Ovarian Cancer risk factors and Their Mechanism of Action

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Abstract—Ovarian cancer continues to be one of the deadliest and lethal form of gynecological cancer affecting younger and older woman. Understanding various factors that could lead to ovarian cancer and how they are able to drive its progression, metastasis and survival might help in its treatment and prevention. This paper aims to review different risk factors both genetic and environmental that could lead to the development of ovarian cancer and their mechanism of action. The research methods used in this study follows the principles outlined by [1]. It is a comprehensive literature review on ovarian cancer risk factor. The role of genetics and environmental risk factors in ovarian carcinogenesis and their mechanism of action created a theoretical foundation of the paper. A new model is presented to encapsulate highly dynamic interaction between ovarian carcinogenesis and the mechanism of action of some associated risk factors. The contribution of the study is intended to review and summarize the theoretical and empirical knowledge that should inspire new discussions and directions for further research activity. The model highlights various factors that can trigger the development of ovarian cancer namely; TP53, BRCA genes, Cigarette smoke and Talc powder and how they are able to promote ovarian cancer. Various have been done about how mutation of certain genes and some environmental factors could lead to ovarian carcinogenesis. However, more research is needed to further understand how their mechanism of action. The content of this paper will be useful in devising a better screening, treatment and preventive measure towards the ovarian cancer. This study provides an exciting opportunity to advance our knowledge of ovarian cancer to efficiently aid medical practitioners and researchers to device better prevention and treatment plan to combat ovarian cancer.

Index Terms—Gynecological; Ovarian cancer; Mutation; Metastasis.

I. INTRODUCTION

There is growing literature on ovarian cancer and the factors and associated risk factors [2]-[11]. According to WHO, the risk of ovarian cancer development increases in woman who have ovulated more than once over their lifetime including those who have never children and those who started ovulating at young age or those who reach menopause at an older age [12].

Different effort has also been made to clarify the association of mutation of BRCA gene in advanced ovarian and its development [7]. BRACA1 holds multiple roles such as DNA repair, transcriptional regulation, and mitosis while BRACA2 is used for homologous recombination [13]. Germline mutation of BRCA 1 AND 2 gene can lead to the high-grade serous ovarian cancer [14]. Various research and

cohort study done on the association of TP53 and ovarian cancer has also showed that mutation in tumour suppressor 53 enhance and increase the risk of ovarian cancer. TP53 is a tumour suppressor gene that helps regulates cells and prevents them from growing uncontrollably, and mutation in TP53 can lead to development of ovarian [15]. Mutation of TP53 is commonly found in High grade serous carcinoma [8], [16]. It is also found in low grade mucinous cancer [17].

Cigarette smoking and exposure to environmental agents such as talc and pesticides may also increase the risk of ovarian cancer development [18]. Various cohort study has reported that cigarette smoke smoking is a risk factor for invasive and mucinous ovarian cancer [19], [20]. cancer smoke extract increase growth, migration and invasion of ovarian cancer via cell cycle regulation, apoptosis and EMT and metastasis related cellular markers and signaling proteins [11], [9]. However, there have been controversies about the effect of talc powder on the development of ovarian cancer. Talc is a natural clay mineral fiber that is structurally similar to asbestos which is a known carcinogen. Some shows that perineal application of talc powder causes ovarian cancer [10], [21]. On the other hand, other cohort studies show no relation in talc powder on ovarian cancer [22]- [24]. The use of talc powder could also moderately increase the risk of ovarian cancer development [25].

Ovarian cancer is a deadly disease that has no symptoms and is mostly detected at a later stage. Outlining and understanding the molecular and biochemical mechanism that underlies the role of some risk factor both genetics and environmental factor in ovarian carcinogenesis might aid screening, treatment planning and prevention of the diseases thus in a way decrease the high mortality and modalities associated with the disease.

Fig. 1. Ovarian cancer and associated risk factors

II. RESEARCH METHOD

The research methods used in this study follows the principles outlined by [1]. It is a comprehensive literature review on ovarian cancer risk factor. The role of genetics and environmental risk factors in ovarian carcinogenesis and their mechanism of action created a theoretical foundation of the paper. A new model is presented to encapsulate

highly dynamic interaction between ovarian carcinogenesis and the mechanism of action of some associated risk factors. The contribution of the study is intended to review and summarize the theoretical and empirical knowledge that should inspire new discussions and directions for further research activity

III. BRCA GENE

Series of work has been done to illuminate the role of mutated BRCA gene in the development of advanced ovarian cancer [7]. Mutation of BRCA 1 and BRCA2 are genetic risk factor associated with ovarian cancer. From various article, it is clear enough that they are mostly mutated in the case of high grade serous cancer and 10% hereditary ovarian cancer and are associated risk factor in ovarian cancer development [39]- [42]. Germline mutation of BRCA 1 AND 2 gene can lead to the high-grade serous ovarian cancer [14].

A. Function and Mutation

BRCA I and 2 gene encodes proteins that are necessary for the repair of double stranded DNA breaks (DSBs) by homologous recombination [43]. BRCA gene also function in chromatin remodeling [44]. BRCA gene mutation can be a small insertions or deletions mutation or point mutations which lead to nonsense condon. Most of mutations lead to development of truncated protein with no functional domain. [45]. Approximately 10% of ovarian cancers are associated with homologous recombination defects and genomic instability [40].

B. Mechanism

Studies has shown the relationship between germline BRCA 1 and 2 mutation and development of ovarian cancer however, the reason why their mutation specifically lead to ovarian carcinogenesis remain unclear [46], [47]. It was reported that oestrogen controls the survival of BRCA 1-deficient cells via PI3/NRF2 regulated pathway. This might partially explain hormonally driven tumor in patient carry BRCA1 and 2 mutations [48]. NRF2 is a transcription factor that regulate antioxidant response and also interact with the BRCA 1 protein [49]. Cells with mutated BRCA 1 gene have high reactive oxygen species that in turn impair cell viability and since NRF2 regulate antioxidant response, activation of NRF2 by oestrogen will result in cell survival [47].

C. BRCA 1 and TP53

TP53 mutation or accumulation happen to be the most often detected abnormalities in approximately 80% of BRCA 1 related ovarian cancer and it may be an early event in BRCA 1 related ovarian cancer as shown by LOH study [50], [51]. It has been reported that loss of TP53 gene increases mortality of the embryo in BRCA1 deficient mouse and also proliferation of the epithelial cells to the ovarian surface of the mouse [52], [53].

Fig. 2. BRCA gene and its contribution to cancer

IV. TP53

The research and cohort study done on the association of TP53 and ovarian cancer shows that mutation in tumour suppressor 53 can enhances and increase the risk of ovarian cancer. Mutation of TP53 is commonly found in High grade serous carcinoma [8], [16]. It is also found in low grade mucinous cancer [17]. P53 mutation is also associated with breast cancer but it is less frequent [54]. The presence of mutated TP53 in ovarian cancer was also detected using the report made by Evolutionary Action analyses of The Cancer Gene Atlas data sets that many specific p53 missense and gain-of-function mutations exist and function in high-grade serous ovarian cancer (HGSC) [55]. Using archival paraffin-embedded tissues and automated fluorescent DNA sequencing mutated p53 was also found in sporadic ovarian cancer [56].

A. Function and Mutation

TP53 is a tumor suppressor and also regulate various signaling pathway involve in tumor suppression [57]. TP53 regulating cellular homeostasis, induces DNA repair, cell cycle arrest, senescence and apoptosis [58], [59]. TP53 gene often undergo missense mutation where single nucleotide is substituted by another [60]. TP53 mutation can also be inherited [61]. Many of mutation cause loss of TP53 ability to bind to DNA in a specific manner and may cause TP53 mutants to actively stimulate tumor development [60]. TP53mutation enhances and increases the risk of ovarian carcinogenesis and it is commonly in high grade serous carcinoma [16].

B. Metastasis

TP53 is able to perform its tumour suppression function by suppressing Epithelial-mesenchymal transition (EMT) which is a process that plays a role in tumour progression and metastasis and it is able to do that by repressing transcription factor ZEB1 and ZEB2 that promote EMT and regulating microRNA [62], [63]. However, mutation in TP53 lead to loss of its function and it has been reported that mutant TP53 exerts oncogenic function [63]. Mutant TP53 promotes ovarian cancer cell adhesion to mesothelial cell via Integrin β 4 and Akt signals. Adhesion or attachment to mesothelium is considered the first step to ovarian cancer cell metastasis [64]. Mutant TP53 is also able to stimulate ovarian cell invasion by interacting with Rad21 protein (Ahn, 2017). Mutant TP53 also interact with guanidinoacetate N-methyltransferase (GAMT) and sterol

regulatory element-binding proteins (SREBPs) promoting anabolism of lipid to expedite ovarian cancer growth and progression [8].

C. Platinum resistance:

Genetic mutation is not the only cause of TP53 impairment in cancer. It has been shown that some in high grade serous ovarian cancers (HGSOCs), aggregation of TP53 protein leads to inactivation of TP53 and contribute to platinum resistance in HGSOC cells [59]. It has been reported that TP53 mutation-mediated genomic instability instigates the development of chemoresistance and epithelial ovarian cancer resistance by stimulating the accumulation of chromosome-7 and amplification of multi drug resistance 1 (MDR1) [65].

Fig. 3. TP53 and its contribution to ovarian cancer

V. CIGARETTE SMOKE

Various cohort study carried out shows that smoking is another risk factor that could lead to ovarian cancer development either by increasing increase growth, migration and invasion of ovarian cancer via cell cycle regulation, apoptosis, EMT, metastasis related cellular markers and signaling proteins [11], [9]. Smoking of cigarette is a risk factor for development of invasive and mucinous cancer but its association with other type of ovarian cancer is unclear [19], [20], [66] Long term deviation from smoking could also reserve its effect in ovarian cancer [67].

A. Composition

Cigarette smoke comprises of approximately 500 chemicals such as nitric oxide, nicotine, carbon monoxide, tar, acetaldehyde e.t.c. over 60 compounds in these chemically has been known as carcinogens [68]. Smoking of cigarette has been closely associated with chronic diseases and health problem [69], [70].

B. Metastasis

Cigarette smoking has many adverse effects in the biological system. It includes inflammation and impaired immune function which are the hallmark of cancer development [71], [72]. Cigarette smoke extracts has been reported to promote ovarian cancer growth, invasion, and metastasis. It increases the epithelial-mesenchymal transition (EMT) in BG-1 ovarian cancer cells. EMT is a process in tumor progression that gives tumor cells the ability to separate from the primary tumor and metastasize to distant region in the biological system. Upon treatment with cigarette smoke extracts, EMT-associated

transcriptional factors are upregulated. MMP-9 and cathepsin D are also over expressed [11].

C. Mucinous ovarian cancer

Smoking of cigarette is a risk factor for development of invasive and mucinous cancer but its association with other type of ovarian cancer is unclear [19]. Cotinine which is a major metabolite of nicotine and B(a)P-DNA adduct, a potent B(a)-P mutagen and carcinogen of cigarette smoke have been in ovarian follicular cells. Smoking is highly associated with mucinous ovarian cancer but after discontinuing smoking, the risk will eventually return to normal [73]. The risk of developing mucinous ovarian cancer is in a dose dependent manner but no other subtypes [38].

VI. TALC POWDER

Research studies shows that there are controversies when it comes to the effect of talc powder on the development of ovarian cancer. Some shows that perineal application of talc powder causes ovarian cancer [10], [21]. On the other hand, other cohort studies show no relation in talc powder on ovarian cancer [22], [24]. The use of talc powder could also moderately increase the risk of ovarian cancer development [25].

A. Properties

Talc is a mineral compound made of pulverized hydrous magnesium silicate with a chemical formula $H_2Mg_3(SiO_3)_4$ or $Mg_3Si_4O_{10}(OH)_2$ [74]. It is one of the substances that are widely used in baby powder. Talc is a natural clay mineral fiber that is structurally similar to asbestos which is a known carcinogen [75].

B. Talc and Ovarian cancer

In 2006, IARC categorized the perineal use of talc powder as a possible carcinogen [76]. Talc has been associated with ovarian cancer. Talc fibers have been detected in the ovarian tissue and case control studies has shown 20-25% increased risk of serous tumour in talc powder users [75], [77].

C. Mechanism

Animal studies has shown that talc moves from the vagina via the peritoneal cavity to the ovaries after which it get entrapped in epithelium on the surface of the ovaries causing a response similar to those that occur during ovulation thus, increasing the risk of carcinogenesis. It has also been suggested that talc could initiate granulomas formation which are related to persistent acute inflammatory responses [75]. Another study has reported that estrogen and or prolactin might play a significant role through macrophage activity and inflammatory response to talc [78].

Fig. 4. Cigarette smoke and its contribution to cancer

VII. OTHER ASSOCIATED RISK FACTOR

TABLE I: OTHER FACTORS THAT CONTRIBUTE TO THE DEVELOPMENT OF OVARIAN CANCER

Other factors	Contribution to Ovarian Cancer
1 BRAF Mutation	A study has reported that BRAF mutation exists in 28-35% of serous borderline/Low-grade serous (LGS) ovarian cancer [79].
2 KRAS	It has been reported that KRAS oncogene mutations occur in several Histologic kinds of invasive epithelial ovarian carcinoma, especially stage I tumors, but are mostly common in mucinous ovarian tumor [80]. Another study shows that there is a mutation of KRAS or Braf rarely in invasive ovarian cancer but not in invasive serous carcinoma[81].
3 PTEN	It has been reported that mutation in KRAS, BRAF and PTEN are present in low grade serous ovarian cancer and mucinous endometriod [82]. PTEN mutation are also found more frequent in low grade endometrial endometriod carcinoma than low grade ovarian endometriod carcinoma [83].
4 Organochlorine pesticide	A cohort study shows that organochlorine pesticide plays a feasible role in the pathogenesis of epithelial ovarian cancer among north Indian women population [84]
5 Endometriosis	Endometriosis is associated with a significant increase in the risk factor of clear cell, low grade serous and endometriod invasive ovarian cancer but no association with mucinous or high grade serous invasive ovarian cancer [85]
6 Lead and Nickel	Another study also for the first time reported the accumulation of lead and nickel in the borderline of ovarian tissue and malignant proliferation of the epithelium surface[86]. Lead is a known carcinogenic and it has been linked to inducing carcinogenicity by destabilizing the DNA structure, depleting the cellular antioxidant and inducing oxidative stress and lipid peroxidation [87] ,[88]. Nickel is a carcinogenic metal used in many industry producing stainless steel, jewelry and battery [89]. It act by inhibiting the repair enzyme of the DNA, altering the chromatin structure by histone modification and by hypermethylation of the promoter region of TP16 thus silencing it [90], [91]

VIII. RESULT AND DISCUSSION

Fig. 5. A proposed framework that shows various factors leading to ovarian carcinogenesis and their associated properties, function, composition and Mechanism of actions.

Ovarian cancer is the fifth most common cause of death in female malignant tumor and approximately 22,440 new cases and 14,080 ovarian cancer deaths are estimated to occur in U.S in 2017 [91]. As shown in Fig. 5 there are various factors that has been identifies as a potential risk and contribute to the development and metastasis of ovarian cancer. Over 23% of ovarian carcinoma has been related to hereditary conditions and 65-85% is due to BRCA gene mutation [92]. BRCA I and 2 gene encodes proteins that are necessary for the repair of double stranded DNA breaks (DSBs) by homologous recombination and chromatin remodeling [42], [43]. The mechanism at which it leads to ovarian cancer is unknown however, Cells with mutated BRCA 1 gene have high reactive oxygen species that in turn impair cell viability and since NRF2 regulate antioxidant response, activation of NRF2 by oestrogen will result in cell survival [46]. Mutation and accumulation of TP53 is also associated with BRCA 1 related ovarian cancer as shown by LOH study [49].

TP53 is a tumour suppressor regulating cellular homeostasis, induces DNA repair, cell cycle arrest, senescence and apoptosis [57], [58]. TP53mutation enhances and increases the risk of ovarian carcinogenesis and it is commonly in high grade serous carcinoma [15]. It promotes ovarian cancer cell adhesion to mesothelial cell via Integrin $\beta 4$ and Akt signals. Adhesion or attachment to mesothelium is considered the first step to ovarian cancer cell metastasis [63]. Mutant TP53 is also able to stimulate ovarian cell invasion by interacting with Rad21 protein and also interact with guanidinoacetate N-methyltransferase (GAMT) and sterol regulatory element-binding proteins (SREBPs) promoting anabolism of lipid to expedite ovarian cancer growth and progression [7]. TP53 mutation-mediated genomic instability also instigates the development of chemoresistance and epithelial ovarian cancer resistance by stimulating the accumulation of chromosome-7 and amplification of multi drug resistance 1 (MDR1) [64].

Cigarette smoke is another risk factor and it comprises of approximately 500 chemicals such as nitric oxide, nicotine, carbon monoxide, tar, acetaldehyde etc. Over 60 compounds in these chemically has been known as carcinogens [67].

Smoking could lead to ovarian cancer development either by increasing growth, migration and invasion of ovarian cancer via cell cycle regulation, apoptosis, EMT, metastasis related cellular markers and signaling proteins [10], [8]. It is a risk factor of invasive and mucinous cancer but its association with other type of ovarian cancer is unclear [18]. Cotinine which is a major metabolite of nicotine and B(a)P-DNA adduct, a potent B(a)-P mutagen and carcinogen of cigarette smoke have been seen in ovarian follicular cells. Smoking is highly associated with mucinous ovarian cancer but after discontinuing smoking, the risk will eventually return to normal [72]. The risk of developing mucinous ovarian cancer is in a dose dependent manner but not related to other subtypes [37].

Talc is a mineral compound made of pulverized hydrous magnesium silicate with a chemical formula $H_2Mg_3(SiO_3)_4$ or $Mg_3Si_4O_{10}(OH)_2$ [73]. It is one of the substances widely used in baby powder. It is a natural clay mineral fiber that is structurally similar to asbestos which is a known carcinogen [74]. There are still controversies about the contribution of Talc to the development of ovarian cancer. Some studies show that perineal application of talc powder causes ovarian cancer [9], [20]. There is another cohort studies shows no relation of talc powder to ovarian cancer [21]- [23]. It has also been reported that the use of talc powder could also moderately increase the risk of ovarian cancer development [24]. Animal studies has shown that talc moves from the vagina via the peritoneal cavity to the ovaries after which it get entrapped in epithelium on the surface of the ovaries causing a response similar to those that occur during ovulation thus, increasing the risk of carcinogenesis. It has also been suggested that talc could initiate granulomas formation which are related to persistent acute inflammatory responses [74]. Another study has reported that estrogen and or prolactin might play a significant role through macrophage activity and inflammatory response to talc [77].

Other risk factors have been highlighted in Table I. BRAF gene is also known as proto-oncogene B-Raf and it encode a protein; serine/threonine protein kinase which participates in MAPK/ERK signaling pathway and plays a significant role in cancers [93]. BRAF mutation has been reported to exist in 28-35% of serous borderline/Low-grade serous (LGS) ovarian cancer [78]. Another study shows that there is a mutation of KRAS or Braf rarely in invasive ovarian cancer but not in invasive serous carcinoma [80]. Mutation in KRAS gene has also been reported in several histologic kinds of invasive epithelial ovarian carcinoma, especially stage I tumors, but are mostly common in mucinous ovarian tumor [79]. Mutation in KRAS, BRAF and PTEN are present in low grade serous ovarian cancer and mucinous endometriod [81]. Another study also reported the feasible role of Organochlorine pesticide in the development of epithelial ovarian cancer among north Indian women population [83]. Organochlorine pesticide belongs to a class of hydrocarbon and it said to act as tumor promoter by acting as endocrine disruptors or via hormone mediated effects [94]. Endometriosis also significantly increase in the risk factor of clear cell, low grade serous and endometriod invasive ovarian cancer but no association with mucinous or high grade serous invasive ovarian cancer [84]. Accumulation of lead and nickel has also been reported in

the borderline of ovarian tissue and malignant proliferation of the epithelium surface [85]. Lead is a known carcinogenic and it has been linked to inducing carcinogenicity by destabilizing the DNA structure, depleting the cellular antioxidant and inducing oxidative stress and lipid peroxidation [86], [87]. Nickel is a carcinogenic metal used in many industry producing stainless steel, jewelry and battery [88]. It acts by inhibiting the repair enzyme of the DNA, altering the chromatin structure by histone modification and by hypermethylation of the promoter region of TP16 thus silencing it [89], [90].

IX. CONTRIBUTION AND INSIGHT

Many contributions have been made regarding various factors that could lead to the development of ovarian cancer which is one of the most lethal of the gynecologist cancer. More need to be done regarding how these factors could eventually lead ovarian carcinogenesis so as to better prevent, diagnose and treat it. This paper put together different factors both genetics and environmental, their structure, function, composition, properties as well as the mechanism at which they can cause ovarian cancer. Many of these factors are able to induce ovarian cancer development and metastasis by interrupting many important cellular processes that plays a significant role in the biological system. Cellular processes such as cell cycle, DNA repair, Senescence and Apoptosis are deregulated and inflammation, cell adhesion as well as Epithelial-Mesenchymal transition is also induced by some factors [61], [62], [77]. All of this in a way contributes to ovarian cancer development and metastasis.

X. CONCLUSION

Ovarian cancer remains a significant cause of mortality and morbidity increasingly in women globally. It is a disease that doesn't exactly have a well-established symptom thus diagnosed at later stage. However, several contributions have been made regarding various risk factors that could lead to the development of ovarian cancer. Many of these factors are able to induce ovarian cancer development and metastasis by interrupting many important cellular processes that plays a significant role in the biological system. Cellular processes such as cell cycle, DNA repair, Senescence and Apoptosis are deregulated and inflammation, cell adhesion as well as Epithelial-Mesenchymal transition are also induced by some risk factors. More need to be done regarding the risk factors mechanism of action so as to effectively devise strategies for the prevention and treatment plan.

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