Original Article

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Bioinformatics Based Drug Repurposing Approach for Breast and Gynecological Cancers: *RECQL4/FAM13C* Genes Address Common Hub Genes and Drugs

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ABSTRACT

Objective: The prevalence of breast cancer and gynaecological cancers is high, and these cancer types can occur consecutively as secondary cancers. The aim of our study is to determine the genes commonly expressed in these cancers and to identify the common hub genes and drug components.

Materials and Methods: Gene intensity values of breast cancer, gynaecological cancers such as cervical, ovarian and endometrial cancers were used from the Gene Expression Omnibus database Affymetrix Human Genome U133 Plus 2.0 Array project. Using the linear modelling method included in the R LIMMA package, genes that differ between healthy individuals and cancer patients were identified. Hub genes were determined using cytoHubba in Cytoscape program. "ShinyGo 0.80" tool was used to determine the disease-specific biological KEGG pathways. Drug.MATADOR from the ShinyGo 0.80 tool was used to predict drug-target relationships.

Results: The RecQ Like Helicase 4 and *Family with Sequence Similarity 13 Member C* genes were found to be similarly expressed in breast cancer and gynaecological cancers. Upon KEGG pathway analyses with hub genes, Drug.MATADOR analysis with hub genes related to cancer related pathways was performed. We have determined these gene/drug interactions: NBN (targeted by Hydroxyurea), EP300 (targeted by Acetylcarnitine) and MAPK14 (targeted by Salicylate and Dibutyryl cyclic AMP).

Conclusion: The drugs associated with hub genes determined in our study are not routinely used in cancer treatment. Our study offers the opportunity to identify the target genes of drugs used in breast and gynaecological cancers with the drug repurposing approach.

Keywords: Breast cancer; gynaecological cancers; DEGs; hub genes; drug repurposing; RECQL4/FAM13C

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Key Points

- The aim of the study is to determine the genes commonly expressed in both breast and gynaecological cancers and to identify the common hub genes and drug components.

In our study,

- Primarily, the *RecQ Like Helicase 4* and *Family with Sequence Similarity 13 Member C* genes were found to be similarly expressed in breast cancer and gynaecological cancers.
- Secondly, as a result of Drug.MATADOR analysis with hub genes, we have determined these gene/drug interactions such as NBN (targeted by Hydroxyurea), EP300 (targeted by Acetylcarnitine), and MAPK14 (targeted by Salicylate and Dibutyryl cyclic AMP).
- The drugs associated with hub genes determined in our study are not drugs routinely used drugs in cancer treatment.
- In summary, we offer the opportunity to identify the target genes of drugs used in breast and gynaecological cancers with the drug repurposing approach which is a novelty of our study. It brings together two women's cancer groups (breast and gynaecological cancers) that have not been clinically targeted in the literature and clinic and suggests common genes and new candidate drugs/therapeutics.

Introduction

Among all cancers, the most common and life-threatening cancer in women is breast invasive carcinoma (BRCA) (1). Another type of cancer that affects women's lives is gynecological reproductive system cancers. Although gynecological reproductive system cancers such as ovarian serous cystadenocarcinoma (OV), cervical squamous cell carcinoma (CESC) and uterine corpus endometrial carcinoma (UCEC) are not as common as breast cancer, they also threaten women's lives with increasing death rates (2). There are common risk factors (genetic

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predispositions, hormonal interactions, lifestyle factors) that trigger breast and gynecological cancers, which affect the mammary gland and female reproductive organs, respectively (3). For this reason, the probability of multiple primary cancers in the same breast cancer patient is up to %16 higher in women-related cancers due to common triggering factors and genetic predispositions. For example, a history of breast cancer has been shown to be a risk for the development of women's cancers. Additionally, the incidence of gynecological cancers is high in a woman with primary breast cancer (3, 4).

Due to the common biological and genetic mechanisms between breast cancer and gynecological cancers, we tried to identify the genes that are commonly upregulated or downregulated in these cancers through bioinformatic analysis using multiple and independent patient groups. Based on commonly expressed genes, hub genes were identified and drug components that could target these hub genes were tried to be predicted. According to our knowledge, any bioinformatics-based study has been found in which similarly expressed genes were detected using microarray data from both breast cancer patients and gynecological cancer patients. *RecQ Like Helicase 4 (RECQL4)* and Family with Sequence Similarity *13 Member C* (*FAM13C*) genes were detected as commonly expressed genes in gynecological and breast cancer patients.

RECQL4 and *FAM13C* genes were detected as commonly expressed genes in both gynecological and breast cancer patients in our study. *RECQ* genes encodes helicase enzymes that play roles in the DNA damage response. It has been summarized that expression level differences in the *RECQL4* gene, among other genes belonging to this family, play a role in the development of breast and gynecological cancers (5). It has been summarized that expression level differences in the *RECQL4* gene, among other genes belonging to this family, play a role in the development of breast and gynecological cancers (5-8). In addition, cross-sectional studies in patients with cervical cancer showed that the *RECQL4* gene was upregulated in tumour tissue (5, 9), while in a retrospective study, researchers found that the *RECQL4* gene was similarly expressed at higher levels in tissues of ovarian cancer patients than in normal tissue (5, 10).

The *FAM13C* gene, which was found to be downregulated in all cancer types in our study, is a gene belonging to the FAM family. Although the current literature shows that the *FAM13C* gene is downregulated in cervical and ovarian cancer patients compared to normal tissue (11-13), when the content of the studies is examined, it is seen that there is no study directly targeting the *FAM13C* gene. In addition, a study on endometrial cancers is the only study conducted on direct *FAM* genes to date, and as a result of bioinformatic analysis, it is emphasized that a group of FAM family genes, including FAM13C, may be an important prognostic marker in UCEC patients (14).There have been no studies in which the RECQL4 (upregulated) and FAM13C (downregulated) genes were simultaneously marked, and the common hub genes and possible drug-target components were attempted to be predicted in both breast cancer and all gynecological cancers (ovarian, endometrial and cervical). In this respect, our study has unique value.

Materials and Methods

Data Acquisition and Data Processing

Gene intensity values for BRCA (GSE42568, GSE20685, GSE54002), gynecological cancers such as CESC (GSE63514, GSE5787), OV (GSE54388, GSE14407, GSE27651) and UCEC (GSE17025) were obtained from the Affymetrix Human Genome U133 Plus 2.0 Array [HG-U133_Plus_2] project (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GPL570). GPL570 platform was used with 54.675 probes per patient in the Gene Expression Omnibus (GEO) database (15-23). Robust results were ensured by using independent and multiple datasets available for each cancer type. Gene intensity values of 17 healthy individuals (from GSE42568) and 24 healthy individuals (from GSE63514) were used as the control for gene intensities of breast and cervical cancer patients, respectively (24, 25). The data containing patient gene intensity data used in our study was selected from the data contained in the GPL570 platform in the NCBI GEO database because it is the platform with the highest number of probes per patient. We also aimed to include the highest number of patients as possible.

Statistical Analysis

Raw data of all datasets in the CEL format for each cancer type were utilized. Background correction and "Robust Multi-Array Average" normalization using the "oligo" package was done with the help of the Bioconductor R program (https://support.bioconductor.org/p/9148353/). The linear modelling method in the R LIMMA (version 4.3.1.) package was used separately for all datasets (https://www.bioconductor.org/packages/release/bioc/html/limma.html). By doing this, genes that show different gene expression (DEG) levels, either upregulated or downregulated when comparing healthy individuals and cancer patients were identified (26-28). To control the false discovery rate (FDR), The Benjamini-Hochberg method was used (29). Log2FC≥1 and log2FC≤−1 were accepted for the upregulation and downregulation of mRNA expression, respectively. The *p*-value was accepted as <0.05 for statistical significance.

Determination of Hub Genes and Protein-Protein Interactions (PPI) Network

After identifying DEG of interest, hub genes were investigated using the cytoHubba (30) program, which also identify important nodes and subnetworks of protein structures in the Cytoscape (31) program, an open-source software platform used to visualize complex molecular protein-protein interaction networks and integrate them with chosen attribute data. BioGRID 4.4 database was used to list the proteins interacting with *RECQL4* and *FAM13C* genes (32).

Gene Enrichment Analysis of Hub Genes

"ShinyGo 0.80" (known as a graphical gene-set enrichment tool for animals and plants) web-based tool was used to determine the disease specific functional biological pathways addressed by hub genes by selecting the "KEGG" pathway option (33). Furthermore, "ShinyGo 0.80" program was also utilized for gene annotations and probes that were not associated with any gene and were designated as NA were removed from the list. FDR cut-off was accepted as "0.05".

Predicted Drug-Target Interaction of Hub Genes

Drug.MATADOR, included in the ShinyGo 0.80 online tool, is used to predict drug-target relationships. MATADOR is a database used for predicting the interactions between proteins and chemicals. It is also a manually annotated list of relationships between protein products of such genes and chemicals (http://matador.embl.de) (34). In our study, this tool was used to predict the new candidate drug components.

Ethics Committee Approval

Publicly available data sets were utilized. Therefore, no approval from the ethics committee was required. Publicly available data sets were utilized. Therefore, patient consent was not required.

Results

The overall aim of our study was to determine the common DEGs between gynecological and breast cancers, which are women's cancers that can trigger each other in the clinic and have high hormonal interactions. Furthermore, we also aimed to determine hub genes that show gene interaction networks with defined DEGs. The final goal of the study was to determine which biological pathways that identified hub genes indicate and which drug-target interactions they address. Based on this purpose, firstly, genes commonly expressed in both BRCA, and all gynecological cancers were obtained. Furthermore, hub genes were identified, the biological pathways they indicate were determined, and predicted drug-target interactions were addressed (Figure 1).

Determination of Common DEGs of Both Breast Cancer and Gynecological Cancers

Types of cancers and their dataset numbers, healthy and patient numbers used in analysis and upregulated/downregulated gene numbers can be seen in Table 1. According to our findings, the *RECQL4* gene was shown to be commonly upregulated in all cancer types, including both BRCA and gynecological cancers, and the *FAM13C* gene was commonly downregulated in all cancer types (Table 2). Volcano plots of common DEGs for all cancers can be observed in Figure 2 a-i.

Identification of Hub-Genes and PPI Networks

A total of 3130 proteins, which interact with the protein products of the RECQL4 and FAM13C, were identified from the BioGRID 4.4 database. Using the obtained PPI protein list, hub genes were determined based on closeness (Figure 3a) and degree (Figure 3b) using the CytoHubba plugins of the Cytoscape program. According to these results, the top 20 nodes were identified according to both closeness and degree. Totally, 37 hub genes were determined (Figure 3). Furthermore, KEGG pathway analysis was performed for 37 hub genes. Pathways that may be associated with cancers were cellular senescence, FoxO signalling pathway, ubiquitin-mediated proteolysis and viral carcinogenesis and specifically annotated genes are shown in Figure 4 a-b and Table 3. Upon KEGG pathway analysis, among the 37 genes obtained, those related to defined KEGG pathways were determined and reduced to 11 genes.

Predicted Drug-Target Interactions by Using Common Hub Genes Determined for Breast and Gynecological Cancers

Drug.MATADOR analysis was performed using 11 hub genes *(RAD50, MAPK14, SIRT1, MRE11, NBN, EP300, USP7, DDB1, UBE2O, CDC16, and H2BC6)*. Drugs commonly associated with these hub genes and thus both breast and gynecological cancers were hydroxyurea; acetylcarnitine; salicylate; and dibutyryl cyclic AMP (Figure 5). In Table 4, there were three genes identified for these three drug components, and these were NBN, EP300 and MAPK14. For the gene NBN, hydroxyurea was the suggested interacting agent. However, for EP300, acetylcarnitine was suggested. Finally, both salicylate and dibutyryl cyclic AMP agents were suggested as interacting with the product of the *MAPK14* gene.

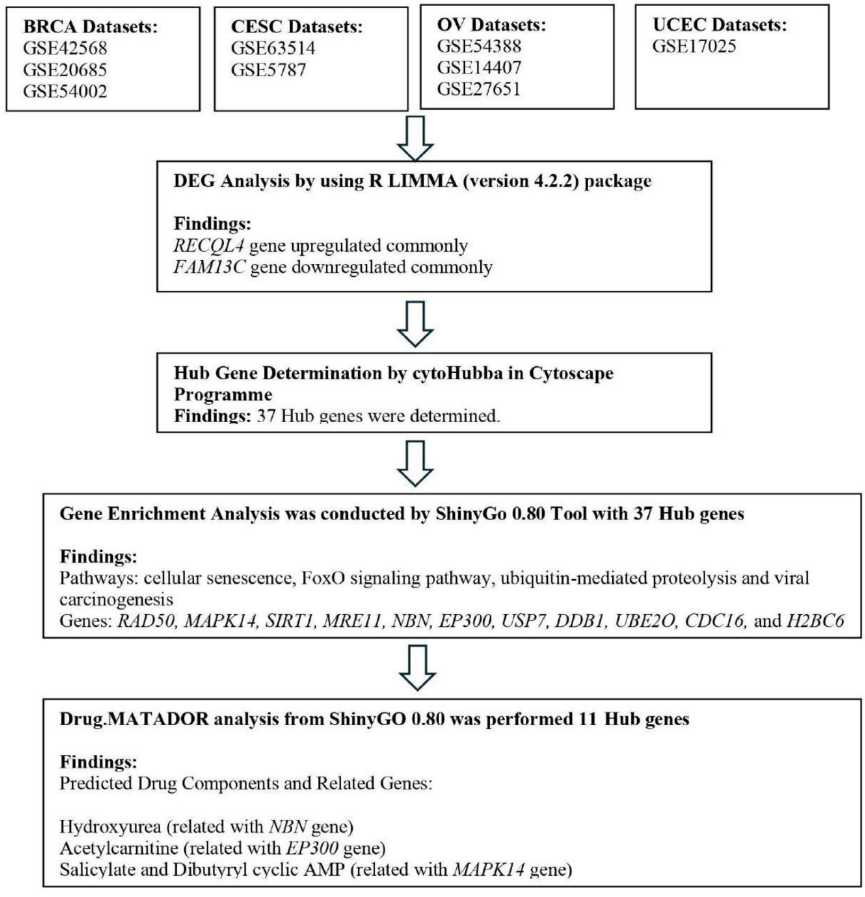

Figure 1. Outline of the study has been shown to clarify the setup of the research

Table 1. Information of breast and gynecological cancer datasets and DEG results

Cancer type	Breast cancer	Breast cancer	Breast cancer	Cervical cancer	Cervical cancer	Ovarian cancer	Ovarian cancer	Ovarian cancer	Endometrial cancers
GSE Code	GSE42568	GSE20685	GSE54002	GSE63514	GSE5787	GSE54388	GSE14407	GSE27651	GSE17025
Number of Samples (tumour/ healthy)	121 (104/17)	327 (327/17)	433 (417/16)	128(104/24)	33 (33/0)	22 (16/6)	24 (12/12)	49 (43/6)	103 (91/12)
Total number of samples	121	17	433	128	57	22	24	49	103
Tumour sample number	104	327	417	104	33	16	12	43	91
Healthy Sample number	17 healthy individuals (from GSE42568)		16	24 healthy individuals (from GSE63514)		6	12	6	12
Downregulated gene number	8563	27584	9919	5003	19460	4483	6161	6787	3311
Non-significant gene number	37872	11125	24141	44248	16550	45696	43224	42371	45724
Upregulated gene number	8240	15966	20615	5424	18665	4496	5290	5517	5640
Total gene number	54675	54675	54675	54675	54675	54675	54675	54675	54675

DEG: Differentially expressed genes

Table 2. Commonly expressed genes in both gynecological cancers (ovarian, cervical and endometrial) and breast cancers in women

Affy IDs of genes	Ensembl gene name (s)	Gene descriptions	Type	Expression pattern of genes in breast cancer	Expression pattern of genes in gynecological cancers
1553015_A_AT	RECQL4 (RECQ4)	RecQ like helicase 4	Protein coding	BRCA: upregulated	OV: upregulated CESC: upregulated UCEC: upregulated
1554547 AT	FAM13C (FAM13C1)	Family with sequence similarity 13 member C	Protein coding	BRCA: downregulated	OV: downregulated CESC: downregulated UCEC: downregulated

Discussion and Conclusion

In our study, the *RECQL4* and *FAM13C* genes were found to be similarly expressed in both breast cancer and gynecological cancers. Considering the proteins in the interaction network of the genes we focused on in our study, the hub genes obtained were primarily determined as 37. As a result of KEGG pathway analyses, pathways associated with cancers were determined as cellular senescence, FoxO signalling pathway, ubiquitin-mediated proteolysis and viral carcinogenesis, and hub genes indicating these pathways were focused on. After performing Drug.MATADOR analysis with the remaining 11 hub genes, we have 3 genes that both indicated a meaningful biological pathway and from which we can make drug-target predictions.

In the literature, instead of focusing on the common genes of breast cancer and all gynecological cancers, there are studies in the literature that analyse common DEGs between breast cancer, OV or UCEC separately. In this context, the only similar study conducted without using bioinformatic analysis is the study conducted by Naghizadeh et al. (35), and in group studies, researchers studied with 200 healthy individual and 200 female patients diagnosed with breast and gynecological cancer. In the study, only demographic data of the patients and statistical correlation data between cancer cases were obtained, with regional restrictions in the Iranian region. No analysis based on genetic-based bioinformatics methods was performed in the study (35). In addition, instead of focusing on the common genes of breast cancer and all gynecological cancers, there are studies in the literature that analyse common DEGs between breast cancer, OV and UCEC. In one study, DEG analyses and biological pathway predictions were made because it is not clear in the literature by which biological and genetic mechanisms breast cancer is associated with UCEC.

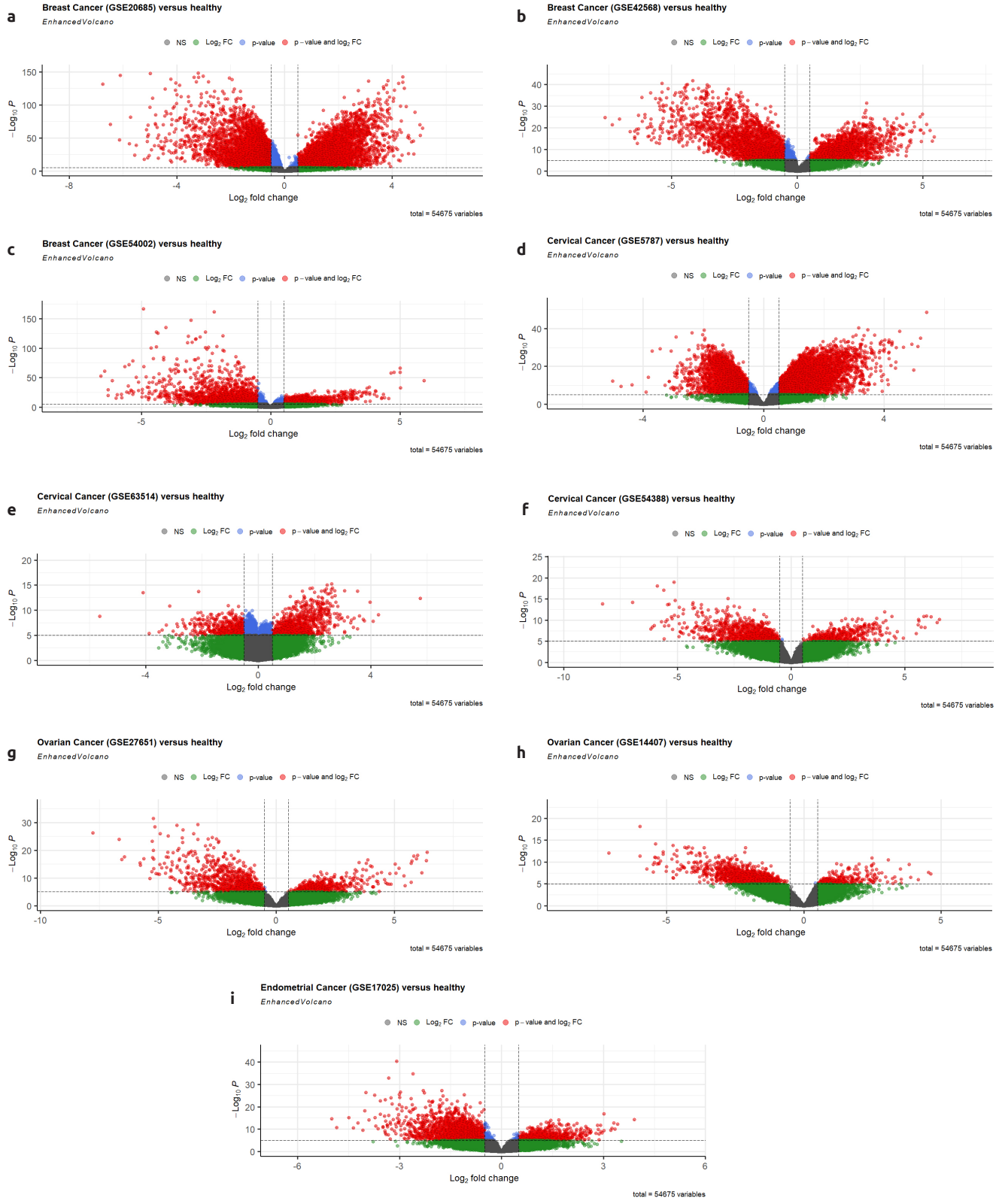

Figure 2. Volcano plot of breast and gynecological cancers. Blue dots indicate *p*-value 10e-6, green dots indicate Log2FC ≤ -1 and ≥1, and red dots show those that are below the p-value of 0.05 and Log2FC thresholds. Gray dots indicate insignificant genes. (a) breast cancer (GSE20685), (b) breast cancer (GSE42568), (c) breast cancer (GSE54002), (d) cervical cancer (GSE5787), (e) cervical cancer (GSE63514), (f) cervical cancer (GSE54388), (g) ovarian cancer (GSE27651), (H) ovarian cancer (GSE14407), (i) endometrial cancer (GSE17025)

Table 3. KEGG pathway genes specifically related to individual pathways

Enrichment FDR	Number of genes	Pathway genes	Fold enrichment	Pathway	Genes
0.019736446	2	41	39.86237	Homologous recombination	*MRE11, NBN*
0.000123199	5	156	26.19162	Cellular senescence	*RAD50, MAPK14, SIRT1, MRE11, NBN*
0.000972628	4	131	24.95202	FoxO signalling pathway	*MAPK14, EP300, SIRT1, USP7*
0.017618289	3	142	17.26434	Ubiquitin mediated proteolysis	*DDB1, UBE2O, CDC16*
0.003510585	4	202	16.18175	Viral carcinogenesis	*DDB1, EP300, USP7, H2BC6*
0.019736446	3	162	15.13294	Hepatitis B	*MAPK14, DDB1, EP300*

FDR: False discovery rate

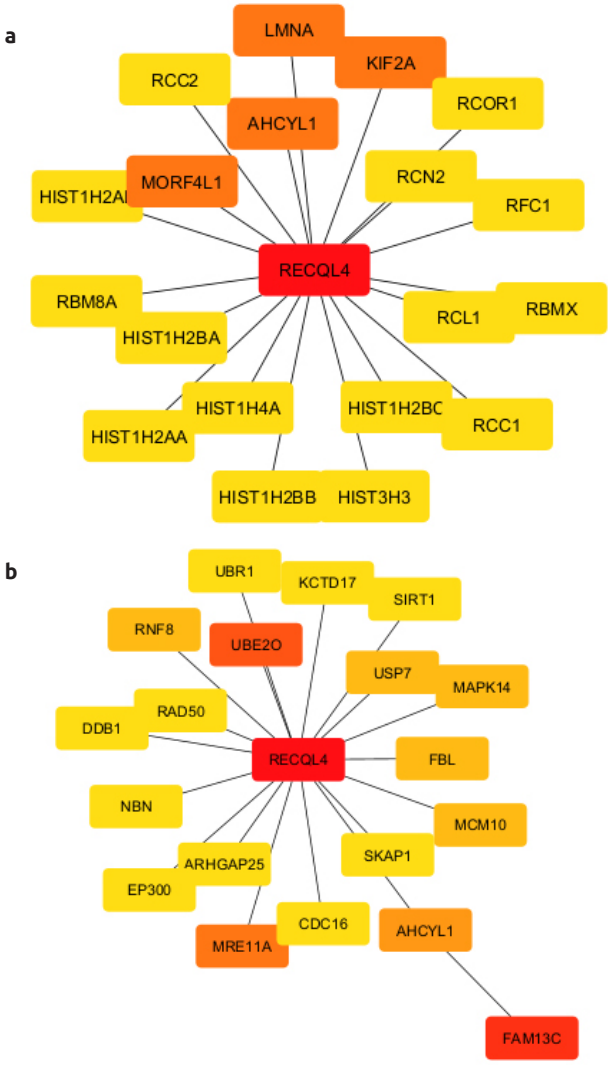

Figure 3. Network of hub-genes identified by closeness (a) and degree (b) in Cytoscape according to PPI network analysis done with CytoHubba plugins of the Cytoscape program, hub genes were determined based on closeness (a) and degree (b). The top 20 nodes were used according to both closeness and degree

PPI: Protein-protein interactions

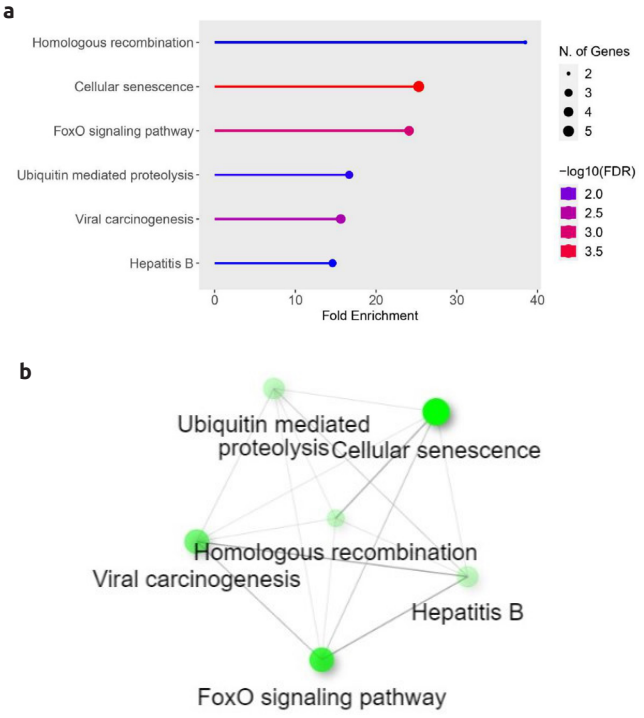

Figure 4. The lollipop chart (a) and network (b) of KEGG pathways in ShinyGO 0.80 According to KEGG pathway analysis from ShinyGO 0.80 online tool, biological pathways related commonly with breast and gynecological cancers are shown with lollipop chart (a) and network (b)

Fifty-seven DEGs were identified in the study, and among these genes, *RECQL4* and *FAM13C* genes, which were found to be commonly expressed in all cancers in our study, were not present (36). In another study, genes commonly expressed between breast cancer patients and both OV and UCEC patients were determined (37). In addition, another study in which bioinformatic analyses were performed using gene density data of breast cancer and ovarian cancer patients focused only on mutations of the BRCA gene (38). In addition, another study in which bioinformatic analyses were performed using gene density data of breast cancer and ovarian cancer patients focused only on mutations of the *BRCA* gene. In one of the current studies conducted

Table 4. Drug-target interaction prediction with common hub genes of both breast and gynecological cancers

Enrichment FDR	nGenes	Pathway genes	Fold enrichment	Drug component	Genes
0.02391172	1	11	189.0991736	Hydroxyurea	*NBN*
0.02391172	1	25	83.20363636	Acetylcarnitine	*EP300*
0.02391172	1	25	83.20363636	Salicylate	*MAPK14*
0.034966622	1	49	42.45083488	Dibutyryl cyclic AMP	*MAPK14*

FDR: False discovery rate

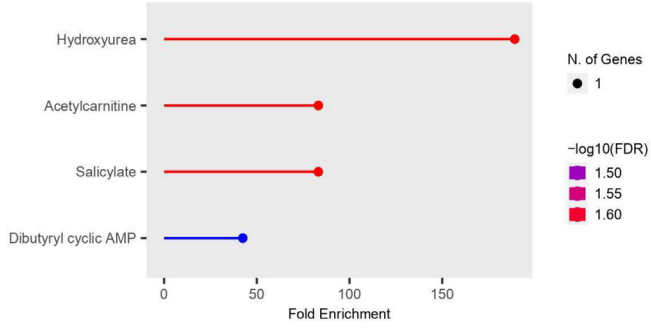

Figure 5. Predicted drug components commonly related to both breast and gynecological cancers. Using Drug.MATADOR analysis from ShinyGO 0.80 online tool, drug-gene target prediction has been made by using common hub genes determined for both breast cancer and gynecological cancers

among gynecological cancers without breast cancer, DEG analyses were performed in patients diagnosed with ovarian, endometrial and vulvar cancer (39). One of the most recent studies on this subject aimed to identify common genes in cervical, endometrial and ovarian cancers and to determined effective and dominant biological pathways through hub genes (40). None of the studies whose findings were summarized above focused on the DEGs we pointed out. For this reason, hub gene analysis and gene enrichment analysis results were also not similar. Additionally, these studies did not perform drug-target prediction analyses, which we focused on in our study.

It is known that the protein product of the *RECQL4* gene, one of the DEGs commonly detected in our study, is a protein that plays a role in the DNA repair mechanism, and it is known in the literature that it has more unique functions in replication and DNA breaks compared to other repair proteins (41). On the other hand, *FAM13C* gene and its protein product belongs to FAM family members and although it has been detected in cancer tissues, it should be further investigated.

Before discussing the drug, components obtained in our study and the hub genes they interact with, information will be given about all hub genes and enriched pathways obtained in the study. It has been well known that the MRN complex (MRE11-RAD50-NBN) creates a DNA damage repair site where there is double strand break. RAD50 (RAD50 double strand break repair protein) and Alterations in MRE11 (MRE11 homolog, double strand break repair nuclease) double strand break repair protein and variants of these genes have been observed in other cancers, including breast, ovarian and endometrial cancers (42, 43). In our study, we also showed MRN complex molecules among the hub genes indicated by DEGs obtained from breast and gynecological cancers.

SIRT1 protein has been shown to be an important protein in cancer progression however it has been newly shown that it contributes to the metastasis of breast cancer with the cooperation of (The Forkhead box O) FoxO protein (44). For instance, overexpression od *SIRT1* gene has been indicated in cervical cancer (45). Furthermore, based on the deacetylating effect of the *SIRT1* gene on histone and non-histone proteins, it is thought that it may contribute to DNA damage and repair, apoptosis, cell cycle regulation and inflammation in gynecological cancers (46). In our study, FoxO signalling pathway is enriched with our hub genes and there should be further studies to identify the roles of the pathway and *SIRT1-FoxO* genes in gynecological cancers.

In our study, the gene identified as the hub gene and closely related to DNA damage and repair mechanism is the damage specific *DNA binding protein 1 (DDB1)* gene. It has been shown that alterations in this gene expression have been related to ovarian and breast cancers (47). Rather than DDB1 alone, mostly DDB1-DDB2 (damage-specific DNA-binding protein 2) complex as a new tumor suppressor has been associated to ovarian cancers (48). On the other hand, DDB2 overexpression has been related to breast cancers (49). The roles in cervical and endometrial cancers remains an open area to be elucidated.

H2BC6 gene has been considered as a cancer biomarker in prostate cancer by NIH Early Detection Research Network (50). Further studies should also be done for breast and gynecological cancers.

Cancer cells are related to the expression of oncogenes and tumor suppressor gene products and the balance between them. When growth factors that cause tumors are not destroyed in the ubiquitin-proteasome system, tumor formation is triggered (51). In our study, the ubiquitin-mediated proteolysis pathway is one of the pathways enriched with our hub genes such as *USP7* and *UBEO2* genes. USP7 (ubiquitin specific peptidase 7) gene has been shown to be involved in ubiquitination process of proteins during the posttranslational protein modifications process and suppression of the overexpression of this gene has led to breast cancer regression in breast cancer cell lines (52). It has been shown that it can be a prognostic factor for ovarian and cervical cancer (53). Furthermore, *UBE2O* gene has also be linked to various cancers such as breast and ovarian cancers summarized in a comprehensive review (54).

Lastly, in our study, cellular senescence has been enriched by our hub genes such as *CDC16* gene. Even though cellular senescence mechanism can be used in cancer regression via cell cycle arrest in cancer cells, there can be a possibility that cells affected by therapy-induced senescence can stay dormant and can enter again in cell cycle process (55). In this regard, according to our opinion, targeting and

inhibiting cell cycle related genes can effectively induce irreversible cellular senescence and it can be a possible prevention for the dormant cells which may re-enter the cell cycle process from the senescent state.

In our study, primarily, *RECQL4* and *FAM13C* genes were found to be similarly expressed in breast cancer and gynaecological cancers. Secondly, as a result of Drug.MATADOR analysis with hub genes, we have determined these gene/drug interactions such as NBN (targeted by Hydroxyurea), EP300 (targeted by Acetylcarnitine), and MAPK14 (targeted by Salicylate and Dibutyryl cyclic AMP).

The *NBN* gene is a gene that encodes the nibrin protein, also known as "Cell Cycle Regulatory Protein P95" and is a component of the MRE11-RAD50-NBN (MRN) complex. *NBN* gene plays an important role in DNA double-strand break repair mechanisms (56). Mutations or expression differences in the *NBN* gene may play a role in cancer processes as they may lead to deficiencies in DNA damage repair mechanisms. Variants of the *NBN* gene have so far been studied among women's cancers using breast cancer patient samples. For example, it has been shown using data from 116 patients that NBN variants may be important as diagnosis markers to be used in tests to detect hereditary breast cancer cases (57). It has also been determined that amplification of the *NBN* gene increased cisplatin and polymerase inhibitors (PARPi) resistance in breast and ovarian cancers (58). In another recent study, various analysis and experiments were conducted to determine whether the NBN gene could be a pan-cancer susceptibility gene. It was shown that pathogenic variants of the *NBN* gene increased the risk of cancer due to disruptions in the DNA damage response in breast, endometrial, ovarian and cervical cancers, respectively, as in many cancers (59). In our study, the *NBN* gene was associated with homologous recombination and especially cellular senescence.

In our study, as a result of drug component prediction analysis, hydroxyurea (hydroxycarbamide) was associated with the *NBN* gene. Hydroxyurea is an anticancer and antineoplastic agent and is known as a DNA replication inhibitor (60). According to Drugbank data, where drug research and clinical use are currently shared with the scientific world, it is frequently used in patients with chronic myelogenous leukaemia and head and neck primary squamous cell carcinoma. It is also a drug used clinically in sickle cell anaemia (https://go.drugbank.com/drugs/DB01005).

The *E1A binding protein P300* (*EP300*) gene encodes the P300 protein. P300 protein plays a role in gene expression by increasing the transcriptional activity of genes by interacting with transcription factors and serving as histone acetyltransferase, allowing histone proteins to be separated from genes during DNA replication (61). In a recently published study, it has been shown that the nucleosome assembly protein 1 like 1 (NAP1L1) protein, which is active through the DEAD-box helicase 5 (DDX5) promoter and acetylated by the EP300 protein, played a role in the progression of endometrial cancers (62). It has been shown that cervical cancer cells secrete lactic acid while performing the aerobic glycolysis mechanism (63, 64). Yang et al. (65) have identified the *EP300* gene among the genes associated with histone lactation modification via the GEPIA2 webtool by using cervical cancer patients' data (65). In addition, in a study trying to determine the effectiveness of poly- (ADP ribose) PARPi therapy on ovarian cancer cells, researchers showed that the *EP300* gene has an important role in this process (66). According to the results of the study, it was found that the histone acetyltransferase mechanism, which was inhibited as a result of the *EP300* gene, developed PARPi-resistance in patient samples (66). In studies conducted on triple negative breast cancer cell lines, it was observed that the *EP300* gene had an oncogenic effect, and with the suppression of the gene, a decrease in the metastatic capacity of the cells, a change in cancer stem cell phenotype, and a regression in the growth of tumour cells were observed (67). In another study, it was determined that the loss of heterozygosity percentages of the *EP300* gene in breast and ovarian cancer cell lines and primary cancer cells were 36% and 49%, respectively (68).

In our study, the drug component associated with the *EP300* gene and predicted to interact with it is acetylcarnitine. Acetylcarnitine is the acetylated form of the amino acid L-carnitine, which is involved in mitochondrial fatty acid metabolism (69). With this structure, Acetylcarnitine is used clinically in the treatment of peripheral nerve lesions, psychiatric diseases such as depression, dementia and neuropathies, according to Drugbank data. Furthermore, according to Drugbank data, Acetylcarnitine is also an agent used in clinical trials for the treatment of diseases such as migraines, type 2 diabetes mellitus chronic hepatitis C, progressive supranuclear palsy. (https://go.drugbank.com/drugs/DB08842).

Mitogen activated protein kinases (MAPKs) play a crucial role in balancing the responses between outside and inside the cell in the homeostasis processes of the cell. *MAPK14* gene is also known as *p38*α gene (https://www.genecards.org/cgi-bin/carddisp.pl?gene=MAPK14). Inhibition of MAPK14 (p38α) has been shown to develop anti-tumoral effects against Taxanes due to increased DNA damage in breast cancer cells in patients and murine models (70, 71). In the study conducted by Katopodis et al. (72) the role of MAPKs in women's cancers (OV, UCEC, CESC, BRCA, and UCS) was investigated, and the study focused on the expression and methylation levels of MAPK11 (p38β) as a result of bioinformatic analysis. In addition, another study has emphasized that the drug called Ralimetinib (LY2228820), known as an inhibitor of p38α (MAPK14) and p38β (MAPK11), is an agent that can target a group of cancer types, including metastatic breast cancers and ovarian cancers (73). In a study conducted in 2023, the role of the p38α signalling pathway in cancer processes was investigated, and according to proteomic analysis, it was shown that the MAPK14 (p38α) protein was important in RNA metabolism, regulated cell adhesion in breast cancer cells, and was effective in DNA replication. Breast cancer cells were used as a role model in this study (74).

Salicylates are known as salts or esters of salicylic acids, and they are frequently used for their analgesic effects. Furthermore, they are also providing anti-inflammatory and antipyretic impact (https://go.drugbank.com/categories/DBCAT000579). For example, aspirin (acetyl salicylate), used as a nonsteroidal anti-inflammatory drug, is a drug often used in people at risk of myocardial infarction (75, 76). However, it has been investigated for a while whether it can be effective in a group of cancer types, including breast and ovarian cancers (77, 78) According to the results of these studies, it has been stated that it can be used effectively in breast cancer patients among women's cancers.

The drug component shown to target the *MAPK14* gene in our study is dibutyryl cyclo-adenosine monophosphate, whose generic name is Bucladesine. Bucladesine, a cyclic nucleotide derivative, acts as an endogenous cAMP and phosphodiesterase inhibitor in the cell. It can be used as a topical product for wound healing for skin ulcers or as a cardioprotective agent (https://drugs.ncats.io/drug/63X7MBT2LQ). According to Drugbank data, there is no study showing whether Bucladesine, which is still in the experimental and research phase, is an effective agent in women's cancers (https://go.drugbank.com/drugs/DB13242#BE0000240).

The drugs mentioned in the discussion section of our article and associated with the hub genes determined in our study are not drugs used in the clinic for the treatment of breast cancer or gynecological cancers. In fact, they are not routinely used drugs in cancer treatment. In this respect, our study offers the opportunity to identify the target genes of drugs used in the treatment of different diseases in the clinic with the drug repurposing approach, which can be used in gene-targeted therapies in the treatment of breast cancer and gynecological cancers. Furthermore, before the trial of these agents on behalf of their cytotoxic effects on cell lines, future molecular dynamics simulations should be done to validate the docked structures to claim that drugs are suitable for the active regions of the target proteins. As a future perspective, total RNA and DNA samples obtained from projects including patient samples and cell lines that include validation of the obtained data should be used for further analysis by using more comprehensive and modern RNA-Seq, whole exome/transcriptome sequencing data.

Ethics

Ethics Committee Approval: Publicly available data sets were utilized. Therefore, no approval from the ethics committee was required.

Informed Consent: Publicly available data sets were utilized. Therefore, patient consent was not required.

Footnotes

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References

1. Xu Y, Gong M, Wang Y, Yang Y, Liu S, Zeng Q. Global trends and forecasts of breast cancer incidence and deaths. Sci Data. 2023; 10: 334. (PMID: 37244901) [Crossref]
2. Vitale SG, Capriglione S, Zito G, Lopez S, Gulino FA, Di Guardo F, et al. Management of endometrial, ovarian and cervical cancer in the elderly: current approach to a challenging condition. Arch Gynecol Obstet. 2019; 299: 299-315. (PMID: 30542793) [Crossref]
3. Ge S, Ma X. Common multiple primary cancers associated with breast and gynecologic cancers and their risk factors, pathogenesis, treatment and prognosis: a review. Front Oncol. 2022; 12: 840431. [Crossref]
4. Maxwell KN, Wenz BM, Kulkarni A, Wubbenhorst B, D'Andrea K, Weathers B, et al. Mutation rates in cancer susceptibility genes in patients with breast cancer with multiple primary cancers. JCO Precis Oncol. 2020; 4: PO.19.00301. (PMID: 32954205) [Crossref]
5. Maity J, Horibata S, Zurcher G, Lee JM. Targeting of RecQ helicases as a novel therapeutic strategy for ovarian cancer. Cancers (Basel). 2022; 14: 1219. (PMID: 35267530) [Crossref]
6. Arora A, Agarwal D, Abdel-Fatah TM, Lu H, Croteau DL, Moseley P, et al. RECQL4 helicase has oncogenic potential in sporadic breast cancers. J Pathol. 2016; 238: 495-501. (PMID: 26690729) [Crossref]
7. Thomassen M, Tan Q, Kruse TA. Gene expression meta-analysis identifies chromosomal regions and candidate genes involved in breast cancer metastasis. Breast Cancer Res Treat. 2009; 113: 239-249. (PMID: 18293085) [Crossref]
8. Zhu X, Chen H, Yang Y, Xu C, Zhou J, Zhou J, et al. Distinct prognosis of mRNA expression of the five RecQ DNA-helicase family members - RECQL, BLM, WRN, RECQL4, and RECQL5 - in patients with breast cancer. Cancer Manag Res. 2018; 10: 6649-6668. (PMID: 30584360) [Crossref]
9. Das M, Prasad SB, Yadav SS, Govardhan HB, Pandey LK, Singh S, et al. Over expression of minichromosome maintenance genes is clinically correlated to cervical carcinogenesis. PLoS One. 2013; 8: e69607. (PMID: 23874974) [Crossref]
10. Guo L, Li Y, Zhao C, Peng J, Song K, Chen L, et al. RECQL4, Negatively regulated by miR-10a-5p, facilitates cell proliferation and invasion via MAFB in ovarian cancer. Front Oncol. 2020; 10: 524128. (PMID: 33014878) [Crossref]
11. den Boon JA, Pyeon D, Wang SS, Horswill M, Schiffman M, Sherman M, et al. Molecular transitions from papillomavirus infection to cervical precancer and cancer: Role of stromal estrogen receptor signaling. Proc Natl Acad Sci U S A. 2015; 112: E3255-E3264. (PMID: 26056290) [Crossref]
12. Feng H, Gu ZY, Li Q, Liu QH, Yang XY, Zhang JJ. Identification of significant genes with poor prognosis in ovarian cancer via bioinformatical analysis. J Ovarian Res. 2019; 12: 35. (PMID: 31010415) [Crossref]
13. Wei M, Bai X, Dong Q. Identification of novel candidate genes and small molecule drugs in ovarian cancer by bioinformatics strategy. Transl Cancer Res. 2022; 11: 1630-1643. (PMID: 35836518) [Crossref]
14. Chi H, Gao X, Xia Z, Yu W, Yin X, Pan Y, et al. FAM family gene prediction model reveals heterogeneity, stemness and immune microenvironment of UCEC. Front Mol Biosci. 2023; 10: 1200335. (PMID: 37275958) [Crossref]
15. Clarke C, Madden SF, Doolan P, Aherne ST, Joyce H, O'Driscoll L, et al. Correlating transcriptional networks to breast cancer survival: a large-scale coexpression analysis. Carcinogenesis. 2013; 34: 2300-2308. (PMID: 23740839) [Crossref]
16. Kao KJ, Chang KM, Hsu HC, Huang AT. Correlation of microarray-based breast cancer molecular subtypes and clinical outcomes: implications for treatment optimization. BMC Cancer. 2011; 11: 143. (PMID: 21501481) [Crossref]
17. Tan TZ, Miow QH, Miki Y, Noda T, Mori S, Huang RY, et al. Epithelial-mesenchymal transition spectrum quantification and its efficacy in deciphering survival and drug responses of cancer patients. EMBO Mol Med. 2014; 6: 1279-1293. (PMID: 25214461) [Crossref]
18. den Boon JA, Pyeon D, Wang SS, Horswill M, Schiffman M, Sherman M, et al. Molecular transitions from papillomavirus infection to cervical precancer and cancer: Role of stromal estrogen receptor signaling. Proc Natl Acad Sci U S A. 2015; 112: E3255-E3264. (PMID: 26056290) [Crossref]
19. Bachtiary B, Boutros PC, Pintilie M, Shi W, Bastianutto C, Li JH, et al. Gene expression profiling in cervical cancer: an exploration of intratumor heterogeneity. Clin Cancer Res. 2006; 12: 5632-5640. (PMID: 17020965) [Crossref]
20. Yeung TL, Leung CS, Wong KK, Gutierrez-Hartmann A, Kwong J, Gershenson DM, et al. ELF3 is a negative regulator of epithelial-mesenchymal transition in ovarian cancer cells. Oncotarget. 2017; 8: 16951-16963. (PMID: 28199976) [Crossref]
21. Bowen NJ, Walker LD, Matyunina LV, Logani S, Totten KA, Benigno BB, et al. Gene expression profiling supports the hypothesis that human

ovarian surface epithelia are multipotent and capable of serving as ovarian cancer initiating cells. BMC Med Genomics. 2009; 2: 71. (PMID: 20040092) [Crossref]

22. King ER, Tung CS, Tsang YT, Zu Z, Lok GT, Deavers MT, et al. The anterior gradient homolog 3 (AGR3) gene is associated with differentiation and survival in ovarian cancer. Am J Surg Pathol. 2011; 35: 904-912. (PMID: 21451362) [Crossref]
23. Day RS, McDade KK. A decision theory paradigm for evaluating identifier mapping and filtering methods using data integration. BMC Bioinformatics. 2013; 14: 223. (PMID: 23855655) [Crossref]
24. Clarke C, Madden SF, Doolan P, Aherne ST, Joyce H, O'Driscoll L, et al. Correlating transcriptional networks to breast cancer survival: a large-scale coexpression analysis. Carcinogenesis. 2013; 34: 2300-2308. (PMID: 23740839) [Crossref]
25. den Boon JA, Pyeon D, Wang SS, Horswill M, Schiffman M, Sherman M, et al. Molecular transitions from papillomavirus infection to cervical precancer and cancer: Role of stromal estrogen receptor signaling. Proc Natl Acad Sci U S A. 2015; 112: E3255-E3264. (PMID: 26056290) [Crossref]
26. R Core Team (2023) R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna. [Crossref]
27. Carvalho BS, Irizarry RA. A framework for oligonucleotide microarray preprocessing. Bioinformatics. 2010; 26: 2363-2367. (PMID: 20688976) [Crossref]
28. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. Limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 2015; 43: e47. (PMID: 25605792) [Crossref]
29. Y Benjamini, Y Hochberg. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Roy Stat Soc. 1995; 57: 289-300. [Crossref]
30. CH Chin, SH Chen, HH Wu, CW Ho, MT Ko, CY Lin. CytoHubba: identifying hub objects and sub-networks from complex interactome. BMC Syst Biol. 2014; 8: S11. [Crossref]
31. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 2003; 13: 2498-2504. (PMID: 14597658) [Crossref]
32. Stark C, Breitkreutz BJ, Reguly T, Boucher L, Breitkreutz A, Tyers M. BioGRID: a general repository for interaction datasets. Nucleic Acids Res. 2006; 34: D535-D539. (PMID: 16381927) [Crossref]
33. Ge SX, Jung D, Yao R. ShinyGO: a graphical gene-set enrichment tool for animals and plants. Bioinformatics. 2020; 36: 2628-2629. [Crossref]
34. Günther S, Kuhn M, Dunkel M, Campillos M, Senger C, Petsalaki E, et al. SuperTarget and Matador: resources for exploring drug-target relationships. Nucleic Acids Res. 2008; 36: D919-D922. (PMID: 17942422) [Crossref]
35. Naghizadeh S, Faroughi F, Mirghafourvand M. Investigating the relationship between breast and gynecological cancers and infertility and its treatments: a case-control study. Eur J Cancer Prev. 2023; 32: 600-607. (PMID: 37283054) [Crossref]
36. MF Rahman, MR Rahman, T Islam, T Zaman, MAH Shuvo, MT Hossain, et al. A bioinformatics approach to decode core genes and molecular pathways shared by breast cancer and endometrial cancer. 2019. [Crossref]
37. Atasever S. Identification of potential hub genes as biomarkers for breast, ovarian, and endometrial cancers. Frontiers in Life Sciences and Related Technologies. 2024; 5: 74-82. [Crossref]
38. Wang Z, Zhang J, Zhang Y, Deng Q, Liang H. Expression and mutations of BRCA in breast cancer and ovarian cancer: Evidence from bioinformatics analyses. Int J Mol Med. 2018; 42: 3542-3550. (PMID: 30221688) [Crossref]
39. Liu Y, Yi Y, Wu W, Wu K, Zhang W. Bioinformatics prediction and analysis of hub genes and pathways of three types of gynecological cancer. Oncol Lett. 2019; 18: 617-628. (PMID: 31289534) [Crossref]
40. Zhang X, Wang Y. Identification of hub genes and key pathways associated with the progression of gynecological cancer. Oncol Lett. 2019; 18: 6516-6524. (PMID: 31788113) [Crossref]
41. Luong TT, Bernstein KA. Role and regulation of the RECQL4 family during genomic integrity maintenance. Genes (Basel). 2021; 12: 1919. (PMID: 34946868) [Crossref]
42. Heikkinen K, Karppinen SM, Soini Y, Mäkinen M, Winqvist R. Mutation screening of Mre11 complex genes: indication of RAD50 involvement in breast and ovarian cancer susceptibility. J Med Genet. 2003; 40: e131. (PMID: 14684699) [Crossref]
43. Otahalova B, Volkova Z, Soukupova J, Kleiblova P, Janatova M, Vocka M, et al. Importance of germline and somatic alterations in human MRE11, RAD50, and NBN genes coding for MRN complex. Int J Mol Sci. 2023; 24: 5612. (PMID: 36982687) [Crossref]
44. Dilmac S, Kuscu N, Caner A, Yildirim S, Yoldas B, Farooqi AA, et al. SIRT1/FOXO Signaling pathway in breast cancer progression and metastasis. Int J Mol Sci. 2022; 23: 10227. (PMID: 36142156) [Crossref]
45. Velez-Perez A, Wang XI, Li M, Zhang S. SIRT1 overexpression in cervical squamous intraepithelial lesions and invasive squamous cell carcinoma. Hum Pathol. 2017; 59: 102-107. (PMID: 27720890) [Crossref]
46. Chen J, Chen H, Pan L. SIRT1 and gynecological malignancies (Review). Oncol Rep. 2021; 45: 43. (PMID: 3364983) [Crossref]
47. Shan Y, Mao B, Jin Y, You Y, Wang Y, Shen K, et al. Expression of DDB1 is associated with subtypes of epithelial ovarian cancer and predicts clinical outcomes. Tissue Cell. 2023; 82: 102072. (PMID: 36934683) [Crossref]
48. Han C, Zhao R, Liu X, Srivastava A, Gong L, Mao H, et al. DDB2 suppresses tumorigenicity by limiting the cancer stem cell population in ovarian cancer. Mol Cancer Res. 2014; 12: 784-794. (PMID: 24574518) [Crossref]
49. Kattan Z, Marchal S, Brunner E, Ramacci C, Leroux A, Merlin JL, et al. Damaged DNA binding protein 2 plays a role in breast cancer cell growth. PLoS One. 2008; 3: e2002. (PMID: 18431487) [Crossref]
50. Jia Z, Wang Y, Sawyers A, Yao H, Rahmatpanah F, Xia XQ, et al. Diagnosis of prostate cancer using differentially expressed genes in stroma. Cancer Res. 2011; 71: 2476-2487. (PMID: 21459804) [Crossref]
51. Liu F, Chen J, Li K, Li H, Zhu Y, Zhai Y, et al. Ubiquitination and deubiquitination in cancer: from mechanisms to novel therapeutic approaches. Mol Cancer. 2024; 23: 148. (PMID: 39048965) [Crossref]
52. Hayal TB, Doğan A, Şişli HB, Kiratli B, Şahin F. Ubiquitin-specific protease 7 downregulation suppresses breast cancer in vitro. Turk J Biol. 2020; 44: 145-157. [Crossref]
53. Ma M, Yu N. Ubiquitin-specific protease 7 expression is a prognostic factor in epithelial ovarian cancer and correlates with lymph node metastasis. Onco Targets Ther. 2016; 9: 1559-1569. (PMID: 27051296) [Crossref]
54. Maffeo B, Cilloni D. The ubiquitin-conjugating enzyme E2 O (UBE2O) and its therapeutic potential in human leukemias and solid tumors. Cancers (Basel). 2024; 16: 3064. (PMID: 39272922) [Crossref]
55. Xiao S, Qin D, Hou X, Tian L, Yu Y, Zhang R, et al. Cellular senescence: a double-edged sword in cancer therapy. Front Oncol. 2023; 13: 1189015. (PMID: 37771436) [Crossref]
56. Varon R, Vissinga C, Platzer M, Cerosaletti KM, Chrzanowska KH, Saar K, et al. Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. Cell. 1998; 93: 467-476. (PMID: 9590180) [Crossref]

57. Zuntini R, Bonora E, Pradella LM, Amato LB, Vidone M, De Fanti S, et al. Detecting variants in the NBN gene while testing for hereditary breast cancer: what to do next? Int J Mol Sci. 2021; 22: 5832. (PMID: 34072463) [Crossref]
58. Wu Z, Li S, Tang X, Wang Y, Guo W, Cao G, et al. Copy number amplification of DNA damage repair pathways potentiates therapeutic resistance in cancer. Theranostics. 2020; 10: 3939-3951. (PMID: 32226530) [Crossref]
59. Belhadj S, Khurram A, Bandlamudi C, Palou-Márquez G, Ravichandran V, Steinsnyder Z, et al. NBN pathogenic germline variants are associated with pan-cancer susceptibility and in vitro DNA damage response defects. Clin Cancer Res. 2023; 29: 422-431. (PMID: 36346689) [Crossref]
60. Koç A, Wheeler LJ, Mathews CK, Merrill GF. Hydroxyurea arrests DNA replication by a mechanism that preserves basal dNTP pools. J Biol Chem. 2004; 279: 223-230. (PMID: 14573610) [Crossref]
61. Thompson PR, Kurooka H, Nakatani Y, Cole PA. Transcriptional coactivator protein p300. Kinetic characterization of its histone acetyltransferase activity. J Biol Chem. 2001; 276: 33721-33729. (PMID: 11445580) [Crossref]
62. Zhu X, Li Y, Shao Z, Lu X, Chen Y. NAP1L1 promotes endometrial cancer progression via EP300-mediated DDX5 promoter acetylation. Mol Cancer Res. 2024; 22: 1011-1021. (PMID: 38953887) [Crossref]
63. Schwickert G, Walenta S, Sundfør K, Rofstad EK, Mueller-Klieser W. Correlation of high lactate levels in human cervical cancer with incidence of metastasis. Cancer Res. 1995; 55: 4757-4759. (PMID: 7585499) [Crossref]
64. Walenta S, Wetterling M, Lehrke M, Schwickert G, Sundfør K, Rofstad EK, et al. High lactate levels predict likelihood of metastases, tumor recurrence, and restricted patient survival in human cervical cancers. Cancer Res. 2000; 60: 916-921. (PMID: 10706105) [Crossref]
65. Yang X, Zhang W, Zhu W. Profiling of immune responses by lactate modulation in cervical cancer reveals key features driving clinical outcome. Heliyon. 2023; 9: e14896. (PMID: 37151676) [Crossref]
66. Cheng A, Rao Q, Liu Y, Huang C, Li J, Huo C, et al. Genomic and expressional dynamics of ovarian cancer cell lines in PARPi treatment revealed mechanisms of acquired resistance. Gynecol Oncol. 2022; 167: 502-512. [Crossref]
67. Ring A, Kaur P, Lang JE. EP300 knockdown reduces cancer stem cell phenotype, tumor growth and metastasis in triple negative breast cancer. BMC Cancer. 2020; 20: 1076. [Crossref]
68. Bryan EJ, Jokubaitis VJ, Chamberlain NL, Baxter SW, Dawson E, Choong DY, et al. Mutation analysis of EP300 in colon, breast and ovarian carcinomas. Int J Cancer. 2002; 102: 137-141. (PMID: 12385008) [Crossref]
69. McCann MR, George De la Rosa MV, Rosania GR, Stringer KA. L-carnitine and acylcarnitines: mitochondrial biomarkers for precision medicine. Metabolites. 2021; 11: 51. (PMID: 33466750) [Crossref]
70. Cánovas B, Igea A, Sartori AA, Gomis RR, Paull TT, Isoda M, et al. Targeting p38α increases DNA damage, chromosome instability, and the anti-tumoral response to taxanes in breast cancer cells. Cancer Cell. 2018; 33: 1094-1110. [Crossref]
71. Madkour MM, Anbar HS, El-Gamal MI. Current status and future prospects of p38α/MAPK14 kinase and its inhibitors. Eur J Med Chem. 2021; 213: 113216. (PMID: 33524689) [Crossref]
72. Katopodis P, Kerslake R, Zikopoulos A, Beri N, Anikin V. p38β - MAPK11 and its role in female cancers. J Ovarian Res. 2021; 14: 84. [Crossref]
73. Vergote I, Heitz F, Buderath P, Powell M, Sehouli J, Lee CM, et al. A randomized, double-blind, placebo-controlled phase 1b/2 study of ralimetinib, a p38 MAPK inhibitor, plus gemcitabine and carboplatin versus gemcitabine and carboplatin for women with recurrent platinum-sensitive ovarian cancer. Gynecol Oncol. 2020; 156: 23-31. (PMID: 31791552) [Crossref]
74. Dan Y, Radic N, Gay M, Fernández-Torras A, Arauz G, Vilaseca M, et al. Characterization of p38α Signaling Networks in Cancer Cells Using Quantitative Proteomics and Phosphoproteomics. Mol Cell Proteomics. 2023; 22: 100527. (PMID: 36894123) [Crossref]
75. Cuzick J, Otto F, Baron JA, Brown PH, Burn J, Greenwald P, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol. 2009; 10: 501-507. (PMID: 19410194) [Crossref]
76. Zundorf U. Aspirin 100 years: the future has just begun (cover illustration). 1997. Leverkusen: BayerAG
77. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol. 2012; 23: 1403-1415. (PMID: 22517822) [Crossref]
78. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology. 1994; 5: 138-146. (PMID: 8172988) [Crossref]