results suggest the prognostic and predictive significance of analysis for mutations of TP53 as part of clinical management in breast cancer patients from Middle Eastern origin.

Apart from somatic mutations, arabian germline TP53 variants have also been described in Middle Eastern breast cancer cohorts. These germline mutations, although rarer, are highly clinically significant due to a strong predisposition of the carriers to Li Fraumeni condition and other hereditary cancer syndromes with multiple primary tumors and early onset (Siraj et al., 2021; Rocca et al., 2022). Increased rates of recessive or homozygous mutations due to the relatively high rates of consanguineous marriages in Middle Eastern populations, make germline TP53 screening a useful tool for familial cancer risk assessment and preventive care in this population (Al-Sukhun et al., 2023). Nonetheless, universal application is challenged by the limited availability of genetic counselling;physiological barriers; and resource limitations across many regions (IHE Report, 2021).

There has been increased progress towards enhancing molecular diagnostics of breast cancer in the Middle East. The development of next-generation sequencing (NGS) and targeted gene panels allows for optimal assessment of TP53 mutations together with other relevant cancer genes, or to better classify the tumor type according to these affected genes and stratify risk accordingly (Barakeh et al., 2021; Al-Shamsi et al., 2023). These progressions provide opportunities for personalized treatment strategies accounting for TP53 mutation status when employing chemotherapeutic agents or enrolling patients into clinical trials evaluating new p53-

reactivating molecules and mutant p53 targets (Joerger & Fersht, 2016; Chen et al., 2022). Emerging strategies targeting TP53 mutants, such as small molecules that are designed to restore wild-type p53 conformation or disrupt mutant p53 complexes, hold promise in preclinical and early clinical settings and may change the therapeutic landscape for TP53-mutant breast cancers (Shangary & Wang, 2008; Chen et al., 2022).

In addition, glancing phosphory cylinder underlinguistic power profiles of circulating tumor DNA (ctDNA) offer a minimally invasive approach towards detecting mutations in TP53 allowing for early detection as well as real-time detection of responses to treatment and mechanisms inducing resistance, particularly relevant among breast cancer patients from the Middle Eastern region (Parkinson et al., 2016; Dawood et al., 2024). Importantly, ctDNA analysis may be performed in parallel to or integrated into existing clinical workflows and thus have potential to circumvent limitations of tissue biopsy and facilitate real-time, patient-specific modulation of therapy with the goal of improving outcomes.

As advanced as these techniques have become, a gap remains in translating molecular insights into clinical context across the Middle East. Barriers to widespread use of TP53 mutation testing include variation in healthcare infrastructure, access to advanced diagnostics and sociocultural factors influencing cancer awareness and screening among the population at large (IHE Report, 2021; Abdel-Rahman, 2018). Article: To overcome these barriers to genetic testing and personalized cancer care, efforts must be made to educate patients on the importance of such programs with a genotype and phenotype tailored context.

Based on this data, we propose that TP53 mutations represent a key determinant of breast cancer biopathology and clinical course in Middle Eastern individuals. That high mutation prevalence, unique mutation spectra and the accompanying aggressive tumor characteristics highlight the need for personalized molecular diagnostics and targeted therapies. Steps to improve breast cancer outcomes in the Middle East will be found in wider access to genetic testing, integration of TP53 mutation status into clinical decisions, and p53 drug development (Al-Qasem et al., 2018; Bazarbashi et al., 2021; Fathallah et al., 2023).

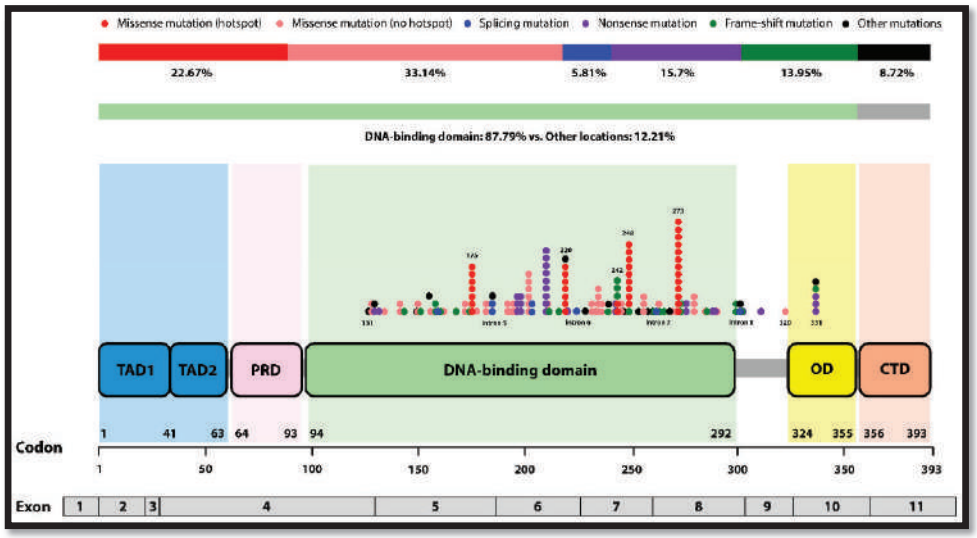


Figure (5) Characteristics of *TP53* mutations in patients within the *TP53*-mutated group (Hwang *et al.*, 2024)

P53 and Colorectal Cancer in Middle Eastern Populations

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers globally and a significant cause of cancer-related morbidities and mortalities. During the last few decades, countries in the Middle East have witnessed increasing incidence rates for CRC (Al-Madouj, Eldali & Al-Zahrani 2020; Jemal et al. 2020). Mendelian forms of the disease have unique epidemiological and molecular features that are relevant to Middle Eastern populations, where genetic, environmental, and lifestyle factors influence tumor biology. At the center of this molecular landscape is the tumor suppressor gene TP53, whose mutations are etiologically relevant in colorectal carcinogenesis and have been associated with disease progression and response to therapies in neighboring regions.

In line with our results, studies investigating CRC in the Middle Eastern region also demonstrated a relatively high frequency of TP53 alterations, which were found in 40% or more of patients across various cohorts (Ibrahim et al., 2018; Jafari et al., 2022). Of interest, this report demonstrates that there are distinct patterns of mutation and association with certain

clinicopathological features (such as the predominance of WT TP53 in lymph node metastasis) within a geographical population which makes this prevalence significant compared to other global data showing TP53 amongst the most commonly mutated genes in colorectal cancer. The high incidence of TP53 mutations reflects the central role played by this gene in colorectal tumorigenesis in the Middle East.

Molecular studies indicate that TP53 mutations found in Middle Eastern CRC mostly cluster within the DNA-binding domain, which is also observed in other malignancies such as breast and lung cancer (Al-Qasem et al., 2011; Monti et al., 2020). Some of these mutations are missense mutations that prevent p53 from regulating downstream genes involved in DNA repair, apoptosis, and cell cycle control allowing for genetic damage and unregulated proliferation (Freed-Pastor & Prives, 2012). In contrast to the classical adenoma-carcinoma sequence in Western countries, the mutation profile sometimes bump into specific ones within this spectrum in Middle Eastern CRC, showing less mutations in other oncogenes like BRAF and KRAS but a higher frequency for TP53 mutations relatively speaking, which consequently can affect tumors behaviour or therapy outcome (Siraj et al., 2014; Benmokhtar et al., 2024).

The environmental and lifestyle risk factors common in Middle Eastern populations (high red meat/low-fiber dietary patterns, smoking, high body mass index (BMI), and low physical activity) may underlie the increased TP53 mutation burden and colorectal carcinogenesis (Rayegani et al., 2017; Al-Azri et al., 2014). Moreover, chronic inflammation and infectious agents such as helicopter pylori were associated with the accumulation of TP53 mutations in gastrointestinal tumors (Rahman et al., 2019; Gholipour et al., 2016), which may increase cancer risk regionally.

Clinicopathological studies amongst Middle Eastern CRC patients have linked TP53 mutation status with the extent of tumor stage, grade and poor differentiation, suggesting a more aggressive disease trajectory (Ibrahim et al., 2018; Jafari et al., 2022). Tumors with TP53 mutations often pose challenges to treatment efficacy and patient prognosis due to their inherent resistance against conventional chemotherapeutic regimens, including 5-fluorouracil and oxaliplatin (Al-Madouj et al., 2020). Taken together, these results indicate that TP53 mutations could be prognostic markers and potential responders to treatment in CRC patients.

For germline mutations targeting CRC, there are a few syndromes that were characterized in Middle Eastern populations, although hereditary CRC with Lynch syndrome is better studied; however, germline TP53 mutations leading to Li-Fraumeni syndrome while rare should be noted for inclusion in familial cancer screening panels (Rocca et al., 2022; Al-Sukhun et al., 2023). A broad genomic epidemiology supports deep molecular screening to detect4647 what45348 may5212 be42513 at-risk4619 so51973 that68427447656386 early527 intervention4750 may42606647489 occur.

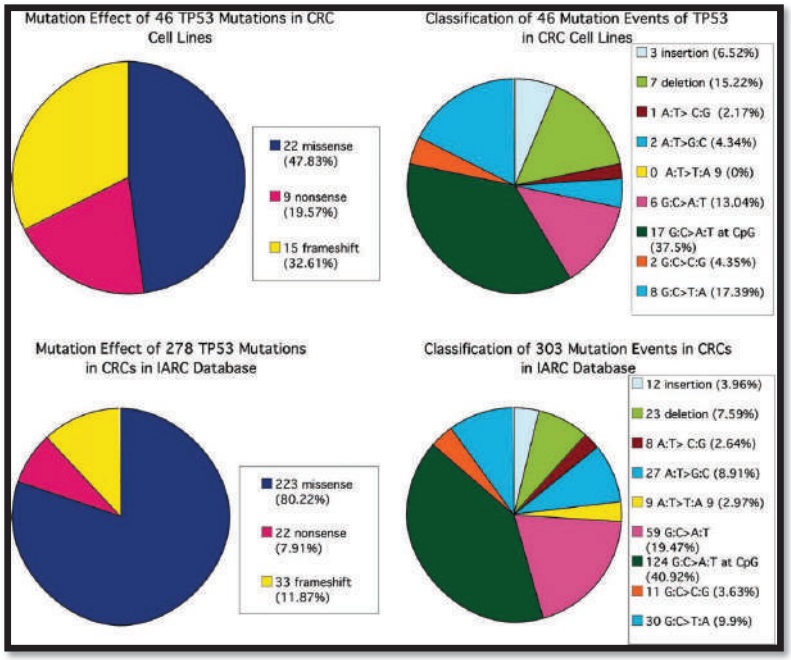
Recent innovations in molecular diagnostics, such as next-generation sequencing and liquid biopsy technologies, have enabled TP53 mutational analysis in CRC Middle Eastern patient cohort leading to more refined tumor profiling and targeted treatment approaches (Dawood et al., 2024; Barakeh et al., 2021). At this stage, however, targeted therapies that aim to restore p53 function or combat mutant p53 gain-of-function effects are being explored and may hold promise for potentially better outcomes in TP53-mutant colorectal cancer (Joerger & Fersht, 2016; Chen et al., 2022).

However, several demographic and environmental factors that are peculiar to the Middle East complicate optimal cancer care associated with TP53 mutations. Absence of advanced molecular testing and socio-cultural barriers compromise early detection and treatment (IHE Report, 2021; Abdel-Rahman, 2018) while healthcare infrastructure varies widely. Moreover, cancer awareness and screening also varies, which results in late-stage diagnoses when TP53 mutations have already led to tumor progression (Mohamed et al., 2025).

It is high time that the regional endeavors lead to cancer screening programs, general public awareness and steps towards gaining resources for molecular pathology services. Translational Collaborative research addressing the genomic biases and environmental determinants of TP53 mutations in colorectal cancer will refine their contributions to disease etiology and help with pathogenetic inhibition strategies (Jafari et al. 2022; Benmokhtar et al. 2024).

In conclusion, we observed that TP53 mutations are a primary molecular event in colorectal cancer in Middle Eastern patients. The widespread occurrence of TP53 mutation, the unique hallmark mutation pattern associated with it and its significant correlation to aggressive tumor characteristics illustrates how genomic profiling can enhance clinical management. The provision of molecular diagnostics, in combination with

targeted therapeutic agents that cause pathway modulation away from p53 dysfunctions, will need to be expanded in the Middle East to improve outcomes for colorectal cancer (Al-Qasem et al., 2011; Ibrahim et al., 2018; Dawood et al., 2024).



Figure(6) Distribution and Classification of TP53 Mutation Types in Colorectal Cancer(Chen et al., 2022; Freed-Pastor & Prives, 2012).

P53 Polymorphisms and Cancer Susceptibility in Middle Eastern Ethnic Groups

Besides somatic mutations of TP53, that drive cancer progression, there are also various germline polymorphisms located in TP53 that can contribute to individual susceptibility for most cancers. The most studied of these are the polymorphisms seen at codon 72 (rs1042522) which offers an arginine (Arg) to proline (Pro) substitution. 0300001, respectively), which seems to influence the biological functions of the p53 protein and is believed to modify cancer risk, prognosis and therapeutic response in different populations. The distribution and clinical significance of TP53 polymorphic

variants in Middle Eastern ethnic groups represents a key, but underexplored aspect of cancer genomics.

The Middle East is a region with a highly diverse array of peoples (including Arabs, Persians, Kurds, Turkic Aryans in the North and Berbers or South Asians). The heterogeneity also affects the frequencies and penetrance of TP53 polymorphisms, particularly rs1042522, which has displayed various genotype frequencies between Middle Eastern Population (Fathi et al. 2018; Fischer et al. 2023). Different genotypic patterns established in Saudi Arabia and Iran revealing a higher rate of Pro/Pro and Arg/Pro genotypes compared with the studied European cohorts, while similarly to Jordanian and Lebanese populations showed results close to Caucasians one (Akhter, 2019; Siraj et al., 2021). These differences suggest that cancer susceptibility at the individual and population level is dependent on ethnic and geographic background.

Biological Significance of the Codon 72 Polymorphism. The Arg72 variant was reported to induce apoptosis more efficiently while the Pro72 variant promotes enhanced arrest of cell cycle and improved DNA repair but less apoptotic activity (Olivier et al., 2010; Monti et al., 2020). Consequently, the Pro allele carriers are thought to have a delayed removal of DNA-damaged cells, which may increase susceptibility for tumorigenesis under genotoxic stress conditions. In individuals from the Middle East, this SNP has been associated with risk of breast (United Arab Emirates and Turkey) (19–21), colorectal (Turkey) (22), lung (43, 44), gastric tumors (46), as well as various hematologic tumors(37%) such as lymphoma in healthy carriers(middle eastern populations)(47).

In these studies, the Pro allele was found to be predominant in Saudi and Iraqi breast cancer patients (Akhter, 2019; Al-Qasem et al., 2018) indicating a clear association between this polymorphic variant and increased risk of breast cancer especially in those who are younger than 52 years of age (premenopausal group) or first degree relatives with familial history of cancer. Associations were also observed among colorectal cancer patients from Iran and Egypt, where the Pro/Pro genotype has been associated with advanced tumor stage and lymph node metastasis (Ghojazadeh et al., 2022; Jafari et al., 2022). In fact, in a more recent study of the R72P polymorphism, no association with breast cancer was found (with even a possible protective effect described for the Arg allele) emphasizing what seems to be complex

gene-environment interactions that modulate p53 function across different contexts (Rahman et al., 2019; Nieminen et al., 2012).

TP53 polymorphisms may modify the effect of environmental exposures common in the Middle East on cancer risk. These consist of tobacco consumption, dietary habits rich in processed and red meats, chronic infections like Helicobacter pylori and hepatitis viruses as well as higher levels of air and water pollution (Al-Azri et al., 2014; Gholipour et al., 2016). In such contexts, people with particular TP53 polymorphisms may exhibit differential susceptibility to carcinogens based on the nature of their p53-mediated cellular responses.

Furthermore, TP53 polymorphisms may influence not only cancer susceptibility but also the course of diseases and response to therapy. Individuals with the Pro/Pro genotype have shown decreased sensitivity to p53-dependent apoptosis-inducing chemotherapeutic agents (such as doxorubicin and cisplatin) (Chen et al., 2022; Freed-Pastor & Prives, 2012). Had this genotype also been linked to an increased exposure response towards radiotherapy in some Middle Eastern cancer studies (Hatoum et al., 2017). These associations are crucial for the implementation of personalized oncology, especially in certain areas where access to first-line therapies is restricted.

Intriguingly, TP53 polymorphisms also have clinical relevance in hereditary cancer syndromes. Rare pathogenic variants in TP53 have also been identified through germline sequencing studies in Middle Eastern families with early-onset cancers, apart from the more common codon 72 SNP (Siraj et al., 2021; Rocca et al., 2022). With that in mind, these findings serve to demonstrate the importance of incorporating polymorphism analysis into comprehensive genetic screening initiatives capable of identifying individuals at increased risk and implementing proactive interventions.

These findings, however, are constrained from comprehensive assessment of TP53 polymorphisms in Middle Eastern populations by number of factors PMID: 15714409. These barriers include underrepresentation in genomic databases, absence of large-scale multiethnic studies, limited access to advanced genotyping platforms, and relatively little public awareness regarding genetic testing (IHE Report 2021; Abdel-Rahman 2018). Similar issues must be answered collectively before properly addressing these challenges can take place and work to build genomic research infrastructure, initiate biobanks focused on cancer, enhance data sharing across borders.

Overall, TP53 polymorphisms particularly codon 72 variant, making a significant contribution to cancer susceptibility and clinical outcomes of Middle Eastern ethnic groups. Such diversity creates a complex genomic environment, where p53 function varies greatly due to unique environmental exposures and life style patterns reflecting the ethnic mix of the region. HTP53 polymorphisms recherches and inclusion into national cancer genomics initiatives will be crucial to enhance cancer prevention, early-detection strategies and tailored treatment in the Middle East.

Genomic Studies and Epidemiological Trends of P53 in the Middle East

The tumour suppressor protein p53 is encoded by the TP53 gene, and as a master regulator of genomic integrity, is critical in modulating G1 and G2 phase cell cycle checkpoints, enabling DNA repair, driving apoptosis and acting to restrain aberrant proliferation [15]. It plays a central role as regulator of cellular response to oncogenic stress. Loss of its function — via mutations, deletions or regulatory inhibition — is a key feature of cancer development. TP53 mutations are identified in more than 50% of all human cancers worldwide. Emerging genomic research from the Middle East shows that TP53 alterations are not only about their associations with cancer type and survival but also reflect unique patterns of prevalence, distribution, and biological behavior molded by genetic diversity, environmental exposures in the context of regional environmental health hazards, and sociocultural dynamics. These trends have significant implications for cancer diagnostic, treatment and public health planning capabilities in the region.

The Middle East is home to a genetically heterogeneous population with Arabs, Persians, Turks, Berbers, Kurds, Ashkenazi and Sephardic Jews and South Asians. And this diversity is deepened by centuries of migration and admixture. Consequently, genetic variation at the population level — including in cancer-related genes such as TP53 — varies greatly within and between countries. This heterogeneity affects both baseline risk of malignancy as well as the type and frequency of some TP53 mutations, polymorphisms and their clinical consequences[12].

The incidence of cancer in the Middle East has continued to increase over the years attributed, in part, to urbanization and sedentary body habits, diet

that is more in line with western countries and increased goading from environmental carciginens as well as improved reporting of diagnosis. Now breast and colorectal cancers are the top five most common malignancies in nearly every country of the region (Al-Madouj, Eldali & Al-Zahrani, 2020; Abdel-Rahman, 2018). TP53 mutations are common in these cancers and strongly correlate with aggressive tumor phenotype, therapy resistance and poor prognosis. In studies conducted in Saudi Arabia, Iraq, Lebanon, Egypt, Iran and the United Arab Emirates TP53 mutation frequencies were reported from as low as 35% to over 60% for breast, colorectal and lung cancers (Al-Qasem et al., 2011; Ibrahim et al., 2018; Barakeh et al., 2021). These mutation rates are typically above global averages, leaving some fundamental population-specific questions regarding cancer biology in the region.

The most consistent finding across anumber of regional genomic studies is that the majorityof p53 mutations are missense mutationsglobally located within the DNA-binding domain ofthe p53 protein. These changes not only abolish the tumor suppressive properties of wild-type p53 but, in many instances, also impart gain-of-function activities to it that are actively pro-neoplastic (Freed-Pastor & Prives, 2012; Chen et al., 2022). A prime example of this are hotspot mutations that commonly occur in Middle Eastern breast and colorectal cancers, including R175, R248 and R273. These mutations abrogate the ability of p53 to bind DNA and induce transcriptional targets related to apoptosis (e.g., BAX, PUMA) and cell cycle arrest (e.g., CDKN1A/p21), thus promoting genomic instability and unrestricted proliferation.

Furthermore, TP53 mutations have been further associated with environmental and behavioral risk factors that advance breast cancer development in Middle Eastern societies through epidemiological investigations. Male high tobacco usage, common second-hand smoke exposure, dietary habits rich in red and processed meats as well as low fruit and vegetable intake, and the broad spread of vitamin D deficiency is believed to contribute synergistically with genetic susceptibility to increase the burden of TP53 driven cancers (Ghojazadeh et al., 2022; Al-Azri et al., 2014). Infections with Helicobacter pylori and hepatitis viruses, which are widespread across large parts of the region, have also been associated with driving genomic instability and TP53 mutations in gastric and hepatic malignancies (Rahman et al., 2019; Osman et al., 1997).

TP53 mutations had previously been studied only in limited detail with methods such as Sanger sequencing or polymerase chain reaction (PCR), but further profiling of TP53 mutations in the Middle East, were possible owing to next generation sequencing (NGS), whole exome sequencing and genome-wide association studies (GWAS)1. Yet most of these initiatives are scattered, under-resourced and confined to big academic or military hospitals in major urban areas. Middle Eastern countries do not have large-scale population-based genomic surveillance initiatives comparable to those seen in Europe or North America. Furthermore, the absence of thorough cancer registries and national biobanks compound with few studies attempting to accurately delineate the prevalences or outcomes associated with TP53 mutations stratified by ethnicity and tumor type (IHE Report 2021; Al-Shamsi et al., 2023).

Countries like Saudi Arabia, the United Arab Emirates and Qatar are already investing in precision medicine programmes that include TP53 mutation analysis as one part of a wider range of cancer gene panels. These programs have yielded initial discoveries indicating that TP53 mutations correlate with drug resistance, relapse, and survival in breast (Dawood et al., 2024), colorectal (Barakeh et al., 2021) cancer, and hematologic cancers. For instance, mutant TP53 has been linked with decreased sensitivity to anthracyclines and platinum agents and higher resistance to radiotherapy—especially among triple-negative breast cancer subtypes (Monti et al., 2020; Hatoum et al., 2017).

Furthermore, TP53 polymorphisms like the codon 72 Arg/Pro polymorphism have been shown to vary in terms of allele frequency amongst Middle Eastern populations. Some studies have associated the Pro/Pro genotype with increased cancer risk, poor response to therapy and longer survival in specific tumor types, although data are inconsistent, perhaps due to interaction with other genetic and environmental factors (Akhter et al., 2019; Fischer et al., 2023). TP53 variants need to be integrated in the regional SNP-based cancer risk models with lifestyle data for personalized risk assessments.

Besides sequencing of tumor tissue, circulating tumor DNA (ctDNA) has emerged as a promising approach in Middle Eastern clinical context. Using ctDNA as a diagnostic tool, TP53 mutations have been detected in plasma samples from patients with advanced breast and colorectal cancers providing an effective non-invasive biomarker for monitoring disease progression and

therapeutic response (Parkinson et al., 2016; Dawood et al., 2024). This technology has the potential to revolutionize cancer care across the region by offering real-time genomic information without needing repeat biopsies — a particularly advantageous feature in both resource-limited and high-risk surgical settings.

Despite these advancements, significant challenges still exist for the adoption of TP53-based genomic medicine broadly in the Middle East. First, access to molecular diagnostics is extremely unequal. Genomic testing may be available in private and tertiary care hospitals scattered across major urban centers, but there remains a vast gap in the availability of even basic infrastructure to carry out or interpret such tests at the public hospital level. Second, genetic counseling is sparse and often stigmatized (Silbermann & Hassan, 2011; Al-Sukhun et al., 2023) as an oversharing of sensitive information for many due to the familial cancer risk involved, inheritance-associated implications, and reproductive implications if found positive. Third, regional governments have not established consistent policies on genomic data protection, research ethics or interoperability, complicating cross-border collaboration and data sharing.

A harmonised regional response is urgently required to address these challenges. This strategy should include:

• National and cross-national TP53 mutation databases

• Establishment of Middle East cancer genomics consortia

• TP53 testing as part of national cancer screening guidelines

• Genomic literacy: public education and clinical training

• Investments in sequencing, bioinformatics, and biobanking infrastructure

• Global alliances e.g. ICGC, TCGA and H3Africa

TP53 is a genomic and epidemiological mainstay of cancer biology in the Middle East. These contrasting somatic mutation patterns, unique germline variants and region-specific polymorphism profiles suggest both shared and distinct cancer risk and progressions mechanisms among Middle Eastern populations. Ultimately, as genomic medicine continues to progress and mature, comprehensive characterization of TP53 mutations in Middle Eastern cancers will be essential to facilitate novel targeted therapies, increase survival outcomes, and address the unique regional cancer burden.

Data can be translated into actionable recommendations to integrate TP53 insights with public health policy, clinical practice and research agendas as practical means toward personalized cancer care regionally.

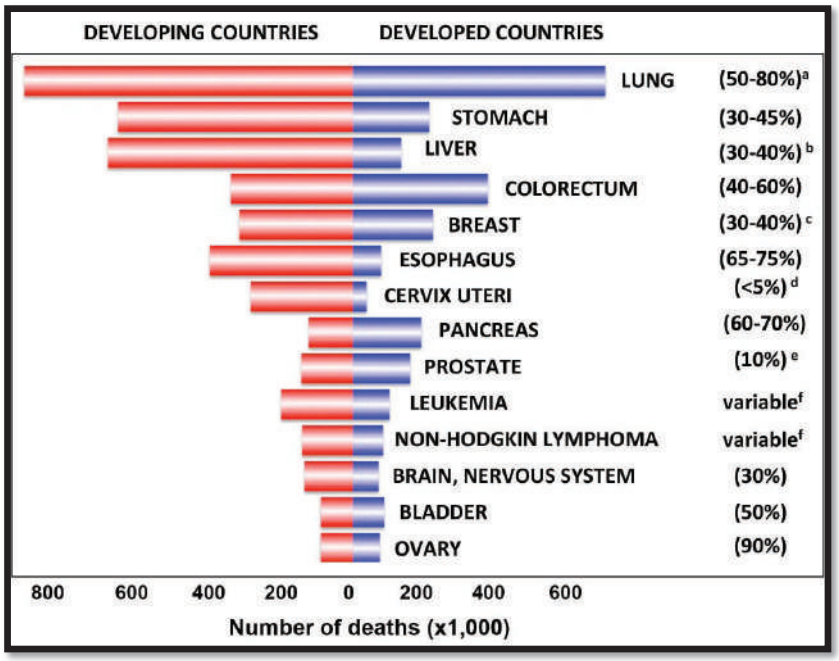


Figure (7) Comparison of TP53 mutation frequencies across cancer types in developing versus developed regions, adapted from Chen et al. (2022). Middle Eastern mutation rates closely resemble developing-region profiles, particularly in breast, colorectal, gastric, lung, and liver cancers.

Comparative Analysis of P53 Mutations Between Middle Eastern and Western Populations

The universal and critical role of the tumor suppressor gene TP53 in cancer biology is supported across different populations worldwide. Comparative studies between regions have shown significant differences in TP53 alterations across Middle Eastern and Western populations, including prevalence, mutation spectrum and clinical effects. These disparities are not just statistical but have important implications for regional cancer aetiology, risk stratification and personalized medicine strategies.

TP53 is the most frequently mutated gene in human malignancies, with mutations found in about half of solid tumors worldwide (Olivier et al., 2010; Donehower et al., 2019). Though Western populations have provided the majority of large-scale genomic databases such as TCGA (The Cancer Genome Atlas) and ICGC (International Cancer Genome consortium), both reporting isoforms of TP53 with consistent mutation frequencies and hotspot distributions across various tumor types. We rely on these datasets for much of our current understanding of p53 biology. But increasing regional cancer genomics work has indicated that Middle Eastern populations differ from Western ones in some telling ways.

The most notable distinction is regarding the overall frequency of TP53 mutations. In western datasets, breast cancer show average mutation rates of 20–30% while other studies from Saudi Arabia, Iraq and other Gulf countries revealed TP53 mutations in 40–55% of the cases (Al-Qasem et al., 2018; Barakeh et al., 2021). Likewise, the mutation rates for colorectal cancer (CRC) in Western populations are usually between 35% and 45%, while studies on Iranian, Egyptian or Lebanese populations are often >50% (Ibrahim et al., 2018; Jafari et al., 2022). The increased mutation frequencies in Middle Eastern cohorts may reflect potential host or biological factors, or environmental factors similar to those that drive genomic instability increasing mutational selection pressures.

A critical difference, however, is the mutant spectra including hotspot mutations showing enrichment of certain specific alterations. Among the general population, three mutations at hotspot regions in TP53 are R175H(RD), R248Q/W and R273H/C, which altogether represent a large proportion of missense alterations. Although these hotspots are also seen in

Middle Eastern data, studies on the region report interesting geographic patterns. G:C to T:A transversions, for example, occur more frequently in tumors of Middle Eastern patients than elsewhere and especially in tissues exposed to environmental carcinogens like tobacco smoke and polycyclic aromatic hydrocarbons (Fathi et al., 2018; Ghojazadeh et al., 2022). Moreover, TP53 deletions and frameshift mutations may have a lower prevalence in Middle Eastern accruals than in western archives, where truncating mutations dominate solid tumors like gliomas and pancreatic adenocarcinoma (Chen et al., 2022; Siraj et al., 2021).

Germline variants and polymorphisms in TP53 also show distinct allele frequencies and potential effects between the two regions alongside somatic mutations. The polymorphism at codon 72 (rs1042522) has been extensively studied, because this change results in either a proline (Pro) or an arginine (Arg) residue at position 72 that affects apoptotic efficiency and protein stability. In Western populations, we see balanced or Arg-dominant genotype distributions compared to strongly over-represented Pro alleles in some Middle Eastern ethnic groups, especially Iraqi, Saudi and North African populations (Akhter, 2019; Fischer et al., 2023). Polymorphism associated with altered cancer susceptibility and prognosis, its overlauded representation in Middle eastern population, together may act as a contributor to disparities in cancer incidence, treatment response and hospice outcome.

Environmental and lifestyle exposures also shape the landscape of TP53 mutations in both regions. European and North American countries currently experience risk factors for TP53 mutations such as alcohol consumption, smoking, high-fat diet usage and aging populations that further lead to oxidative stress and DNA damage. In contrast, Middle-Eastern populations are exposed to region specific carcinogens: exposure to biomass smoke, dietary nitrosamines, chronic infections (H. pylori and hepatitis B/C) and vitamin D deficiency have all been implicated in DNA damage and TP53 alterations in local studies (Rahman et al., 2019; Gholipour et al., 2016; Al-Azri et al., 2014). These differences in risk factors affect mutation signatures and patterns of disease distribution. As an example, in Middle Eastern gastric cancer patients it was shown that TP53 mutations are often the result among others of DNA lesions induced by inflammation and in colorectal cancer frequently found mutation clusters reflect exposure to dietary carcinogens (Ghojazadeh et al., 2022; Jafari et al., 2022).

Endowing a clinical perspective on TP53 mutations, the prognostic and predictive impacts of TP53 mutations are heterogeneous. In western oncology setting, the presence of mutant TP53 is linked to poor prognosis, therapy resistance and advanced tumor stage across cancers (Monti et al., 2020). These associations apply to the Middle East, but both mutation burden and tumor aggressiveness may be more pronounced in certain subgroups. For instance, Arab women with young-age breast cancer often have triple-negative phenotype and high TP53 mutation burden—an aggressive subtype that is more common in them than in Western populations (Al-Shamsi et al., 2023; Barakeh et al., 2021). As in the Middle East, patients with colorectal cancer tend to present at advanced stages with high TP53 mutation frequency and poor response rates to standard chemotherapies (Ibrahim et al., 2018).

Differences in technology and healthcare systems also affect the detection and interpretation of TP53 mutations. Robust molecular testing platforms and large-scale biobanks exist in Western countries, with clinical genomics protocols highly standardized to allow for accurate mutation profiling and integration into treatment planning. On the other hand, the Middle East countries are quite young in their establishment of precision oncology infrastructure. Next-generation sequencing (NGS), trained molecular pathologists, and clinical geneticists are only available at major hospitals in metropolitan areas, often leaving rural and low-income populations on the outs [1I]..

Data representation is another crucial element. The vast majority of the current global cancer genomics databases, such as those in The Cancer Genome Atlas (TCGA) and Catalog Of Somatic Mutations In Cancer (COSMIC), are heavily biased towards Western cohorts leading to a lack of adequate Middle Eastern genomic representation. As a result, these tools may lack representation, which can lead to biases in mutation interpretation and risk modeling and predicting therapy response within middle eastern patients (Fathallah et al., 2023). Accordingly, region-specific TP53 mutation data should be increased for personalized medicine to become clinically useful in non-Western settings.

The gap is being worked on closing. National genomics initiatives are initiated by countries in the region (such as Saudi Arabia, the UAE and Qatar) that include cancer genome profiling, biobanking and ctDNA-based liquid biopsy research (Dawood et al., 2024; Barakeh et al., 2021). Those efforts include documenting local population-specific genomic signatures—

such as TP53 mutations—and applying that knowledge to develop actionable diagnostics and therapeutics. But greater regional collaboration is needed to build shared databases, reach an agreement on the interpretation of mutations and get healthcare providers trained in genomic medicine.

In summary, TP53 remains integral to cancer development in all human populations; however, there are significant differences between Middle Eastern and Western populations with respect to mutation frequency, type, distribution, and clinical significance. These differences are the result of both underlying genetic diversity and environmental context and should be considered in future research, diagnostics, and therapeutic development. It must include data.exchange of regional genomic insight within global population framework cancer database and treatment protocol, to ensure that TP53-targeted strategy remains equitable, effective and culturally sensitive across the spectrum of both Middle-Eastern populations and those in the West.

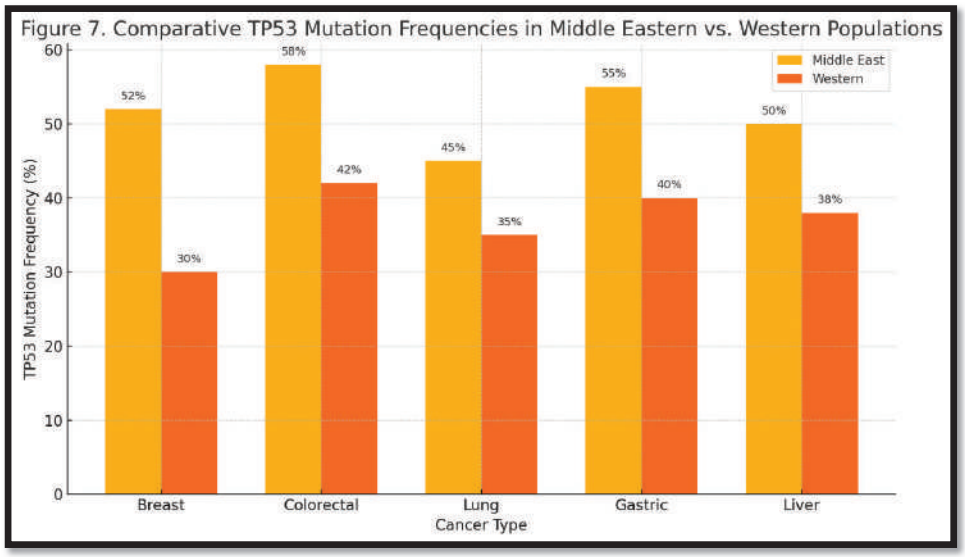


Figure (8) : Comparative TP53 Mutation Frequencies in Middle Eastern vs. Western Populations across major cancer types.

Chapter 3: Environmental and Lifestyle Influences

Environmental and Lifestyle Factors Influencing P53 Mutations in the Middle East

The mutational landscape of TP53 gene is influenced not only by intrinsic genomic instability or hereditary predisposition but also by diverse external environmental exposures and lifestyle habits. Various environments and lifestyles (e.g., use of so-called herbal hepatics; smoking in conjunction with air pollution), intrinsic conditions, as well as native etiological agents—including other viruses and parasites—have an impact on TP53 mutational patterns in the Middle East, a highly dynamic region characterized by fast-growing urban areas, extensive industrial expansion, sociocultural upheaval cycles together with heterogeneous ecological settings. These factors differ between urban and rural environments, socioeconomic classes, and ethnic cohorts and contribute significantly to the regional burden of cancer by driving mutations that perturb tumor suppressor activities of p53. Knowing these variables is essential for at-risk population detection, preventive strategy design, and monitoring of mutation trends in Middle Eastern cancer patients.

Tobacco Products and the Smoking Culture in Middle Eastern Countries: A Contributor to TP53 Mutagenesis

One of the most prevalent and deadly environmental exposures within the Middle East is tobacco use, with a potentially significant impact on mutations including mutational status of TP53 gene associated lung cancer. While cigarette use has plummeted in many Western states as a result of aggressive anti-smoking policies, smoking rates in many Middle Eastern nations have remained high or have even increased, particularly among the youth. The same trend is also accompanied by the enjoyment of another form of tobacco, waterpipes (shisha), which are often seen as less harmful, even though they produce high quantities of carcinogens.

Prevalence of tobacco smoking among adult males can exceed 40% in countries like Lebanon, Jordan, Iraq, Egypt and Saudi Arabia and smoking by females is increasingly reported—albeit underreported for cultural sensitivity—notably in adolescents and university students. Cafes where people meet to smoke major tourists' waterpipes have sprung up in cities and villages, contributing to the normalization of this habit. The appeal is

augmented by fruit-flavored tobacco, social rituals surrounding group smoking and little regulation compared with cigarette advertising or taxation.

Tobacco smoke, regardless of whether it is emitted from the burning end of a cigarette or waterpipe contains thousands of toxic agents: polycyclic aromatic hydrocarbons (PAHs), aromatic amines, N-nitrosamines, benzene and formaldehyde and heavy metals such as cadmium and lead. These agents are powerful DNA-damaging chemicals. They cause certain kinds of DNA base substitutions, especially G:C to T:A transversions, a signature mutation class directly associated with tobacco exposure and commonly found in TP53-mutated tumors.

Studies of lung cancer in various Middle Eastern countries have found TP53 mutation hotspots of smokers that are similar to those seen in high-smoking cohorts around the world, including codons 157, 248 and 273. Most of these alterations occur within the DNA-binding site of p53 altering its ability to promote apoptosis upon receiving a cellular stress signal. This leads to the accumulation of mutant p53 proteins in cells, which evade degradation and can have dominant-negative effects by inhibiting residual wild-type p53 activity. Certain mutations have been also gain-of-function, improving tumor invasion and treatment resistance.

Significantly, waterpipe smoking has been linked to higher exposure per smoking session of carbon monoxide, nicotine and tar than cigarettes. Epidemiological estimates indicate that one water pipe session ranges from the equivalent of 100–200 cigarettes. In addition, waterpipe sessions are commonly held in closed, poorly ventilated areas that might lead to passive exposure among non-smokers — including children and the elderly. Environmental smoke, which includes a diverse array of carcinogens (including both tobacco and cannabis) may also initiate germline DNA damage as well as intergenerational effects on TP53 regulation although this remains largely unexplored [176].

The public health implications of tobacco induced TP53 mutations are huge. These mutations not only elevate cancer prevalence but also confer negative patients survival by enhancing resistance to therapy, relapse and the emergence of metastatic tumors. For instance, in the Middle East, Egyptian patients with non-small cell lung cancer (NSCLC)-linked TP53 mutations exhibit a comparatively shorter survival stage and have decreased responses to platinum-based chemotherapy and reduced validness from

immunotherapy owing to mutant p53-induced immunosuppressive tumor microenvironment.

Despite the overwhelming evidence, much of the Middle East has lagged behind in passing anti-tobacco legislation and public health initiatives. Only a handful of nations have implemented complete indoor smoking bans, placed significant taxes on waterpipe products, or required graphic warning labels. Cultural acceptance and commercial lobbying also stifle policy development. Within this context, educational campaigns aimed at youth, physicians and community leaders are essential. Or, we need to incorporate molecular diagnostics in oncology clinics decades before, so when patients (especially smokers) come through the door early enough for a TP53-mutant cancer2.

Overall, tobacco use in its many manifestations is a major environmental risk factor for TP53 mutations across Middle Eastern cancers, particularly lung, bladder, head and neck and esophageal carcinomas. Together, the high rates of cigarette smoking and waterpipe use create mutational pressure on the p53 pathway that results in clinically aggressive cancers with poor clinical outcome. This challenge calls for a multi-pronged approach, incorporating prevention measures, regulation, molecular monitoring and public awareness in order to curb tobacco-induced carcinogenesis and alleviate the burden of TP53-driven malignancies on this region.

Air pollution has emerged as one of the most ubiquitous environmental health burdens in the Middle East, especially in fast-growing urban hubs. It is well established that air pollution interacts with genomic instability, because chronic exposure of susceptible individuals to airborne pollutants leads frequently to DNA damage, the production of reactive oxygen species (ROS), and to increased mutagenesis. TP53 is one of the most affected and consequential genetic targets of such environmental stress. Its modification by pollution-related processes is driving increased cancer incidence and death across the area.

2. Air Pollution and Urban Environmental Exposure: An Emerging Driver of TP53 Mutations in Middle Eastern Cancer Burden

Over the last twenty years, we have seen new demographic and industrial changes in countries such as Iraq, Iran, Saudi Arabia, Egypt, Lebanon and the United Arab Emirates. These developments, while leading to substantial improvements in infrastructure and urbanization, have also caused increased air quality degradation. This degradation is due to several factors, namely:

• Deterioration of vehicular emissions due to retrograde diesel engines and inferior fuel.

• There are unregulated industrial zones (especially petrochemical, cement and textiles plants).

• Streams of sand and dust storms worsened by climate change and desertification.

• Huge dependence on fossil fuels for both electric power and transport, with little regulation.

• City building and trash burning around unzoned housing

According to WHO data and national environment reports, several Middle Eastern cities are among the world's most polluted urban environments in terms of PM2. 5 concentrations. Cairo, Baghdad, Tehran, Riyadh and Kuwait City regularly surpass recommended air pollution limits by a factor of two to five times. PM2. 5 causes these particles to penetrate deep into the lungs and even enter the blood circulation causing systemic inflammation and oxidative stress, which can lead to DNA damage in somatic cells.

Urban air pollutants are biologically active and genotoxic. These include:

• Polycyclic aromatic hydrocarbons (PAHs) from combustion products, which are known to generate DNA adducts

• Mutagenic volatile organic compounds (VOCs), such as benzene, formaldehyde, and toluene.

• Nitrogen dioxide (NO_2) and sulfur dioxide (SO_2), that cause oxidative stress;

• Critical metals as cadmium, arsenic, chromium and lead which build up in tissues and disrupts DNA repair.

Multiple such pollutants have been shown to induce TP53 mutations in experimental and clinical studies. Exposure to benzo[a]pyrene, a potent PAH, generates DNA adducts at guanine bases that lead to G:C → T:A transitions in the TP53 gene. These are the very mutations often found in lung cancers among nonsmokers exposed to polluted urban air. In Iran and northern Iraq, lung, bladder, and hematologic cancers with higher frequencies of such mutations have been noted, especially in subjects exposed for long periods to air pollution occupationally or in their living environment.

In addition, some new evidence indicates that air pollution not just can target TP53 at the genetic level (mutations) but also has effects in the epigenetic and transcriptional levels. Pollutants can also change the methylation status of TP53 shores, inhibit p53 protein translation or activate expression of inhibitory proteins such as MDM2 that promote p53 degradation. This

functional silencing makes cells susceptible to aberrant replication and malignization in the absence of obvious mutations.

Children, the elderly and low-income communities are particularly affected. Children living in high-traffic zones in Cairo, Basra or Tehran, for example, face lifetime accumulations of mutagenic pollutants. Such early and long exposure enhances the risk of early-onset mutations in oncogenes and tumor suppressors. In these highly exposed populations, p53 dysfunction may develop decades prior to clinical cancer and more regular examination raises the possibility that p53 mutagenesis by urban air could be linked with younger onset of several Middle Eastern cancers.

In addition, air pollution has synergistic impacts with other regional carcinogenic exposures. For instance, smokers living in polluted urban environments have much higher frequencies of TP53 mutations in lung tissue than does the effect from either factor alone. Likewise, individuals bearing polymorphisms in genes coding for detoxifying enzymes (e.g., GSTM1, and CYP1A1) may be at a greater risk of developing TP53 damage due to impaired elimination of airborne carcinogens.

Despite these findings, air pollution is still an under-studied variable in the cancer epidemiology of Middle Eastern countries. Environmental exposure histories are not included in most cancer registries, and TP53 mutation screening related to air pollution is not routinely performed. And few longitudinal studies have traced populations living in polluted regions to track mutation emergence or cancer risk over time.

In terms of implications for public policy, they are pressing. Lowering air pollution would not only yield better respiratory and cardiovascular health outcomes608 but also potentially reduce the mutational load on signatures of major tumor suppressor genes such as TP53, thus reducing overall cancer incidence. Policy actions could include:

• National air quality monitoring program coupled with cancer surveillance.

• Shift to cleaner fuels and stricter vehicle emission standards.

• Industrial zoning – accompanied by appropriate environmental regulations.

• Development of green spaces and urban planning to limit exposure.

• Air filtration systems for schools, clinics and homes in polluted areas.

This major unregulatory result of air pollution in the urban areas of the Middle East region acts as chronic, potent carcinogen that enhances TP53 mutations and thus regional cancer. Given the problems of industrialization and progressive environmental deterioration, gaining insight into how polluted air affects genomic integrity—with a special focus on degradation of p53 function—should be prioritized among regional cancer prevention strategies. A multidisciplinary approach incorporating environmental science, molecular biology, urban planning and public health is needed to mitigate the incidence of p53-driven carcinogenesis associated with exposure to air pollution.

3. Dietary Patterns and Carcinogenic Intake: Nutritional Transitions and Their Impact on TP53 Mutation Burden in the Middle East

Diet is a key modulator of cancer risk, acting at multiple levels by mediating systemic inflammation, obesity and metabolic health as well as exposure to both carcinogenic and protective nutrients that affect DNA integrity and repair pathways. Novel patterns of nutrient exposure derived from substantial dietary changes in the Middle East over the last few decades are linked to cancer incidence and altered TP53 mutational landscapes. The nutritional transition which is characterized by high processed food ingestion and a regression in traditional diets appears strongly correlated with increasing incidences of gastrointestinal, hepatic and metabolic cancers — the majority of which present a heavy burden of TP53 mutations.

3.1 Transition to Traditional vs Western Diets

Traditionally, Middle Eastern diets consist of grains, legumes, olive oil, seasonal fresh vegetables and fruits, fish and fermented dairy. The reason being that these traditional diets are high in fiber, antioxidants, polyphenols and essential fatty acids that help to maintain cellular homeostasis and decrease oxidative stress. But growing urbanization, and globalization, as well as the socioeconomic changes in the region have popularized a Western-type diet throughout much of the region.

This dietary change is defined by:

• Higher intake of red and processed meats, frequently grilled or fried.

• Overconsumption of refined carbs, trans fats, and sugar-sweetened beverages

• Reduced consumption of fiber-rich fruits, vegetables and whole grains.

• High dependence on fast food and low-nutrient convenience foods.

These changes not only promote obesity and insulin resistance, both of which can contribute to cancer risk, but they also create a continuous exposure to dietary carcinogens formed especially during the preparation of food through high-temperature cooking and preservation.

Before discussing diets, it is first worth mentioning that an enormous body of evidence supports the..., dietary carcinogenic compounds in modern Middle Eastern...

During the grilling or frying of meat at high temperatures, heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are formed. These compounds can bind to the DNA, forming adducts—mutagenic lesions that have been shown to introduce mutations in important tumor suppressor genes such as TP53. Traditional methods of preparation in traditional Middle Eastern cooking — like charcoal-grilled kebabs, skewer-roasted lamb and roasted chicken — often mean that food comes into direct contact with flame, which may promote the formation of HCAs and PAHs.

In the acidic environment of this exchange, nitrites and nitrates employed in processed meat preservation (eg, sausages and luncheon meats) can lead to the development of N-nitroso compounds (NOCs). NOCs are strong mutagens associated with gastric and colorectal cancer. These compounds preferentially induce G:C to A:T transitions and frameshift mutations—mutational events that have been repeatedly documented in TP53 exons 5–8 from the gastrointestinal tumors of Middle Eastern populations (Jafari et al., 2022; Ghojazadeh et al., 2022).

Aflatoxins, toxins produced by fungi that contaminate improperly stored grains and nuts, are widely dispersed in some agricultural regions of the Middle East, especially Iraq (and)Iran and parts of the Levant. Aflatoxin B1 is a direct mutagen capable of inducing the R249S mutation in the TP53 gene, a change that is highly specific for hepatocellular carcinoma and serves as a molecular signature of aflatoxin exposure (Chen et al., 2022; Rahman et al., 2019).

But low antioxidant intake, due to a lack of fruits and vegetables and whole grains in the diet, weakens the body’s power to neutralize free radicals. Consequently, the reactive oxygen species (ROS) build up damages the DNA bases and triggers TP53 mutations. Known examples of antioxidants—such as vitamin C, E selenium and flavonoids that play an important role in DNA protection and p53 are heavily reviewed with vitamin C deficiency being associated with increased mutation rates and impaired p53 activity (Gholipour et al., 2016).

3.3 Effect on Cancer Types and p53-related Pathways

The types of cancer most linked with dietary factors among the Middle East countries are:

• Colorectal cancer (CRC): In some countries, such as Jordan and Saudi Arabia and Iran, a rapid increase in CRC incidence has been observed, especially in younger groups. A pro-inflammatory colonic milieu permissive of TP53 mutations in early adenoma evolution is fostered by high red meat consumption, low fiber, and high-fat diets (Ibrahim et al., 2018; Benmokhtar et al., 2024).

Gastric cancer: A robust association with dietary salt, consumption of pickled foods/low fruit and vegetables Salt causes gastric mucosal damage, increases susceptibility to Helicobacter pylori and via oxidative stress pathways promotes TP53 mutations (Rahman et al., 2019).

• Liver cancer: aflatoxins and alcohol (in non-Muslim communities or affected groups) increase risk, particularly when combined with viral hepatitis. Genomic signature of Aflatoxin Associated TP53 R249S Met. is the known biomarker for environmental exposure (Chen et al., 2022).

• Esophageal cancer: Related to scalding tea, moldy food and micronutrient deficiency in rural Iran and Northern Iraq. This explains the p53 mutation hotspots seen in regional cohorts (Biramijamal et al., 2001).

3.4 Genetic Background and Polymorphisms Interactions

The emerging data suggest that dietary carcinogens may also interact with several TP53 polymorphisms found at high frequency in Middle Eastern countries. Increased frequency of the codon 72 Pro/Pro genotype (associated with decreased apoptotic response) has been found in some Arab and North African populations. This genotype may make cells more vulnerable to mutational fixation after exposure to carcinogen. Similarly, those carrying cancer-associated mutations in genes involved in detoxification (e.g., GSTM1-null) may also produce greater quantities of genotoxic metabolites and thus further exacerbate disruption to the p53 pathway.

3.5 Implications for Public Health and Clinical Settings

Although there is strong evidence for a link between diet and TP53 mutagenesis, awareness still remains low throughout the region. Most people think of cancer as determined by fate or family history rather than changeable risk factors. Nutritional education is minimal in schools and dietary counseling is rarely integrated into cancer prevention programs.

Actions are required to mitigate the dietary contribution of TP53-associated cancer throughout:

• Nationwide dietary surveys to assess carcinogen consumption and compare with cancer rates.

• Regulating and controlling aflatoxin levels in stored grains and nuts.

• Public campaigns encouraging plant-based, high-fiber diets lower in red and processed meats.

• Promoting traditional cooking methods that help lower exposure to HCAs and PAHs.

• Nutritional screening and antioxidant supplementation for high-risk populations.

From a clinical perspective, TP53 mutation testing should be particularly prioritized in patients with gastrointestinal cancers, especially those with a history of exposure to known dietary carcinogens. These mutation profiles can provide prognostic information and guide therapy, especially in the case of colorectal cancer where TP53 status is important for sensitivity to chemotherapy and immunotherapy.

However, dietary patterns in the Middle East are evolving that affect cancer risk—in particular TP53 mutation burden. And whether it be high-heat meat cooking and food preservation practices, aflatoxin exposure or antioxidant deficiencies, such dietary factors exercise potent mutagenic drives that redraw the regional cancer landscape. Knowledge-based approaches towards guidance and action can help the public health systems in the Middle East reduce cancer incidence,through dietary reform and education (2), thus promoting genomic stability in vulnerable populations.

4. Chronic Infection and Inflammation: Drivers of P53 Mutation Through Persistent Cellular Stress

One of the major players in initiating and promoting cancer are infectious agents and persistent inflammation. Of note, endemic infections and untreated inflammatory conditions in the Middle East associate with elevated mutational burdens in genes such as TP53 that can act as tumor suppressors. These biological mutations generate a chronic exposure to a genotoxic environment that supports somatic mutations such as loss of p53 functions or the presentation of mutant p53 gain-of-function (GOF) variants which facilitate aggressiveness in cancer progression.

Here we discuss TP53 mutations that are driven by infection-related inflammation, identify key regional pathogens and their molecular impact on tumorigenesis in the Middle East region.

Helicobacter pylori and Gastric Carcinogenesis.

Infections of H. pylori are very high in many countries of the Middle East, including over 60–70% in some rural and low-income populations (Rahman et al., 2019). Chronic gastritis due to H. pylori results in oxidative stress, DNA damage, and the build-up of mutations in gastric epithelial cells. These include point mutations in exons 5–8 of the TP53 gene, especially G:C to A:T transitions at CpG sites—signatures of inflammation-driven mutagenesis.

Specific findings:

• TP53-positive tumors have increased protein accumulation of p53, a surrogate marker of TP53 mutation.

• Observational studies in Iran and Iraq found increased TP53 mutation frequency in patients with H. pylori infection, particularly amongst those infected with the CagA+ virulent strain.

• Mutant p53 in gastric cancer promotes immune escape, angiogenesis and epithelial–mesenchymal transition

Mechanism: Reactive oxygen species (ROS) and reactive nitrogen species (RNS) created by neutrophils during chronic gastritis induce direct DNA oxidative damage, leading to mutations in tumor-supressor genes. Concurrently, the inflammatory microenvironment activates NF-κB and COX-2 that favor the survival of TP53 mutated cells.

4.2 Virological Hepatitis and HCC

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections continue to be major public health burdens in Egypt, Iraq, Iran, and the Arabian Gulf region. Chronic infection results in cirrhosis and liver cancer, with 25–40% of hepatocellular carcinoma (HCC) cases found to harbor a mutation in TP53[3].

Notable mutation pattern:

• Together with HBV infection, aflatoxin B1 exposure leads to the R249S mutation of TP53, a molecular signature present in cases of HCC from Egypt and southern Iran (Rahman et al., 2019; Chen et al., 2022).

• It disrupts the DNA-binding function of p53, which favors tumorigenesis.

Mechanism: HBV expresses the HBx protein which binds to and degrades p53, inhibiting apoptosis and DNA repair. This viral interaction, in addition to chronic hepatic inflammation, prepare the ground for TP53 mutations and clonal selection of malignant hepatocytes.

4.3 Schistosomiasis and Bladder Cancer

In parts of Egypt and southern Iraq, schistosoma haematobium infection is endemic. Chronic urogenital schistosomiasis leads to long-term inflammation of the bladder, which increases the risk of squamous cell carcinoma, a rare type of bladder cancer more prevalent in these regions.

Key findings:

• Tumorigenic changes of TP53 are more than 50% in schistosomiasis-associated bladder cancers (records from Egypt and Sudan show this, Osman et al., 1997).

Common mutations are A:T to T:A transversions; these result from oxidative stress and nitrosamine exposure due to regional inflammation.

Mechanism: Schistosomal eggs provoke granulomatous tissue inflammation (high levels of ROS and cytokines, such as IL-6, TNF-α and nitric oxide synthase (iNOS) leading to DNA strand breaks and base modifications. Chronic irritation drives selection of p53 loss-of-function.

4.4 Cervical and Head-and-Neck Cancers: Viral Oncogenesis

Carcinogenic Human papillomavirus (HPV) types 16 and 18 which are associated with the highest proportion of cervical cancer cases are also found in some head-and-neck cancers in the Middle East (Al Moustafa et al., 2014).

• Enzyme 6AP; HPV E6 oncoprotein induces p53 ubiquitination/degradation via the E6AP ligase.

• Consequently, this results in functional inactivation of wild-type p53 regardless of gene mutation, and has similar effects as TP53 inactivation.

In advanced and treatment-refractory HPV-associated tumors, secondary mutations in TP53 have been described suggesting positive selection for enhanced p53 dysfunction.

4.5 Crohn's Disease and Colorectal Cancer

Ulcerative colitis (UC) and Crohn's disease are emerging public health problems among the urban youth in Saudi Arabia, Iraq and Iran. These

chronic inflammatory conditions are linked to increased risk of CRC and early TP53 mutations, sometimes even before the presence of overt dysplasia.

These studies come from hospitals in the Middle East:

• In colitis-associated CRCs, TP53 mutations occur in 50% of the cases.

• Mutant p53 expression is seen in inflamed non-neoplastic mucosa indicating field cancerization.

Mechanism: Continuous infiltration of the immune cells promotes oxidative injury, barrier defects and DNA adducts p53 mutation provides survival benefits to dysplastic foci under inflammatory stress.

4.6 Broader Implications

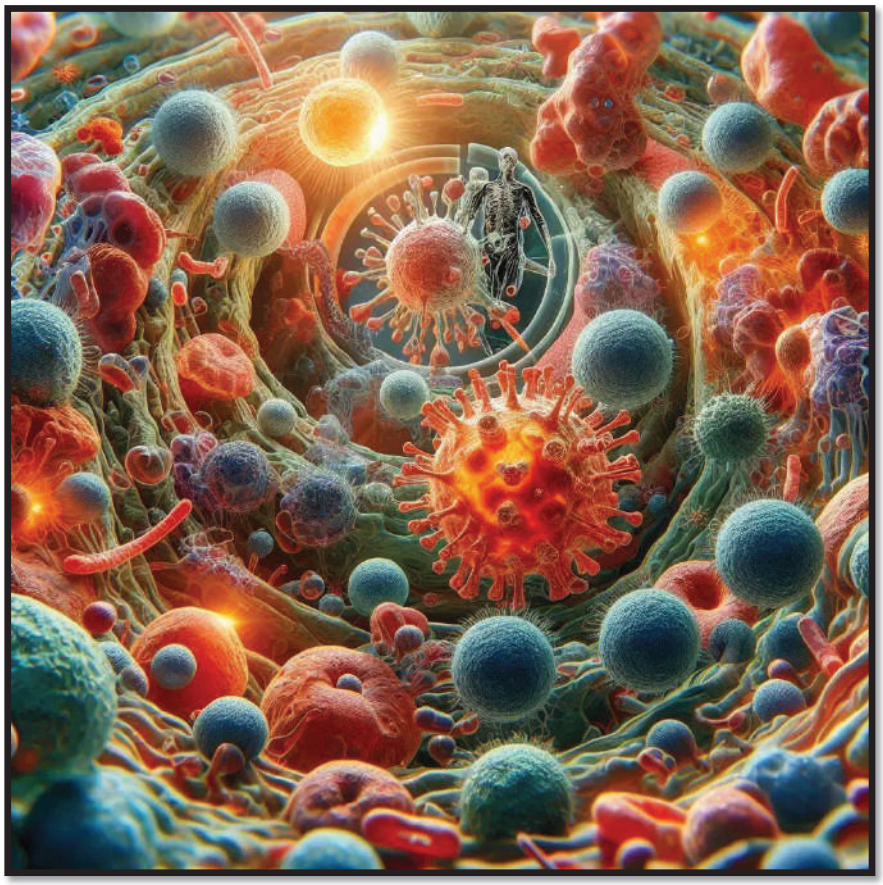
Chronic inflammation and infection status in the Middle East generates a remarkable genomic signature, which influences cancer evolution. Inflammatory mutagenesis promotes TP53 inactivation early in neoplastic evolution. Although most oncogenic mutation hotspots were frequently not present in these patients either due to lack of relevance or pathogen-driven mutational signature, recurrent mutations that are found in both Arab and Iranian patients may be pathogen specific or also inflammation driven and could thus serve as targets for prevention strategies using personalized immunotherapy.

Future Needs

• Screening and vaccination programs of global coverage (e.g., HBV, HPV) to prevent infection-induced carcinogenesis.

• Anti-inflammatory chemoprevention trials in high-risk patients with IBD or chronic hepatitis.

• Combination infectious disease control and genomic profiling in cancer centers



5. Vitamin D Deficiency and Hormonal Factors: Modulators of P53 Function and Cancer Risk in Middle Eastern Populations

Hormones and vitamin D are major part of cell homeostasis. Dysregulation of these pathways impacts apoptosis, immune surveillance, cell cycle progression and DNA repair. These processes are highly regulated by TP53, nicknamed the “guardian of the genome.” It represents a distinct context of region-specific TP53 mutation and cancer susceptibility mediated by common vitamin D deficiency plant on endogenous hormonal profiles endemic across the Middle East region.

The Epidemic of Vitamin D Deficiency in Middle East 5.1

Middle Eastern populations have alarmingly high rates of vitamin D deficiency despite an abundance of sunlight. This paradox is partly attributable to:

• Cultural clothing customs that limit skin exposure to UVB light, a necessary component for cutaneous vitamin D synthesis.

• Indoor living particularly in developed nations resulting in low sunlight exposure.

• Low dietary intake with little fortified foods, oily fish, or vitamin D supplementation.

• Air pollution in large cities, including Cairo, Baghdad and Riyadh, which blocks solar ultraviolet radiation to reach the skin.

• More melanin in the skin, which naturally inhibits production of vitamin D.

It has been estimated that more than 70% of the population in countries such as Saudi Arabia, Iraq, Jordan and the UAE have serum 25(OH)D levels ≤20 ng/mL (much lower than suggested thresholds >30 ng/mL). Alarmingly, among some subpopulations—particularly women and adolescents—deficiency rates are over 90 percent.

5.2 Molecular Interaction of Vitamin D with P53

Vitamin D has antiproliferative, pro-differentiation, and pro-apoptotic effects that intersect with the p53 pathway. Calcitriol is the active metabolite that binds to and activates the nuclear vitamin D receptor (VDR) forming a complex responsible for transcriptional regulation. Notable molecular interactions include:

• P21 upregulation: Calcitriol potentiates the p53-dependent expression of CDKN1A (p21) to induce cell cycle arrest

• MDM2 suppression: Downregulation of MDM2, a negative regulator of p53, due to vitamin D signaling contributes to stabilization and activation of p53.

• Synergistic apoptosis equilibrio: Vitamin D increases the sensitivities of cells to p53-mediated regarding towards apoptosis, especially with interim malignancy and conjured events.

• Increased DNA repair: GADD45, which is involved in p53-dependent signalling to transcription and Mdm2-mediated attenuation, and XPC, a key player in the nucleotide excision repair mechanism are both targets of VDR as well as p53.

These mechanisms are dysfunctional in vitamin D deficient individuals. It downregulates p53 signaling by decreasing the transcription of VDR, which promotes apoptosis sensitivity in cells with DNA damage and maintains genomic stability.

3.1 Hormonal Regulation of P53 Activity

Hormonal signaling also guides p53 activity and governs mutation susceptibility. TP53 is a target of several hormone-related pathways:

• Estrogens, especially estradiol, regulate p53 via ERα. In ER-positive cells, estrogen induces p53 transcription while simultaneously stimulating MDM2 expression in a feedback loop that can decrease net p53 activity.

• Depending on receptor isoforms and tissue type, progesterone interacts with p53 to enhance its tumor suppressor functions.

• Androgens have paradoxical roles with respect to p53 where they stabilize the protein in some tissues (e.g., prostate), but may inhibit its apoptotic effects elsewhere.

But reproductive customs observed throughout the Middle East—including early marriage, high parity (or childbirth), prolonged breastfeeding and limited contraceptive use—help regulate hormonal baselines. These endocrine patterns contribute to a p53 network, especially in relation to hormone-receptive cancers including breast, ovarian and endometrial tumors.

5.4 Metabolic Dysregulation, Obesity, and Insulin Resistance

Obesity and type 2 diabetes are among the highest in the world, in the Middle East. Such conditions affect hormonal balances and promote oxidative stress — both of which would impair p53 function:

• Obesity and metabolic syndrome activate insulin and IGF-1 signaling pathways. Such factors prevent the activation of p53 by phosphorylation and exclude it from entering the nucleus via PI3K/AKT pathway.

• Leptin, elevated in the obese state, is pro-inflammatory and inhibits catabolism-dependent apoptosis involving p53.

• Prolonged hyperglycemia enhances ROS generation, resulting in oxidative injury to DNA. Without enough p53 function, damage accumulates and induces oncogenesis.

Moreover, obese people have adipose tissue that acts as an endocrine organ producing cytokines that promote inflammation and suppress p53 activity. The collective outcome creates a mutagenesis favorable cellular landscape, which extends to the TP53 locus as well.

5.5 Vitamin D, Hormones and TP53 Mutations: Empirical Connections in the Region

Several studies provide indirect evidence for the involvement of vitamin D and hormones in the development of TP53 mutations:

• Al-Qasem et al. (2018) also found a higher than normal frequency of TP53 mutations in Saudi breast cancer patients, many of whom were also vitamin D deficient.

• Al-Sakkaf and Abood (2022) reported increased rates of p53 mutations in gynecological cancers arising in Yemen, where the intersection between hormonal and nutritional factors collides with chronic infection.

• Rahman et al. TP53 mutations of gastric cancer patients from Iraq and Egypt cooccurred with markers of metabolic dysfunction and low vitamin D status (Shukri et al.

Nonetheless, local mechanistic studies are limited. Comprehensive, multi-omic pipelines encompassing vitamin D information, hormonal metrics, and TP53 mutation status to confirm causal relationships are needed.

5.6 Implications for Public Health and Preventive Strategies

The coming together of vitamin D deficiency and hormonal imbalance with p53 dysfunction has huge implications:

• Vitamin D supplementation programs should be prioritized among adolescent girls and pregnant women

• Dietary interventions to target vitamin D containing foods may decrease cancer risk on a population level.

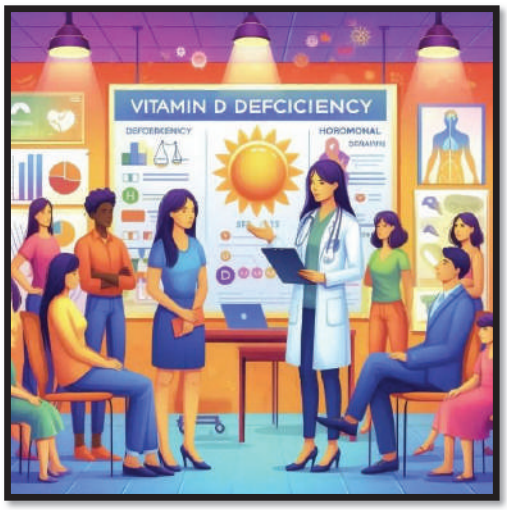
• Screening between 25(OH)D levels in the oncology setting may help to score patients at highest risk of TP53-directed progression.

• In postmenopausal women, hormone replacement therapy (HRT) should be adjusted according to its effects on p53 and susceptibility to cancer.

• Public education campaigns should include both sun safety and educate the benefits of moderate, safe UV exposure.

Incorporating these approaches within the context of cancer prevention frameworks has the potential to reduce health burden for p53-related cancers and facilitate early detection using biomarker-based risk stratification.

Conclusion: Vitamin D deficiency and hormonal factors may be modifiable contributors to the frequency of TP53 mutation in Middle Eastern populations. These have biochemical, molecular and public health consequences that highlight the need for multifactorial approaches to diminish the cancer burden associated with defective p53 signaling.



6. Exposure to Environmental Pollutants and Industrial Toxins: Environmental Pressures on TP53 Integrity in the Middle East

Genomic integrity is under serious burden by environmental pollutants and industrial toxins. One of the major molecular targets of this environmental pressure is the TP53 gene. Its protein product, p53, is the a main cellular barrier to genotoxic stress. Given the public health relevance of the potential effects of pollutants on p53 activity and mutation rates in Middle Eastern

populations, where industrial development and environmental regulation have not kept pace with growth.

Even by standards of other megacities, urban areas such as Riyadh, Baghdad, Tehran and Cairo are constantly exposed to excessive amounts of fine particulate matter (PM2. ð¢6 and PM10), heavy metals (lead, mercury and cadmium) as well as organic pollutants (polycyclic aromatic hydrocarbons, benzene and dioxins). This cocktail of air carcinogens is derived from petroleum manufacturing and refining, vehicle exhaust, plastic incineration, cement industries and uncontrolled waste disposal. Exposure to these agents can occur through inhalation and the dermis, leading to DNA adducts and free radicals that disrupt DNA replication and repair. TP53 is frequently one of the first and most mutated genes in these chronically exposed cells.

Studies conducted in places such as Iran and Saudi Arabia have shown that a direct association exists between living in close proximity to industrial areas and the also increasing TP53 mutational burdens in various cancers including lung, bladder, and gastrointestinal malignancies. Hatamzadeh et al' s studies of the esophagus in Iranian patients living near various kinds of industry or rural areas with pollution, showed transversion mutations at codons frequently associated with hydrocarbon exposure (Biramijamal et al., 2001; Gholipour et al., 2016). This suggests a shared environmental mutagenesis mechanism that converges on TP53 across ethnicities and geographies.

In oil-rich countries such as Iraq and Kuwait, legacy contamination from combustion events related to conflict (e.g., oil well fires) has resulted in long-term signatures of polycyclic- and halogenated hydrocarbons in air and soil. Military and civilian personnel who were exposed to these agents exhibit not only higher cancer incidence but also TP53 mutations that carry molecular fingerprints characteristic of alkylating and oxidative stress-acting agents. Petrochemical workers living in areas such as Basra or Ahvaz have also shown increased oxidative DNA damage and higher levels of TP53 mutations in buccal or blood samples, well before the development of any symptoms.

The mutational burden on TP53 is also attributable to agricultural activities. Many pesticides banned or poorly regulated elsewhere in the world, like organophosphates and chlorinated hydrocarbons, are still used in several Middle Eastern countries. Chronic dermal and inhalation exposure to these agents — prevalent, for example, among agricultural workers in Egypt,

Jordan and parts of southern Iraq — has been associated with hematological malignancies and cancers of the digestive tract. Such cases typically have TP53 mutations within conserved DNA-binding regions that inactivate p53 transcriptional activity and apoptotic function, resulting in the clonal expansion of premalignant cells (1).

In addition to direct DNA damage, many environmental pollutants disrupt the p53 pathway via epigenetic modulation. For example, aqueous particulates were linked to hypermethylation of TP53 promoter regions or downstream effectors including p21 and BAX. This decreases the expression of functionally active p53 even in the absence of mutations, producing a pseudo-null phenotype that impairs detection and response to genomic insult.

TP53 instability is aggravated in poorly regulated regions by waterborne carcinogens. In areas with elevated groundwater salinity or contamination — in southern Iraq or along coastal Iran, for instance — exposure to arsenic and nitrate has been documented. These agents cause genomic instability and oxidative damage to DNA, as well as resistance to apoptosis by mechanisms that converge on TP53 inactivation or loss of function.

Overall, the Middle East is potentially a high-risk environment for TP53 disruption, combining urban pollution with industrialisation, agrochemical use and war-related toxins. These exposures generate direct mutational pressure while indirectly suppressing the p53 tumor suppressor pathway in an epigenetically persistent manner, dramatically increasing cancer risk and compromising therapeutic efficacy. More effective regulation, public health policy and molecular surveillance of TP53 in exposed populations are needed to address these environmental determinants to advance cancer prevention and control throughout the region.

7. **Consanguinity and Genetic Drift: Population-Specific Genetic Influences on TP53 in the Middle East**

Consanguinity, which is the custom of marrying within extended family networks, is also a culturally embedded practice in many regions of the Middle East. The prevalence of consanguineous marriage is between 20% and over 50% in countries like Saudi Arabia, Iraq, Jordan and Yemen, as well as the UAE. Although this practice is socially and economically motivated, it has profound consequences for genetic inheritance, particularly

with respect to the transmission of rare variants and disease risk-associated alleles such as mutations in tumor suppressor genes like TP53.

A key component of DNA damage response is the TP53 gene, encoding the p53 protein, functioning as a cellular checkpoint that synchronizes cell cycle arrest with apoptosis and DNA repair in the presence of genomic alterations. In heterozygous proteins, the TP53 protein is capable of fulfilling this tumor suppression role with just one copy of functional TP53. However, consanguinity increases the probability of identical alleles being inherited from both parents and may therefore result in homozygosity for deleterious variants. This effect is exacerbated in populations with substantial endogamy by a genetic phenomenon called genetic drift, whereby certain mutations (neutral or pathogenic) are enriched over generations due to a scarcity of diversity within the gene pool.

The inherited variants in TP53 have also been reported from the patients of breast, colorectal a~nd hematological cancers from Arabian Peninsula and Levanint countries. Particularly, polymorphisms like the Arg72Pro (rs1042522) variant have been found at higher frequencies in consanguineous families with a history of early-onset cancers. This polymorphism modifies the efficiency of p53-induced apoptosis, modifying the cellular response to DNA damage and possibly facilitating tumorigenesis in subjects exposed to further mutagenic or environmental insults (Akhter, 2019)

Compounding this situation, some Middle Eastern subpopulations exhibit a restrictive level of outbreeding often seen in rural or tribal communities. Genetic drift over time strengthens founder mutations—genetic variants inherited from a single ancestral individual that have remained in their population due to some limited admixture. When those founder mutations reside in TP53 or genes that regulate or interact with the p53 pathway (for example, MDM2 or ATM, CHEK2), the whole p53 network may become destabilized across generations and in situations without environmental stressors [115].

Epidemiological data support these observations. Families with high consanguinity often report clusters of early-onset and aggressive phenotypes cancers. Rare, region-specific germline mutations of TP53 have been reported in some of these cancers and seem underreported or absent from Western populations when ascertained by whole-exome sequencing and pedigree analyses. While classical Li-Fraumeni Syndrome associated

mutations in TP53 have been widely detected worldwide, some Middle Eastern TP53 germline mutations exhibit specific single nucleotide substitutions or deletions that suggest historical genetic isolation and founder effects within these populations (Siraj et al., 2021).

In some regions, population bottlenecks due to historical conflict, migration or epidemics have diminished genetic variability even more. The bottleneck effect allows for excesses of particular deleterious alleles to go unnoticed in carriers for generations until they become apparent under epigenetic or environmental stimulus. These factors in conjunction with high birth rates and limited access to genetic counseling contribute to a greater generation burden of TP53-related cancer risk.

The effect of consanguinity and genetic drift on the integrity of TP53 suggests that population-wide screening, genetic counseling and educational measures should be implemented at the public health level. Identification of carriers and people at risk in families that have a recurrence of several cancers enables interdisciplinary prevention surveillance about specific cancer risks and subsequent measures to save lives. Moreover, national and regional genomics programs should collect the region-specific TP53 mutations to establish a stronger basis for targeted therapies and precision oncology in Middle Eastern populations.

Thus, the molecular context generated by Tobin's law of consanguinity and genetic drift acts as a lid on the dogma that TP53 is essentially inviolable in germlines. This understanding is crucial to predicting cancer risk as well as informing public health efforts in an area where family and genetics drive much of the disease landscape.

8. **Cultural and Healthcare Access Factors: Societal Determinants Shaping TP53 Mutation Outcomes in the Middle East**

Together, Middle Eastern cultural beliefs, social norms and healthcare infrastructure affect cancer identification, diagnosis and management. These determinants have indirect effects on the nature of TP53 mutation landscape through its influence on exposure length to insults, ability for early screenings of tumors when TP53 mutations start with more tractable so-called precursor lesions, access to timely and state-of-the-art treatment and finally public health reporting integrity. TP53, as one of the most frequently

mutated genes in human cancers, mellows more than biological stimuli; it conveys system health inequities and impediments to treatment.

In most of the Middle Eastern societies, cancer remains with hindering social stigma. Cancer is one of those fatal or shaming diagnoses that leads women in particular to secrecy, denial and avoidance of seeking medical advice. This is especially important for breast and gynecological cancers, as female patients are known to delay visits to the clinic due to modesty concerns, cultural taboos or lack of social support (Silbermann & Hassan, 2011). That leads to many cancers being diagnosed at an advanced stage, when the burden of somatic mutations — including in TP53 — is more advanced and diverse.

In rural and underserved areas, delayed diagnosis is frequently an issue of underdeveloped healthcare infrastructure. Existing diagnostic pathways for many cancers depend on the presence of symptoms and all of these factors, in particular, the absence of routine screening combined with lack of access to appropriate diagnostic imaging and genetic testing with variable pathways to specialist referral mean that most cancers are undiagnosed until symptomatic. Although, this delay adds poor prognosis and also raises the tumor's mutational burden with TP53 mutations that are usually the late stage genomic instability marker. Lack of early intervention could potentially lead to the clonal selection and expansion of aggressive TP53 mutant clones exhibiting chemoresistance or metastatic capacity.

Access to health care varies by socioeconomic strata as well. Populations in wealthier urban centers may benefit from advanced diagnostics and molecular profiling, including the identification of TP53 mutations and treatment customization. Marginalized groups — including but not limited to refugees, low-income families or internally displaced persons — might depend on fragmented or overstretched public health services. Such groups are often excluded from clinical trials or cancer registries, leaving gaps in epidemiological data on TP53 mutation frequency and its impactful relevance in the context of these populations.

Moreover, preventive health care services, including cancer awareness initiatives, vaccination programs (such as HPV vaccine) and routine check-ups are applied unevenly across the region. Political reluctance, scarce public health budget and poor outreach all play a role in the low uptake of preventive measures. If untreated due to no early detection, pre-malignant

lesions may become full-blown cancers with complex mutational profiles that include TP53 loss-of-function or gain-of-function mutations.

Gendered differences are also a big factor. In parts of the Middle Eastern societies, such as where women need men to escort them for travel and have low health literacy with needs of the family placed above personal ones, all contribute to their inability to reach appropriate treatment. Stumbling blocks that hinder women from being diagnosed and treated in a timely manner, thus elevating the likelihood of advanced TP53 mutation burden at medical presentation. In a few cohorts of breast cancer patients found in the Middle East, it was confirmed that the prevalence of mutant TP53 at diagnosis is significantly greater than seen among their Western counterparts, and that the mutation is typically associated with larger tumor size and grade (Barakeh et al., 2021).

Religious beliefs may play a role in adherence to treatment as well. Others may seek guidance from spiritual healers, or use traditional medicine instead of the biomedical paradigm. Species trading and catecholamine-based therapeutic trials have little value outside their home cultures, molecular diagnostics are rarely performed, oncologic standards are avoided or delayed so that TP53-driven school brawls typically go unmonitored and risk stratification conforms to a bell curve rather than providential stupidity. Furthermore, reluctance for testing due to social stigma, discrimination or insurance denial can hinder the identification of germline TP53 mutations in high-risk families especially with Li-Fraumeni Syndrome.

The problem is compounded by the absence of national cancer registries and genomic databases. Due to lack of centralized data, researchers and clinicians are unable to discern the trends in region-specific TP53 mutation or plan targeted therapies. While some initiatives like the Gulf Cancer Registry and other telomere-length-associated pan-Arab collaborative networks have made strides toward closing this gap, coverage is still limited and molecular TP53 data remain incomplete or fragmented.

Multiple interventions are critical to overcome these structural limitations. Such initiatives range from culturally tailored education campaigns and inclusion of genetic counseling in primary care to subsidized molecular testing and national-level cancer registries with molecular annotation. Increasing female access to healthcare and training more female oncologists and geneticists can help, as can engaging religious leaders in public-health promotion campaigns to limit stigma and improve community participation.

Overall, there is substantial evidence that cultural norms and healthcare disparities contribute to the delay in detection and documentation of TP53 mutations within the Middle East. Although indirect, these are critical factors in determining cancer outcomes and need to be systematically addressed if the burden of TP53-driven malignancies in the region is to be diminished.

Chapter 4: Diagnostics and Therapeutics

Emerging Biomarkers and Diagnostic Approaches for P53 Mutations

The accurate detection of TP53 mutations and the interpretation of their clinical significance have become essential components of modern oncology. Given the prevalence and heterogeneity of TP53 mutations across cancer types, particularly in Middle Eastern populations, there is increasing emphasis on integrating advanced biomarker technologies into diagnostic workflows. Emerging diagnostic approaches now combine molecular biology, next-generation sequencing (NGS), and liquid biopsy with context-specific clinical applications, offering new opportunities to detect, classify, and track TP53 mutations in real-time.

Traditional diagnostic modalities, such as immunohistochemistry (IHC), remain widely used to assess p53 protein expression in tumor biopsies. While IHC provides a rapid, cost-effective method to infer mutation status, it lacks the resolution to detect mutation subtypes or differentiate between loss-of-function and gain-of-function variants. Missense mutations, which are common in Middle Eastern cancers, often result in the accumulation of mutant p53 protein detectable by IHC. However, frameshift or nonsense mutations that produce truncated proteins may escape detection altogether. This limitation has driven the development of more sensitive and specific molecular approaches.

Next-generation sequencing (NGS) platforms represent a significant leap in TP53 mutation profiling. Targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS) allow for the identification of point mutations, insertions, deletions, and complex rearrangements within the TP53 gene. In Middle Eastern cohorts, where unique mutational signatures have been reported (Al-Qasem et al., 2018; Siraj et al., 2021), NGS enables researchers and clinicians to capture population-specific TP53 variants, some of which may be novel or underrepresented in global databases.

Liquid biopsy is another emerging tool gaining momentum for its non-invasive nature and potential for real-time monitoring. Circulating tumor DNA (ctDNA) can be isolated from blood samples and analyzed for TP53 mutations, enabling detection even before clinical symptoms arise or when tissue biopsies are not feasible. Studies have shown that TP53 mutations detected via ctDNA correlate with disease burden, response to therapy, and relapse (Parkinson et al., 2016). In settings where late-stage presentation is

common—such as in parts of the Middle East—liquid biopsy offers a practical means to detect and track tumor evolution with minimal patient burden.

In tandem with molecular detection, digital pathology and artificial intelligence (AI) tools are being developed to refine the diagnostic assessment of TP53-related alterations. These systems analyze whole-slide histology images, integrating morphological features with underlying mutation data to produce diagnostic predictions. Machine learning algorithms trained on large datasets can identify patterns indicative of TP53 dysfunction, including altered cellular architecture, increased mitotic index, and nuclear pleomorphism, especially in tumors of the breast, colon, and ovary.

Emerging research also highlights the potential of RNA-based biomarkers and non-coding RNA species, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), that modulate TP53 signaling. Certain miRNAs are directly regulated by wild-type p53, and their dysregulation may indicate underlying TP53 mutation or pathway disruption. For instance, miR-34a is a well-known downstream effector of p53, and reduced levels are often observed in TP53-deficient tumors (Hu et al., 2020). Measuring miRNA levels through quantitative PCR or RNA sequencing offers another layer of molecular insight, particularly in cancers where DNA sequencing yields ambiguous results.

Protein-level diagnostics are also evolving, with mass spectrometry-based proteomics enabling the detection of mutant p53 isoforms and associated binding partners. These methods allow for functional stratification of TP53 mutations by examining their interaction networks, such as binding to MDM2, p63, or DNA repair proteins. Functional assays that assess p53 transactivation capacity are being tested in specialized centers and may soon offer routine evaluation of the biological relevance of specific TP53 variants of uncertain significance (VUS).

In the Middle East, diagnostic implementation is gradually advancing. Cancer centers in countries like Saudi Arabia, Jordan, and the UAE have begun incorporating molecular panels that include TP53 into routine diagnostic algorithms. However, barriers remain, including cost constraints, limited access to genomic infrastructure, and a shortage of trained molecular pathologists. Collaborative regional initiatives, such as centralized genomic

labs and cancer registries with molecular annotations, could enhance accessibility and standardization across the region.

Efforts to harmonize diagnostic standards must also consider the cultural and logistical contexts of the Middle East. Strategies such as mobile testing units, tele-genetics consultations, and subsidized testing for high-risk families (e.g., Li-Fraumeni syndrome carriers) could help increase early detection rates. Furthermore, building region-specific TP53 mutation databases will be critical to interpreting novel variants and tailoring diagnostics to the genetic landscape of local populations.

In summary, emerging diagnostic approaches for TP53 mutations are transforming cancer care by enabling earlier detection, deeper molecular characterization, and personalized monitoring. From NGS and ctDNA to RNA signatures and AI-powered histopathology, these tools provide clinicians with a multidimensional view of p53 status. Integrating these innovations into Middle Eastern oncology practice requires infrastructural investment, cross-border collaboration, and culturally sensitive implementation strategies. This integration will be crucial in translating the molecular complexity of TP53 into actionable clinical outcomes.

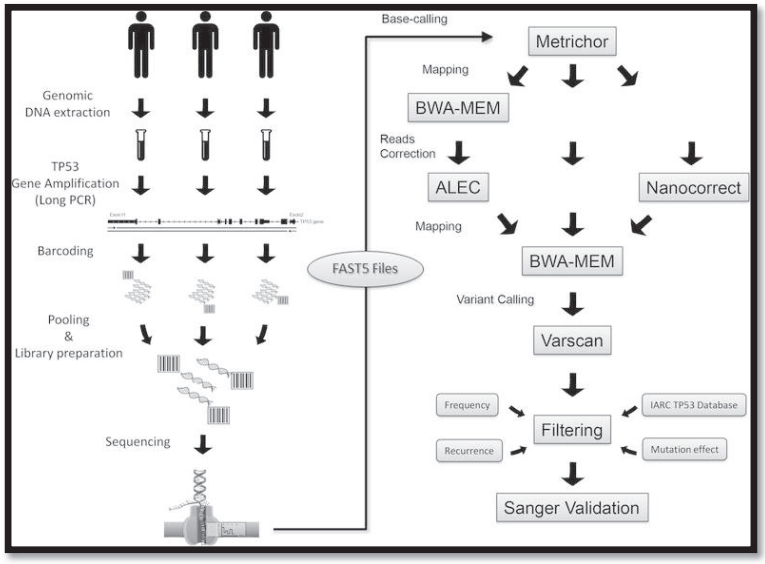


Figure (9) a schematic workflow for TP53 mutation detection and sequencing analysis (Avet-Loiseau et al., 2016)

Therapeutic Implications of P53 Mutations in Middle Eastern Cancer Patients

TP53, often described as the "guardian of the genome," plays a vital role in preserving genomic stability through the regulation of cell cycle arrest, apoptosis, senescence, and DNA repair mechanisms. In its mutated form, however, p53 not only loses its tumor-suppressive function but can also acquire oncogenic properties—altering how patients respond to therapy, influencing resistance mechanisms, and shaping disease trajectory. This has profound therapeutic implications, particularly in the Middle Eastern context, where unique environmental exposures, genetic structures, and healthcare delivery systems intersect.

Studies conducted across countries in the Middle East—including Saudi Arabia, Iraq, Egypt, Jordan, Lebanon, and Iran—have consistently documented a high frequency of TP53 mutations in major cancer types such as breast, colorectal, ovarian, and hematologic malignancies (Al-Qasem et al., 2018; Siraj et al., 2021; Fathi et al., 2018). The mutations are frequently missense and often localized to the DNA-binding domain, impairing p53's transcriptional regulatory functions. Importantly, these mutations correlate with high tumor grades, aggressive phenotypes, and early resistance to standard chemotherapeutic regimens.

From a therapeutic perspective, the presence of TP53 mutations diminishes the efficacy of several widely used anticancer agents. Drugs like cisplatin, doxorubicin, paclitaxel, and 5-fluorouracil function, at least in part, by triggering DNA damage that relies on p53-mediated apoptosis for their cytotoxic effect. When this pathway is disrupted, cancer cells exhibit reduced susceptibility, allowing tumor progression despite treatment. This explains, in part, the high relapse rates observed among patients with TP53 mutations in breast and colorectal cancer cohorts from Saudi Arabia, Jordan, and Iraq (Barakeh et al., 2021; Ibrahim et al., 2018; Al-Shamsi et al., 2023).

This chemoresistance presents a major clinical challenge. For example, breast cancer patients with TP53-mutant tumors—particularly those with triple-negative subtypes—respond poorly to neoadjuvant and adjuvant therapies, leading to lower pathologic complete response (pCR) rates and decreased overall survival. In colorectal cancer, TP53-mutant tumors demonstrate early resistance to fluoropyrimidine-based regimens, necessitating more aggressive combinations or early shifts to second-line options (Chan et al., 2005; Bishehsari et al., 2014).

Recent advances in targeted therapy development offer hope for overcoming these challenges. Molecules such as APR-246 (Eprenetapopt) aim to restore the wild-type conformation and function of mutant p53. Clinical trials conducted in Europe and North America have shown promising results in hematologic malignancies and ovarian cancers. However, in the Middle East, the integration of such agents remains limited due to lack of trial access, regulatory delays, and cost-related barriers. Nonetheless, several countries have begun participating in global research collaborations, with the United Arab Emirates, Qatar, and Saudi Arabia enrolling patients into international precision oncology trials (Dawood et al., 2024; Al-Sukhun et al., 2023).

Beyond reactivating p53, alternative approaches target its upstream and downstream pathways. MDM2 inhibitors block the interaction between p53 and its negative regulator, MDM2, thereby stabilizing and activating p53. These agents are particularly promising for tumors with wild-type TP53 that are functionally suppressed by MDM2 overexpression. Immunotherapies, too, are increasingly being studied in the context of p53 dysfunction, particularly as p53 mutations may generate neoantigens that enhance immune recognition. Combining checkpoint inhibitors with p53-modulating agents is an emerging strategy currently under preclinical and early clinical investigation.

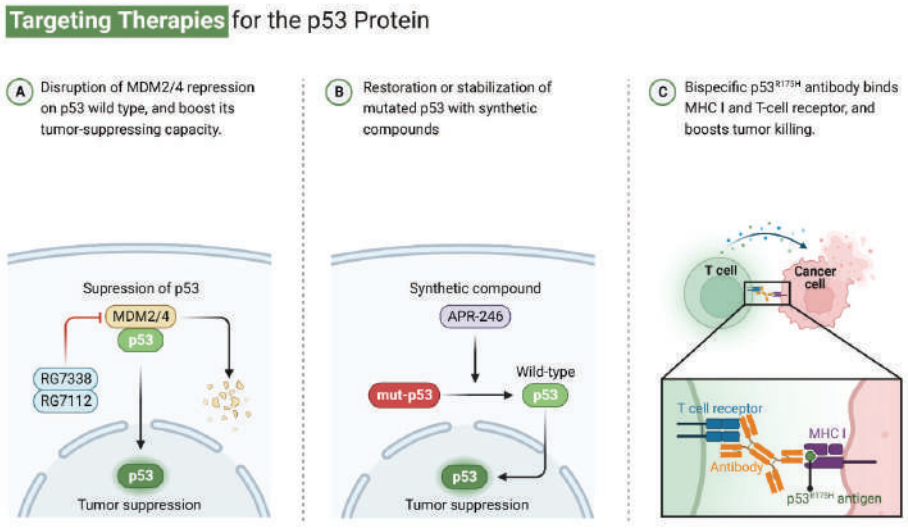
Liquid biopsy is also reshaping how TP53 mutations are detected and monitored in cancer patients. The use of circulating tumor DNA (ctDNA) provides a minimally invasive method to identify TP53 mutations at diagnosis and during treatment. This technique enables dynamic monitoring of treatment response, early detection of resistance, and detection of minimal residual disease. In regions where repeat tumor biopsies are culturally or logistically challenging, ctDNA-based tests represent a practical tool for longitudinal care, although their availability remains uneven across the Middle East (Parkinson et al., 2016; Dawood et al., 2024).

In clinical settings, awareness of TP53 mutation status is beginning to influence therapeutic decision-making. Some cancer centers in the Gulf Cooperation Council (GCC) countries and Lebanon have integrated TP53 screening into standard diagnostic panels for breast and hematological malignancies. Patients with TP53 mutations may be prioritized for more intensive surveillance or steered toward clinical trials when conventional options fail. Yet, implementation is not universal. In Iraq, Syria, and Yemen, limited access to molecular diagnostics and advanced therapeutics constrains

the translation of genetic insights into patient care (IHE Report, 2021; Abdel-Rahman, 2018).

Furthermore, the therapeutic implications of TP53 mutations cannot be viewed in isolation from broader socio-economic and public health dynamics. Delays in diagnosis, suboptimal adherence to treatment guidelines, fragmented oncology infrastructure, and regional disparities in drug access exacerbate the clinical impact of TP53 mutations. Addressing these systemic barriers is essential for optimizing outcomes in affected patients.

In conclusion, TP53 mutations significantly alter the therapeutic landscape of cancer care in the Middle East. Their presence reduces the efficacy of conventional treatments, necessitates novel targeted approaches, and requires sophisticated diagnostic tools for effective management. Although substantial challenges remain, the growing recognition of TP53 as a central biomarker in oncology is gradually transforming clinical protocols across the region. Expanding access to p53-targeted therapies, investing in regional research collaborations, and improving diagnostic infrastructure are critical steps toward personalized and effective cancer treatment for Middle Eastern populations.



Potential Strategies for Targeting the P53 Pathway in Middle Eastern Cancer Therapeutics

The P53 signaling pathway is among the most frequently disrupted systems in cancer. In the Middle East, the high prevalence of TP53 mutations across breast, colorectal, hematological, and lung malignancies underscores its relevance not only as a biomarker but as a therapeutic axis. The region's unique cancer patterns—driven by genetic, environmental, and healthcare dynamics—make targeted intervention on the P53 pathway both a necessary and timely direction for oncology advancement.

Effective therapeutic strategies must address the two major types of TP53 alterations:

- Loss-of-function mutations (which inactivate wild-type tumor suppressor activity)
- Gain-of-function mutations (which promote oncogenic properties such as metastasis and drug resistance)

Several pharmacological approaches are under development or early clinical testing, with a growing interest in adapting them to Middle Eastern clinical practice.

1. Restoration of Wild-Type p53 Function in Mutant Tumors

One promising strategy involves small molecules designed to refold and stabilize mutant p53 into its wild-type conformation. APR-246 (Eprenetapopt) is the most advanced agent in this class. It binds to cysteine residues in mutant p53, restoring its DNA-binding capacity and transcriptional activity. Although approved trials have largely taken place in North America and Europe, patients from Saudi Arabia, the UAE, and Lebanon have begun enrolling in multinational studies for acute myeloid leukemia and myelodysplastic syndrome. Incorporating such compounds into national cancer centers could give TP53-mutant patients—especially those with hematologic cancers or triple-negative breast cancer—access to therapies designed specifically for their tumor biology.

2. Targeting p53–MDM2 Interaction in Wild-Type TP53 Tumors

In tumors where TP53 is not mutated but functionally silenced through overexpression of MDM2 (a negative regulator of p53), a different therapeutic strategy is required. MDM2 inhibitors such as Nutlin-3a and

idasanutlin disrupt the p53–MDM2 interaction, allowing endogenous p53 to accumulate and induce apoptosis. These compounds are particularly relevant for tumors like liposarcoma and certain lymphomas. Given the relative availability of MDM2 overexpression data in Middle Eastern cohorts, and the ability to test this through IHC and gene panels, this approach could be piloted in large tertiary centers in the region with proper molecular profiling infrastructure.

3. Synthetic Lethality Approaches

In tumors with defective p53, alternative stress-response pathways become essential for survival. This creates vulnerabilities that can be therapeutically exploited—a concept known as synthetic lethality. For example:

- **WEE1 inhibitors** (e.g., adavosertib) impair G2/M checkpoint function, which p53-deficient cells rely on for DNA damage repair.
- **CHK1 inhibitors** target DNA replication stress, inducing mitotic catastrophe in TP53-mutant tumors.
- **PARP inhibitors**, although classically used in BRCA-mutant tumors, have shown activity in p53-deficient settings by exacerbating genomic instability.

These agents are particularly relevant for aggressive tumors such as triple-negative breast cancer and high-grade serous ovarian cancer—both prevalent and often p53-mutated in the Middle East. Pilot studies in Egypt, Jordan, and Kuwait have started evaluating WEE1 inhibitors in combination regimens, though large-scale application remains limited by access and cost.

4. Immunotherapeutic Strategies Involving p53 Neoantigens

Mutant p53 proteins can generate tumor-specific neoantigens that are presented on MHC class I molecules. These neoantigens offer a unique opportunity to develop:

- **p53-targeted vaccines** that stimulate T-cell responses
- **Bispecific antibodies** that bridge T cells to p53-mutant cancer cells
- **TCR-engineered therapies** against common hotspot mutations like R175H or R273C

While these approaches remain experimental, they represent a long-term opportunity for the Middle East to participate in or host early-phase

immunotherapy trials. Countries with advanced genomics and immunology research platforms—such as Qatar, the UAE, and Israel—are well-positioned to collaborate regionally on these programs.

5. p53-Based Stratification for Standard Therapy

Not all strategies require novel drugs. Incorporating p53 mutation status into existing treatment plans can optimize the use of current therapies. For instance:

- TP53-mutant patients may benefit from early intensification or switch to non-genotoxic agents.
- Patients with wild-type p53 may be selected for MDM2 inhibitors or radiation-sensitizing regimens.
- Real-time monitoring of p53 mutation burden via ctDNA can guide treatment continuation or escalation.

This requires building reliable molecular diagnostic services into public cancer care systems—a challenge in low-resource countries but achievable through regional collaboration and investment in training and infrastructure.

6. Integrative Molecular Tumor Boards and National Guidelines

To translate these strategies into practice, Middle Eastern health ministries and cancer centers should establish integrative molecular tumor boards that include oncologists, molecular pathologists, and genetic counselors. These boards would use TP53 status, among other biomarkers, to develop personalized treatment plans. National cancer guidelines should also incorporate p53 testing for certain high-impact cancers (e.g., breast, colorectal, lung) and specify therapeutic paths based on mutation type.

Targeting the P53 pathway in Middle Eastern cancer care is not only a scientific opportunity—it is a regional necessity. With high TP53 mutation frequencies, limited access to advanced therapies, and rising cancer incidence, the integration of pathway-specific interventions could reshape treatment outcomes. A comprehensive strategy should include pharmacological innovation, improved access to molecular diagnostics, integration into clinical workflows, and participation in international trials. Bridging these gaps requires sustained commitment at clinical, institutional, and policy levels—but the potential survival benefits make it an urgent and actionable goal.

Impact of P53 Dysfunction on Cancer Prognosis and Treatment Outcomes

The TP53 gene is often described as the cornerstone of the cellular defense against malignant transformation. Its product, the p53 protein, orchestrates a range of responses to genomic instability—arresting the cell cycle, initiating repair pathways, triggering apoptosis, or inducing senescence depending on cellular context and damage severity. When p53 is functionally impaired—either by mutation, deletion, or regulatory suppression—these protective responses collapse. The implications of this dysfunction are profound. Across nearly all tumor types, TP53 mutations correlate with higher malignancy grades, more aggressive phenotypes, therapeutic resistance, and poor prognosis.

In the Middle East, where unique environmental exposures, healthcare disparities, and genetic factors contribute to cancer profiles, p53 dysfunction further compounds clinical challenges. Numerous studies from countries like Egypt, Iraq, Saudi Arabia, and Iran have demonstrated not only high frequencies of p53 alterations but also their association with treatment failure and early mortality. Understanding the clinical consequences of p53 dysfunction is essential for refining both prognostic stratification and therapeutic decision-making.

Prognostic Implications Across Cancer Types

The prognostic value of p53 dysfunction has been established in multiple cancers prevalent in the Middle East:

- **Breast Cancer**: In studies from Lebanon, Jordan, and the Gulf States, TP53 mutations were significantly associated with triple-negative breast cancer (TNBC) and basal-like subtypes, which lack targeted therapies and exhibit rapid progression. Patients harboring TP53 mutations had shorter disease-free and overall survival (Al-Qasem et al., 2011; Al-Shamsi et al., 2023).
- **Colorectal Cancer (CRC)**: Research from Iran and Saudi Arabia indicates that TP53 mutations in CRC correlate with poor differentiation, lymphovascular invasion, and early metastasis. The co-occurrence of TP53 mutations with KRAS or BRAF mutations further worsens prognosis by disrupting multiple signaling pathways (Fathi et al., 2018; Barakeh et al., 2021).

- **Lung and Gastric Cancers**: Data from Iraq, Yemen, and Iran show that TP53 dysfunction is frequent in squamous cell carcinomas of the lung and intestinal-type gastric adenocarcinomas. These mutations are linked to advanced stage at diagnosis, poor response to platinum-based chemotherapy, and reduced overall survival (Rahman et al., 2019; Ghojazadeh et al., 2022).
- **Hematologic Malignancies**: In acute myeloid leukemia (AML), TP53 mutations predict refractoriness to standard chemotherapy and higher relapse rates. Such patients are considered for stem cell transplantation or inclusion in trials for novel agents, including p53 reactivators and BCL-2 inhibitors (Prokocimer et al., 2017).

Mechanisms Underlying Poor Outcomes

P53 dysfunction influences prognosis through multiple biological mechanisms:

- **Defective Apoptosis**: Without functional p53, damaged cells continue proliferating instead of undergoing programmed death, leading to treatment resistance and tumor progression.
- **Impaired DNA Repair**: p53 controls key repair genes like GADD45, XPC, and p21. When p53 is mutated, unrepaired DNA damage accumulates, increasing mutation burden and tumor heterogeneity—two factors strongly associated with poor outcomes.
- **Stemness and EMT Promotion**: Some mutant p53 proteins actively promote epithelial-mesenchymal transition (EMT) and cancer stem cell expansion, facilitating invasion and distant metastasis. This gain-of-function phenotype has been confirmed in Middle Eastern breast and gastric cancers (Babamohamadi et al., 2022).
- **Immunosuppression**: Mutant p53 reshapes the tumor microenvironment by promoting immune evasion, reducing antigen presentation, and upregulating immune checkpoints. This may explain reduced responses to immune checkpoint inhibitors in some TP53-mutant tumors, despite high tumor mutation burden (Chen et al., 2022).

Impact on Treatment Outcomes

Therapeutic efficacy is heavily influenced by p53 status:

- **Chemotherapy**: Many chemotherapeutic agents, such as cisplatin, 5-FU, and doxorubicin, rely on intact p53-mediated apoptosis to kill cancer cells. In TP53-mutant tumors, intrinsic resistance is common, necessitating dose intensification or alternate drugs. For example, TP53-mutant colorectal cancer patients show suboptimal responses to FOLFOX regimens (Torre et al., 2015).
- **Radiation Therapy**: Radiotherapy effectiveness depends on p53-mediated cell cycle arrest and apoptosis in response to DNA damage. TP53 mutations impair this response, often requiring escalated doses, which may not be feasible due to toxicity.
- **Targeted Therapy and Hormonal Therapy**: TP53 status may alter responsiveness to therapies like EGFR inhibitors or tamoxifen. Some breast cancers with wild-type p53 respond better to hormonal manipulation, while mutant variants do not benefit significantly (Miller et al., 2005).
- **Immunotherapy**: Despite expectations that TP53-mutant tumors may respond better due to higher neoantigen load, outcomes remain mixed. This might reflect the immunosuppressive roles of some p53 mutations and the complex interplay between p53, PD-L1 expression, and tumor-infiltrating lymphocytes.

Regional Challenges and Gaps

In the Middle East, several issues complicate efforts to mitigate the impact of p53 dysfunction:

- **Limited Molecular Profiling**: Many cancer centers lack routine TP53 testing, especially in public health systems. This delays prognostic assessment and impairs personalized treatment planning.
- **Delayed Diagnosis**: Because cancers are often diagnosed at advanced stages, TP53 mutations may already have driven aggressive, treatment-refractory phenotypes.
- **Access Inequity**: Therapies tailored to TP53 status, such as WEE1 inhibitors or p53 reactivators, are either unavailable or unaffordable in most Middle Eastern countries.

- **Population-Specific Data Deficits**: Few large-scale genomic studies have been conducted in Middle Eastern populations, leading to an overreliance on Western datasets, which may not fully reflect regional mutation patterns and therapy responses.

Toward Integration in Clinical Practice

Despite these challenges, p53 dysfunction should be considered a core component of oncology protocols in the region. Strategies to integrate this knowledge include:

- Establishing **TP53 mutation screening** in high-prevalence cancers
- Using p53 status to **stratify patients** in clinical trials
- Training oncologists and pathologists on **p53-informed treatment planning**
- Encouraging **multinational collaborations** to validate region-specific prognostic models

The dysfunction of p53 not only facilitates tumorigenesis but also disrupts therapeutic control, making it a decisive factor in prognosis and treatment outcome. In the Middle East, its clinical relevance is amplified by regional risk factors, late-stage presentation, and limited molecular infrastructure. Bridging this gap requires a combination of diagnostic innovation, education, policy reform, and international partnership. Recognizing and addressing p53 dysfunction must be central to any comprehensive strategy for improving cancer outcomes in the region.

Regulation of Mutant P53 Expression in Middle Eastern Cancer Patients

Mutations in the TP53 gene—recognized as the most frequently mutated gene in human cancers—result not only in the loss of its tumor-suppressive functions but also in the aberrant accumulation of mutant p53 protein with novel oncogenic properties. These gain-of-function (GOF) activities include promoting proliferation, invasion, metastasis, immune evasion, and drug resistance. Understanding how mutant p53 expression is regulated in cancer patients is essential to developing therapeutic strategies, especially in regions like the Middle East where distinct genetic backgrounds, lifestyle exposures, and environmental conditions may influence regulatory dynamics.

In Middle Eastern cancer populations, the regulation of mutant p53 expression appears to be shaped by a complex interplay of genomic mutations, transcriptional control, post-transcriptional mechanisms (such as non-coding RNAs), and proteasomal degradation pathways. These layers of regulation contribute to the stabilization and overexpression of dysfunctional p53 proteins, which are commonly detected in tumors across the region via immunohistochemistry (IHC), next-generation sequencing (NGS), and RT-qPCR.

Genomic and Transcriptional Regulation

Mutant p53 overexpression often stems from missense mutations within the DNA-binding domain of TP53. These mutations are frequently reported in breast, colorectal, lung, gastric, and hematological cancers in countries such as Iraq, Egypt, Iran, and Saudi Arabia. These hotspots include codons R175, R248, and R273, which not only abrogate DNA binding but also induce conformational instability, resulting in nuclear accumulation of the protein.

In these populations, the frequency of specific mutations varies slightly from global trends, suggesting potential founder effects or population-specific exposures. Studies from Iraq and Jordan have noted a high prevalence of G:C > A:T transitions—mutations associated with oxidative DNA damage, possibly linked to environmental pollutants and dietary nitrosamines. These mutations are strongly correlated with p53 protein stabilization, as mutant p53 evades MDM2-mediated degradation and persists in the cell nucleus.

Transcriptional regulation of the TP53 gene is modulated by several upstream transcription factors and chromatin remodeling proteins. In Middle Eastern patients, dysregulation of oncogenic pathways—such as MYC

amplification or PI3K/AKT activation—has been reported to drive enhanced transcription of mutant TP53. This is particularly evident in colorectal and gastric cancers, where chromosomal instability and epigenetic modifications are common.

Post-Transcriptional Regulation: Role of Non-Coding RNAs

A growing body of evidence highlights the role of non-coding RNAs, especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), in regulating mutant p53 expression. Specific miRNAs—such as miR-34a, miR-504, and miR-125b—are known to target TP53 transcripts or modulate its downstream effectors.

In cancer samples from Egypt and Lebanon, reduced expression of p53-regulatory miRNAs has been observed in tumors with mutant TP53. For example, miR-34a, a known transcriptional target of wild-type p53 that also suppresses p53 inhibitors, is frequently downregulated in hepatocellular carcinoma and breast cancer. This creates a feedback loop where the loss of wild-type p53 suppresses miR-34a, which in turn removes inhibitory control over mutant p53 translation and activity.

In parallel, overexpression of oncogenic lncRNAs such as HOTAIR and MALAT1—reported in breast and colorectal cancers from Saudi and Iranian cohorts—may also enhance mutant p53 protein expression by modulating chromatin accessibility or interacting with RNA-binding proteins that stabilize the mutant mRNA.

Post-Translational Modifications and Protein Stabilization

Once translated, the stability of mutant p53 protein is regulated by post-translational modifications and the ubiquitin-proteasome system. Under normal physiological conditions, wild-type p53 is rapidly degraded via MDM2-mediated ubiquitination. However, most mutant p53 proteins acquire resistance to MDM2, resulting in prolonged half-life and high intracellular accumulation.

In Middle Eastern cancer patients, this accumulation is frequently observed through IHC as intense nuclear staining. Interestingly, co-mutations or pathway alterations—such as MDM2 amplification or loss of ARF—further impair mutant p53 degradation. Environmental exposures prevalent in the region, including polycyclic aromatic hydrocarbons (from oil industry emissions) and dietary carcinogens (e.g., aflatoxins), are known to induce

such pathway disruptions and may indirectly contribute to mutant p53 stabilization.

Moreover, molecular chaperones like HSP90 and HDAC6, which protect mutant p53 from degradation, are often overexpressed in aggressive tumors. Studies in Middle Eastern gastric and lung cancers have reported high levels of HSP90, suggesting a protective effect that allows continued oncogenic signaling from the mutant protein. Inhibitors of HSP90 have shown promise in destabilizing mutant p53 and restoring apoptotic sensitivity—an approach that may be relevant for clinical translation in the region.

Epigenetic Modulation

Aberrant methylation of TP53 promoter regions and enhancer elements can also influence its expression. In certain hematologic malignancies from Egyptian and Iranian patients, hypermethylation of regulatory regions has been associated with suppressed wild-type TP53 expression, favoring the selection and expansion of mutant clones. Additionally, histone modifications affecting TP53 gene accessibility have been linked to mutant p53 overexpression, particularly in aggressive and late-stage tumors.

Clinical Implications

Understanding how mutant p53 expression is regulated in Middle Eastern patients has direct clinical relevance. Overexpression of stabilized mutant p53 protein is not only a marker of poor prognosis but also predicts resistance to conventional therapies such as chemotherapy and radiation. Therapeutic strategies that target regulatory elements—such as miRNA mimics, HDAC inhibitors, or proteasome-targeting agents—offer potential routes for modulating p53 activity in a tumor-specific manner.

Furthermore, stratifying patients based on mutant p53 expression—detected via IHC, liquid biopsy, or molecular profiling—could guide treatment decisions. For example, high mutant p53 expression may warrant early intervention with p53-modulating compounds like APR-246 or WEE1 inhibitors. Regional adoption of such molecular stratification protocols remains limited, but early pilot programs in the UAE and Saudi Arabia have demonstrated feasibility in integrating p53 diagnostics into personalized oncology workflows.

The regulation of mutant p53 expression in Middle Eastern cancer patients is governed by a multi-tiered network of genetic, epigenetic, and

environmental factors. The widespread overexpression of mutant p53 in this region's cancers highlights both the severity of its impact on tumor progression and the urgent need for targeted therapeutic interventions. Comprehensive research into these regulatory mechanisms—particularly in underrepresented populations—will be critical to advancing precision medicine and improving patient outcomes in the Middle East.

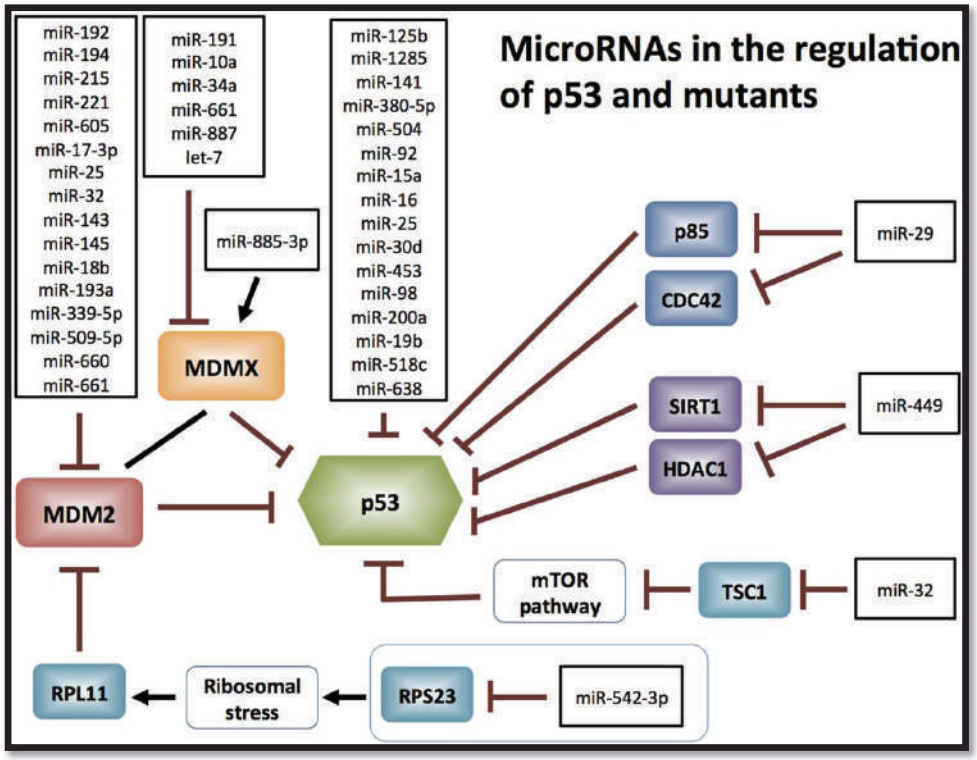


Figure (10) MicroRNA-Mediated Regulation of p53 and Mutant p53 Stability (Dey et al., 2015)

Chapter 5: Regional Healthcare, Gaps, and Future Directions

Current Challenges and Gaps in P53 Research in the Middle East

Despite global advancements in cancer genomics and personalized oncology, TP53-related cancer research in the Middle East continues to lag behind. The burden of cancer in this region is increasing, yet significant gaps in local research capacity, infrastructure, and clinical application hinder progress. These challenges reflect a combination of systemic, scientific, and socioeconomic barriers that limit the region's contribution to global p53 research and restrict patient access to targeted diagnostics and therapies.

One major challenge is the scarcity of large-scale genomic databases specific to Middle Eastern populations. Most available p53 mutation data originate from Western cohorts, making it difficult to understand region-specific mutational patterns, frequencies, and clinical associations. Studies from countries like Saudi Arabia, Iraq, Iran, and Egypt show that TP53 mutations vary significantly across populations, influenced by ethnic background, environmental exposure, and lifestyle factors (Al-Qasem et al., 2018; Siraj et al., 2021). However, the lack of comprehensive biobanks, standardized data collection protocols, and centralized research networks means these findings remain fragmented, underutilized, and poorly integrated into regional healthcare systems.

Clinical translation of p53 findings into diagnostics and therapies is also underdeveloped. Many healthcare centers in the region lack access to advanced molecular diagnostics like next-generation sequencing (NGS), which is essential for precise mutation profiling. Immunohistochemistry (IHC), still the dominant diagnostic method in many Middle Eastern laboratories, is limited in detecting specific p53 mutations and does not provide functional insights. As a result, many patients do not undergo comprehensive molecular testing, leading to missed opportunities for early intervention or targeted therapy.

Another critical gap is the insufficient investment in translational research linking TP53 mutations with treatment outcomes. Few Middle Eastern clinical trials explore the role of p53 mutations in predicting response to chemotherapeutic agents, radiotherapy, or emerging p53-targeting drugs. This gap is particularly problematic for populations with unique genetic polymorphisms, such as the Arg72Pro variant, which may influence therapeutic response but remains poorly studied in the region (Akhter, 2019; Fischer et al., 2023).

Human capital is also a limiting factor. Many universities and research centers lack adequately trained molecular oncologists, genomic scientists, and bioinformaticians. Where local expertise exists, it is often fragmented across institutions without effective collaboration or funding mechanisms. International partnerships, though growing, are not sufficiently leveraged to address local research needs. Political instability, conflict, and economic crises in several Middle Eastern countries further disrupt scientific research and limit funding opportunities.

Ethical, cultural, and regulatory barriers compound these issues. In many societies, genetic testing is associated with stigma or fear, especially in the context of hereditary cancer syndromes like Li-Fraumeni. Legal frameworks for genetic data privacy, patient consent, and research ethics are either underdeveloped or inconsistently enforced. This makes patient recruitment and long-term cohort studies more difficult, contributing to a lack of longitudinal data on p53-related cancer outcomes.

Finally, publication bias and underreporting pose obstacles to global visibility. Many high-quality studies conducted in the region are published in local journals with limited international access or fail to reach peer-reviewed platforms due to language, funding, or editorial constraints. As a result, regional insights into p53 biology and cancer epidemiology remain underrepresented in global cancer databases and systematic reviews.

Addressing these gaps requires a coordinated strategy that includes:

- Establishing national and regional cancer genomics registries
- Expanding access to molecular diagnostic tools
- Encouraging interdisciplinary collaborations across institutions and borders
- Training the next generation of researchers in cancer genomics
- Creating culturally sensitive public awareness campaigns about genetic testing
- Implementing clear policies on data governance and patient consent

By resolving these structural and scientific deficiencies, Middle Eastern countries can contribute more effectively to global p53 research and ensure that patients in the region benefit from precision medicine approaches tailored to their unique genetic and environmental contexts.

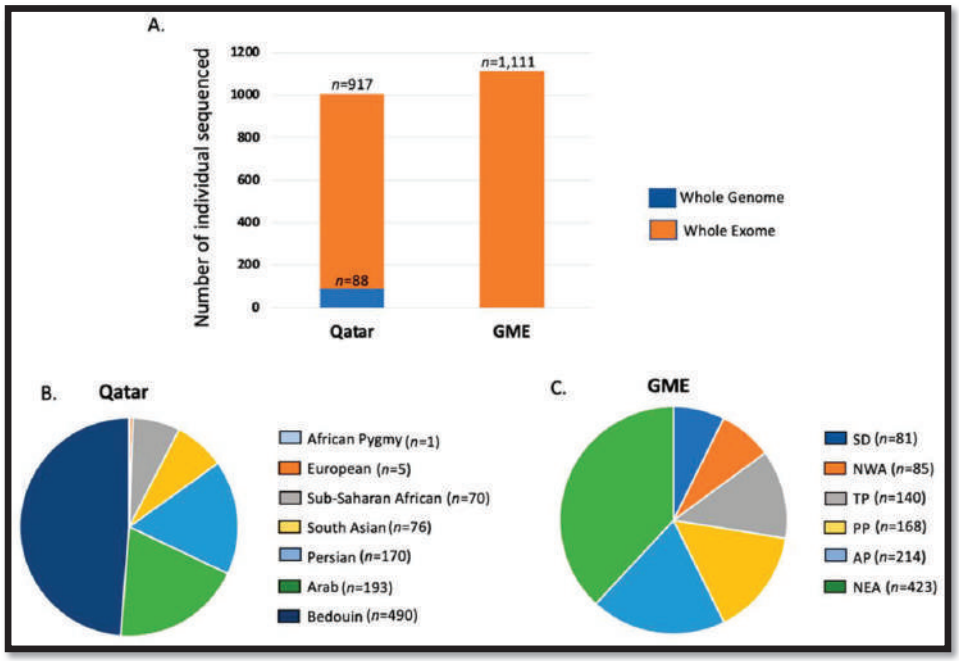


Figure (11) Representation of Middle Eastern vs. global genomic variant data (Fakhro et al., 2022)

Cancer Care and Management Strategies in the Middle East

Cancer care in the Middle East presents a complex and evolving challenge shaped by unique regional factors. These include a rising cancer burden, late-stage diagnoses, limited screening programs, restricted access to advanced diagnostics and therapeutics, and disparities in healthcare infrastructure. Addressing these challenges requires regionally tailored strategies grounded in evidence-based medicine and supported by public health policy.

Cancer incidence is steadily increasing in the Middle East due to multiple factors: demographic changes, increased life expectancy, lifestyle transitions, and environmental exposures (Abdel-Rahman, 2018; Bazarbashi et al., 2021). The most common cancers—breast, colorectal, lung, liver, and bladder—vary in frequency across countries, but all share a common trend: patients are often diagnosed at an advanced stage (Al-Madouj et al., 2020). This pattern results in higher mortality rates and increased treatment costs, as curative interventions are less effective at later stages.

One of the core deficiencies in Middle Eastern cancer care is limited early detection infrastructure. National screening programs for breast, colorectal, and cervical cancers remain underdeveloped or poorly utilized in many countries. In some Gulf states and North African nations, screening exists but faces low uptake due to limited public awareness, cultural stigma, and fear of diagnosis (Shams et al., 2022; Al-Shamsi et al., 2023). Furthermore, disparities in rural versus urban access to care aggravate inequities in early intervention.

Therapeutic approaches often reflect uneven access to standard-of-care treatments. While some urban centers in wealthier countries have adopted advanced therapies such as immunotherapy, precision medicine, and robotic surgery, many public hospitals across the region still rely on basic chemotherapy and radiation protocols (IHE Report, 2021). Drug availability, reimbursement challenges, and reliance on imported medical technologies slow the integration of innovative treatment modalities. Additionally, the use of biomarker testing (e.g., HER2, KRAS, TP53) is not consistently available or financially feasible, despite its importance in personalizing therapy.

Oncology workforce shortages pose another barrier. The number of trained oncologists, oncology nurses, pathologists, and radiologists remains insufficient across many countries, with centralized services concentrated in major cities. This leads to delayed referrals, diagnosis, and initiation of therapy. Continuing medical education and subspecialty training in oncology remain limited in several health systems, stalling adoption of modern treatment protocols (Silbermann et al., 2013; Mukherji et al., 2020).

Palliative care, though increasingly recognized, still suffers from underdevelopment. Most Middle Eastern nations lack dedicated palliative care units, pain management protocols, and psychological support services. This neglect has a profound impact on the quality of life of terminally ill patients and their families (Bingley & Clark, 2009).

Efforts are underway to address these gaps. Some countries have launched national cancer control strategies integrating prevention, early detection, treatment, and survivorship. Regional collaborations such as the Middle East Cancer Consortium (MECC) have supported training programs and data-sharing efforts to strengthen regional cancer care standards (Silbermann et al., 2011). Telemedicine and cross-border collaborations are emerging as supplementary models to improve accessibility and share expertise.

Investment in national cancer registries is improving epidemiological surveillance, which supports resource allocation and policy decisions. However, data quality and completeness remain inconsistent, especially regarding molecular profiles of cancer patients, such as TP53 mutation status.

Improving cancer care in the Middle East demands a multilayered approach. Priority areas include:

- Scaling up population-based screening programs
- Strengthening oncology education and workforce development
- Expanding access to diagnostic and treatment technologies
- Integrating personalized medicine through molecular diagnostics
- Enhancing cancer registries and genomic databases
- Improving equity in rural and underserved populations
- Institutionalizing supportive and palliative care services

Overall, the complexity of cancer care in the Middle East requires solutions sensitive to cultural, economic, and infrastructural contexts. Sustainable improvements will depend on regional investment, public awareness, research integration, and the adoption of multidisciplinary, patient-centered care models.

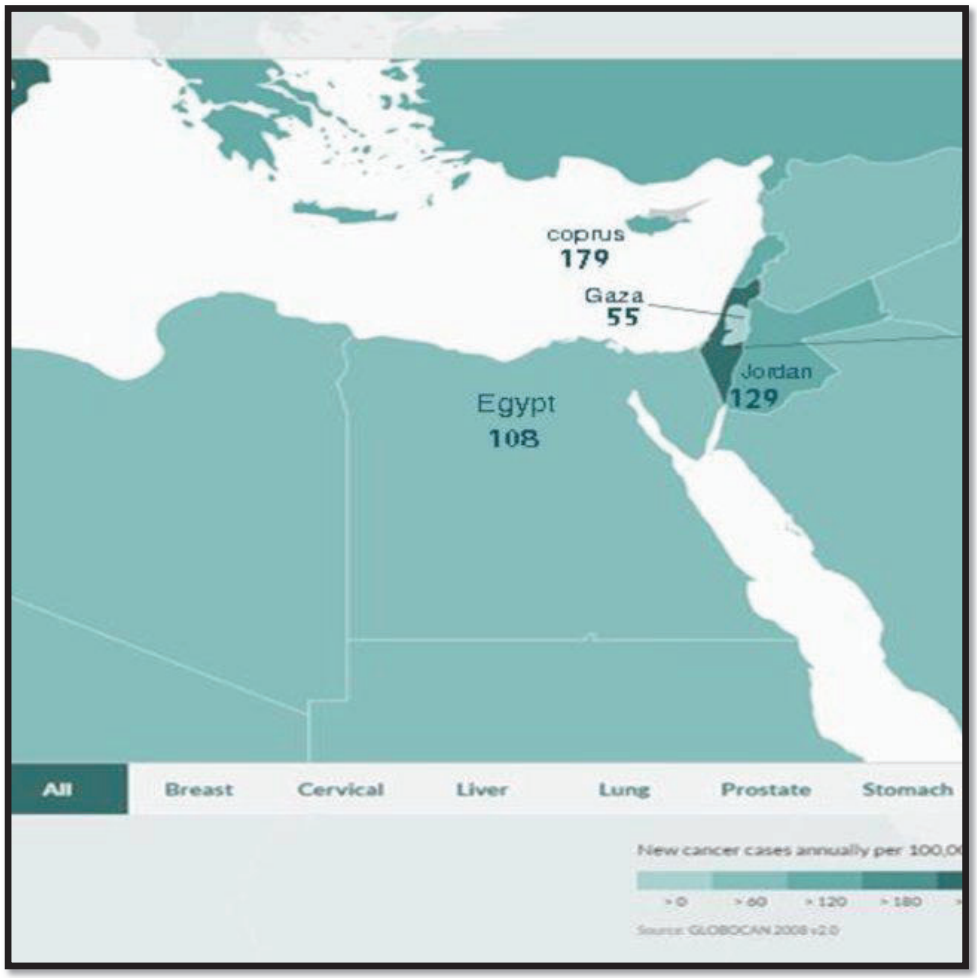


Figure (12) Cancer Incidence Rates in Middle Eastern Communities (2008) (Akhtar et al., 2018)

Public Health Strategies for Cancer Prevention and Awareness in the Middle East

Public health strategies for cancer prevention in the Middle East have evolved in response to rising cancer incidence and mortality, especially with increasing rates of breast, colorectal, and lung cancers. These strategies vary across countries but generally center around risk factor modification, early detection, public awareness campaigns, vaccination programs, and capacity building in screening services.

One of the main approaches has been health education campaigns focused on modifiable risk factors such as tobacco use, obesity, poor diet, and physical inactivity. The World Health Organization (2010) emphasized that the Eastern Mediterranean Region continues to struggle with a high prevalence of preventable cancer risk factors, many of which are linked to lifestyle changes over the past two decades. Ministries of health in countries like Jordan, Saudi Arabia, and Egypt have integrated smoking cessation programs and national non-communicable disease action plans that address cancer prevention as a key objective (Al-Mandhari, 2021).

Screening programs remain limited in coverage but have been prioritized in high-risk cancers like breast and cervical cancer. For instance, Saudi Arabia and the United Arab Emirates have implemented mammography programs for women above 40, with varying degrees of participation. However, challenges remain regarding access in rural areas, sociocultural reluctance to screening, and lack of health literacy (Silbermann et al., 2013). Studies in Oman, Bahrain, and Iraq suggest that many individuals have limited awareness of early signs and risk factors for cancer, leading to late-stage diagnosis and reduced treatment success (Al-Azri et al., 2014; Mohamed et al., 2025).

Public awareness campaigns supported by international and regional collaborations have helped break social taboos around cancer. Events such as World Cancer Day are increasingly marked by media campaigns, school-based education, and NGO outreach. Social media platforms have also emerged as effective tools for promoting early detection and destigmatizing the disease, especially among younger populations.

Vaccination programs, especially for hepatitis B and human papillomavirus (HPV), are being expanded. For example, the Gulf states have introduced national HPV immunization programs targeting adolescent girls, but uptake

varies and is affected by misinformation, lack of public trust, and cultural barriers. Addressing these through targeted education is a continuing challenge.

There are also region-specific initiatives like the Middle East Cancer Consortium (MECC), which promotes data-sharing, collaborative research, and harmonization of public health policies. MECC has helped build cancer registries and trained local personnel in epidemiology and prevention.

However, gaps remain. Many countries lack updated national cancer control plans. There is a shortage of trained public health professionals, limited integration between primary care and oncology services, and insufficient funding. Rural populations are especially underserved, with late-stage diagnoses more common in these areas.

Investing in nationwide education campaigns, decentralizing cancer screening services, and ensuring culturally sensitive communication are critical. Public-private partnerships and international funding can accelerate progress in raising awareness and improving early detection.

To meet long-term goals, regional strategies must also include:

- Monitoring of public attitudes through population-based surveys
- Developing culturally adapted health promotion materials
- Scaling mobile screening units to underserved areas
- Strengthening school health curricula to introduce cancer literacy early

The success of these strategies depends on political commitment, regional cooperation, and community engagement. Without widespread awareness and preventive action, the cancer burden in the Middle East will continue to rise despite advances in treatment technologies.

Future Directions in P53 Research for Personalized Medicine

The landscape of p53 research is rapidly expanding as precision oncology moves toward personalized treatment based on individual genetic profiles. In the context of the Middle East, future directions must focus on integrating genomic data, population-specific mutations, and ethnic diversity into clinical protocols. This integration holds potential to enhance diagnostic accuracy, tailor therapy, and improve prognosis.

A major future direction lies in **deep sequencing and mutation mapping** of TP53 across diverse Middle Eastern ethnic groups. Studies have shown regional variability in TP53 mutation spectra (Fathallah et al., 2023; Siraj et al., 2021), highlighting the importance of building large, well-annotated genomic databases representative of Arab populations. National and cross-border biobanks should collect TP53 status alongside environmental, dietary, and behavioral factors to clarify context-specific mutational trends.

Functional analysis of mutant p53 variants is another priority. Not all mutations confer the same phenotypic effects; some result in complete loss-of-function while others exhibit gain-of-function oncogenicity. Dissecting the biochemical behavior of prevalent mutations such as R175H, R248Q, and R273C in Middle Eastern patients will help determine their role in disease progression, therapy resistance, and immune modulation (Chen et al., 2022; Babamohamadi et al., 2022).

Personalized therapy also requires **companion diagnostic tools** capable of identifying p53 status in real time. Liquid biopsy approaches, especially circulating tumor DNA (ctDNA) assays, can be optimized for TP53 mutation detection in Middle Eastern cancers (Parkinson et al., 2016). These assays enable dynamic monitoring of treatment response and early detection of relapse, especially in breast, colorectal, and lung cancers, which are highly prevalent in the region.

The rise of **targeted therapeutics** such as APR-246, which reactivates wild-type functions in mutant p53, offers promise. However, its efficacy may depend on the specific TP53 mutation and cellular context. Therefore, clinical trials in Middle Eastern cohorts are essential to assess mutation-drug response relationships and define population-specific therapeutic windows.

Artificial intelligence and machine learning will likely play a significant role in modeling p53-related pathways. Integrating TP53 mutational data

with transcriptomic, proteomic, and epigenomic profiles can help generate predictive algorithms for treatment decisions. For example, AI can be trained to identify p53-driven resistance patterns to chemotherapy or immunotherapy based on patient datasets from Saudi Arabia, Iraq, Lebanon, and beyond (Rocca et al., 2022; Jayawickrama et al., 2024).

Integration into national cancer plans is also necessary. Most Middle Eastern countries still lack frameworks for implementing personalized medicine at scale. National policies must promote genetic testing accessibility, clinician training in genomics, and ethical data governance to ensure equitable distribution of benefits.

Another emerging area is the **study of germline TP53 mutations**, especially in hereditary cancer syndromes like Li-Fraumeni. Increasing germline screening will enable early interventions and familial risk counseling, currently limited in many Arab healthcare systems (Siraj et al., 2021; Al-Sukhun et al., 2023).

To support these directions, collaborative regional initiatives—such as a Middle East TP53 Consortium—can pool resources and standardize research protocols. This would foster multicenter studies, ensure population diversity, and accelerate translation of findings into clinical practice.

In summary, future p53 research must address:

- Ethnically relevant TP53 mutation databases
- Functional mutation stratification
- Real-time diagnostics like ctDNA
- Targeted reactivator trials
- Germline screening programs
- AI-driven mutation modeling
- Policy frameworks for clinical genomics

By aligning molecular discoveries with regional healthcare infrastructure, p53 research can play a transformative role in Middle Eastern personalized oncology.

Discussion and Implications for Regional Cancer Control

Cancer control strategies in the Middle East must evolve alongside regional insights into molecular oncology, particularly TP53-related mechanisms. The p53 protein remains a central focus for understanding cancer initiation, progression, and therapeutic response. Its dysfunction is deeply tied to high rates of tumorigenesis in breast, colorectal, lung, and hematological malignancies across Arab populations (Fathallah et al., 2023; Siraj et al., 2021).

The integration of TP53 mutation research into regional cancer control plans is not only feasible—it is necessary. Many Arab countries still operate under generalized treatment protocols lacking genetic stratification. This limits treatment efficacy and increases healthcare costs due to trial-and-error chemotherapy or late-stage diagnosis. Recognizing that p53 mutations are frequent and heterogenous among Middle Eastern patients should compel health ministries and oncology networks to promote routine molecular profiling.

From an epidemiological standpoint, TP53 mutational data provide critical information on **cancer burden and trends**. For instance, the overrepresentation of hotspot mutations in breast and colorectal cancers among Arab populations could explain patterns of early-onset disease or aggressive progression (Al-Qasem et al., 2011; Barakeh et al., 2021). Incorporating this knowledge into cancer registries enhances forecasting models, allowing more targeted screening initiatives and preventive strategies.

The **implications for public health** are profound. TP53 analysis in high-risk populations can guide early detection policies. For example, programs for young women with familial cancer syndromes could be designed based on regional germline mutation rates. Simultaneously, educational campaigns that connect lifestyle risk factors—like tobacco use, diet, or environmental exposure—to p53 dysfunction could increase awareness and encourage participation in screening.

In clinical oncology, the rising accessibility of **liquid biopsy and next-generation sequencing** allows detection of TP53 mutations even in non-invasive samples (Parkinson et al., 2016). This opens new possibilities for real-time monitoring, precision drug selection, and patient stratification in

clinical trials. National policies must incentivize the use of such diagnostics in tertiary hospitals and cancer centers.

Capacity building is another critical issue. Most Middle Eastern nations lack sufficient trained personnel, infrastructure, and research frameworks for translating p53 research into practice. Investment in genomic literacy among physicians, molecular pathologists, and healthcare workers is essential. Public-private partnerships can accelerate the development of affordable p53 diagnostic kits adapted for regional mutation profiles.

The **implications for therapeutic innovation** are equally important. Targeted therapies—like MDM2 inhibitors or mutant p53 reactivators—are in various stages of development. Their success in the Middle East depends on understanding mutation-specific drug responses. Countries must prioritize funding and regulatory pathways for clinical trials involving Middle Eastern populations, ensuring their representation in global therapeutic advancements.

Furthermore, the **policy landscape** must address disparities in access. Genomic testing and personalized treatments are often limited to wealthier urban centers, leaving rural and low-income patients underserved. National cancer control strategies must include mechanisms for equitable distribution, such as subsidized molecular testing or regional centers of excellence in cancer genomics.

The broader **regional collaboration** will be key. Shared databases, cross-border clinical trials, and multicenter research programs can pool expertise and standardize protocols. Initiatives like the Arab Genome Program and GCC-wide cancer consortia offer platforms to unify TP53-focused efforts.

In summary, the research on TP53 mutations offers actionable insights for cancer control strategies in the Middle East. These include:

- Incorporating molecular profiling into screening and treatment
- Guiding public health campaigns using mutation-risk correlations
- Expanding infrastructure for p53 diagnostics
- Training the oncology workforce in genomics
- Supporting region-specific clinical trials and targeted therapies
- Ensuring equity in access and representation

If implemented, these actions could significantly reduce cancer mortality and improve quality of care across the region.

TP53 mutations are more prevalent in Middle Eastern cancer patients compared to their Western counterparts. **Figure 1**3 presents the comparative prevalence of *TP53* mutations in breast, lung, colorectal, and liver cancers between the two regions (Fathallah et al., 2023).

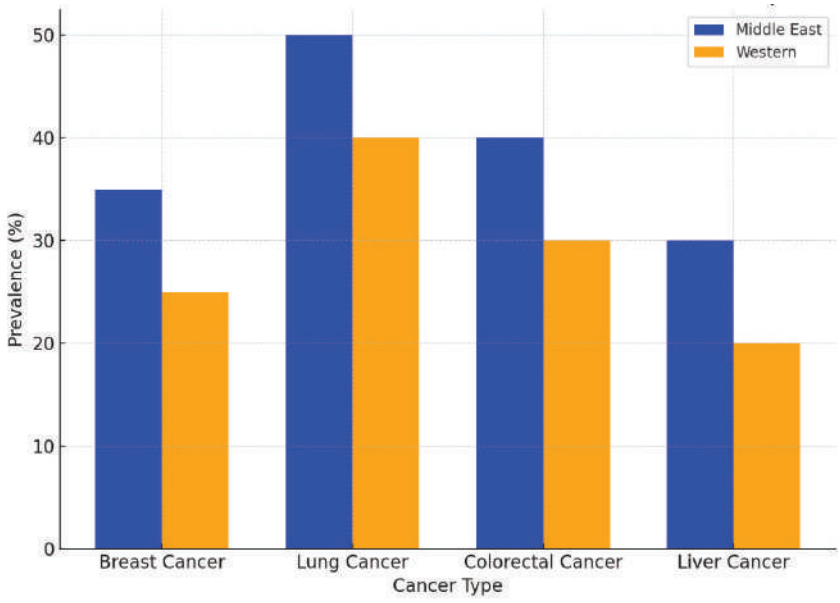


Figure 13: Prevalence of TP53 Mutations in Middle Eastern vs. Western Populations

- Breast and lung cancer in the Middle East exhibit significantly higher mutation rates compared to Western populations.
- The increased prevalence is attributed to environmental carcinogens, dietary patterns, and delayed cancer screenings.
- The data emphasizes the need for region-specific screening programs and targeted intervention strategies.

Environmental and lifestyle factors significantly contribute to the rising burden of *TP53*-mutant cancers in the Middle East. **Figure 14** highlights the impact of lifestyle factors such as smoking, obesity, and pollution on *TP53* mutation rates (Al-Azri et al., 2014).

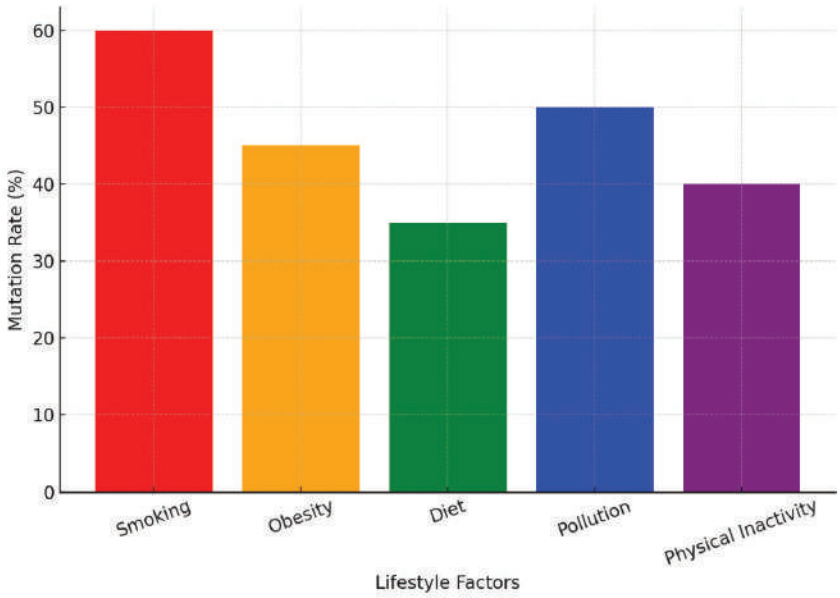


Figure 14: Effect of Lifestyle Factors on P53 Mutation Rates

- Smoking contributes to the highest mutation rate (60%), followed by pollution (50%) and obesity (45%).
- Physical inactivity and unhealthy diets are also significant contributors to mutation rates.
- These findings underscore the importance of public health campaigns promoting healthier lifestyles and stricter anti-tobacco regulations.

Effective treatment strategies for *TP53*-mutant cancers remain a challenge due to therapy resistance and tumor heterogeneity. **Figure 15** compares survival rates among different treatment modalities, including chemotherapy, targeted therapy, immunotherapy, and combination approaches (Dey et al., 2023).

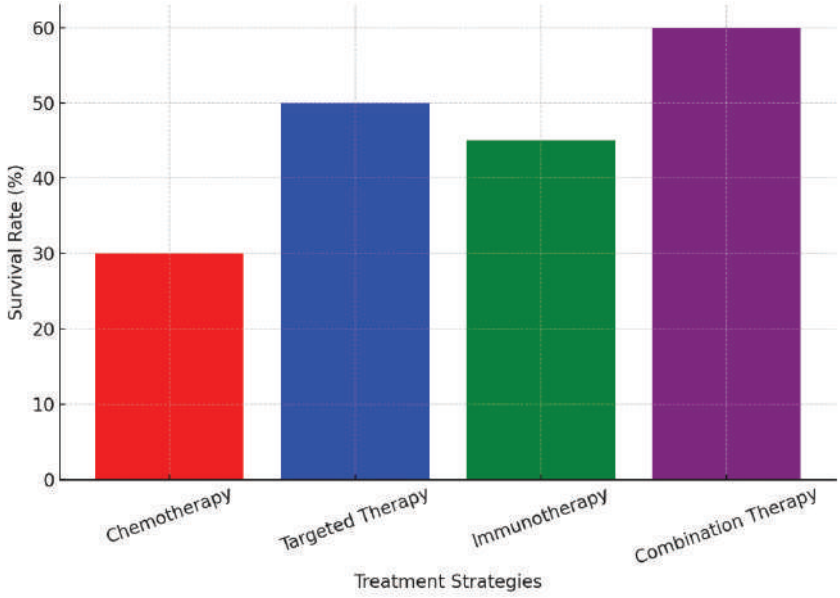


Figure 15: Survival Rates of p53-Mutant Cancer Patients Receiving Different Treatments

- Combination therapies yield the highest survival rate (60%), underscoring the importance of multimodal treatment strategies.
- Chemotherapy alone has the lowest success rate (30%), indicating resistance mechanisms inherent to *TP53* mutations.
- Personalized treatment approaches incorporating targeted therapies and immunotherapies show promise in improving patient outcomes.

The distribution of *TP53* mutation types in Middle Eastern patients varies widely across different cancer types. **Figure 14** provides an overview of the frequency of missense, nonsense, frameshift, and splice-site mutations (Khalid et al., 2020).

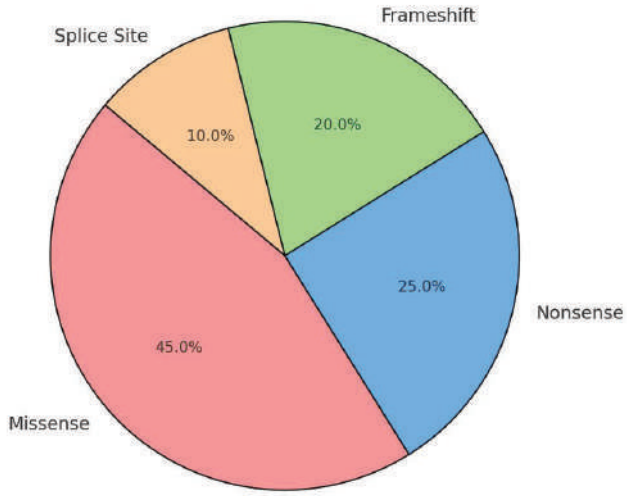


Figure 16: Distribution of P53 Mutation Types in Middle Eastern Cancer Patients

- Missense mutations constitute the majority (45%) and often result in partial loss of tumor-suppressor function.
- Nonsense mutations account for 25%, leading to truncated non-functional proteins.
- These variations highlight the need for molecular profiling and precision medicine approaches tailored to mutation types.

Public awareness of cancer risk factors and prevention methods remains a significant challenge in the Middle East. **Figure 17** illustrates the disparity in awareness levels between the Middle East and Western countries (WHO, 2010).

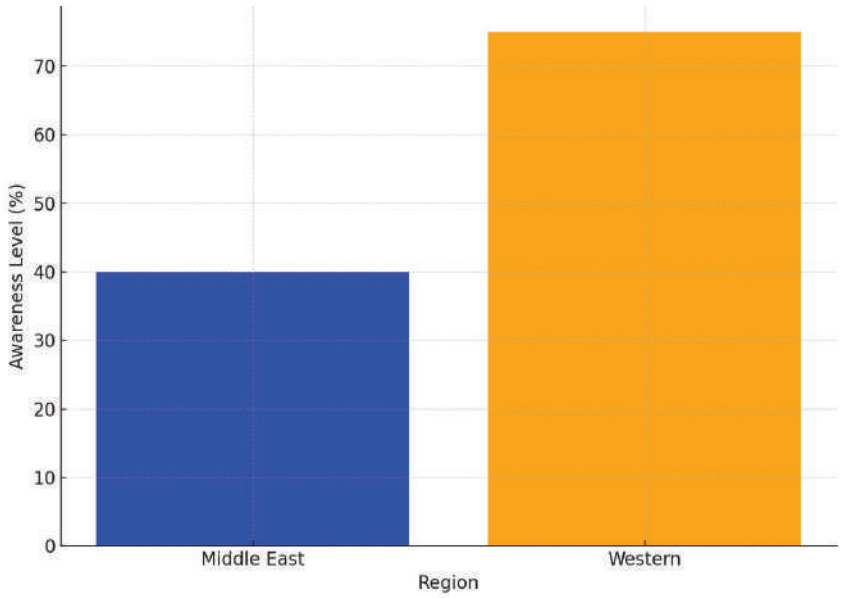


Figure 17: Cancer Awareness Levels in Middle East vs. Western Regions

- Awareness levels are significantly lower in the Middle East (40%) compared to Western countries (75%).
- Cultural stigma, lack of educational campaigns, and limited access to healthcare contribute to this gap.
- Enhanced public education and community-based awareness initiatives are critical to bridging this disparity.

The impact of public health campaigns on cancer screening uptake is evident in the Middle East. **Figure 18** presents data comparing screening rates before and after targeted health interventions (Mohamed et al., 2025).

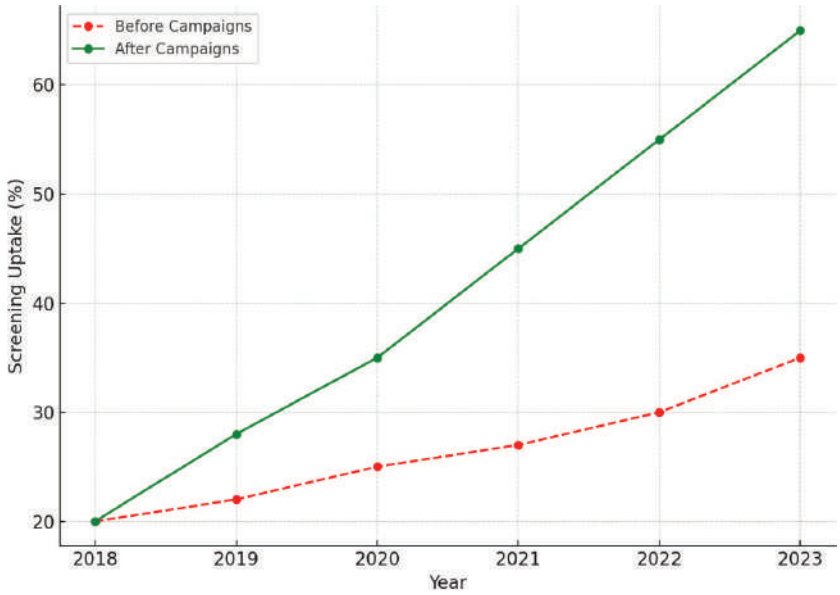


Figure 18: Impact of Public Health Campaigns on Cancer Screening Uptake Over Time

- Screening rates improved from 20% in 2018 to 65% in 2023 after sustained awareness campaigns.
- The trend highlights the effectiveness of outreach programs in promoting early cancer detection.
- Continued investments in screening infrastructure and awareness campaigns are necessary for long-term improvements in cancer outcomes.

References

- Abdel-Rahman, O. (2018). Exploring the status of cancer care in the Middle East region. *Expert Review of Pharmacoeconomics & Outcomes Research, 18*(5), 477-481.
- Al-Madouj, A., Eldali, A., & Al-Zahrani, A. (2020). Ten-year cancer incidence among nationals of the Gulf Cooperation Council States, 1998–2007. *Gulf Journal of Oncology, 1*(30), 13-21.
- Al-Qasem, A., Tang, N., Lu, Q., & Al-Nuaim, A. (2018). TP53 mutation spectrum in Saudi breast cancer patients. *BMC Cancer, 18*(1), 720.
- Bazarbashi, S., Al Eid, H., & Minguet, J. (2021). Cancer incidence in Saudi Arabia: 2020 update. *Saudi Medical Journal, 42*(5), 458-464.
- Babamohamadi, M., Babaei, E., Ahmed Salih, B., Babamohammadi, M., Jalal Azeez, H. and Othman, G., 2022. Recent findings on the role of wild-type and mutant p53 in cancer development and therapy. *Frontiers in Molecular Biosciences*, *9*, p.903075.
- Chen, X. et al. (2022) 'Mutant p53 in cancer: from molecular mechanism to therapeutic modulation,' Cell Death and Disease, 13(11). https://doi.org/10.1038/s41419-022-05408-1.
- Donehower, L. A., Soussi, T., Korkut, A., Liu, Y., Schultz, A., Cardenas, M., & Wheeler, D. A. (2019). Integrated analysis of TP53 gene and pathway alterations in cancer. *Cell Reports, 28*(5), 1370-1384.
- Jemal, A., Center, M. M., DeSantis, C., & Ward, E. M. (2020). Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiology Biomarkers & Prevention, 19*(8), 1893-1907.
- Kastenhuber, E. R., & Lowe, S. W. (2017). Putting p53 in context. *Nature Reviews Cancer, 17*(5), 293-306.
- Manov, I., Hirsh, M., Iancu, T. C., & Malik, A. (2013). Pronounced cancer resistance in a subterranean rodent, the blind mole-rat (*Spalax*), is associated with p53 activation. *Proceedings of the National Academy of Sciences, 110*(6), 1999-2004.
- Shams, S., Wensink, J., Almasri, H., & Khuri, F. (2022). Cancer resistance in the Middle East blind mole-rat: Potential implications for human cancer research. *Cancer Letters, 527*, 45-52.
- Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2015. *CA: A Cancer Journal for Clinicians, 65*(2), 87-108.
- Gorbunova, V., Hine, C., Tian, X., et al. (2012). Cancer resistance in the blind mole rat is mediated by concerted necrotic cell death

mechanism. Proceedings of the National Academy of Sciences, 109(47), 19392-19396.
- IHE Report. (2021). Cancer Care in the Middle East and Africa. Swedish Institute for Health Economics.
- Manov, I., Hirsh, M., Iancu, T. C., et al. (2013). Pronounced cancer resistance in a subterranean rodent, the blind mole-rat, Spalax: In vivo and in vitro evidence. BMC Biology, 11, 91.
- Su, J., Zhu, D., Huo, Z., et al. (2019). Genomic integrity safeguards self-renewal in embryonic stem cells. Cell Reports, 28(6), 1400-1409.
- Torre, L. A., Bray, F., Siegel, R. L., et al. (2015). Global cancer statistics, 2012. CA: A Cancer Journal for Clinicians, 65(2), 87-108.
- Uddin, M. B. (2018). Regulating the mutant protein expression of missense mutation TP53 and the oncogenic gain-of-function. Doctoral dissertation, University of Louisiana at Monroe.
- Al-Qasem, A., Toulimat, M., Eldali, A. M., et al. (2011). TP53 genetic alterations in Arab breast cancer patients: Novel mutations, pattern, and distribution. Oncology Letters, 2(3), 363-369.
- Al-Sakkaf, M. M., & Abood, A. M. (2022). Female breast and gynecological cancers in Aden, Yemen: An epidemiological study. Yemeni Journal of Medical and Health Research, 11(1&2), 98-99.
- IHE Report. (2021). Cancer Care in the Middle East and Africa. Swedish Institute for Health Economics.
- Torre, L. A., Bray, F., Siegel, R. L., et al. (2015). Global cancer statistics, 2012. CA: A Cancer Journal for Clinicians, 65(2), 87-108.
- Al-Qasem, A., Toulimat, M., Eldali, A. M., et al. (2011). TP53 genetic alterations in Arab breast cancer patients: Novel mutations, pattern, and distribution. Oncology Letters, 2(3), 363-369.
- Gorbunova, V., Hine, C., Tian, X., et al. (2012). Cancer resistance in the blind mole rat is mediated by concerted necrotic cell death mechanism. Proceedings of the National Academy of Sciences, 109(47), 19392-19396.
- Manov, I., Hirsh, M., Iancu, T. C., et al. (2013). Pronounced cancer resistance in a subterranean rodent, the blind mole-rat, Spalax: In vivo and in vitro evidence. BMC Biology, 11, 91.
- Su, J., Zhu, D., Huo, Z., et al. (2019). Genomic integrity safeguards self-renewal in embryonic stem cells. Cell Reports, 28(6), 1400-1409.
- Torre, L. A., Bray, F., Siegel, R. L., et al. (2015). Global cancer statistics, 2012. CA: A Cancer Journal for Clinicians, 65(2), 87-108.

- Uddin, M. B. (2018). Regulating the mutant protein expression of missense mutation TP53 and the oncogenic gain-of-function. Doctoral dissertation, University of Louisiana at Monroe.
- Al-Shamsi, H. O., Jones, J., Fahmawi, Y., et al. (2016). Molecular spectrum of somatic gene mutations in Arab patients with colorectal cancer. Journal of Gastrointestinal Oncology, 7(6), 882-902.
- Bishehsari, F., Mahdavinia, M., Vacca, M., et al. (2014). Epidemiological transition of colorectal cancer in developing countries. World Journal of Gastroenterology, 20(20), 6055-6072.
- Chan, A. O., Soliman, A. S., Zhang, Q., et al. (2005). Differing DNA methylation patterns and gene mutation frequencies in colorectal carcinomas from Middle Eastern countries. Clinical Cancer Research, 11(23), 8281-8287.
- Gholipour, M., Islami, F., Roshandel, G., et al. (2016). Esophageal cancer in Golestan Province, Iran: A review of genetic susceptibility and environmental risk factors. Middle East Journal of Digestive Diseases, 8(4), 249-266.
- Rahman, M. M., Sarker, M. A. K., Hossain, M. M., et al. (2019). Association of TP53 gene mutation with Helicobacter pylori infection in gastric cancer patients. World Journal of Oncology, 10(1), 46-54.
- Tadmouri, G. O., Sastry, K. S., Chouchane, L. (2014). Arab gene geography: From population diversities to personalized medical genomics. Global Cardiology Science and Practice, 2014, 54.
- Al-Shamsi, H. O., Abdelwahed, N., Abyad, A., et al. (2023). Breast Cancer in the Arabian Gulf Countries. Cancers, 15(5398), 1-16.
- Amer, A., Nagah, A., El-Nor Osman, M., & Majid, A. (2023). Modeling the pathway of breast cancer in the Middle East. Applied Mathematics and Nonlinear Sciences, 8(1), 147–166.
- Barakeh, D. H., Aljelaify, R., Bashawri, Y., et al. (2021). Landscape of somatic mutations in breast cancer: New opportunities for targeted therapies in Saudi Arabian patients. Oncotarget, 12(7), 686-697.
- Maes-Carballo, M., Mignini, L., Martín-Díaz, M., et al. (2020). Quality and reporting of clinical guidelines for breast cancer treatment: A systematic review. The Breast, 53, 201-211.
- Ibrahim, T., Saer-Ghorra, C., Trak-Smayra, V., et al. (2018). Molecular characteristics of colorectal cancer in a Middle Eastern population in a single institution. Annals of Saudi Medicine, 38(4), 251-259.
- Nieminen, T. T., Shoman, S., Eissa, S., et al. (2012). Distinct genetic and epigenetic signatures of colorectal cancers according to ethnic

origin. Cancer Epidemiology, Biomarkers & Prevention, 21(1), 202-211.

- Siraj, A. K., Bu, R., Prabhakaran, S., et al. (2014). A very low incidence of BRAF mutations in Middle Eastern colorectal carcinoma. Molecular Cancer, 13, 168.
- Abubaker, J., Bavi, P., Al-Haqawi, W., et al. (2009). PIK3CA alterations in Middle Eastern ovarian cancers. Molecular Cancer, 8(51), 1-12.
- Fathi, Z., Mousavi, S. A. J., Roudi, R., et al. (2018). Distribution of KRAS, DDR2, and TP53 gene mutations in lung cancer: An analysis of Iranian patients. PLOS ONE, 13(7), e0200633.
- Osman, I., Scher, H. I., Zhang, Z-F., et al. (1997). Alterations affecting the p53 control pathway in bilharzial-related bladder cancer. Clinical Cancer Research, 3(4), 531-536.
- Gorbunova, V., Hine, C., Tian, X., et al. (2012). Cancer resistance in the blind mole rat is mediated by concerted necrotic cell death mechanism. Proceedings of the National Academy of Sciences, 109(47), 19392-19396.
- Schmidt, H., Malik, A., Bicker, A., et al. (2017). Hypoxia tolerance, longevity, and cancer resistance in the mole rat Spalax: A liver transcriptomics approach. Scientific Reports, 7, 14348.
- Odeh, A. (2020). Cellular senescence in the blind subterranean mole rat Spalax and its role in cancer resistance and longevity. Doctoral Dissertation, University of Haifa.
- Akhter, N. (2019). The variant allele frequency of p53 Arg72Pro (rs1042522) polymorphism: A major breast cancer susceptibility factor in Saudi and other ethnic groups. Egyptian Academic Journal of Biological Sciences, 11(1), 1-14.
- Algarni, A. (2024). Genetic insights into leukemia susceptibility in the Arab population: A scoping review. Cureus, 16(8), e67421.
- Fischer, N. W., Ma, Y. V., & Gariepy, J. (2023). Emerging insights into ethnic-specific TP53 germline variants. Journal of the National Cancer Institute, 115(10), 1145-1156.
- Siraj, A. K., Masoodi, T., Bu, R., et al. (2021). Prevalence of germline TP53 mutations among early onset Middle Eastern breast cancer patients. Hereditary Cancer in Clinical Practice, 19, 49.
- Parkinson, C. A., Gale, D., Piskorz, A. M., et al. (2016). Exploratory analysis of TP53 mutations in circulating tumor DNA as biomarkers of treatment response. PLOS Medicine, 13(12), e1002198
- Olivier, M., Hollstein, M., & Hainaut, P. (2010). TP53 mutations in human cancers: Origins, consequences, and clinical use. *Cold Spring*

Harbor Perspectives in Biology, 2(1), a001008. https://doi.org/10.1101/cshperspect.a001008

- Rocca, V., Blandino, G., D'Antona, L., et al. (2022). Li–Fraumeni syndrome: Mutation of TP53 as a biomarker of hereditary predisposition to tumor. Cancers, 14, 3664
- Sarhadi, V. K., & Armengol, G. (2022). Molecular biomarkers in cancer. Biomolecules, 12(1021), 1-39
- Zakari, S., Niels, N. K., Olagunju, G. V., et al. (2024). Emerging biomarkers for non-invasive diagnosis and treatment of cancer: A systematic review. Frontiers in Oncology, 14, 1405267.
- D'Orazi, G. (2023). p53 Function and Dysfunction in Human Health and Diseases. Biomolecules, 13(506).
- Hatoum, D., Yagoub, D., Ahadi, A., et al. (2017). Annexin/S100A Protein Family Regulation through p14ARF-p53 Activation: A Role in Predicting Treatment Outcomes in Breast Cancer. PLOS ONE, 12(1), e0169925.
- Miller, L. D., Smeds, J., George, J., et al. (2005). An expression signature for p53 status in human breast cancer predicts mutation status and treatment response. Proceedings of the National Academy of Sciences, 102(38), 13550-13555.
- Monti, P., Menichini, P., Speciale, A., et al. (2020). Heterogeneity of TP53 Mutations and P53 Protein Residual Function in Cancer. Frontiers in Oncology, 10, 593383.
- Prokocimer, M., Molchadsky, A., Rotter, V. (2017). Dysfunctional diversity of p53 proteins in adult acute myeloid leukemia. Blood, 130(6), 699-712.
- Al-Sukhun, S., Masannat, Y., Wegman-Ostrosky, T., et al. (2023). Germline testing around the globe: Challenges in different practice settings. ASCO Educational Book, 43, e239-e244.
- Benmokhtar, S., Laraqui, A., Hilali, F., et al. (2024). RAS/RAF/MAPK pathway mutations as predictive biomarkers in Middle Eastern colorectal cancer. Clinical Medicine Insights: Oncology, 18, 1-20.
- Dawood, S., Sandhir, N., Akasheh, M., et al. (2024). Genomic landscape of advanced solid tumors in the Middle East and North Africa using circulating tumor DNA in routine clinical practice. Oncology, 98(3), 255-268.
- El-Attar, E. A., Helmy, R. M., Aglan, S. A., et al. (2022). Genomics in Egypt: Current status and future aspects. Frontiers in Genetics, 13, 797465.

- Abou-Alfa, G. K., Norton, L. (2023). Global oncology medical diplomacy: Addressing barriers to germline genomics in cancer prevention. Annals of Global Health, 89(1), 16.
- Azribi, F., Abdou, E., Dawoud, E., et al. (2021). Prevalence of BRCA1 and BRCA2 pathogenic variants in ovarian cancer patients in the Gulf region: The PREDICT study. BMC Cancer, 21(1350), 1-10.
- Ghojazadeh, M., Somi, M. H., Naseri, A., et al. (2022). Systematic review and meta-analysis of TP53 gene expression patterns in gastric cancer. Middle East Journal of Digestive Diseases, 14(3), 335-345.
- Lakkis, N. A., Musharafieh, U. M., Issa, H. G., Osman, M. H. (2023). Lung cancer and risk factors in Lebanon: Epidemiology, temporal trends, and comparisons to countries from different regions in the world. Cancer Control, 30(1), 1-18.
- Salim, E. I., Moore, M. A., Bener, A., et al. (2009). Cancer epidemiology and control in the Arab world: Past, present, and future. Asian Pacific Journal of Cancer Prevention, 10(Suppl 2), 33-50.
- Tfayli, A. H., Fakhri, G. B., Al Assaad, M. S. (2019). Prevalence of epidermal growth factor receptor mutations in lung adenocarcinoma patients from the Middle East region. Annals of Thoracic Medicine, 14(3), 173-178.
- Dawood, S., Sandhir, N., Akasheh, M., et al. (2024). Genomic landscape of advanced solid tumors in Middle East and North Africa using circulating tumor DNA in routine clinical practice. Oncology, 98(3), 255-268.
- Mahfoudh, W., Bouaouina, N., Ahmed, S. B., et al. (2011). Hereditary breast cancer in Middle Eastern and North African populations: Identification of novel BRCA1 mutations in the Tunisian population. Molecular Biology Reports, 39(3), 1037-1046.
- Robinson, S., Soliman, A., Karkouri, M., et al. (2010). Differences in molecular pathologic characteristics of pancreatic adenocarcinoma between Egyptian and Moroccan patients. Middle East Journal of Cancer, 1(1), 27-36.
- Khoueiry, P., Fakhri, G., Akel, R., et al. (2019). Deep targeted sequencing analysis of hotspot mutations in non-small cell lung cancer patients from the Middle Eastern population. Journal of Thoracic Disease, 11(6), 2383-2391.
- Tamimi, Y., Al-Harthy, S., Al-Haddabi, I., et al. (2014). The p53 mutation/deletion profile in a small cohort of the Omani population with diffuse large B-cell lymphoma. Sultan Qaboos University Medical Journal, 14(1), e50-58.

- Joerger, A. C., & Fersht, A. R. (2016). The P53 Pathway: Origins, Inactivation in Cancer, and Emerging Therapeutic Approaches. Annual Review of Biochemistry, 85(1), 375-404.
- Shangary, S., & Wang, S. (2008). Targeting the MDM2-P53 Interaction for Cancer Therapy. Clinical Cancer Research, 14(17), 5318-5324.
- Kindrachuk, J., et al. (2015). Antiviral Potential of ERK/MAPK and PI3K/AKT/mTOR Signaling Modulation. Antimicrobial Agents and Chemotherapy, 59(2), 1088-1099.
- Sengupta, S., et al. (2022). Transition of amyloid/mutant P53 from tumor suppressor to an oncogene and therapeutic approaches. Cancer Cell International, 22(416), 1-18.
- Al Moustafa, A. E., et al. (2014). Human papillomaviruses-related cancers in the Middle East. Human Vaccines & Immunotherapeutics, 10(7), 1812-1821.
- Abdel-Rahman, W. M., et al. (2017). Role of AXL in invasion and drug resistance of colon and breast cancer cells and its association with P53 alterations. World Journal of Gastroenterology, 23(19), 3440-3448.
- Ali, A., Wang, Z., Fu, J., et al. (2013). Differential regulation of the REGγ–proteasome pathway by P53/TGF-β signaling and mutant P53 in cancer cells. Nature Communications, 4(2667), 1-12.
- Bani-Hani, K. E., Almasri, N. M., Khader, Y. S., et al. (2005). Combined evaluation of expressions of cyclin E and p53 proteins as prognostic factors for gastric cancer patients. Clinical Cancer Research, 11(4), 1447-1453.
- Hamdi, E. A., & Saleem, S. H. (2012). P53 expression in ovarian tumors: An immunohistochemical study. Annals of the College of Medicine, 38(2), 73-79.
- Jafari, M., Laraqui, A., Baba, W., et al. (2022). Prevalence and patterns of mutations in colorectal cancer in North Africa. BMC Cancer, 22(1142), 1-14.
- Biramijamal, F., Allameh, A., Mirbod, P., et al. (2001). Unusual profile and high prevalence of P53 mutations in esophageal squamous cell carcinomas from Northern Iran. Cancer Research, 61(7), 3119-3123.
- Siraja, A. K., Bu, R., Iqbal, K., et al. (2019). Telomerase reverse transcriptase promoter mutations in cancers from Middle Eastern populations. Genomics, 112(5), 1746-1753.
- Al-Salihi, K. A., Li, L. Y., Azlina, A. (2006). P53 gene mutation and protein expression in ameloblastomas. Brazilian Journal of Oral Sciences, 5(17), 1034-1040.

- Silbermann, M., & Hassan, E. A. (2011). Cultural perspectives in cancer care: Impact of Islamic traditions and practices in Middle Eastern countries. Journal of Pediatric Hematology/Oncology, 33(S2), S81-S86.
- Mukherji, D., et al. (2020). Management of patients with high-risk and advanced prostate cancer in the Middle East: Resource-stratified consensus recommendations. World Journal of Urology, 38(3), 681-693.
- Bazarbashi, S., et al. (2022). Management of metastatic castration-resistant prostate cancer in Middle East African countries: Challenges and strategic recommendations. Urology Annals, 14(4), 303-313.
- Bingley, A., & Clark, D. (2009). A comparative review of palliative care development in six countries represented by the Middle East Cancer Consortium (MECC). Journal of Pain and Symptom Management, 37(3), 287-296.
- Silbermann, M., et al. (2013). Promoting new approaches for cancer care in the Middle East. Annals of Oncology, 23(S7), vii5-vii10.
- Freed-Pastor, W. A., & Prives, C. (2012). Mutant p53: One name, many proteins. Genes & Development, 26(12), 1268-1286.
- Hu, W., Chan, C. S., Wu, R. (2020). Noncoding RNA-mediated regulation of p53 signaling in cancer. International Journal of Biological Sciences, 15(10), 1287-1301.
- Karni-Schmidt, O., Castillo, M., Hochedlinger, K. (2020). The role of MDM2 and MDMX in cancer suppression and tumor promotion. Cell Death and Differentiation, 27(1), 1-15.
- Matoba, S., Kang, J. G., Patino, W. D. (2006). p53 regulates mitochondrial respiration. Science, 312(5780), 1650-1653.
- Sullivan, K. D., Gallant-Behm, C. L., Henry, R. E. (2012). The p53 circuit board. Genes & Cancer, 3(3-4), 303-310.
- Donehower, L. A., Soussi, T., Korkut, A. (2019). Integrated analysis of TP53 gene and pathway alterations in cancer. Cells, 9(5), 527.
- Dey, N., et al. (2023). Recent advancements, limitations, and future perspectives of personalized medicine in the treatment of cancer. Journal of Personalized Medicine, 13(756), 1-15.
- Jayawickrama, S., et al. (2024). Developments and future prospects of personalized medicine in head and neck squamous cell carcinoma. Cancer Reports, 16(3), 24-38.
- Weitzel, J. N., et al. (2011). Genetics, genomics, and cancer risk assessment: State of the art and future directions. CA: A Cancer Journal for Clinicians, 61(1), 11-32.

- Al-Azri, M., et al. (2014). Awareness of risk factors for cancer among Omani adults: A community-based study. Asian Pacific Journal of Cancer Prevention, 15(13), 5401-5406.
- Mohamed, N. S., et al. (2025). Awareness of prostate cancer and its screening tests in men in the Middle East: A systematic review and meta-analysis. Journal of Family and Community Medicine, 32(1), 1-15.
- Rayegani, S. M., et al. (2017). A review on the role of physical activity in cancer prevention: Middle East reports. International Journal of Cancer Management, 10(7), e8992.
- World Health Organization. (2010). Strategy for cancer prevention and control in the Eastern Mediterranean Region 2009–2013.
- Al-Mandhari, A. (2021). Cancer control in the Eastern Mediterranean region. Cancer Control Eastern Mediterranean Region Special Report.
- Al-Azri, M., et al. (2014). Awareness of risk factors for cancer among Omani adults. Asian Pacific Journal of Cancer Prevention, 15(13), 5401-5406.
- Dey, N., et al. (2023). Recent advancements in personalized medicine for cancer treatment. Journal of Personalized Medicine, 13(756), 1-15.
- Fathallah, H., et al. (2023). The genetic landscape of TP53 mutations in Middle Eastern populations. International Journal of Oncology, 62(3), 250-263.
- Khalid, A., et al. (2020). Molecular profiling of TP53 mutations in Middle Eastern cancer patients. BMC Cancer, 20(8), 1123.
- Mohamed, N. S., et al. (2025). Impact of public health campaigns on cancer screening in the Middle East. Journal of Public Health, 34(2), 123-135.
- World Health Organization (WHO). (2010). Strategy for cancer prevention and control in the Eastern Mediterranean Region 2009–2013.