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Associations of Menopause and Cancer in Global Scenario in post-menopausal women

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KEYWORDS

Breast cancer, Cervical cancer, Menopause, Ovarian cancer, Uterine cancer

ABSTRACT

Cancer is one of the deadliest causes of morbidity and mortality around the world. Menopause is the permanent cessation of menses results in permanent amenorrhea. Menopause causes a vast change in women's life e.g., physiological and psychological changes. Menopause is not the cause for cancer but it's a factor to cancer as age increases. The dual burden of cancer and menopause hampers many women globally. There are various other risk factors e.g., obesity, high BMI, sedentary lifestyle, unhealthy food habits, smoking, alcohol consumption, age at menopause etc can raise the probability of malignant disease. Some of these risks factor can be changed, whereas some cannot. Among all the reproductive organ cancers, breast cancer is the most common, followed cervical cancer and other cancers in developing countries. Women who attain late menopause after the age of 55 years are more prone to reproductive and other cancers (e.g., uterine cancer, ovarian cancer and breast cancer). In developing countries, women lack basic knowledge which tends to make them more vulnerable to dangerous diseases. Cancer is a major concern over there. Early screening, proper diagnosis and medication are effective measure to control cancer. This review study is in contrast to menopause and its association to recent trends in cancer in a global scenario. It describes current burden, prevalence, prevention, early diagnosis of cancer globally and theoretical analysis of female reproductive cancer among menopausal women.

Introduction

Cancer is considered as the 2nd deadliest causes of morbidity and mortality after cardiovascular death across the world (Sharma and Pattanshetty, 2017; Omran *et al.*, 2018), with increasing number of new cases and deaths every year (Szabo *et al.*, 2019). The burden of cancer is spreading unexpectedly all over the world in all income groups due to the growing population and longevity. There is a large population of middle aged women in menopausal years, among whom the prevalence of cancer is the most (Torre *et al.*, 2017). Menopause is the permanent cessation of menses which results from ovarian failure, as defined by the WHO (Kumari *et al.*, 2017). Studies found that menopause is not the cause for cancer but it may be a factor associated with cancer with increasing age and rise more in mid age (Lobo *et al.*, 2014; Surakasula *et al.*, 2014; Macdonald *et al.*, 2018). Women who attain late menopause after the age of 55 are more prone to cancer (Lobo *et al.*, 2014; Surakasula *et al.*, 2014). This is also the same for girls who attain puberty before twelve, hence the more the exposure of estrogen, the higher the risk of breast cancer (Lobo *et al.*, 2014). Some of the biological processes of aging may be also involved in the pathogenesis of cancer and age related diseases. There are many environmental factors that influence these biological processes and those can be modified resulting slowed aging and the onset of cancer may be delayed or even prevented (Surakasula *et al.*, 2014; Torre *et al.*, 2017; Macdonald *et al.*, 2018).

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According to the data of 2012, breast cancer is the most common cancer followed by colorectal cancer, cancer of lungs, cervical cancer and cancer of stomach, endometrium and ovarian cancer (Lobo *et al.*, 2014). There are various risk factors that can raise the probability of developing female reproductive cancers. According to the WHO, common cancers seen among women are of reproductive organs, breast cancer is the most common, followed by the cancer of cervix in developing countries like India (Shakir, 2018; Szabo *et al.*, 2019). Breast cancer is found to be the most common cancer in UK and most deaths occur due to late medical approach with ineffective treatment (Macdonald *et al.*, 2018). Globally 44000 new cases of cervical cancer are registered yearly but it is a preventable cancer with an early diagnosis (Shakir, 2018). In the year 2018 there were about 2.1 million breast cancer cases registered worldwide which accounts almost one in four cancer cases among women (Szabo *et al.*, 2019). The total number of cancer cases expected to rise is 24 million in 2035 which was 6.7 million in 2012 (Lobo *et al.*, 2014; Kumari *et al.*, 2017). Studies revealed that cancer rates are 1.8 times more in developed countries than developing countries, with the exception of cervical cancer. Risk factors associated with cancer are smoking, consumption of alcohol, increased body weight, sedentary lifestyle, change in reproductive pattern, late age at first child birth, lesser childbirth, exposure to radiation, excess sunburn, irregular menstrual period, more exposure to hormones, age, more exposure to environmental pollution, environmental physical and chemical agents, chronic infectious condition, unhealthy dietary habits, induced abortion, non-parity etc. (Lobo *et al.*, 2014; Surakasula *et al.*, 2014; Torre *et al.*, 2017). Genetic factors also contribute significantly to the risk of various cancers (Lobo *et al.*, 2014). Unhealthy lifestyle practices can be easily modified to prevent the incidence of cancer, e.g., lifestyle modification, balanced diet, daily exercises, skipping tobacco and alcohol can decrease the risk of cancer (Lobo *et al.*, 2014; Macdonald *et al.*, 2018). Numerous prevention and early detection interventions are proven to reduce cancer and mortality (Torre *et al.*, 2017). Proper screening and risk assessment can be helpful in preventing cancer and mortality if implemented worldwide, e.g., cervical cancer can be easily controlled with screening through Pap smear method or Human papilloma virus (HPV) analysis at beginning stage (Lobo *et al.*, 2014; Shakir, 2018). High risk women should be aware of such programs/techniques and opt for screening regularly and earlier in the life. Hence, this review study has been done to emphasis different risk factors of menopause associated with cancer. This can bring into light the present global scenario of cancer among menopausal women in population.

Statement and objectives of the present review study

Menopause makes women life more complex and it doubles if one has cancer. Menopause may be induced early because of cancer but it may not be same for the opposite. The objectives of the present review study are aimed to determine the association between cancer and menopause and its impact on health among adult women. This manuscript also describes global cancer status, risk factors, prevalence of cancer of reproductive organ among menopausal women. Management of menopausal complaints after cancer may not be that easy as well. It needs holistic and multidisciplinary approach along with individualized care. The increasing cancer burden is pronounced more in low and middle income countries due to inadequate access to early detection and proper treatment and with increasing age menopausal women may be associated with high risk of developing cancer. This study will limelight the present situation of this disease and adds more to the present knowledge.

Uterine/endometrial cancer and menopause

Endometrial cancer is one of the most common gynecological malignant cancers among women with high mortality rate (Torre *et al.*, 2017; Clarke *et al.*, 2018). It accounts about 5% cancer incidence and 2% of mortality among women across the globe, seen more among developed countries than

developing countries (Torre *et al.*, 2017; Clarke *et al.*, 2018). Northern America and region of Europe experience the highest rate of uterine cancer whereas Melanesia, Eastern Europe, Caribbean records highest mortality rate (Torre *et al.*, 2017; Clarke *et al.*, 2018). Risk factors associated with endometrial cancer are higher BMI, central adiposity, genetic factors, Lynch syndrome (hereditary non-polyposis colorectal cancer), history of cancer, early age at menarche, breastfeeding, nulliparity, late age at menopause, hypertension, long-term hormonal exposure, estrogen therapy, high blood sugar, PCOS and life style factors such as sedentary life, smoking, alcohol consumption, unhealthy food pattern also had a impact on endometrial cancer (Torre *et al.*, 2017; Clarke *et al.*, 2018; Wu *et al.*, 2019). Women who attain menopause at a later age have higher hormone levels and are exposed to estrogen for long time which is associated to various health issues. The association of age at menopause and increased risk of endometrial cancer is still controversial. Studies also showed that increased weight, later age at puberty and higher parity were associated with late menopause. Moreover, a low level of progesterone with anovulatory cycles is seen among women with late menopause, which may also result to endometrial cancer risk (Wu *et al.*, 2019). Wu *et al.* (2019), analyzed that women who exceeded 46.5 years without attaining menopause risked to endometrial cancer (Clarke *et al.*, 2018; Wu *et al.*, 2019). Post menopausal bleeding (PMB) is a common symptom of endometrial cancer seen among 2/3 of menopausal women (Clarke *et al.*, 2018). Endometrial cancer lacks in early detection and no population based screening was found till date. It is curable with surgery with a 5 year survival rate. Women with PMB go through various clinical examinations like transvaginal ultrasound, hysteroscopy, biopsy, dilation and many more. The risk of endometrial cancer among women with PMB is 3% to 25% varies from person to person. The prevalence of PMB was 90% in women with endometrial cancer found in a review analysis study (Clarke et al., 2018).

Ovarian/ fallopian cancer and menopause

Ovarian cancer is a highly fatal health condition worldwide, is the 5th leading cause of cancer death in women (Franco, 2012). It accounts for about 4% of cancer prevalence and mortality worldwide and highest cases are found among Europe, Northern and Eastern Europe whereas death rates are higher among these countries along with Melanesia (Torre *et al.*, 2017). It has a 5 year survival rate with 36%-46% among women (Perez-Lopez *et al.*, 2017). Each histological range of ovarian cancer is allied with different history of clinical nature, epidemiologic factors, genetic and family history (Perez-Lopez *et al.*, 2017). Familial influence of breast or ovarian cancer is found to be important risk factors, some ovarian cancers cluster heredity which easily develop sooner than non genetic tumors (Perez-Lopez *et al.*, 2017; Torre *et al.*, 2017). The existence of ovarian cancer in one first degree relative increases women's risk by 5% and it increases by 7% if there are more than one (Perez-Lopez *et al.*, 2017). Other risk factors are long term menopausal hormone therapy, BMI, excess body fat deposition, increasing age, low parity, not using oral contraceptives, environmental factors (Franco, 2012; Perez-Lopez *et al.*, 2017; Torre *et al.*, 2017), whereas the use of oral contraceptives for a long duration is estimated to reduce the risk of ovarian cancer by 30% (Perez-Lopez *et al.*, 2017; Torre *et al.*, 2017). Trans vaginal ultrasound and biomarker testing are two screening methods for ovarian cancer used in developed countries include U.S and U.K. Due to early non specific symptoms and late stage presentation most of the cases are diagnosed at later stages of this disease and thus making survival rate low (Perez-Lopez *et al.*, 2017; Torre *et al.*, 2017) and the prime intervention as surgery and chemotherapy (Perez-Lopez *et al.*, 2017). Symptoms such as abdominal pain, swelling etc occurs later in life in ovarian cancer patients (Franco, 2012) whereas asymptomatic women without genetic predisposition are difficult to treat (Perez-Lopez *et al.*, 2017). According to Franco (2012), ovarian cancer risk increased with increasing height, weight and BMI. The taller the woman, the greater is the risk of ovarian cancer, the same with weight and BMI too, if all other factors for ovarian cancer remain constant. At various stages of life in women different types of ovarian cancer may develop. Epithelial

ovarian carcinoma is most common in post-menopausal women which arise from ovarian surface, fallopian tubes or peritoneum (Perez-Lopez *et al.*, 2017). Based on clinical and molecular studies there are two different carcinogenic trajectories, type I and type II. Low grade serous, clear cell, low grade endometrioid, mucinous cancers and Brenner tumors fall under type I category. From genetic point of view type I are stable whereas, type II are instable with high p53 mutation prevalence. High grade epithelial serous, endometrioid, undifferentiated cancers and mixed mesodermal malignancies fall in type II which can arise from extra-ovarian tissues, fallopian tubes (Perez-Lopez *et al.*, 2017).

Cervical cancer and menopause

It is the fourth most common diagnosed genital cancer worldwide with fourth leading cause of cancer mortality as well. In developing countries, cervical cancer is the second most commonly diagnosed cancer succeeded by breast cancer and third leading cause of cancer related mortality (Torre *et al.*, 2017). There are about 510,000 new cases every year, in which 80% accounts for developing countries as mentioned by the WHO and half of these cases end in death (Kumari *et al.*, 2017). In India, cervical cancer accounts for 17% cause of mortality which is one quarter of global cervical cancer rate (Sharma and Pattanshetty, 2018). In India one woman dies of cervical cancer in every 8 minutes (Kumari *et al.*, 2017). The cervical cancer accounts for 15% of all cancer in women (Kumari *et al.*, 2017). The main cause of cervical cancer is human papilloma virus (HPV) which is responsible for 70% of cervical cancers around the world (Torre *et al.*, 2017), commonly seen among middle aged women (Jabbari *et al.*, 2019). In developing countries 1/53 women and in developed countries 1/100 women suffer from this disease (Sharma and Pattanshetty, 2018). The WHO recommends women of 30 years and more to perform Pap smear every 10 years and countries who implemented such strategies have eradicated cervical cancer drastically. It is the most common method used for diagnosing cervical cancer (Lobo *et al.*, 2014; Jabbari *et al.*, 2019). Different studies suggests that people has inadequate knowledge and aware on cervical cancer. Socio-economic factors, cultural barriers, attitude and perception of women on cervical cancer can be a risk factor to it (Jabbari *et al.*, 2019). As gynaecologists suggests cancer of cervix is an ideal malignancy for screening for premalignant epithelial anomalies, as it meets both test and disease criteria. Early detection of this disease is easy as it has a long latent stage which provides sufficient time for diagnosis (Shakir, 2018). Several researchers have reported that determinants associated with the risk of cervical cancer are age, educational status, early marriage, marital status, early age of child birth, number of sex partners, employability, financial status, presence of malignancy, chronic disease, habit of smoking, family history of cancer, perception on health, health status, food pattern, likelihood of screening (Sharma and Pattanshetty, 2018; Jabbari *et al.*, 2019). Kumari *et al.* (2017) reported that presents various complaints among cervical cancer women were postmenopausal bleeding, watery discharge, blood stained discharge, contact bleeding, foul smelling, lower abdominal pain, and backache. Vaginal itching and not washing genitals were found to be associated to cervical cancer (Sharma and Pattanshetty, 2018). Studies found that post-menopausal bleeding was most frequent grievance among cases of cervical cancer and post-menopausal women were diagnosed at advanced stage of cervical cancer (Kumari *et al.*, 2017). As women get older they neglect the risk of cancer incidence and try avoiding screening (Jabbari *et al.*, 2019) and age is highly associated with the prevalence of cervical cancer (Shakir, 2018). The prevalence of pre-malignant and malignant lesions was common in post-menopausal women when compared to the counterpart pre-menopausal women. Further, squamous intraepithelial lesions are more common in post-menopausal women (Shakir, 2018). The prevalence of pre-malignant and malignant lesions was common in post-menopausal women when compared to the counterpart pre-menopausal women. Further, squamous intraepithelial lesions are more common in post-menopausal women. Borker *et al.*, (2013) observed that many post-menopausal women don't feel to clean genitals as they don't have menses now. Many women don't know the exact way to clean the genitals. They even don't feel to

visit a doctor for the complaints since they thought that it is non treatable. Hence screening with pap smear is crucial for early detection of cervix cancer.

Breast cancer and menopause

Breast cancer is the most frequently diagnosed cancer among female worldwide. It is a disease of older women (more than the age of 20) with leading death cause of cancer (Torre *et al.*, 2017; Heer *et al.*, 2020). Around the world most cases of breast cancer are seen in North America, New Zeleand, Northern Europe and Western Europe whereas higher mortality rates are seen in developing countries than in developed countries e.g., sub-Saharan Africa (Torre *et al.*, 2017). The incidence of breast cancer is rising in India (22.9%) and is now the second most commonly diagnosed cancer in women after cervical cancer (Surakasula *et al.*, 2014; Lobo *et al.*, 2014). Global burden of breast cancer will increase over 2 million new cases/years by 2030 (Surakasula *et al.*, 2014). Breast cancer alone contributes 25.2% of the cases, and the top three contribute more than 43% of all cancer cases (Lobo *et al.*, 2014). Breast cancer may be increased with prolonged use of standard doses of estrogen in combination with certain progestogens; estrogen alone either decreases the risk or increases it marginally with very prolonged use (10–15 years). Breast cancer mortality has significantly decreased in countries where a national screening program is available (Surakasula *et al.*, 2014; Szabo *et al.*, 2019). The rate of breast cancer survivors is increasing gradually due to early detection and disease specific death in developed countries. Many women experience menopausal complaints, estrogen deficiency during or after the period of breast cancer treatment (Santen *et al.*, 2017). The experience of menopause, menopausal symptoms and cancer is different women to women. The joint burden of cancer and menopause hampers many women globally (Surakasula *et al.*, 2014; Szabo *et al.*, 2019). Some of the un-modifiable risk factors to breast cancer are genetic factors, age, sex, family history, menstrual cycle, use of radiation, dense breast tissue. Other prevailing risk factors related to lifestyle are nulliparity, late pregnancy, unable to breast feed child, induced abortion, recent use of oral contraceptive pills, use of hormone therapy in menopause, use of alcohol, high BMI, sedentary life (Surakasula *et al.*, 2014). Study revealed that the incidence of breast cancer was seen more among post-menopausal women with excess body weight (Heer *et al.*, 2020) than pre-menopausal women. Younger age at menarche increases the risk of breast cancer among menopausal women, whereas late menopause increases the risk of breast cancer. The risk is increased by 3% every year with later menopause. Late age at first full term pregnancy is associated with higher risk to breast cancer, while early age at first full term pregnancy is not. High parity and practicing breast feeding is believed to reduce the risk of breast cancer (Surakasula *et al.*, 2014). Weight at a young age decreases the risk of breast cancer whereas after menopause high BMI increases the risk of breast cancer. Weight gain during 40-50 years of life is associated with high risk of post-menopausal breast cancer. Pre-adolescence girls with low weight have higher mammographic density when they grew up adults, and mammographic density is counted as one of the highest risk factor associated to breast cancer. Hence, leaner women may be prone to breast cancer due to low level of adiposity in the mammary gland which alters breast tissue maturation making it more susceptible to cancer (Duverger *et al.*, 2016). The rate of breast cancer mortality has been reduced in developed countries where it is detected earlier, screening program is performed with mammography and with improved treatments women are living longer even after diagnosed with breast cancer (Lobo *et al.*, 2014; Szabo *et al.*, 2019). Women were diagnosed with breast cancer, menopausal symptoms are more persistent along with effects of cancer treatment and may be more severe and annoying compared to natural menopause. After cancer, diagnosing menopause can be troublesome as ovulation may start again many years after long delayed menses and raised follicle stimulating hormone (Surakasula *et al.*, 2014).

Conclusion

Menopause marks the end of woman's reproductive cycle which is due to hormonal changes. The hormonal changes and the menopause can be factors responsible for cancer. Cancer is an age related disease that develops over a long period of time. This complex process leads to mortality and impact millions of women around the world. Menopausal women should be offered evidence-based education on cancer and its precautionary measures. It is necessary to understand the role of risk factors associated to the prognosis of cancer including factors that are modifiable and may contribute to prevent the progression of cancer thereby improving survival of menopausal women.

Recommendations

Awareness program on cancer should be organized, eg. health camps. Access to health care facility for menopausal women should be established for early diagnosis. Separate clinic for screening cancer should be there in every district hospitals.

Awareness on help seeking and early approach to medical should be encouraged for older adults.

Media can be more focus on cancer causing agents and thus can influence public creating awareness.

Intervention measures should be taken to improve menopausal health eg. counseling, guiding on mental health, nutrition, sanitation etc.

Menopausal women in rural areas should be properly guided about menopausal symptoms and they should be made aware of common life threatening diseases. Health care professionals can be engaged for the said purpose as they have access to remotest area of the village and are trained.

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