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*Review Article*

# Genomics and splicing events of type II endometrial cancers in the black population: racial disparity, socioeconomic and geographical differences

Flavia Zita Francies[1], Rahaba Marima[1], Rodney Hull[1], Thulo Molefi[2], Zodwa Dlamini[1]

*[1]SAMRC/UP Precision Prevention & Novel Drug Targets for HIV-Associated Cancers (PPNDTHAC) Extramural Unit, Pan African Cancer Research Institute (PACRI), University of Pretoria, Faculty of Health Sciences, Hatfield 0028, South Africa; [2]Department of Medical Oncology, University of Pretoria, Faculty of Health Sciences, Hatfield 0028, South Africa*

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**Abstract:** Endometrial cancer, also known as uterine cancer, is the most common gynaecological malignancy with burgeoning incidence and mortality rates globally. Racial disparity, socioeconomic and geographical differences are important determinants of endometrial cancer incidence and mortality. Endometrial cancer is mainly categorised as type I and type II. Although less prevalent, type II is the most aggressive form of the disease and typically diagnosed at a late stage, contributing to higher mortality. Black women are at higher risk of developing aggressive, type II disease. Type I tumours are related to higher levels of circulating estrogen with lower-grade tumours that have a good prognosis and frequently related to PTEN mutations. In comparison, type II tumours are estrogen-independent, typically have poor prognosis and associated with the p53, HER2, PPP2R1A, FBXW7 and PIK3R1 mutations. The risk of developing type II malignancy is higher in women with Lynch syndrome as a result of mutations in the MMR gene family. Genetic modifications contribute to aberrant alternative splicing events that are related to tumour development, progression and resistance to therapy. Alternative splicing events are rapidly emerging as potential biomarkers and therapeutic targets. Type II endometrial cancer lacks targeted therapy and biomarkers for novel therapeutic strategies. Recent advances have illustrated a number of molecular targets that are currently explored for the treatment of advanced, late-stage endometrial cancer. The aim of this review is to outline 1) the epidemiology of type II endometrial cancer in black women, 2) discuss the correlated risk factors that contribute to the development of type II endometrial cancer and 3) the associated molecular mechanisms and genetic factors underlying the disease, and 4) aberrant splicing events and biomarkers with therapeutic potential as novel drug targets.

**Keywords:** Endometrial cancer, racial disparity, socioeconomic and geographical differences, estrogen, obesity, alternative splicing, biomarkers

## Introduction

Gynaecological cancers are the second most common cancers in women following breast cancer. Endometrial cancer, the most common uterus cancer, is the sixth most frequently diagnosed cancer among women globally [1]. Endometrial cancer is the presence of malignant cells formed in the endometrium, which is the lining of the uterus, and is the most common gynaecological cancer in women in high-income countries such as the United States (US) [2, 3], although the aggressive disease type is primarily observed in the black population [4]. The endometrium consists of a basal and functional layer which is the endometrial lining. In women who are of reproductive age, estrogen and progesterone are required to maintain the normal functional layer that is shed during menstruation. Several risk factors are associated with endometrial cancer such as early menarche, late menopause, obesity and anovulation can cause an increase in estrogen levels and enlarge the endometrial lining leading to endometrial hyperplasia or endometrial cancer [5, 6]. The endometrial lining will be shed as heavy menstrual or irregular bleeding and often leads to early detection, particularly in menopausal women [5]. Diagnostic hysteroscopy with endometrial biopsy are recommend-

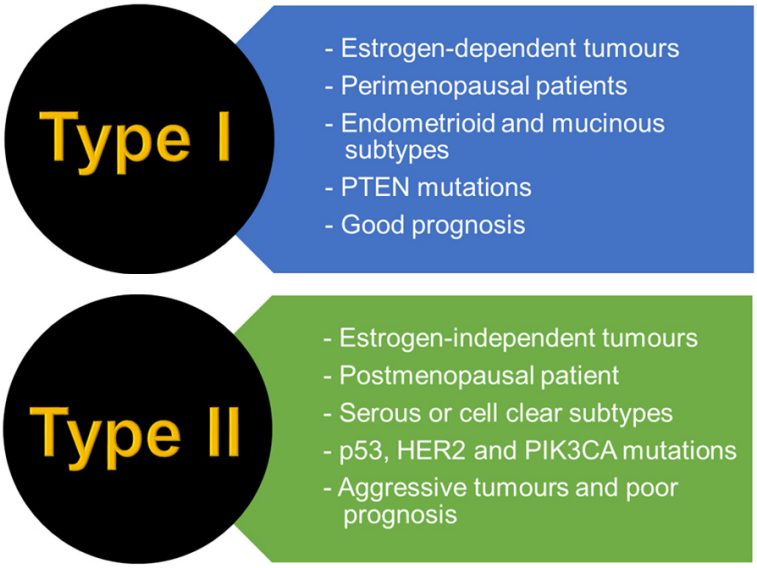


**Figure 1.** Endometrial cancer subtypes. Type I endometrial cancer is typically caused by excess levels of estrogen and have favourable prognosis. In contrast, type II is often diagnosed in black women with an aggressive outcome [3, 11].

ed for postmenopausal women with irregular or abnormal bleeding to detect malignancy at early stages [7].

Endometrial cancer is categorised into several histological subtypes based on cellular differentiation. These subtypes are endometrioid carcinoma, mucinous adenocarcinoma, adenocarcinoma, serous carcinoma, clear-cell carcinoma, neuroendocrine carcinoma, mixed cell adenocarcinoma and, undifferentiated and dedifferentiated carcinoma [3, 5, 8]. Of these subtypes, adenocarcinoma is the most frequently diagnosed type of endometrial cancer. Additional to subtype categorisation, endometrial cancer is further classified into types I and type II that are based on its association with estrogen levels (**Figure 1**). Type I tumours are generally caused by excess estrogen levels in the body. These tumours are typically lower grade that are correlated with Kras, Phosphatase and tensin homolog (PTEN) and PIK3CA mutations and have favourable prognosis [5, 9]. In contrast to type I, type II cancers are fast growing tumours that metastasize and not associated with excess estrogen levels. Type II cancers are commonly high-grade adenocarcinomas that are poorly differentiated and associated with TP53 and human epidermal growth factor 2 (HER2) mutations. These tumours have a high rate of recurrence and metastasis; therefore, type II endometrial cancers have poor prognosis. Type I tumours occur more frequently and account for about 90% of endometrial cancers, and type II accounts for the remaining 10% [5, 10, 11].

The incidence rate of endometrial cancer is on the rise. A racial disparity has been reported in endometrial cancer with varying incidence rates in several ethnic groups. However, black women, in particular, have shown an increase in incidence of aggressive type II tumours that are higher graded compared with white women [12, 13]. The aim of this review is to outline 1) the epidemiology of type II endometrial cancer in black women, 2) discuss the correlated risk factors that contribute to the development of type II endometrial cancer and 3) the associated molecular mechanisms and genetic factors underlying the disease and 4) aberrant splicing events and biomarkers with therapeutic potential as novel drug targets.

## Epidemiology

Endometrial cancer, also known as corpus uteri, is diagnosed in 382 069 women globally every year and contribute to an estimated 23.5% of mortality (**Table 1**) [14]. The lifetime risk of developing endometrial cancer in different regions is presented in **Table 1**. The International Agency for Cancer Research (IACR) reported the highest incidence rate of endometrial cancer in North America with 20.5 age-standardised rate (ASR) per 100 000 and lowest being South-Central Asia with 2.5 ASR per 100 000. Polynesia had the highest mortality rate with 4.7 ASR per 100 000 and the lowest was 0.74 ASR per 100 000 in Northern Africa (**Figure 2**) [14]. In 2018, the IACR stated endometrial cancer as the 20$^{th}$ leading cancer in Africa. However, this lifetime risk may vary in different age and ethnic groups. For instance, the National Cancer Registry (NCR) in South Africa estimates the lifetime risk of endometrial cancer for women to be 1 in 145. The risk, how-

**Table 1.** Incidence, mortality rate and cumulative risk of endometrial cancer globally

| REGION | INCIDENCE (NEW CASES) | CUM. RISK 0-74 (%)* | MORTALITY | CUM. RISK 0-74 (%)* |
|---|---|---|---|---|
| Global | 382 069 | 10.1 | 89 929 | 0.21 |
| Africa | 12 919 | 0.41 | 5 568 | 0.19 |
| East Africa | 3 782 | 0.39 | 1 966 | 0.22 |
| West Africa | 2 993 | 0.40 | 1 625 | 0.24 |
| North Africa | 3 620 | 0.46 | 760 | 0.09 |
| Southern Africa | 1 375 | 0.57 | 601 | 0.24 |
| North America | 65 208 | 2.55 | 11 898 | 0.38 |
| Latin American and Caribbean | 29 353 | 0.92 | 7 493 | 0.22 |
| South America | 18 357 | 0.84 | 5 156 | 0.22 |
| Central America | 8 310 | 1.05 | 1 363 | 0.18 |
| Caribbean | 2 686 | 1.17 | 974 | 0.39 |
| Asia | 148 764 | 0.64 | 34 460 | 0.15 |
| East Asia | 95 704 | 0.86 | 17 276 | 0.15 |
| West Asia | 10 031 | 1.07 | 2 423 | 0.24 |
| South-East Asia | 20 796 | 0.67 | 6 570 | 0.22 |
| South-Central Asia | 22 233 | 0.29 | 8 191 | 0.11 |
| Europe | 121 578 | 1.97 | 29 638 | 0.36 |
| Central and East Europe | 54 657 | 2.33 | 13 790 | 0.49 |
| West Europe | 26 737 | 1.55 | 6 507 | 0.24 |
| North Europe | 16 922 | 1.97 | 3 881 | 0.31 |
| South Europe | 23 262 | 1.78 | 5 460 | 0.28 |
| Oceania | 4 247 | 1.77 | 872 | 0.28 |
| Australia and New Zealand | 3 713 | 1.83 | 732 | 0.26 |
| Melanesia | 440 | 1.30 | 118 | 0.38 |
| Polynesia | 54 | 1.92 | 17 | 0.56 |
| Micronesia | 40 | 1.66 | 5 | 0.09 |

*The cumulative risk, at age 0 to 74 years, of being diagnosed with or mortality from endometrial cancer. Cancer data for America is presented separately for North America and Latin American and the Caribbean by GLOBOCAN. Data adapted from [14].

ever, varies based on ethnicity. In South Africa, Asian women have an estimated risk of 1 in 69, 1 in 165 for black women, 1 in 127 for mixed race women and 1 in 114 for white women [15]. Despite cancer surveillance data in Africa, under-reporting of cancer cases from public and private hospitals is a challenge. Cancer incidence estimates from South Africa show that 28% of under reporting has been observed in private hospitals due to withholding of data and should be quantified to reflect accurate cancer burden in the country. Therefore, improved cancer surveillance in both the private and public hospitals will be advantageous for accurate reporting of cancer incidence rates [16].

*Geographical disparities*

Endometrial cancer is mostly prevalent in high-income countries compared to low- and middle-income countries. Factors that contribute to the geographic variations may include access to high quality healthcare and number of oncologists available in low-, middle- and high-income countries [17]. For instance, an estimated 36% of US counties are situated further than 50 miles from the nearest gynaecologic oncologist [18]. Majority of women in low- and middle-income countries experience similar or severe geographical barriers in accessing quality healthcare. In 2018, approximately 87% new cases of endometrial cancer were recorded in high-income countries [6, 14]. Lortet-Tieulent et al. (2018) showed the highest incidence rates of endometrial cancer was recorded in North America and Europe [6]. The high incidence rate in these countries could be attributed to lifestyle risk factors such as obesity which is associated with almost 50% of endometrial cancer cases [5]. Of a total 43

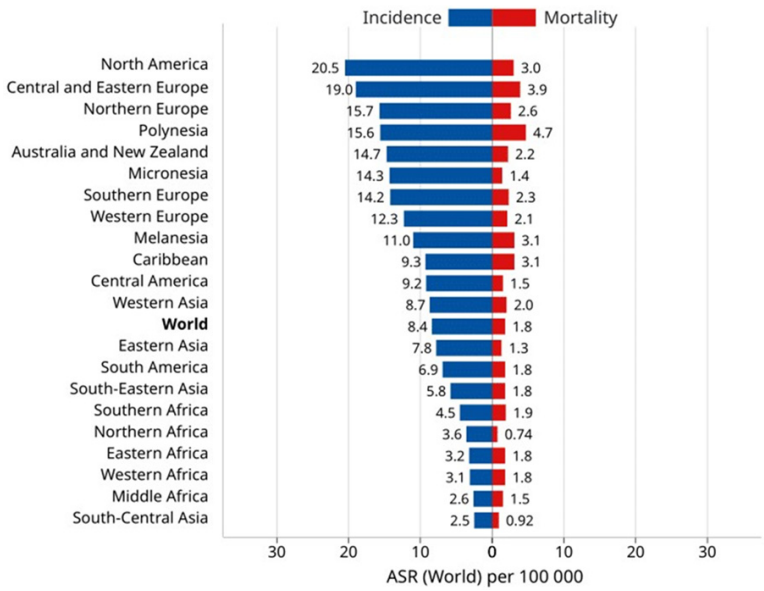


**Figure 2.** Global data for endometrial cancer. Age-standardized rate (ASR) for world incidence and mortality rate of endometrial cancer [14].

countries that were studied, the incidence rate was rapidly growing in 26 countries in this epidemiology study [6]. However, the mortality rate is steadily increasing steeper than the incident rate due to the rise in advanced endometrial cancers and increased life expectancy in high-income countries [19]. Some countries showed a decline in incidence rate in women below the age of 50 years [6]. Although, the median age of diagnosis is 63 and occurs predominantly in postmenopausal women. About 10% of cases are diagnosed in women less than 40 years [20].

*Socioeconomic disparities*

Socioeconomic inequalities are observed across all cancer incidence, mortality and survival rates. Variations in health outcome are influenced by socioeconomic status (SES) measured by a range of factors including income, social class and education. Individuals with a higher SES typically have a favourable health outcome compared to individuals with lower SES due to lack of access to healthcare. Late diagnosis of disease, poor health and reduced survival rates are observed in people with lower SES [21]. Madison et al. (2004) showed that women from higher household incomes are less likely to present with advanced, aggressive type II endometrial cancer. Black women from lower SES lack healthcare insurance and are less likely to receive chemotherapy, radiation therapy and hysterectomies as primary treatments compared to white women with higher SES [22]. Furthermore, Long et al. (2013) elucidated that difference in histology and SES contribute to the vast difference in incidence and mortality observed in endometrial cancer [23]. Endometrial cancer diagnosis in black women with lower SES had a 2.5 times higher likelihood of dying from the disease. Regardless of stage and grade of endometrial cancer, black women are twice likely to receive delayed treatment for endometrial cancer resulting in poor prognosis indicating a potential influence of SES [23].

SES influences the incidence and biology of endometrial cancers regardless of racial disparity. An important indicator of SES is the level of education. A European population-based study with over 5500 women evaluated the influence of education and immigration status by comparing it to the incidence of endometrioid and non-endometrioid endometrial cancer [24]. Not surprisingly, the results illustrated a significant correlation of higher incidence of advanced stage disease and low education levels. Although, immigrant women did not have a higher incidence rates despite low education levels [24]. This further indicates a geographical influence in developing endometrial cancer. SES negatively contributes to poor outcomes and lower survival rates in endometrial cancer due to other factors that are closely attributed to lower SES such as increased smoking, higher body mass index (BMI) and obesity leading to the development of other important co-morbidities [25].

*Racial disparities*

Additional to socioeconomic and geographical differences, racial disparity is an important determinant in endometrial cancer. An epidemiological study conducted on endometrial cancer patients elucidated the incidence in different ethnic backgrounds. Black patients, or women with African descent, had the highest incidence rate with 6.3 per 100 000 and the

lowest was 4.5 per 100 000 in South Asian women [26]. Reflecting the incidence rate, black women have twice the mortality rate compared to their white counterparts. This could be due to the high prevalence of the aggressive type II disease in the black population. Furthermore, the SES, co-morbidities and lack of effective treatment in this population can be attributed to high incidence and mortality rates [27]. A large study with 10647 endometrial cancer patients illustrated that 24.4% of black women had an aggressive serous carcinoma and 24.9% carcinosarcoma compared to 16.3% and 16% in white women, respectively. Additionally, white women had higher rates of stage I disease (45.8%) [4]. The aggressive histology observed primarily in the black population may explain the poor outcomes and reduced survival rates.

Genetic differences are another factor that are influenced by racial disparity in endometrial cancer. The aggressive type II endometrial cancer that is often prevalent in the black population is associated with certain genetic components. Mutations in p53 gene are frequently observed in patients with type II endometrial cancer. Genomic studies have elucidated the recurrence of p53 and PIK3R1 mutations in black women and most likely related to the aggressive type II endometrial cancer and unfavourable prognosis [23, 28]. Mutations in PTEN and PIK3CA were associated with favourable prognosis and most commonly detected in early stage endometrial cancers in white women [28]. Moreover, the upregulation of HER2 is often observed in black women and correlated with treatment resistance and poor survival in aggressive endometrial cancer. Genomic studies scrutinising HER2 expressions have shown that 70% of black women have higher levels of HER2 expression compared to 24% in white women [23]. In contrast, PTEN mutations and microsatellite instability is associated with type I endometrial cancer with favourable prognosis and is frequently detected in white women. An estimated 22% of PTEN mutations and 16% microsatellite instability was detected in white women compared to 5% and 13% in black women, respectively [23, 28]. These results highlight that genetic factors are also indicative of racial disparities in the development of aggressive, type II endometrial cancer.

**Risk factors**

Endometrial cancer is a multifactorial disease. Type I and type II disease is attributed to numerous risk factors such as ethnicity, age, obesity, BMI, endogenous exposure to estrogen, oral contraceptive usage, early menarche, late menopause, parity, family history and genetic predisposition [29]. An overlap of risk factors for both subtypes have previously been reported. However, evidence arising from a large epidemiologic study suggest that type II endometrial cancer are mostly correlated with obesity, age, diabetes, ethnicity, menopause, genetic predispositions and other primary cancers [13, 29-31]. Understanding the risk factors and the aetiology of the aggressive type II disease is essential in implementing preventive strategies.

*Ethnicity and age*

Ethnicity is a strongly correlated risk factor for aggressive subtypes of endometrial cancer. Incidence rates have been shown to differ in ethnic groups. Cote et al. (2015) showed the significantly increasing trend of endometrial cancer in black and Asian women compared to white women [12]. Black women are at higher risk of developing the aggressive and higher graded type II endometrial cancer with poor prognosis, elevated risk of recurrence and mortality. The aggressive type II endometrial cancer incidence rate is closely associated with non-white women, advanced age and obesity [13, 29]. Regardless of the tumour subtype, the 5-year survival rates in black women are also significantly lower [12]. The American Cancer Society reported that black women have a 62% 5-year survival rate compared to the white counterpart with 83%. This difference is 5-year survival between the ethnic groups were attributed to early detection in white women. Due to the racial disparity, black women generally had poor survival rates [32].

Age is a key risk factor that influences the developing endometrial cancer. Endometrial cancer risk increases with advanced age and postmenopausal women are highly likely to be diagnosed compared to premenopausal women with only 4% of diagnosis before the age of 40 [33]. A recent study by Clarke et al. (2020) detected endometrial cancer in 85.7% of postmenopausal women over the age of 45

years (mean age was 55 years) with abnormal uterine bleeding. In premenopausal women, also aged over 45 years, the rate of endometrial cancer detected was 14.3%. Endometrial cancer in these women were correlate with age and high BMI [34]. Women enrolled in this study were aged between 45-86 years and a higher rate of atypical hyperplasia and endometrial polyps were detected in women with higher BMI and advanced age [34]. In contrast, an estimated 2-14% of women younger than 40 years of age are diagnosed with malignancy of the endometrium. Younger women with the disease are likely to have excess endogenous levels of estrogen or defects in the mismatch DNA repair pathway or other known risk factors [35]. A study by Giannella et al. (2019) and Pennant et al. (2017) both detected a prevalence of 1.3% endometrial cancer in premenopausal women [36, 37]. The incidence of endometrial cancer in young women may increase with more than one concurrent risk factors present. Women with endometrial hyperplasia of the non-atypical and atypical type had an increased risk of cancer progression of 10% and 40%, respectively [36]. Therefore, it is vital to screen young women for hyperplasia that may progress to malignancy.

*Obesity*

Endometrial cancer risk is strongly associated with higher body mass index (BMI) and obesity, and accounts for approximately 27% of endometrial cancer [38]. The risk of endometrial cancer is elevated in women who have a higher BMI and are obese as young adults or in middle age [39]. In adipose tissue, androgen is converted to estrone which is a form of estrogen that contributes to the development of endometrial intraepithelial neoplasia leading to malignancy [5, 13]. Endogenous estradiol and estrogen levels are higher in obese women compared to women with normal BMI [40]. The incidence rate of endometrial cancer is rapidly growing in urbanised population where obesity poses a major health challenge. Over the past few decades, the incidence rate of obesity has drastically increased with enhanced BMI's observed in populations such as South Asia, South East Asia, Latin America and the Caribbean [41]. Obesity has escalated from 30% to 38% in women from 1980 to 2013 [6]. This increase in BMI and obesity may be a negative contributor to the increase in incidence in endometrial cancer and is correlated with type I endometrial cancer than type II. Although, type II patients were also categorised as obese indicating the role of other risk factors [13]. The rate of obesity has slightly decreased in the 2000s in high-income countries, most likely due to the prevention strategies and intervention policies to fight the healthcare burden [41]. Black women, however, are still disproportionately affected by obesity. Cultural norms, environmental factors, SES, psychological stress and lifestyle factors contribute to this trend in black women [42]. Physical activity and promoting healthy eating is an important strategy that can reverse obesity and modify the risk of developing endometrial cancer by 59% [6, 41].

Increased BMI and obesity contributed to 34% of the cases of newly diagnosed endometrial cancer globally in 2012. Additionally, obesity is a major risk factor for other metabolic syndrome such as diabetes and insulin resistance which is also associated with endometrial cancer [6]. With the increasing prevalence of obesity globally, prevalence of diabetes is also on the rise. The risk of endometrial cancer increases by 72% in diabetic women [40]. Cote et al. (2015) have reported a twofold risk increase in women who are diabetic with enhanced rates in black women in the US [29]. Mechanisms related to insulin resistance, hyperglycaemia and chronic inflammation caused by obesity-related hormonal imbalance in diabetic patients could contribute to the development of endometrial cancer [40, 43, 44]. Insulin and insulin-like growth factor (IGF) signalling pathways are known to enhance cell proliferation and mediators of the inflammatory pathway overturns tumour suppressor activity [44, 45]. Prolonged insulin therapy may increase the risk of endometrial cancer. The correlation of pre-existing diabetes and endometrial cancer is particularly important and useful for screening women at high risk and for early detection.

*Reproductive factors*

Reproductive factors such as early menarche, late menopause, null parity, term of pregnancy and childbearing history influence the risk of endometrial cancer. Early menarche, before the age of 12, and late menopause, after the age of 55, both significantly increase the risk by

two-fold [20]. Evidence supports the positive link between polycystic ovary syndrome (PCOS) and the risk of endometrial cancer. The main characteristics of PCOS is that the ratio of luteinizing hormone to follicle stimulating hormone is high. This leads to chronic anovulation and thick endometrium with follicular cysts. Due to chronic anovulation, the endometrium is exposed to estrogen for longer periods leading to hyperplasia and eventually endometrial cancer [20]. This risk can be modified by administering progestogens in women with PCOS that allows regular shedding of the endometrium and in turn, regulates the circulating estrogen levels [46]. This is similar to the increased risk observed in pregnant women with preeclampsia, a condition thought to increase androgen levels and regulate estrogen. Therefore, increasing the risk of endometrial cancer in women who suffer from preeclampsia [47].

Reproductive factors such as parity, number of full-term pregnancies, age of first pregnancy and breast feeding may also play an important protective role against endometrial cancer. A 44% decrease in risk was observed in women whose last birth was at the age of 40 compared to women who were 25 years at last birth [46]. Prolonged exposure to progesterone during pregnancy reverses the effects of estrogen on the endometrium and hence, reduces the risk. Another study showed that older age at first birth was closely associated with the risk reduction of type I tumours and the risk reduction for type II tumours were observed in women with shorter time since previous birth [47]. Furthermore, 11% decrease in risk was associated with breast feeding [46]. Widely promoting breast feeding and regulating hormone levels in women with PCOS may alleviate the risk associated with endometrial cancer in high risk women.

*Family history and genetic predisposition*

Regardless of age, women with family history of endometrial cancers are more susceptible to developing the disease and are likely to be screened at regular intervals for early detection. The risk of endometrial cancer can also be evaluated based on risk of familial clustering of cancers such as breast, ovarian, colorectal and cervical [48-50]. This risk may increase with one or more affected first-degree relatives. With a positive family history, the risk is shown to increase risk 2 fold with a first or second degree relative affected by endometrial cancer [49]. Studies have shown the risk of endometrial cancer with a positive family history of colorectal cancer [48, 51, 52]. A colorectal cancer diagnosis of a first degree relative increases a women's risk of endometrial cancer by 17% and could indicate inherited or sporadic genetic anomalies [49]. In a recent study, only 2% of women reported family history of endometrial cancer. These women with positive family history also had other risk factors such as obesity, early menarche and underwent postmenopausal hormonal replacement therapy [53]. Obtaining comprehensive family history and assessing other important risk factors is necessary to evaluate an individual's risk of developing endometrial cancer.

DNA repair mechanisms play a vital role and act as guardians of the genome. Germline mutations in the DNA mismatch repair genes gives rise to Lynch syndrome, an autosomal dominant inherited disorder, and contributes to about 2-6% of endometrial cancers [49, 54]. Germline mutations in MLH1, MSH2, MSH6 and PMS2 results in Lynch syndrome. The risk of developing endometrial cancer in women with Lynch syndrome is increased by 27-57% [46]. Therefore, a personal or family history of Lynch syndrome may predispose women to endometrial cancer [49]. For instance, germline mutations in MSH6, a mismatch repair gene, contributes to an increased risk of 26% in women older than 70 years and 44% in women who are 80 years old [51]. Similarly, a positive family history of a first degree relative with breast cancer predisposes women to a twofold increased risk of type II endometrial cancer. This could be attributed to BRCA1/2 familial mutations which is known to cause ovarian cancer or the use of tamoxifen during the treatment of breast cancer. Tamoxifen is widely used as an anti-estrogen treatment for estrogen-positive breast cancer but has a positive correlation with the development of endometrial cancer [50, 55].

Another risk factor that contributes to genetic predisposition of endometrial cancer is the presence of single nucleotide polymorphisms (SNPs). A recent study has identified SNPs in 6

genes namely HNF1B, KLF, EIF2AK, CYP19A1, SOX4 and MYC that are significantly correlated to the development of endometrial cancer. Evidence shows that women harbouring SNPs in these genes have 2.09 times higher risk of the disease [56]. Identification of variants or SNPs in genes associated with endometrial cancer can be utilised for risk prediction, targeted treatment and to implement prevention strategies for women at risk.

### Molecular biomarkers in endometrial cancer

Despite the current knowledge in type II endometrial cancer, there is still a need to develop more effective regimens that will not just ease the physical burden, but the socio-economic burden in endometrial cancer patients. Such regimens may include the identification of sensitive and specific biomarkers. There is currently no reported biomarker in endometrial cancer for diagnostic or prognostic purposes. Given the establishment of new genomic classifications of endometrial cancers, the use of biomarkers to drive therapeutic approaches will be the basis for individualised cancer care in the future. Diagnostic, prognostic and anticancer therapy potentials of these biomarkers will be a great breakthrough in the fight against endometrial cancer, type II in particular [57].

As defined by the US National Cancer Institute (NCI), a biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease'. The World Health Organisation defines a biomarker as 'any substance, structure or process that can be measured in the body or its products that can influence or predict the incidence of outcome or disease. In medicine, biomarkers can be used for screening, diagnosis, prognosis and treatment purposes. There are different types of biomarkers, some of which overlap. Such examples may include gene-based biomarkers that also function as biomarkers in their protein expressed form [58]. Based on these definitions, a biomarker not only includes tumour protein markers, but also genes and chromosomes. Studies of genes with abnormal expression in endometrial cancer have identified various i) oncogenes (KRAS, HER2, epithelial growth factor receptor (EGFR), phosphatidylinositol 3-kinase catalytic subunit (PI3KCA) and fibroblast growth factor receptor 2 (FGFR2)), ii) the tumour suppressors (PTEN, p53, p21 and cyclin-dependent kinase inhibitor 2A (CDKN2A)), iii) mismatch repair genes (the hMLH1, hMSH2, hMSH6, PMS1 and PMS2, that may lead to microsatellite and genome instability), iv) apoptosis related genes (the BCL 2 gene family) and the v) hormone receptors' expression levels (expression levels of estrogen receptor (ER) and progesterone receptor (PR)) [57, 58]. Moreover, abnormal gene expression can be a result of deleterious mutations in these specific genes that are associated with type I and type II endometrial cancer (**Figure 3**) [59]. The difference in ER signalling in type I and II endometrial cancer is also important. The PR is required for the inhibition of endometrial cell proliferation that is due to estrogen signalling and downregulates the activities of estrogen by preventing the transactivation of ERα [60, 61]. Cell proliferation markers such as high Ki-67 indices in serous carcinoma and high levels of angiogenesis factors such as the vascular endothelial growth factor A (VEGF-A) have also been linked to endometrial cancer [62]. Interestingly, Townsend et al. (2019) also identified Jagged2 (JAG2), Aurora Kinase A (AURKA), Phosphoglycerate Kinase 1 (PGK1), and Hypoxanthine Guanine hosphoribosyltransferase 1 (HPRT1) as potential biomarkers, as these genes have been found to be upregulated and also show significant impact on overall endometrial cancer patient survival, particularly HPRT1 and AURKA [63]. Specific to type II endometrial cancer, genetic alterations in p53, HER2, p16 and E-cadherin have been documented [64, 65]. Furthermore, Singh et al. (2011) showed that TP53 was increasingly expressed in African-American women than in their Caucasian counterparts with endometrial cancer. In this study, the 5-year survival rate dropped to 52% from 85% [66]. Genetic alterations which include perturbations in the alternative splicing events are rapidly emerging as potential diagnostic, prognostic and therapeutic targets.

Endometrial cancer type I and type II are associated with different biomarkers that determine the prognosis and beneficial in predicting response to therapy. Molecular alterations that are specific to disease type can be identified using genetic profiling for clinical utility. For instance, lymph node metastasis is associated with the over expression of cell

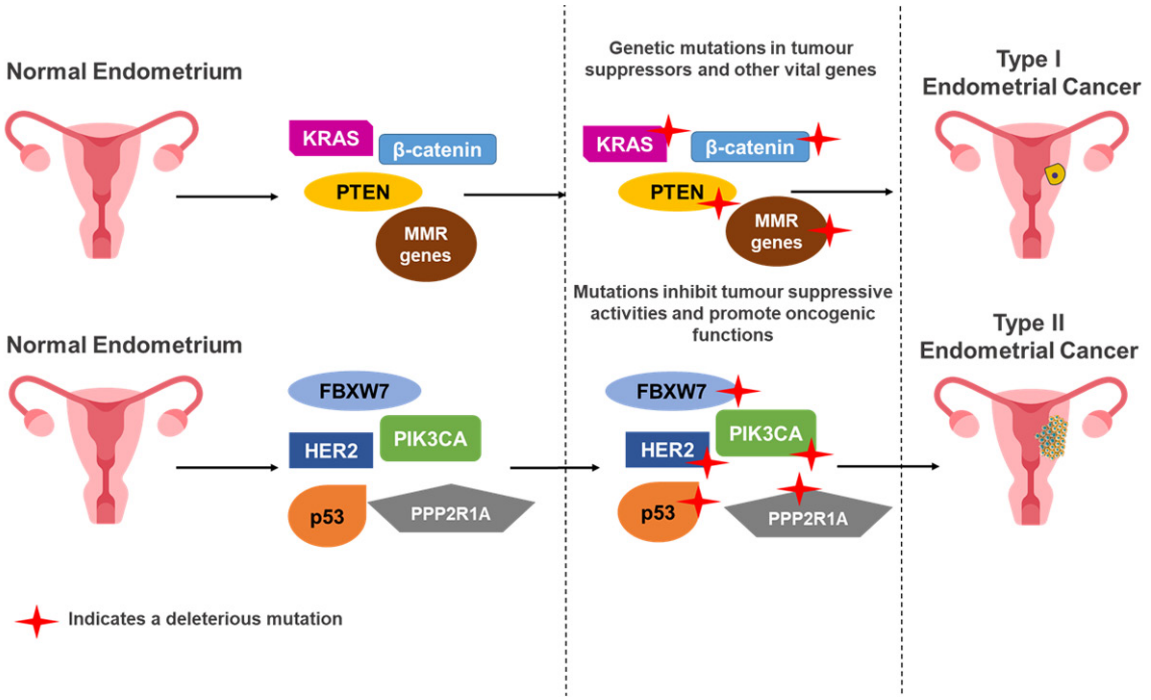


**Figure 3.** Biomarkers in endometrial cancer. Mutations in oncogenes, tumour suppressors, mismatch repair (MMR) genes and hormone receptors genes lead to abnormal expression resulting in malignant transformation. Mutations in these genes are associated with type I and type II endometrial cancer.

cycle checkpoints genes, CDC2 and MAD2L1, and the transcriptional regulator, ZIC2 zinc finger protein. These biomarkers can be utilised to predict prognostic outcomes in patients with endometrioid endometrial cancer [67]. Furthermore, hormone receptors in advanced endometrial cancer is closely correlated to clinical response. Evidence shows that the presence of ER and PR respond differently to hormone therapy [68]. A previous study reported that treatment response was strongest in ERα endometrial tumours. A lack of clinical response was observed in PRα and PRβ tumours. Despite these response results, approximately 26% of endometrial cancers lacking ER responded to hormonal therapy and, in contrast, the absence of PR resulted in a 32% clinical response [68]. This is particularly relevant for aggressive, type II endometrial cancers with poor prognosis that lack ER and PR. On the contrary, patients harbouring HER2 deletion or amplification, typically prevalent in type II cancer, show no response to anti-HER2 treatment [69]. Recent data, however, shows enhanced clinical response and progression-free survival in response to anti-HER2 treatment in patients with type II endometrial cancer [70-72]. Although, further validations of clinical response to anti-HER2 is warranted. These results highlight the importance of molecular characterisation of endometrial cancers to facilitate clinically beneficial outcomes.

### Alternative splicing in endometrial cancer

Alternative splicing is carried out by the spliceosome, which consists of five small nuclear ribonucleoprotein (snRNP) particles. These snRNP particles are U1, U2, U4, U5, and U6 snRNPs that assemble at each intron around splice sites [73]. The spliceosome recognizes each splice site that consists of a consensus sequence around each exon-intron junction [74, 75]. Additional sequence components in exons or introns can work as enhancers or silencers to regulate the binding of splicing factors. The splicing factors can then either promote or inhibit the recognition of a given exon by the spliceosome. Two main nuclear RNA-binding protein families may regulate splicing, particularly in cancer-related genes. These two families are the heterogeneous nuclear ribonucleoprotein (hnRNP) and the serine/arginine-rich protein (SR) family [76, 77].

Alternative splicing is an important regulation mechanism in the processing of mRNAs after transcription. Pre-mRNA produces different mRNAs through different splicing methods to translate into different proteins with unique functions [78, 79]. About 95% of all human genes undergo alternative splicing and this contributes to protein diversity [79, 80]. This ubiquitous process has been shown to play a crucial role in cellular health and cancer biology [81, 82]. There are different types of alternative splicing events and these can be distinguished as (a) alternate acceptor site (AA), (b) alternate donor site (AD), (c) alternate terminator (AT), (d) alternate promoter (AP), (e) exon skip (ES), (f) mutually exclusive exons (ME), and (g) retained intron (RI) [83].

There is increasing evidence that aberrant alternative splicing is closely related to the development of cancer. Aberrant alternative splicing events can thus be targeted as cancer biomarkers. Although, one of the limits with this approach may be in concentrating on fewer genes than in whole genome analysis. Whole genome analysis of alternative splicing events may aid to overcome this limitation by targeting events of this process as biomarkers to improve overall endometrial cancer patient care. Wang et al. (2019) constructed a model based on the Prognostic-Related Alternative Splicing Events (PASEs) and splicing factors using whole genome analysis of alternative splicing events [78]. This has assisted in promoting the prognosis of endometrial cancer patients. Additionally, miRNA regulation has also been shown to influence splicing events that control the cell fate [84].

The effective diagnosis and prognosis of endometrial cancer, particularly type II is limited by a lack of sensitive and specific biomarkers. A single gene can undergo various types of alternative splicing events and also be regulated by different splicing factors. This complicates the study of the regulatory networks between alternative splicing events and splicing factors and further complicates identifying and defining potential alternative splicing biomarkers. Using whole genome sequencing analysis, Wang et al. (2019) revealed that aberrant expression of splicing factors is associated with the overall survival of endometrial cancer patients [78]. Furthermore, research has shown that alternative splicing of ERα and PR closely correlate with the occurrence and development of endometrial cancer [85]. Recently, a newly identified splicing factor, YT521, was shown to promote the alternative splicing of VEGF-A. This leads to an upregulation of VEGF-165 variant, thereby promoting endometrial cancer invasion [86].

Alternative splicing contributes to various aspects of tumour development, tumour progression and resistance to therapeutic treatments. A significant portion of cancer-associated genes are regulated through alternative splicing, indicating a pivotal role alternative splicing plays in the production or activation of oncogenes and tumour suppressors [78]. As an important biological process, understanding alternative splicing in cancer might contribute to better understanding of the malignant transformation and identify novel pathways that are particularly relevant to tumorigenesis. Understanding the molecular origins of cancer-associated alternative splicing isoforms will aid to understand the basis of cancer and simultaneously provide opportunities to improve the efficiencies, sensitivity and specificity of the anti-cancer treatments that will kill rapidly dividing cells rather than normal cells. For instance, targeting alternative splicing isoforms selectively expressed by cancer cells and not by normal cells may be suitable therapeutic targets and could also suggest precise personalized therapy (**Figure 4**) [87]. Molecular targeted therapy, particularly targeting alternative splicing events in endometrial cancer holds promising therapeutic approaches since current standard treatments are not responsive [88]. With the increased endometrial cancer type II mortality rates and lack of effective treatment, there is a need for new treatment options and alternative splicing targeted therapy is promising [89-96]. In addition to ERα, PR and VEGF, other identified and potential biomarkers in type II endometrial cancer with targeted alternative splicing may include HER2, F-box/WD repeat-containing protein 7 (FBXW7), Protein Phosphatase 2 Scaffold Subunit Alpha (PPP2R1A), p53, PTEN and PIK3CA.

*HER2*

HER2 is one of the four human epidermal growth factor transmembrane cell surface receptors [97]. HER2 amplification leads to oncogenic functions and is closely associated

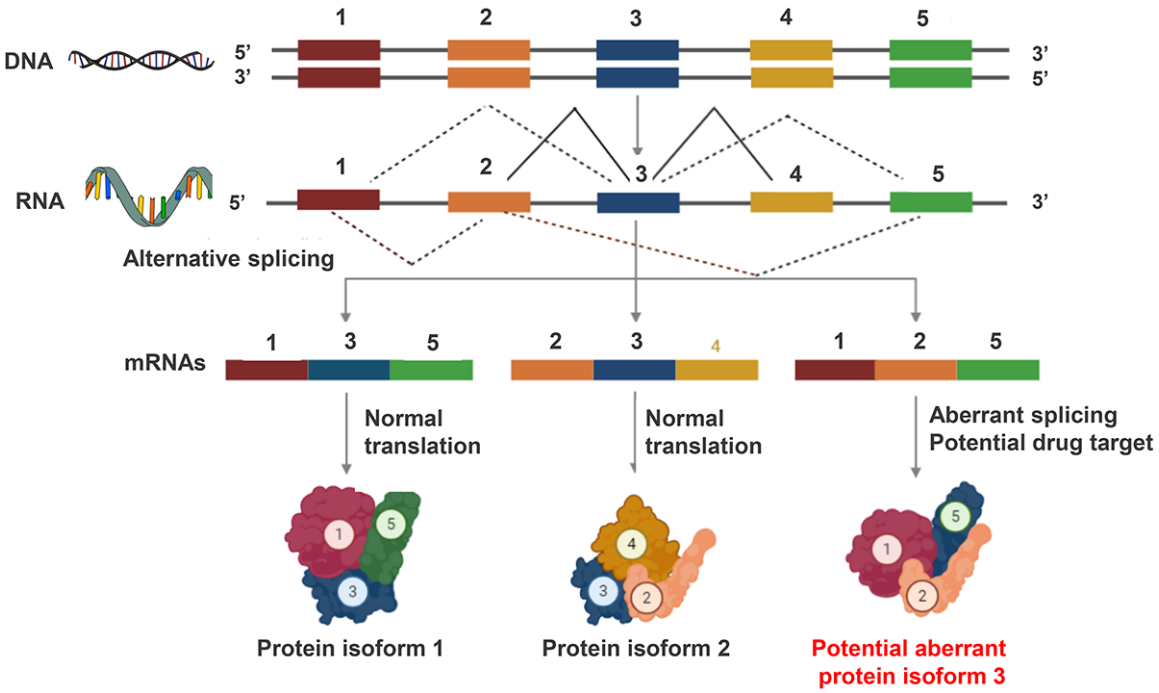


**Figure 4.** An overview of alternative splicing. Alternative splicing is a molecular mechanism that produces protein isoforms with different cellular functions. Defects in alternatively spliced isoforms may modify these functions and promote tumourigenesis. Due to aberrant splicing, the defective isoforms may serve as potential biomarkers for cancer diagnosis or prognosis, or potential drug targets [124].

with type II endometrial cancer with unfavourable prognosis. The prevalence of HER2 gene alterations is widely prevalent in type II endometrial tumours compared to type I [88]. Alternative splicing has revealed three different splice variants of HER2 with conflicting roles in tumour biology. These isoforms are i) Δ16HER-2 (which results from exon 16 skipping), this isoform increases transformation of cancer cells and is related to treatment resistance [98], ii) second isoform is Herstain (results in the retention of intron 8), and iii) p100 is the third isoform (resulting from the retention of intron 15) (**Figure 5**). The second and third splice variants act antagonistically to Δ16HER-2, as they inhibit tumour cell proliferation [99, 100]. HER2 overexpression in endometrial cancer has been reported and the precise roles of its splice variants p100, X5, Δ16HER-2, CTF-611, CTF-687, HER2-B and Herstatin in endometrial cancer remains to be elucidated, as they have been in breast cancer [101].

*FBXW7*

FBXW7 isoforms have also been implicated in cancer [102]. FBXW7 is a tumour suppressor that degrades various oncoproteins. These oncoproteins include c-Myc, c-Jun, cyclin E, different members of the Notch family Aurora-A, mTOR and KLF5 [103]. Loss of function or mutation of FBXW7 has been reported in various human cancers, including endometrial cancer. Frequent mutations in the WD40 repeats alters the function of FBXW7 and contributes to its oncogenic properties (**Figure 6**). These mutations are commonly detected in type II endometrial cancers [104]. FBXW7α, FBXW7β, and FBXW7γ are the 3 different FBXW7 mammalian isoforms. These isoforms differ in their 5'-UTR and N-terminal coding regions and have distinct cellular localizations. This restricts their interactions with their partners. FBXW7α is localized in the nucleoplasm, while FBXW7β in the cytoplasm, and FBXW7γ is nucleolar [105]. FBXW7α is abundantly expressed in proliferating cells and performs most of the known functions of FBXW7.

*PPP2R1A*

PPP2R1A is another gene whose alternative splicing events have been implicated in endometrial cancer. Particularly in type II, about 40% of these tumours are associated with het-

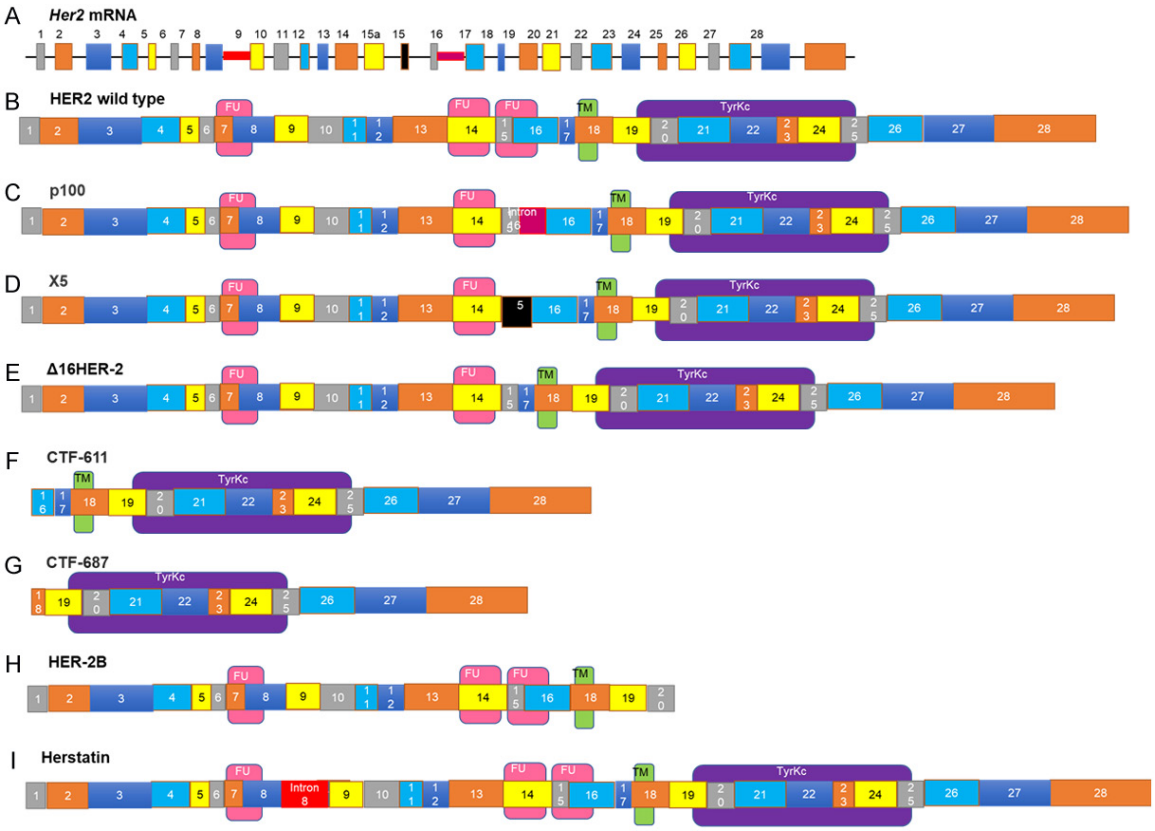


**Figure 5.** Isoforms of HER2. The HER2 gene (A) is spliced to give rise to multiple variants as well as the wild type (B). The region between exons 14 and 16 give rise to many variants, some of which are involved in endometrial cancers. (C) The p100 isoform results from the retention of intron 15. (D) The X5 isoform which splices in part of intron 14 (E). The Δ16HER-2 results from the skipping of exon 16. This isoform increases transformation of cancer cells and is related to treatment resistance. In addition to these splice variants there are 2 further variants produced by alternative translation initiation in exon 15 and 17, CTF-611 (F) and CTF-687 (G). (I) The HER-2B isoform is produced with the exclusion of exon 17. The last isoform (H) Herstatin is formed by the inclusion of intron 8 [101].

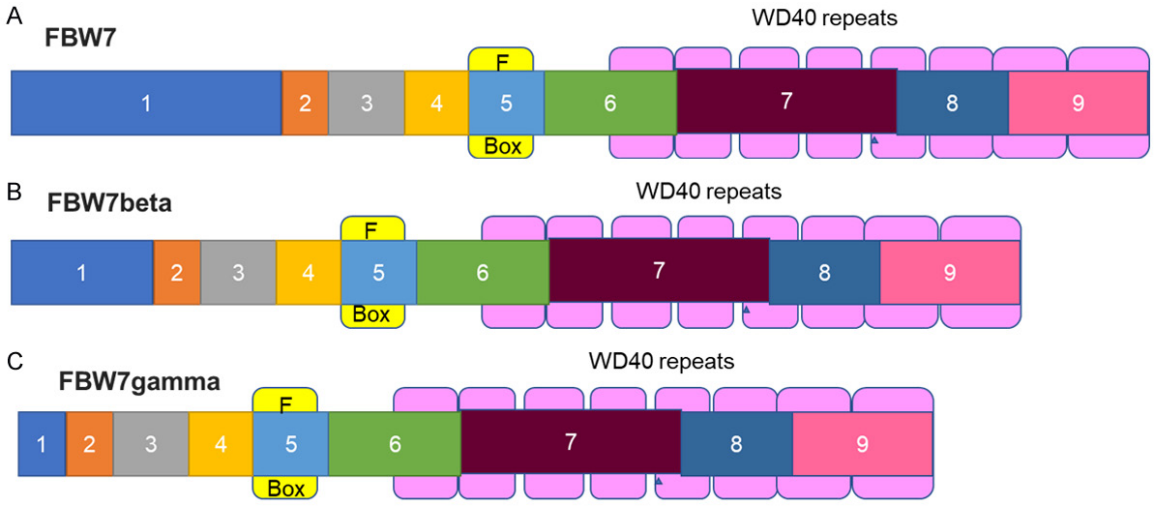


**Figure 6.** Alternate splicing of FBXW7. There are three isoforms of FBXW7 - FBXW7α, FBXW7β and FBXW7γ. The isoforms differ in their 5'-UTR and N-terminal coding regions and have distinct cellular localizations. The domain structure of these isoforms remains the same and the changes in the N-terminal lead to changes in the cellular localisation [125].

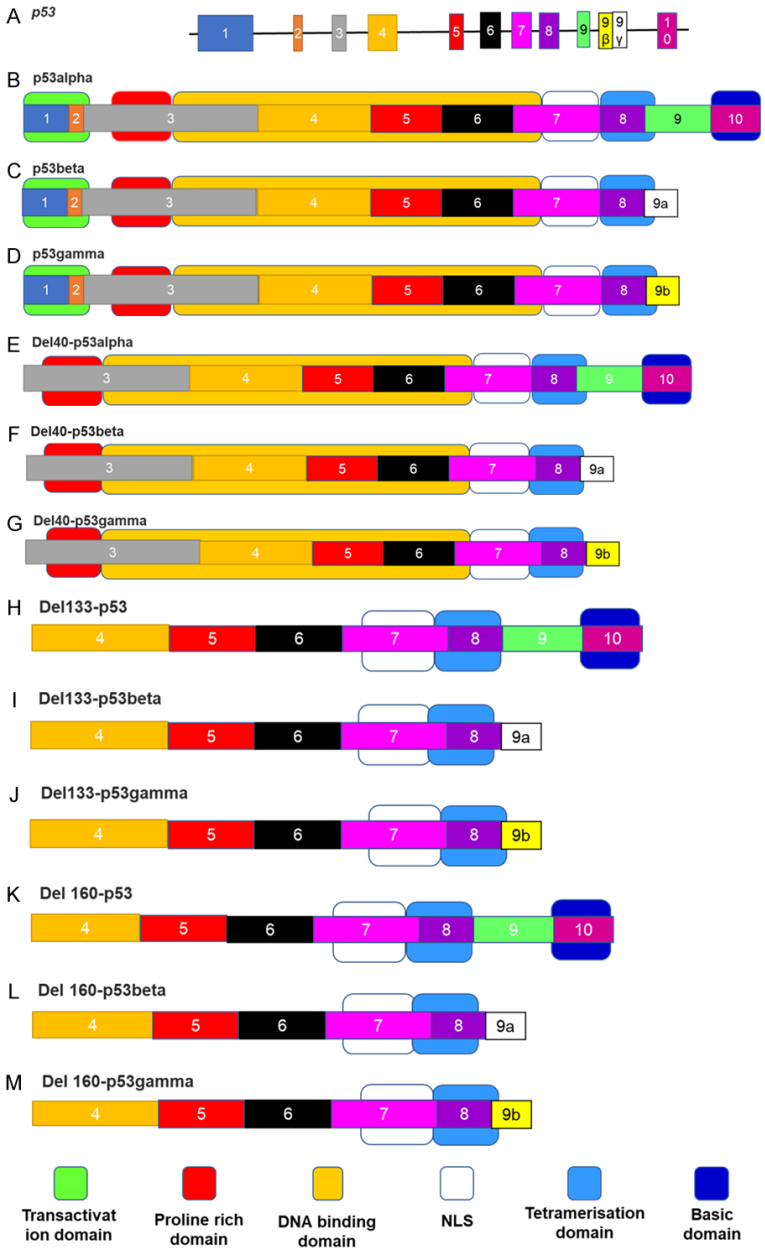


**Figure 7.** Splice variants of p53. Twelve isoforms of p53 have been identified. Alternate splice variants of p53 arise due to the use of alternative translation sites or promoters. The isoforms share a DNA binding domain. The alpha, beta and gamma variants differ in the use of alternate exon 9 splice sites, that lead to an exclusion of exon 10 and the loss of the Basic C terminal domain. Further variants arise due to deletions of the N terminus due to the exclusion of exons 1, 2 and 3. This leads to progressive losses of the Transactivation and proline rich domains [107].

erozygous missense mutations in PPP2R1A, a variant PPP2R1 isoform and tumour suppressor gene that encodes the alpha subunit of PP2A [88, 99]. Evidence supports that association of PPP2R1A mutations with aggressive type II endometrial cancer and unfavourable outcomes. Patients with serous endometrial cancers harbouring PPP2R1A mutations show poor 5-year survival compared to patients without the PPP2R1A mutation [88]. Further validations of 5-survival year of patients with and without PPP2R1A mutations are warranted.

*p53*

p53 mutations are frequent in most cancers. In endometrial cancer, p53 mutations are correlated with high grade tumours and advanced disease. An estimated 57.7-92% of TP53 mutations occur in type II tumours [88]. In humans, about 12 different protein-encoding transcripts of the p53 gene have been identified. These p53 isoforms have been potentially identified as predictive and prognostic markers in cancer patient care (**Figure 7**) [106, 107]. Furthermore, the p53 splice variants have emerged as possible active contributors in cancer development and progression [108]. For instance, p53β and p53γ protein expression is associated positively with overall survival (OS), chemotherapy response and mutational markers for survival in the aggressive blood cancer acute myeloid leukaemia [109].

Contrary to other studies, p53γ was not directly linked to the OS but was proportionally linked to prognosis of breast cancer disease [110]. Such data highlights the complexity of alternative splicing events in different cancers and therefore cannot be approached with the same regimens. This calls for a clear unique patient model underpinning the molecular basis of the diseases, targeting alternative splicing, and therefore thriving towards person-

alized, unlike generalized, medicine. Increased p53 expression in endometrial cancer type II has been reported, however, the precise roles of the different isoforms in type II endometrial cancer would be beneficial to these patients.

*PIK3CA and PTEN*

The phosphoinositide 3-kinase (PI3K) signalling pathway is vital in regulating cell proliferation, cell cycle control and apoptosis. Deleterious mutations in PIK3CA and PTEN have a negative effect on the PI3K pathway which often observed in type II endometrial cancers. PTEN mutations are found in almost 25% of cases of hyperplasia and up to 80% of endometrioid cases [111, 112] with 67-84% mutations detected in type I [104]. PTEN mutations are, therefore, significantly linked to type I rather than type II endometrial cancer, however, a significant number of PTEN mutations are detected in type II endometrial cancer. For instance, 2.7-22.5% PTEN mutations are reported in type II serous carcinoma, 11-21% in type II clear cell carcinoma and 19-33.3% in type II carcinosarcoma [104]. PTEN negatively regulates class I PIK3 enzymes. These enzymes play a role in the PI3K signalling pathway. PIK3 is highly dysregulated in cancer, leading to elevated PI3K signalling, uncontrolled cell proliferation and tumour development [113]. Endometrial cancer has been reported to harbour genetic alterations in components of the PIK3 signalling pathway, PIK3CA oncogene and the tumour suppressor PTEN in particular. Deletions in the coding region of PTEN gives rise to several minor splice variants such as PTEN-L, -M and -O (**Figure 8**). A number of the splice variants are known to be associated with cancer [114]. PIK3CA gene encodes the PIK catalytic subunit p110α. Unlike the p110β isoform, p110α alterations are more common in endometrial cancer [115, 116]. Furthermore, these class I isoforms have been targeted for and are currently on clinical trials with regards to treatment of endometrial cancer patients [117, 118]. This highlights the use of alternative splicing molecular markers as cornerstone markers not just in diagnosis and prognosis, but also in the anticancer treatment of type II endometrial cancer.

**Challenges and limitations**

Early diagnosis is key in treating endometrial cancer and lowering mortality rates. The typical diagnosis of type II endometrial cancer in black women poses a major healthcare challenge particularly in resource restrained settings. Racial disparities in endometrial cancer is well recognised [12]. But high-risk black women may be at a disadvantage in receiving optimal and effective treatment. Endometrial cancer in young women generally have a favourable outcome due to early detection. Evidence shows that young black women have 19% worse survival rates compared to white women after adjusting for pathologic difference in the two groups. Likewise, a 24% survival rate was detected in black women with early stage tumours [119]. Black women are affected with lower survival rates at across all subtypes due to socioeconomic factors and limited access to standard healthcare [12]. It is imperative to identify women with high risk factors, particularly young black women in resource limited setting, to prevent the onset of endometrial cancer and implement early treatment strategies.

Histological classification of endometrial cancer subtypes is vital for determining treatment options and evaluating prognosis. Challenges with inconsistent classification based on histology of endometrial cancer tissue and tumour heterogeneity can lead to inaccurate treatment and risk stratification. Furthermore, rare histotypes and diversity within tumours pose an additional challenge in precise categorisation of tumour subtypes which are essential to evade over or under treating patients [4, 120]. Diagnostic reproducibility and accurate subtyping are poor in the aggressive, grade 3 endometrial tumours, specifically type II endometrial cancers [4]. Talhouk and McAlpine (2016) argue that molecular classification of endometrial tumours in conjunction with histopathology may have added benefits [120]. Molecular classification is relevant for choosing treatment options based on subtypes [121]. Additional to subtyping, women with inherited endometrial cancer may also benefit from molecular classification [120].

Other challenges associated with endometrial cancer include screening and prevention of

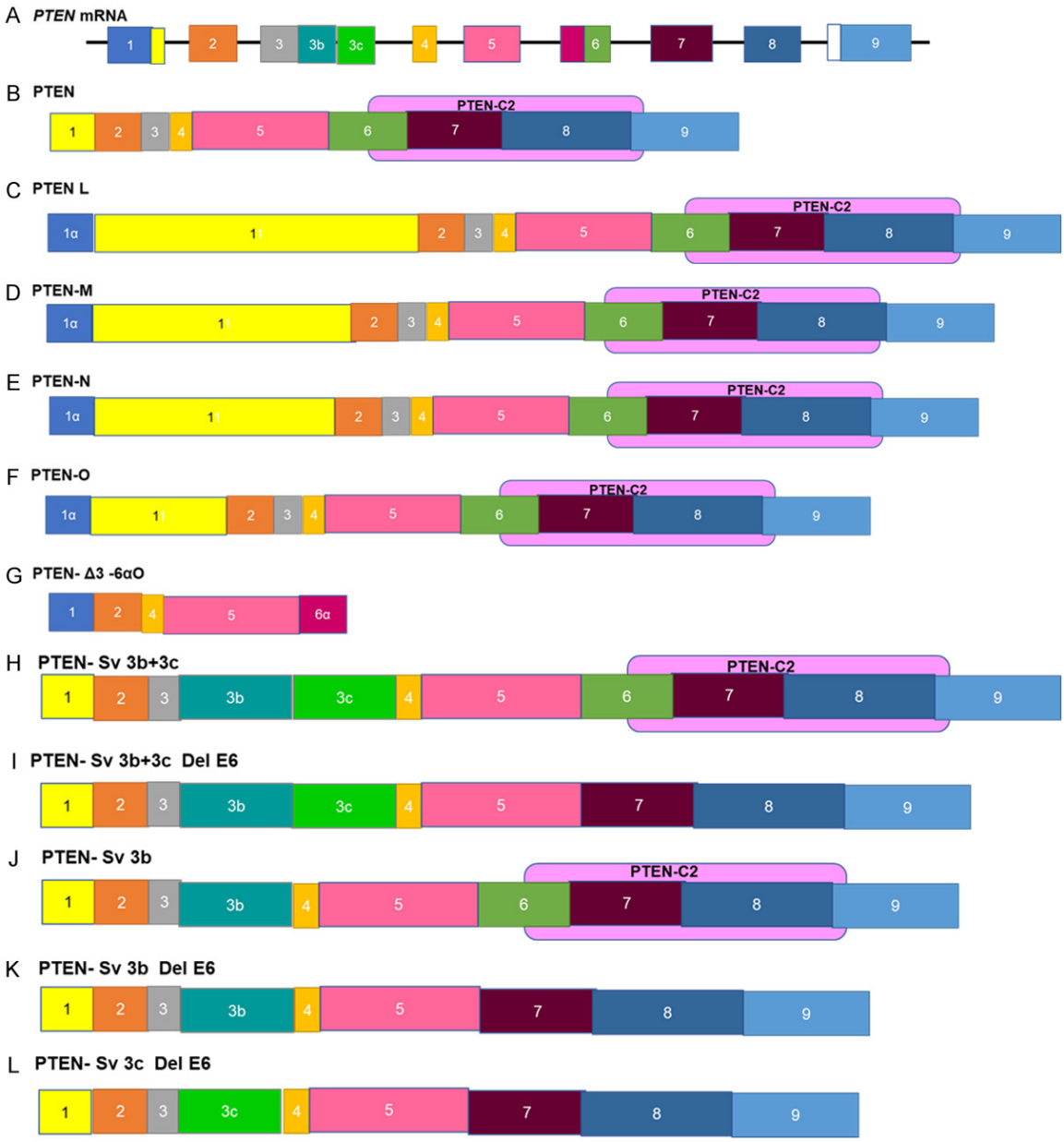


**Figure 8.** PTEN splicing and the generation of splice variants. Multiple isoforms of PTEN have been identified. These isoforms are produced from the PTEN mRNA (A) including the wildtype (B). Four of these variants (PTEN-L, -M, -N and -O) are translational variants (C-F). These variants contain an additional sequence of varying length at the N-terminus and differ in functions and sub-cellular localization. A short non-functional variant (G) has also been identified. Isoform (H) and (J) are produced by including intron 3b and 3c, and 3b, respectively. Isoforms (I, K and L) are produced by the deletion of exon 6. Other isoforms have been identified in samples from old individuals and cancer patients. These variants contain insertions around exon 3 accompanied in some variants by deletions of exon 6 [114].

women on tamoxifen treatment for breast cancer and women with predisposition of endometrial cancer. Estrogen signalling resulting from tamoxifen can cause abnormal bleeding. Since screening of asymptomatic women is not recommended, malignancy of the endometrium is these women are not prevented and screening strategies are implemented on the onset of symptoms [122]. In the instance of hereditary endometrial cancer, endometrium biopsies are used to screen women aged 35 and above as recommended by the American Cancer Society. In selected patients, however, endometrial biopsies may not be useful for detect-

ing malignancy [122]. In such cases, transvaginal ultrasounds are recommended, although this should be conducted at the physicians discretion since it has not shown any benefits in asymptomatic patients [123].

## Conclusions

Endometrial cancer is on the rise with alarming incidence and mortality rates attributed to numerous risk factors. Racial disparity has been reported in endometrial cancer. Black women are at a disadvantage with higher risk of developing the aggressive form of the disease. The rise in obesity among black women further increases the risk of endometrial cancer due to rise in diabetes and increased levels of circulating estrogen. Due to knowledge deficit and equal access to standard healthcare, black women are at risk of delayed diagnosis. By improving early diagnosis, the rapid detection of late-stage disease in black women can be possible and lead to better disease management. The lack of biomarkers for targeted therapy pose as a major challenge in the treatment, specifically of type II endometrial cancer with reduced overall survival rates. Identification of biomarkers that may assist in diagnosis, prognosis and novel therapeutic options would alleviate the burden of endometrial cancer. Additionally, public health efforts are warranted to encourage healthy lifestyle with adequate physical exercise to maintain a healthy weight and increase awareness of endometrial cancer, particularly in black women in rural areas. Modifiable risk factors may reduce the risk of developing endometrial cancer. Prevention and early detection of disease could potentially attribute to lower incidence and mortality rates and successful treatment outcome, respectively.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Zodwa Dlamini, SAMRC/UP Precision Prevention & Novel Drug Targets for HIV-Associated Cancers (PPNDTHAC) Extramural Unit, Pan African Cancer Research Institute (PACRI), University of Pretoria, Faculty of Health Sciences, Hatfield 0028, South Africa. E-mail: Zodwa.Dlamini@up.ac.za

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