The impact of genetics and the environment on cancer risk in Indigenous Australians: a narrative review

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Summary

Aboriginal and Torres Strait Islander (hereafter respectfully named Indigenous) Australians are diagnosed with some cancers substantially more frequently than non-Indigenous Australians implying a different risk factor landscape. Additionally, poorer outcomes for certain cancers are exacerbated by lower cancer screening rates and later diagnoses compared to non-Indigenous Australians. An improved understanding of cancer causation would allow better shaping and targeting of screening programs for those at the highest risk. A narrative review of relevant environmental and genetic risk factors for various cancers in Indigenous populations was undertaken. Research databases were interrogated in June 2024, with information extracted. Further peer-reviewed and grey literature was identified by specific searchers and citation snowballing. The results show that many distinct risk factors exist in environmental, sociocultural, educational, behavioural and metabolic domains; these complex and frequently interacting risks include direct and indirect social and cultural factors. Identified gaps include limited published literature on the genetic determinants of cancer, decreased levels of effective cancer surveillance for Indigenous Australians, a paucity of culturally appropriate cancer health education programs for both Indigenous community members and health providers, and the historical absence of an Indigenous Australian focus and contribution to research on cancer causation. Indigenous Australian co-designed research is needed to address the gaps contributing to cancer prevention and screening development. Empowerment of national Indigenous Australian leadership in partnership with researchers and service providers is needed to develop tailored health interventions and reduce the existing and future challenges of the cancer burden on Indigenous communities.

Keywords: Cancer; Social determinants; Indigenous health; Aboriginal and Torres Strait Islander health; Australia; Rural health; Cancer screening; Cancer risk

Introduction

Aboriginal and Torres Strait Islander (hereafter respectfully referred to as Indigenous) Australians are disproportionately affected by cancer, both in the incidence of certain aggressive cancers and poorer subsequent outcomes. Overall, age-standardised rates of cancer increased by 12% for Indigenous Australians from 2010 to 2019, compared to a 10% decline for non-Indigenous Australians.[1] For specific cancers, incidence is elevated for cervical, uterine, head and neck, oesophageal, stomach, liver, pancreatic and lung cancers as well as cancers of unknown primary site among Indigenous Australians compared to non-Indigenous Australians using 2013 data, while lower or the same for other cancers (bladder, breast [female], colorectal, kidney, melanoma, non-Hodgkin's lymphoma and thyroid).[1] These differences in cancer incidence suggest differences in environmental or genetic risks that lead to cancer development. Overall, the risk of progression and death has been observed to be generally worse for Indigenous compared to non-Indigenous Australians for an equivalent stage of diagnosis. Although improving cancer treatment is important to reduce eventual mortality, cancer risk reduction is the most important approach to reducing both mortality and treatment-related morbidity and requires interventions at multiple levels.[2]

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To date, most explorations of cancer among Indigenous Australians have focused on the epidemiology of cancer, as well as experiences of, and access to cancer care.[3,4] A review of the contribution of environmental and genetic factors to cancer causation or the complex interplay between genetic and environmental risk factors in cancer incidence specific to Indigenous Australians has not previously been published. This is despite considerable knowledge regarding genetic and environmental risk factors for cancer amongst the general population. For example, the International Agency for Research on Cancer (IARC) has assessed multiple agents for their carcinogenicity and lists agents associated with each cancer by anatomical site.[5] Environmental factors such as exposure to asbestos, UV radiation, and benzene (commonly found in smoke from bushfires and household products like glue, paint, and solvents) are also factors known to contribute to cancer risk. Furthermore, in applying the Dahlgreen and Whitehead and Lowitja Institute evaluation frameworks on holistic approaches to cancer risk, environmental factors may not just include traditional determinants (such as those defined by the European Parliament's Public Health Committee).[6–8] Other aspects may include geographical, social and cultural factors that allow the environment to interact with individual cancer risk. Individual factors, defined as metabolic, behavioural and comorbid factors such as tobacco smoking, alcohol consumption, poor diet, obesity, hypertension, heart disease and diabetes are known to affect cancer risk.[9–12] Smoking has a well-documented association with lung, lip, oral, pharyngeal and oesophageal cancers, while diabetes has been associated with digestive cancers.[4] These determinants, together with environmental risk factors, can also synergistically drive cancer risk, as is the case with smoking and asbestos exposure in markedly increasing the risk for mesothelioma. Understanding the relevant environmental and individual risk factors relevant to cancer development among Indigenous Australians is pertinent to addressing inequity in cancer risk and subsequent mortality, as this helps inform expanding cancer screening access through the Australian Cancer Plan and various programs, including BreastScreen Australia and National Bowel Cancer Screening.[13,14]

There is a relative dearth of research into the genetic determinants of cancer among Indigenous Australians despite an increasing understanding of the contributions of genetic alterations to human health and disease. Genetic risk factors for cancer can be defined as gene mutations that increase the risk of cancer development. Advanced sequencing technologies can detect very single base changes in the DNA sequence amongst the billions of bases that constitute the genome. From these data and using knowledge of the structure and function of proteins for which the genes act as assembly instructions, the likely impact of these changes on cancer risk can be predicted. Mutations, deletions, rearrangements, or amplifications of DNA in genes that code for proteins with key roles in cellular homeostasis have been shown to contribute to risk for specific cancers. However, despite this advancing knowledge in oncological genetics, the conduct of genomic studies to assess the influence of such gene changes in Indigenous Australians is in its infancy, as it is for many Indigenous peoples the world over.[15–18] The contribution of genetics to differential cancer development between Indigenous and non-Indigenous Australians deserves exploration.

This narrative review aims to provide a summary of the various individual, environmental and genetic determinants of key prominent cancers in Indigenous Australians including breast, cervical, hepatocellular and lung cancers. It also discusses how these determinants interact to predispose individuals to cancer and analyses this risk in the context of access to preventive and screening-related healthcare among Indigenous Australians. In doing so, it aims to identify gaps in both the current literature and service provision thereby guiding future research and policy development for Indigenous Australians.

Methods

Study design

The design for the narrative review was devised by the study authors and includes the contribution of Indigenous Australian authors (AB, MR, LP) for their perspectives from a cultural and academic lens. The interpretation of study findings and revisions to the review were undertaken with these considerations in mind.[19,20]

Search strategy and selection criteria

The search strategy was based on the methods of the PRISMA for Scoping Reviews (PRISMA-ScR) checklist and was undertaken across multiple databases.[21] The search defined genetic factors as related to genetic alterations leading to cancer risk and environmental factors were defined as inclusive of traditional determinants but also encompassing infections, geographical and sociocultural factors. Individual factors were also included as they related to environmental and genetic risk. The search terms for 'Indigenous Australians' included 'Aboriginal and Torres Strait Islander', 'Aboriginal', 'Torres Strait Islander', and 'First Nations Australian'. Other search terms included cancers (emphasis on 'lung', 'breast', 'cervical' and 'hepatocellular' but inclusive of gastric/oesophageal/colorectal/pancreatic, genitourinary, head and neck). Genetic risk factors were defined as genetics ('genetics', 'genomics', 'genetics risk', 'sequencing', 'mutational profile'), environmental ('infections' including Hepatitis B/C/HPV/*Helicobacter pylori*, 'environmental pollution',

'occupational carcinogen', 'socioeconomic', 'cultural', 'geography') and behavioural/metabolic, also known as individual ('smoking', 'alcohol', 'overweight', 'obesity', 'physical activity', 'dietary') risk factors.

A search was undertaken between 15 and 30 June 2024 of bibliographic databases including PubMed, Web of Science, Google Scholar, the Australian Institute of Health and Welfare (AIHW) and the Australian Indigenous Health Bulletin. Further articles, government surveillance data, cancer registry data and grey literature were identified through specific sub-searches and citation snowballing. Inclusion criteria defined all English language articles related to Indigenous Australian cancer development regarding the risk factors identified in the search terms. Articles were excluded if they could not be accessed as full text, did not relate to cancer, did not relate to the search terms, or were published in languages other than English. Given the anticipated limited literature available specific to environmental and genetic cancer risk in Indigenous Australians, there were no date restrictions for the search and all eligible articles were included from database inception.

Data extraction

Data and information extracted from the articles that were included in this review were explored using the narrative reanalysis framework described by Hall and Leeder.[22] For this, sub-phenomena within each article were identified based on uniqueness and relevance. Forward citation was used to expand and explore sub-phenomena of interest, and the resulting content was reanalysed using a qualitative content analysis approach. In analysing the sub-phenomena of interacting determinants, information on individual risk factors was found to differ in degree and context from that which is understood about cancer in the general population.[23,24]

Results

We screened 473 unique records and included 33 relevant articles for final review following the application of the exclusion criteria, 26 were environmental (inclusive of individual [behavioural/metabolic] or geographical, cultural and social) factors and 7 were genetic factors (Fig. 1).

All included articles were available in full text and in English. One article was within a government report. The eligible studies were predominantly observational in design (n = 21), with four meta-analyses included (Appendix 1). A further four studies were experimental in design and another four explored environmental determinants from a qualitative perspective. Further snowballing of literature to inform the proximal and distal determinants of cancer risk was derived from reviews and governmental and non-governmental documents. Eligible records were published from 1998 to 2023.

Environmental risk factors and Indigenous Australians (inclusive of individual factors)

The environment in which people live has profound effects on their cancer risk and subsequent longevity. Cancer results from the accumulation of many genetic and epigenetic changes within the cell, with subsequent aberrations in cellular proteins leading to disturbances in cell function. Environmental as well as individual factors, including genetic predispositions, contribute to the development of cancer. Multiple risk factors can increase the likelihood of developing disease; some risk factors can also increase the severity of the disease and the likelihood of developing complications. While estimates vary between 30 and 50% of cancers are considered preventable if exposure to factors that increase the risk of cancer is avoided.[25] This section reviews known risk factors for cancer and then what is known about these various risk factors among Indigenous Australians.

Tobacco

Smoking is known to harm almost every organ system in the body. For more than 50 years, tobacco has had a known association with lung cancer, as well as with other cancers, including those of the mouth and oropharynx, trachea, oesophagus, stomach, liver, pancreas, bladder and uterine cervix.[1,26–28] Tobacco smoke contains in excess of 60 carcinogens. Although unburned tobacco is less carcinogenic, it still has at least 16 carcinogens, meaning alternative methods of tobacco consumption still carry cancer risk.[29] Even one to four cigarettes a day has significant adverse health consequences.[30] Smoking rates are significantly raised amongst Indigenous Australians, who also have high rates of lung, head and neck, oesophageal, liver and cervical cancers.[1,26] Passive smoking is another important consideration with people having significant exposure having almost twice the risk of lung cancer diagnosis and death.[31,32]

Indigenous Australians were introduced to tobacco after colonisation, sometimes through trading and as a sign of goodwill, but also as part of the rations that indentured Indigenous labourers received.[33] Many variables feed into smoking development among Indigenous Australians, including disproportionately high rates of mental illness, socioeconomic circumstances (i.e. lower employment, and insecure housing) and societal (racism, incarceration, marginalisation) factors.[34]

Rates of smoking among Indigenous people were very high, of the order of 50% in 2004–5. In association with concerted efforts through the Tackling Indigenous Smoking (TIS) initiative to reduce the uptake of smoking and persuade smokers to quit, rates of

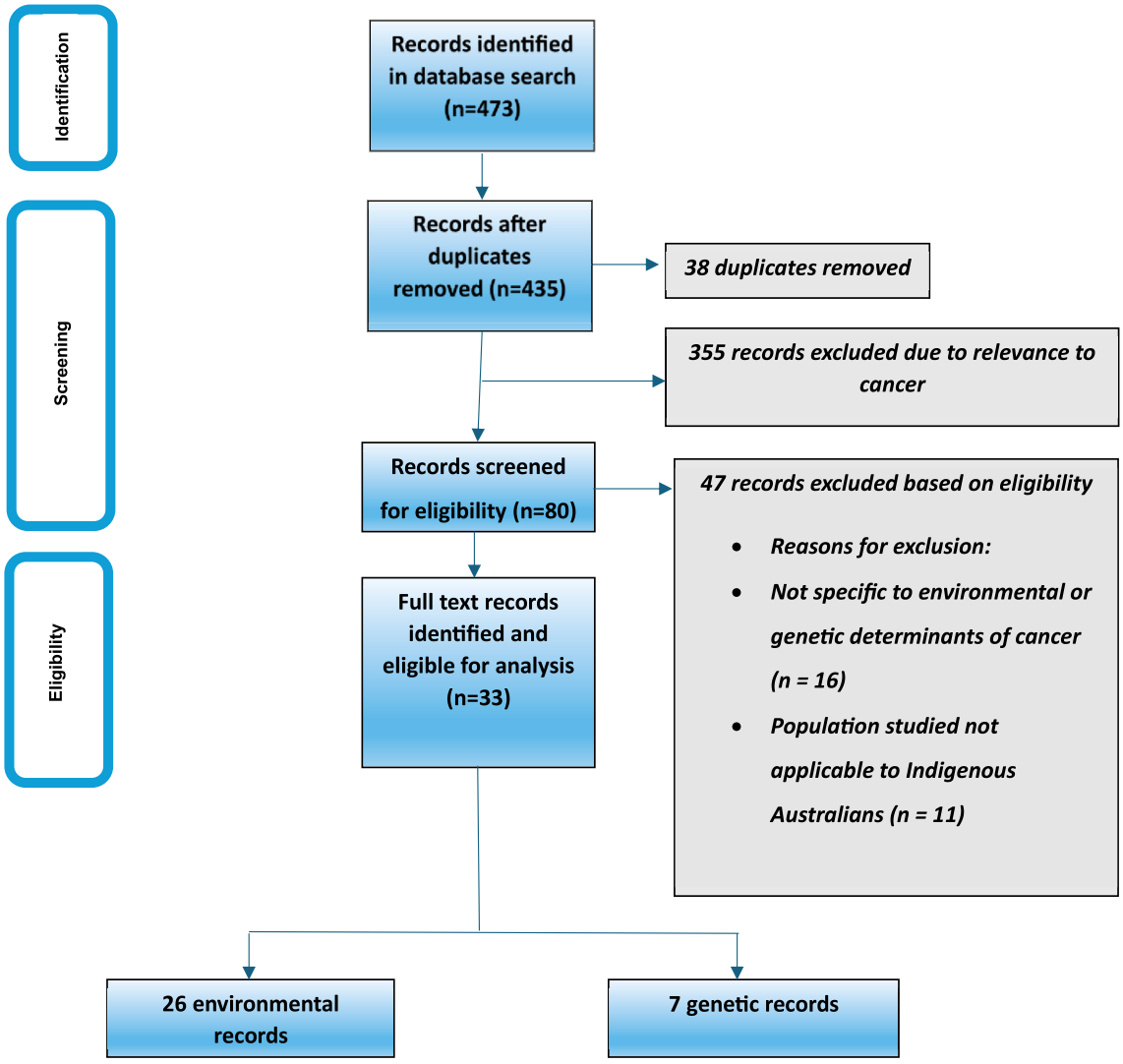

Fig. 1: **Flowchart database search for narrative review.**

Indigenous tobacco smoking have declined, and smoking prevalence has decreased from 54.5% in 1994 to 34.1% in 2022–2023.[35] However, rates remain well above the smoking rate of 11% for the whole Australian population in 2022, demonstrating that sustained efforts in this area are needed.[26]

Alcohol

Ethanol has been classed as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) with seven well-established alcohol-related cancer types, including liver, breast, mouth and throat (oropharyngeal, laryngeal), colorectal and oesophageal cancers.[5,36] The magnitude of the risk is related to the amount of alcohol consumed and its type, but even low levels of consumption incur some increase in risk. Alcohol does not have a minimum dose which does not manifest carcinogenic effects in the human body.[37] Regarding the mechanism of causation, ethanol is causally linked to cancer via several mechanisms. The ethanol metabolite acetaldehyde can cause DNA damage and block DNA synthesis and repair.[38] Additionally, both ethanol and acetaldehyde can disrupt DNA methylation and alter the regulation of genes involved in cancer causation and prevention. Ethanol can also induce inflammation and oxidative stress leading to lipid peroxidation and further indirect DNA damage.[38] Excessive alcohol consumption can result in injury and disease with consequent mortality across many physical and mental health conditions, with cancer only one of these.

Harmful alcohol consumption (defined as more than 10 standard drinks per week or >4 standard drinks on a day with 1 standard drink = 10 g of ethanol) is not

pervasive among Indigenous Australians[26] with estimates that Indigenous Australians are 1.3 times more likely to abstain from alcohol than non-Indigenous people.[39] More recent analysis suggests considerable variation in rates of alcohol consumption among Indigenous Australians depending on sampling strategies.[40] In post-colonial Australia, alcohol has been used as a means of exchange with Indigenous Australians for sex or labour, as well as for enjoyment.[41] For Indigenous Australians, it has also been recognised as a means of escape, solace and obtunding the reality of systemic discrimination, including stigma, racism and socioeconomic disparities.[42] Much of this is a consequence of intergenerational trauma and dispossession from traditional lands and the forcible removal of children from their families and communities following colonial policies.[43] Australian Bureau of Statistics (ABS) data indicate Indigenous Australians are 1.2 and 1.3 times more likely to consume alcohol at levels that pose risks to their health on individual drinking occasions as well as over their lifetimes than non-Indigenous people, with men having more risky alcohol consumption than women.[39,44] However, according to the AIHW, drinking that puts health at risk declined from 48% to 33% between 2010 and 2023 among Indigenous Australians.[26]

Despite this reassuring decline, there are challenges in addressing harmful alcohol consumption, particularly when multiple risk factors need to be addressed simultaneously.[45] Among Indigenous Australians that have chronic Hepatitis B, cirrhosis or hepatocellular carcinoma (HCC), hazardous alcohol use has been recorded to occur in up to 72% of cases, contributing to lower survival compared to non-Indigenous Australians when factoring in other determinants.[46–48] The difficulty in estimating HCC incidence relating to hazardous alcohol use among Indigenous Australians is impacted by lower surveillance in this population, influenced by systemic factors such as the availability of specialist services and rurality of residence.[49] It is evident that more prevention strategies and early intervention efforts are needed to limit hazardous alcohol consumption, along with better access to treatment and care for alcohol dependence for Indigenous Australians; reducing alcohol risks would also help lessen the development of HCC.

Physical inactivity

The health benefits of exercise occur across many conditions with physical activity important for the prevention, management and treatment of chronic diseases as well as social and emotional well-being. Physical inactivity is a major contributor to the burden of disease in Australia, including among Indigenous Australians. Physical activity is inversely associated with cancers of the oesophagus (adenocarcinoma), liver, lung, kidney, gastric cardia, endometrium, colon, rectum, head and neck, bladder, and breast, as well as myeloid leukemia and myeloma. Higher levels of physical activity before a diagnosis also reduced the risk of eventual cancer mortality.[50,51] Aside from indirect action through weight reduction or control, exercise impacts cancer risk and progression mechanistically through multiple pathways inclusive of; cellular proliferation control, favourable energy metabolism, and heightened immune responses to tumour formation.[52] A range of peptides termed myokines are produced from working muscle, with emerging tumour suppressive roles for some.[53]

Traditionally, Indigenous Australians had high levels of daily activity involved with finding renewable food and other resources, sustaining the spiritual connection to Country, and maintaining familial and cultural practices. Physical activity levels among Indigenous Australians have reduced over time,[54] unsurprising given the disruption of a traditional more migratory lifestyle and enforcement of a more settlement-based sedentary one. Furthermore, financial constraints, community and family obligations, and concerns for discrimination and safety have all been identified as contributors to physical inactivity among Indigenous Australians.[55,56] Indigenous physical inactivity levels differ by age, sex and remoteness. According to ABS data, Indigenous children up to the age of 17 years are more physically active and likely to meet recommended physical activity thresholds than adults.[32] In contrast, Indigenous adults are less likely than non-Indigenous peers to be sufficiently active for optimum health. In a 2012–13 study, Indigenous adults in non-remote areas who were sufficiently active were less likely to be obese (31%) than those who were inactive (56%). Barriers to participation in physical activity for Indigenous Australians from this study included concerns over negative social stereotyping or judgement in public spaces, cost and accessibility.[57] However, sports, connection with family and community, and engagement in group and family-based activities strongly motivate participation rates and evidence indicates that gender differences in preferences need to be considered when designing physical activity programs for Indigenous Australians.[57,58]

Sun exposure

Cumulative sun exposure without appropriate protection can be associated with the development of skin cancer, through exposure to ultraviolet radiation (UVR). Non-melanoma skin cancers (NMSC), including basal cell carcinoma and squamous cell carcinoma, are usually found in sun-exposed areas like the head and neck, whereas primary melanoma lesions appear more often in the periphery and torso.[59,60] Despite these differences, both melanoma and NMSC incidence are proportional to UVR exposure. Sun exposure during childhood years and intense intermittent exposure also increases the

risk of melanoma.[61,62] Melanoma and NMSC occur less frequently in those with higher skin pigmentation.[1,63] The decreased frequency among populations with higher melanin content may be related to the level of ultraviolet A cytotoxicity resistance conferred by melanin.[64] Alternatively, it may be explained by higher levels of melanin resulting in a greater absorption of UV radiation, thereby reducing the risk of DNA damage that can lead to melanoma. Despite their decreased frequency of skin cancer, the same exposure risks for melanoma and NMSC exist for Indigenous Australians dispelling the myth that melanoma and NMSC do not occur among Indigenous Australians although its incidence is lower.[65] For example, melanoma in New South Wales had an age-standardised incidence of 16.7 vs 50.8 per 100,000 in Aboriginal and non-Aboriginal people respectively.[66] Detecting skin cancer in dark pigmentation can also be more difficult, compounded by the underrepresentation of pigmented skin in dermatology textbooks.[67] Misunderstanding of cancer risk and the lack of awareness among healthcare providers can lead to later presentations, resulting in Stage II or higher disease.[68] Associated with the later presentation of skin cancer among Indigenous Australians are other environmental and sociocultural factors, including rurality and socioeconomic disadvantage.[69] Furthermore, attributing cancer development to ionising radiation alone is often difficult when comorbidities such as tobacco smoke and hazardous alcohol use exist in clusters that contribute to cancer risk.[70,71]

Dietary factors

A healthy and balanced diet is important for good physical and mental health. Good nutrition can help prevent or delay cardiovascular disease, type 2 diabetes and other chronic diseases including cancer.[72] Australian Dietary Guidelines detail the foods, food groups and dietary patterns that provide the nutrients required for optimal health and well-being, and to protect against chronic disease.[73] Most Australians do not meet the Australian Dietary Guidelines and consume diets high in discretionary foods, sugar, salt and fat, but containing inadequate fresh fruit and vegetables.[74] Dietary guidelines for preventing all types of cancer recommend the consumption of foods mainly from plant sources with five or more servings of fruits and vegetables daily. Vegetables appear more protective than fruits for cancer specifically.[75] The guidelines also stress the importance of limiting the intake of high-fat food, particularly from animal sources. High animal fat diets are documented as increasing the risk of colorectal and breast cancer whereas certain monounsaturated fatty acids from vegetable sources are likely protective.[76] In addition to links with obesity, direct mechanisms may include modification of inflammatory pathways, hormonal signalling, immune function and the gut microbiome.[77,78] A proper diet is important during cancer therapy with numerous studies indicating that malignancy is accompanied by various micronutrient deficiencies such that cancer patients have special nutritional needs.[79]

Indigenous Australians experience a higher rate of illness which is related to a lack of access to affordable, healthy, and fresh food (that is, food insecurity).[80] Food insecurity can lead to obesity and malnutrition and a high rate of comorbidities including diabetes, cardiovascular and chronic kidney disease.[81,82] Indigenous Australians have been noted to have lower rates of fruit and vegetable consumption than non-Indigenous Australians, while malnutrition resulting from poor fruit and vegetable intake contributes to the development of cancers including non-Hodgkin lymphoma, renal cell, oesophageal, gastric and head and neck cancers.[83,84] Indigenous Australians have also been reported to consume more processed and red meat, which has been linked with increased rates of colorectal, lung, breast, hepatocellular and endometrial cancers.[85,86] Access to and cost of fruit and vegetables, particularly in remote areas is an issue, with these components of a healthy diet showing the biggest price differential by remoteness.[81,87] A transition from traditional bush foods to the provision of takeaway foods in remote communities contributes to food insecurity and cancer risk.[81,88] This has been further exacerbated by additional stresses on supply chains such as the COVID-19 pandemic.[89]

Overweight and obesity

Overweight and obesity are major health problems globally, resulting in both morbidity and reduced life expectancy through increasing the risk of many health conditions, including cardiovascular disease, type 2 diabetes, renal diseases, some cancers, respiratory and joint problems, sleep disorders and social problems. Excess weight or adiposity is a common risk factor for cancer onset, progression, and mortality. A range of putative mechanisms have been identified inclusive of insulin resistance and dysfunctional IGF-1 signalling, sex hormone biosynthesis and signalling, impacts on inflammation and cytokine biology and the direct effects of adipocyte-secreted adipokines.[90] Cancers known to be associated with obesity include breast, endometrial, oesophageal (adenocarcinoma), renal, hepatocellular, and colorectal cancers,[46,91,92] with emerging evidence for prostate cancer, many haematological malignancies and renal cancer.[93] The incidence of obesity-related cancers in Australia has increased by birth cohort across all age groups.[94] Based on ABS data, Indigenous Australians have a disproportionately high rate of obesity based on body mass index (BMI), with 71% of individuals over the age of 15 being overweight or obese in 2018–19.[35] The highest burden (76%) is found in those in inner regional areas of Australia. There has been little specific analysis of the interaction between cancer incidence and obesity

among Indigenous Australians although in the Indigenous population obesity has been noted to co-exist at high levels with other cancer risk factors including lower levels of physical activity, poorer nutritional quality, type 2 diabetes, and hepatitis B carriage until recently.[46] This is in addition to other markers of disease risk such as harmful alcohol consumption and psychosocial distress, attributed to the intergenerational impacts arising from colonisation and prejudice on Indigenous Australians.[95–97] All in turn are linked to lower engagement with self-care and healthcare and, consequently, poorer health outcomes.[45,98]

Infections

Infectious agents can play a significant role in the development of some cancers, with cancer-causing infections responsible for up to 25% of cases in low- and middle-income countries.[25] Many infectious agents that cause or contribute to cancer in humans have now been characterised in Indigenous Australians,[99] including hepatitis B virus (HBV) and C virus (HCV) which are associated with hepatocellular carcinoma, and human papillomavirus (HPV) which is associated with cervical and oropharyngeal cancers. These viruses are mostly spread via horizontal or sexual transmission. Horizontal transmission occurs by parenteral contact with blood or blood products (e.g. shared needles, blood transfusions, or healthcare procedures). These viral infections may also uncommonly be transmitted vertically from an infected mother to her live infant. Also very prevalent is *H. pylori*, which causes long-term inflammatory changes in gastric cells, increasing the risk of peptic ulceration, gastric adenocarcinomas and lymphoma.[100]

Both HBV and HCV, which are prevalent among Indigenous Australians, can cause genomic instability which in combination with the high rate of hepatic cirrhosis (of which the most common contributors are alcohol, metabolic-associated fatty liver disease, and HBV and HCV) can lead to cancer.[47] The HBV integrates its own DNA into the host cell genome and, when transcribed can lead to widespread genetic alterations within the cell (insertions, deletions, translocations, amplifications).[101] Human genes reported to be frequently altered are *TERT, MLL4, CCNE1, NTRK2, IRAK2* and *MAPK1*, the mutation of many of which can lead to malignant transformation of cells.[102] The HCV is an enveloped virus with an exclusively cytoplasmic life cycle without integration into the host genome like HBV and so increases cancer risk by somewhat different mechanisms. The HCV mediates the interplay of host, environmental and viral factors to promote inflammation and produce an oncogenic environment. It can induce genomic instability by interfering with DNA repair and manipulating a variety of genes that regulate crucial processes of cell cycle progression.[103]

According to AIHW data, hepatocellular carcinoma (HCC) was the 7th most common cancer diagnosed in Indigenous Australians compared to only 16th in the non-Indigenous population in 2018. Indigenous Australians are 2.4 times more likely to be diagnosed and 2.4 times more likely to die of HCC than non-Indigenous Australians.[1] Rates of HCC transformation from chronic hepatitis B and C have been documented to range from 0.2% in individuals <50 years of age without cirrhosis to 8% in hepatitis B cirrhosis and 5% in hepatitis C cirrhosis.[104] Chronic hepatitis B affected up to 6.8% of the Torres Strait Islander Australian community in one study, and from 2.5 to 6% of Indigenous Australian communities in Central Australia, largely attributed to vertical transmission before the implementation of universal vaccination.[46,105–107] This compares with a prevalence of 0.061% in the overall Australian population based on Commonwealth estimates.[108] Horizontal transmission of HBV infection in children is also well described in Indigenous children in remote Australia, enhanced by overcrowding and skin abrasions.[46] Sexual transmission and intravenous drug use are also important means of spread.[109,110]

From a 2023 surveillance report, Indigenous Australians have age-standardised rates of hepatitis C seven times that of non-Indigenous Australians (156.2 per 100,000 vs 21.7 per 100,000).[111] Hepatitis C infections are largely spread by blood transmission associated with injecting drug use with Indigenous people who inject drugs at higher risk than their non-Indigenous counterparts.[112,113] The risk of cancer development should be considered in the context of multiple environmental factors including incarceration, smoking and alcohol use in addition to polysubstance misuse.[112,114,115]

The introduction of an effective hepatitis B vaccine and the adoption of screening of all Australian infants and the passive use of hepatitis B immunoglobulin for infants born to mothers with chronic hepatitis B infection has seen marked reductions in chronic hepatitis B in Indigenous Australians born since 2000. However, those infected before widespread vaccination are still at high risk of hepatocellular carcinoma.[116] Efforts to improve the uptake of hepatitis B vaccination, improve the understanding of treatment and implement regular liver screening in those with chronic hepatitis B have been implemented in some Indigenous settings.[45,117] These efforts are important to reduce the risk for HCC.

Varying strains of human papillomavirus are associated with cancer, particularly types 16, 18, and 45 for cervical cancer and 16 and 18 for head and neck cancer which are all now covered by vaccination programs in young people. Consequently, rates of cervical cancer have dropped dramatically with smaller gains in head and neck cancer due to the prevalence of smoking as an

alternative aetiology. In 2023 ABS data, vaccination rates were slightly lower in Indigenous Australian populations, with 80.9% and 75.0% of Indigenous girls and boys respectively relative to 84.2% and 81.8% of girls and boys in the whole population having received at least one dose of HPV vaccine by their fifteenth birthday. This difference was largely accounted for by lower rates in remote areas.[86] The most recent comparative data available (2011–2015) from AIHW found a higher incidence remained in Indigenous women, with an age-standardised incidence rate of 19.9 new cases per 100,000 for Indigenous women compared to 10.0 new cases per 100,000 women in the whole population.[118] This illustrates the ongoing importance of optimising vaccination and cervical cancer screening programs for the Indigenous population.

According to the AIHW, Indigenous people are 1.5 times more likely to be diagnosed with gastric cancer and 1.8 times more likely to die relative to the non-Indigenous population.[1] *Helicobacter pylori*, which is associated with gastric cancer, can be readily detected by a non-invasive breath test and eradicated by a combination of proton pump inhibitors and antibiotics.[119] An early study from Western Australia (WA) found *H. pylori* carriage to be 2 to 3 times higher in the Indigenous population relative to the non-Indigenous population with infection present in 91% of rural/remote inhabitants compared to 60% in the urban community.[120] A more recent WA study has observed that *H. pylori* infection remains significantly more common in Indigenous people.[100] Given that *H. pylori* infection usually occurs during childhood makes a compelling case for targeted eradication strategies for remote Indigenous Australians.

As described, Indigenous Australians experience higher rates of infectious diseases which contribute to the risk of cancer. The high rates of infectious diseases are informed by further determinants which include but are not limited to vaccine administration equity, activities that increase the risk of exposure (sexual practices, incarceration, intravenous drug use), stigma and discrimination, and suboptimal culturally safe preventive health education.[121–125]

Environmental pollution and occupational carcinogens

Urban air pollution and indoor smoke from household solid fuels are known to increase cancer risk in exposed populations, particularly lung cancer, the most common cancer in the Indigenous Australian population.[1] This increased cancer risk is postulated to be due to the increased absorption and metabolism of carcinogens through inhalation.[126] Indigenous Australians have been reported to have a higher exposure to particulate air pollution compared to non-Indigenous Australians.[127] Occupational exposure to carcinogenic substances can occur through a variety of chemicals used in agriculture and the environment. The small number of Indigenous Australians makes it difficult to reach conclusions regarding increased risk and incidence from these risk factors. However, one study identified a cluster of cases of malignant mesothelioma associated with the mining and contamination of asbestos around Wittenoom in WA.[128] There were 39 cases (77% male) of malignant mesothelioma among Indigenous Western Australians of which 26 (67%) were a direct result of the mining of crocidolite at Wittenoom and contamination of the surrounding lands. Indigenous Australians consistently had higher 10-year incidence rates than non-Indigenous Australians. Exposure to many of these potential carcinogens is contributed to by inadequate housing, overcrowding, and lack of ventilation.[127]

Geographical, social and cultural determinants of health

Many risk factors for cancer classified as 'environmental' are exacerbated by poverty and exclusion stemming from historical displacement, frontier violence and continuing discrimination (sociocultural factors). Much of the stark inequity in healthcare outcomes in the present day stems from the generational dispossession of lands inhabited by Indigenous Australians following colonisation and the subsequent discrimination and forcible removal of children from their historical communities and families.[43] Colonisation, racism and a lack of cultural safety in health services continue to negatively impact Indigenous people and these factors create barriers that impact access to healthcare services, including the diagnosis and ongoing engagement for cancer-related care. Family disruption can result in disconnection from culture and community, leading to suboptimal health communication in kinship circles, separation of affected individuals from primary carers, increased risk of behavioural and juvenile delinquency concerns, increased drug dependence, mental health concerns and resulting socioeconomic disadvantage. According to AIHW data, almost half of Indigenous Australians were living in socioeconomically disadvantaged areas in 2016, compared to only 5% who lived in advantaged areas.[129]

The effect of decreased purchasing power parity that results from this disadvantage has flow-on impacts on features of an individual's composite lifestyle and also has effects on health-seeking behaviours including cancer screening. The cost and availability of caregivers to look after the usual dependents of affected individuals while accessing cancer screening, particularly for those from remote communities, can be burdensome.[130] Cancer screening requirements have to be balanced with family and community obligations, which can take priority; moreover, screening opportunities can be infrequent in more remote settings. Likely as a consequence, breast screening, cervical screening,

and bowel cancer screening rates are all lower in Indigenous populations.[1,131,132] Indigenous Australian health services have reported that the bowel screening kit is complicated and not culturally appropriate for their Indigenous patients, leading to a low uptake.[133]

Other comorbidities such as dialysis requirements and diabetes which are experienced at a higher rate in Aboriginal communities need to be concurrently managed when undertaking screening.[14,134] Such factors are not evident in AIHW data on rates of cancer detection, prevalence and incidence among Indigenous Australians. Even after such issues are addressed, ensuring cultural safety, food security and safe and Aboriginal-friendly accommodation is a priority for patients accessing cancer screening in remote rural areas.[135]

Differential exposure to cancer risk occurs across geographical, social and cultural demographics. The proportion of Indigenous people in the population increases with remoteness and there are considerable differences in the living environments of Indigenous Australians across Australia.[136] The climate can exert a significant influence, particularly in the northern Australian summer where extremes of heat make undertaking many forms of physical activity challenging. Low cancer health literacy impacts many Indigenous Australians' understanding of the basis of disease, prevention and health-seeking and in part reflects low educational attainment rates and inadequate culturally appropriate health education programs.[137] This is perpetuated by a lack of geographical access, high financial costs, and institutional cultural barriers stemming from previous intergenerational discrimination embedded in colonisation policies, including education.[81,89,138–140] Socioeconomic and diet-related risk factors impact perinatal, postnatal, and childhood nutrition and contribute to premature disease through mechanisms such as insulin resistance, glucose intolerance, obesity, hypertension, high blood triglycerides, and premature cardiovascular disease.[141] Modifiable conditions such as smoking, hazardous alcohol consumption, obesity, and type II diabetes mellitus which impart heightened cancer risk, can potentially be reduced through health promotion and improved linkages with service delivery. This raises the need for effective multi-component health programs to improve community outcomes and incorporate the following elements: effective assessment and feedback, addressing community priorities, addressing both individual and community issues, long-term partnerships, community engagement and capacity building, cultural competence, involvement of respected Indigenous Australian educators, engagement with Indigenous Community Controlled Organisations, integration with existing services, and involving a dedicated appropriately trained workforce.[142–144]

Genetic drivers of cancer

Ultimately, all cancer is caused by changes in genes. There are two distinct categories of genomic change. The first, germline mutation, is responsible for inherited cancer risk and affects genes associated with cellular DNA repair to prevent cancer initiation. The second, somatic mutation, relates to damage sustained by genes throughout life and impacts genes, which control the way cells grow and multiply (termed somatic driver mutations). Germline mutations contribute to approximately 9% of inherited cancer risk, while somatic driver mutations contribute up to three-quarters of the risk.[145] Some well-described examples of germline mutations include *BRCA1* and *BRCA2* which affect proteins involved in DNA repair resulting in higher cancer risk.[146] Understanding germline mutations is necessary to evaluate population cancer risk. For example, the *BRCA1* and *BRCA2* genes markedly increase a woman's lifetime cancer risk of breast cancer by as much as 87% and ovarian cancer by as much as 44% by age 70.[147,148] However, the contribution of these genes to breast cancer rates in Australia is low (less than 5% of all breast cancers) given the rarity of these gene mutations.[149] Further examples of DNA repair genes involved include *p53*, *BRCA*, *PALB2*, *CHEK2*, *ATM* and mismatch repair genes. Inherited defects in these genes that are usually the target of somatic mutations and directly drive cancer development are rare except for changes in the retinoblastoma protein.[81] These germline pathogenic variants that confer cancer risk not only lead to a higher lifetime cancer risk but also often result in cancer onset at a much younger age than in the general population.

Whereas germline mutations are inherited, somatic driver mutations can develop through exposure to chemicals, radiation, and infection, or because of interactions with the environment. The DNA changes that occur in somatic mutations can vary from point mutations that affect just one nucleotide, such as the *BRAF* gene mutations that are involved in the formation of almost half of all melanomas, through to chromosomal rearrangements, when segments of DNA are rearranged, deleted, or copied such as the *BCR-ABL* rearrangement leading to chronic myeloid leukemia. When germline cancer risk mutations are present, this compromise in DNA integrity by damage from such carcinogens in the environment (e.g. chemicals in tobacco smoke, ultraviolet rays from the sun, and viruses) can then be left unrepaired due to defective DNA repair machinery resulting from the inherited defect. This then leads to an accelerated rate of somatic mutations. Hence, cancer development can be influenced by interactions between inherited genetic and environmental risk.[150]

Considering the number of non-heritable somatic driver mutations required for full cancer causation, this varies by cancer type. Occasionally cancer causation can be driven by single mutations. For example, a type of

leukaemia called promyelocytic leukaemia largely results from a mutation affecting the retinoic acid receptor alpha (*RARA*) gene.[151] In other cases, somatic driver mutations in certain key genes are central to cancer causation but usually require the presence of other mutations for full cancer development. This includes amplification of the *HER2* gene that then produces excessive quantities of HER2 protein causing aggressive breast cancers. Similarly, genetic mutations are thought to contribute to the estimated 1 in 3 women and 1 in 10 men who develop lung cancer who have never smoked[152] with mutation, rearrangement and/or amplifications leading to constitutive activation of oncogenes being more common in never-smokers with lung cancer compared to smokers (78–92% vs 49.5% respectively).[153] Further, never-smokers appear to have different mutations but in the same genes as ever-smokers (deletions in exon 19 vs substitutions in exon 21 of *EGFR* respectively).[154] An explosion of genomic data has revealed numerous cancer-causing (driver) mutations exist in lung cancers from both people who do and do not smoke. These include mutations in *KRAS, EGFR, EML-4-ALK, ROS, RAF/MEK, ERK1/2, HER2, MET, IL1RAP, HER2, NRF2, ACSS2, FGFR, BRAF* and more.[155]

However, many solid tumours result from a small number of mutations in a collection of important growth control genes occurring over time in the same cell. For most large bowel cancers to form, for example, a series of mutations in different genes is normally required for a full cancer to develop.[156] Understanding which genes may result in malignancy if mutated is important in ascertaining the contribution genetics has on cancer development among Indigenous Australians and the range of treatments that may be effective. The converse is also true. For example, though no underlying genetic cause was found for a cluster of vulval cancer in East Arnhem land, it has informed opinion in the utility of further genetic testing compared with public health measures to reduce exposures to HPV streamlining of cancer screening.[157–160]

Epigenetics refers to the modification of gene expression rather than the alteration of the genetic code itself.[161] By changing how DNA is packaged, epigenetic changes can alter how much protein a gene makes which then affects cellular behaviour. There has been longstanding recognition of the influence of fetal exposure to environmental factors on the later development of disease across the lifespan, potentially through epigenetic mechanisms.[103] Understanding has been steadily increasing regarding how life adversities in the nutritional or social environment (including trauma) impact the risk of developing disease across the life course. Given evidence of published data linking familial nutrition and generational obesity and diabetes, both of which are associated with cancer development, it is necessary to explore epigenetics in addition to the genetic determinants of cancer.[162–164] Cellular processes such as apoptosis initiation, regulation of RNA, reactivation of tumour suppressor genes or repression of cancer genes may be epigenetically modified by the impact of nutritional intake, which can increase downstream cancer risk.[165–169] Therefore better identification of potential genetic and epigenetic mechanisms in cancer development is needed to inform future interventions, including among Indigenous Australians.

Increasing understanding of genetics in cancer for Indigenous Australians

The Indigenous population has a history of continuous settlement within Australia for over 40,000 years. Consequently, Indigenous Australian genomes have evolved in relative isolation over many thousands of years, although genetic drift due to small population sizes and climatic changes across that time will have exerted influence. More recently, Indigenous genomes will have been influenced by relatively abrupt exposure to new toxins, altered diets and the impacts of colonisation through Western cultural imprints onto nutrition and physical activities. There will also have been, impacts from interactions with surrounding Pacific communities, the Stolen Generation, rape and forced marriages.[170–172] Studies in other populations have focused on how stress and ancestral malnutrition can be associated with cancer development in later generations.[173] Given the lack of information pertaining to Indigenous Australians, further research on cancer risk across generations, analysing both genetics and epigenetics is overdue.

Considering germline mutations specifically, there is a scarcity of studies that have analysed genetic determinants of cancer among Indigenous Australians. Even descriptions of familial cancer in Indigenous Australians are infrequent. This paucity of studies may reflect either lower rates of testing and so a lack of available results or may reflect lower rates of germline mutation carriage with the lack of positive Indigenous pedigrees which may reduce motivation for further research efforts in this area. Feasibly, poorer access of Indigenous Australians to genetic services, limited genetic literacy and reluctance to take up testing, long-term distress and disengagement from cancer screening and the lack of Indigenous Australian stakeholders in genetic counselling and research relevant to their peoples could underlie the absence of data.[104,174–179]

Our search identified no publications on genetic breast cancer risk in Indigenous Australians based on *BRCA1* or *BRCA2* or other testing. However, recently presented unpublished data revealed a four-times lower germline mutation rate for breast cancer risk genes among Indigenous Western Australians compared to non-Indigenous people from 2001 to 2016 including a complete absence of BRCA1 mutations.[180] This was

despite only minor differences in testing being offered, accepted and conducted and may contribute to the lower incidence of breast cancer among Indigenous compared to non-Indigenous Australians.[181]

The other common area of inherited cancer risk is that of Lynch syndrome, which arises due to mutations in genes involved in correcting faulty DNA repair and confers a 50% lifetime risk of colorectal, endometrial and other cancers. A single Indigenous family carrying Lynch syndrome was noted in the literature, one of twenty families with a defect identified from a new program testing colorectal tumours after their removal.[179]

Regarding somatic mutations, there is precedent from other ancestrally diverse populations to further investigate the contribution of changes to cancer driver genes amongst Indigenous Australians. For example, the spectrum of somatic substitution patterns and driver mutations appear to be significantly different in HCC between certain ancestry groups (Japanese, American, Asian and Europeans), which could also be true for HCC in Indigenous Australians.[182]

One study of remoteness and age-matched Indigenous and non-Indigenous Western Australians with breast cancer demonstrated a significantly higher rate of HER2 amplification in the Indigenous relative to the non-Indigenous population (22 vs 12%, $p = 0.013$).[183] This is clinically important as patients with these tumours respond extremely well to HER2-targeted agents. A second study from the Northern Territory reported a similar finding. Although alterations to the HER2 gene were not specifically reported, 41% v 22% ($p < 0.001$) of Indigenous and non-Indigenous tumours were reported as being HER2 positive respectively, a state largely driven by HER2 gene amplification.[184] No other breast cancer studies were identified.

No published somatic mutation data for Indigenous Australian lung cancer have been published. Since data on never-smokers among Indigenous Australians is lacking at present, it is unknown if they harbour similar mutations to general populations or a different conserved set of mutations that would make them more amenable to certain targeted treatments.[154] The impetus behind concern at the lack of Indigenous Australian genetic information is that international studies have shown that the genomic landscape is significantly distinct in different ethnic groups.[185,186] For example, Native Americans are reported to have significantly higher rates of insertions and deletions than other races, Asians have significantly higher rates of *EGFR, RET* and *HER2* variations, and White Northern Americans have higher rates of *KRAS*,[187] indicating the existence of population-specific molecular signatures in lung cancers. Similarly, no studies of B-raf status in Indigenous Australians with melanoma were apparent, another important marker for treatment targeting.

Discussion

Our review of 33 articles (published between 1998 and 2023) demonstrates that cancer risk among Indigenous Australians is highly multifactorial with interacting determinants. This review highlighted that environmental exposures and individual factors—including pollutant and occupational carcinogen exposures and tobacco, alcohol, physical inactivity, dietary inadequacies and pro-carcinogenic infections, play a significant role in cancer risk. The literature identified persistently high smoking rates, a legacy of colonisation compounded by socioeconomic and cultural disadvantage, are strongly linked with lung, head and neck, oesophageal, and other cancers. Similarly, although the review indicated Indigenous Australians often report higher overall abstinence from alcohol, those who consume it do so at levels that significantly increase the risk of liver, oesophageal, and additional cancers via mechanisms such as DNA damage and chronic inflammation. It showed that declining physical activity—from traditional bush lifestyles to more sedentary patterns—and dietary transitions away from nutrient-dense bush foods toward processed, energy-dense meals further contribute to rising obesity rates and elevate risks for colorectal, breast, and hepatocellular cancers. Furthermore, it demonstrated infections such as HBV, HCV, HPV and *H. pylori*, also promote carcinogenesis by inducing chronic inflammation and genomic instability.

Geographical, social, and cultural determinants were found to further exacerbate these risks. Historical dispossession, intergenerational trauma, forced family separation, and continuing discrimination have entrenched poverty, reduced purchasing power, and limited access to culturally safe healthcare services were all identified. These challenges result in lower rates of cancer screening and delayed diagnoses, particularly in remote communities where competing family and community obligations further hamper access to care.

This review highlighted that germline mutations in DNA repair genes (e.g., BRCA1, BRCA2, p53, PALB2, CHEK2, ATM) account for a relatively small proportion of inherited cancer risk, while somatic driver mutations—acquired from exposures such as tobacco chemicals, UV radiation, and infections—play a major role. Epigenetics further influences cancer risk by modulating processes such as apoptosis, RNA regulation, and tumour suppressor gene function, imprinted by early-life adversities, including nutritional deficits and trauma that predispose individuals to later disease.

It indicates genetic testing may identify people at much higher risk of cancer. It may identify those who may be suitable for screening (through biomarkers or imaging) to allow early treatment or offer opportunities for prophylactic intervention, either surgical (for example mastectomy and oophorectomy among individuals with *BRCA1&2* mutations), or chemo-preventative (such as

raloxifene or tamoxifen in women with *BRCA1&2*) that reduce risk. Counselling and potentially testing of family members gives further opportunity to reduce disease burden. Given the complexities of treatment decision-making, multidisciplinary teams are recommended for advice and management with appropriate cultural support, and to allow a person-centred approach that optimises patient outcomes and efficient health care delivery.[188]

Several gaps pertaining to cancer risk among Indigenous Australians that require addressing in future research are evident. These include cancer under-reporting and delayed diagnoses that likely result from structural and systemic shortcomings, including poor access to genetic services and insufficient epidemiological data that capture the true incidence and prevalence of various cancers within these communities. Much of this relates to identified structural obstacles in healthcare access.[177,179] Though there have been some studies on Indigenous Australians' views on access to cancer services, there is limited further evidence in understanding the quantifiable contribution of these gaps in the development of cancer risk.[189]

The review also identified limited literature related to culturally appropriate and tailored cancer prevention and screening education, despite this being featured in a strategic objective of the Australian Cancer Plan for Achieving Equity in Cancer Outcomes for Aboriginal and Torres Strait Islander People.[190] The absence of interventions designed with Indigenous cultural contexts in mind reduces the effectiveness of public health strategies aimed at improving early detection and reducing cancer morbidity.

There is also an evident lack of contributions from Indigenous Australians in cancer research. Few studies have been led or co-designed by Indigenous researchers, and Indigenous perspectives are underrepresented.[191,192] This limits the development of interventions and health policies that are truly responsive to the community's needs, as well as the application of principles of Indigenous data sovereignty. Any further research into cancer risk should be codesigned and led by Indigenous Australians as guided by the principles of the Framework for Governance of Indigenous Data.[193] This framework also aligns with Indigenous data sovereignty principles which protects Indigenous data in such research and provides ownership of data that is pertinent to their community's health. Indigenous-led cancer research results in greater self-determination and advocacy for issues that directly impact Indigenous health and is particularly needed given deficiencies in past research practices involving Indigenous Australians. Future research approaches that incorporate robust Indigenous community consultation and examine the environmental and genetic determinants of cancer in relation to one another will provide a more holistic understanding of cancer risk, aligning with established Indigenous research methodologies.

We also identified sparse published literature examining the genetic determinants of cancer among Indigenous Australians. Data on both germline mutations (e.g., alterations in BRCA1, BRCA2, p53, and other DNA repair genes) and somatic driver mutations remain limited. For example, only one study documented challenges in identifying Lynch syndrome in an Indigenous family, and there is an absence of published genetic data—such as on BRCA mutations or detailed somatic mutation profiles (e.g., HER2 amplification or EGFR status)—in Indigenous populations.[179] This gap suggests that much remains unknown about how unique genomic alterations may contribute to cancer risk for Indigenous Australians.

Further genetic and epigenetic risk may be further determined through future studies. The National Centre for Indigenous Genomics (NCIG) aims to bring the benefits of genomic medicine to Indigenous Australians by creating Indigenous genomic data resources that can harness pre-existing knowledge about cancer risk factors to inform Indigenous Australians.[194] It has an Indigenous Australian-led board with an established policy framework in line with the National Centre for Indigenous Genomics Statute of 2021.[194] The NCIG is assembling genomes from Indigenous Australians to assess their alignment with the existing human reference genome and ascertaining the number of Indigenous Australian reference genomes needed given the potential differences among Indigenous Australians across Australia. By exploring the genomic variation within Indigenous Australians compared to the world, the NCIG estimates up to ~25% of all genomic alterations appear to be unique to Indigenous Australians. This further consolidates the view that Indigenous Australians have unique genomic profiles that will likely require precision cancer medicine that is tailored to their specific genomic architecture.[195] Furthermore, the clinical significance of these 12–25% genome alterations that are private to Indigenous Australians is unknown. More culturally sensitive and inclusive work is needed to explore this, especially in the context of disparities in health including cancer.[178]

We also note that the policy and planning environment with respect to Indigenous Australians and cancer has been evolving, with significant advances in the last decade. The National Aboriginal and Torres Strait Islander Cancer Framework and the Australian Cancer Plan outline national strategies to address cancer disparities within the Indigenous Australian population and include a focus on prevention, early diagnosis, culturally safe care, and community support throughout the cancer continuum.[13] Additional resources have been given to Indigenous Australian-led initiatives in cancer, through working closely with the

National Aboriginal Community Controlled Health Organisation and affiliates, specifically in Indigenous cancer research.

To help promote and ensure Indigenous leadership, the Aboriginal and Torres Strait Islander Quality Appraisal Tool (QAT) has been promoted to help ensure research with Indigenous Australians is undertaken appropriately.[19] Harfield et al. have acknowledged this challenge, noting that they will update the tool so that it can better meet its purpose to advance Indigenous knowledge and the discourse of Indigenous epistemologies.[196] However, the tool has often proved challenging to use in practice both for primary research and reviews of the literature.[20,197] Furthermore, Henningham et al. reviewed 91 articles on Indigenous Australians and cancer and noted that a lack of Indigenous-led research and consultation was reported in the majority of articles, only 10 (11%) demonstrated success across seven (50%) or more questions of the QAT. The QAT was not completed for this narrative review, and we acknowledge that greater ease of use and familiarity with an updated tool can improve future reviews.[20]

Conclusion

Genetic and environmental (including geographic, sociocultural and individual) risk factors interact to create a complex cancer risk environment for Indigenous Australians. There remains an overall deficit in understanding the specific genetic and environmental risk factors in Indigenous Australians due to a lack of population-specific research. This in turn is impairing the ability of health services to provide tailored prevention and screening strategies for the Indigenous population to reduce cancer incidence and conduct more effective screening programs. Gaps identified from this review included limited published literature on the genetic determinants of cancer, both germline and somatic, a decreased level of surveillance of cancer among Indigenous Australians, structural obstacles in Indigenous Australian's access to healthcare, a paucity of culturally appropriate health education programs related to cancer and the absence of a previous Indigenous Australian focus and contribution to cancer research. At a research level, Indigenous Australians remain systemically disadvantaged, and this impacts policy initiatives around reducing the incidence and early detection of cancer and engagement in health care across multiple cancers. Policies recognising and addressing these factors could improve healthcare access and delivery to better serve the needs of Indigenous Australians and better funding, and relevant policy initiatives developed with Indigenous peak body input are underway. Inclusion of research that is culturally and practically relevant to Indigenous Australians can improve Indigenous Australian cancer literacy, cancer detection and healthcare engagement, including addressing the barriers to accessing cancer screening. This can only occur with the involvement of, and leadership inclusive of Indigenous Australians.

Contributors

AN, KM, AR, ST conceived and conceptualised study design with advice from AB and MR. **AN, KM and ST** performed literature searches. **AN** and **KM** undertook data collection and screening. **AN, ST, AR, AB** performed data interpretation with input from MR and LP. **AN, KM, AR, AB, ST** were involved in writing and revising drafts. **All authors** reviewed and approved the final draft of the paper.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

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