Rules of Tumor Cell Development and Their Application to Biomarkers for Ovarian Cancer

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Purpose/Objectives: To apply the Hanahan and Weinberg conceptual framework for tumor development to the specific biomarkers observed or expressed in ovarian cancer.

Data Sources: Data-based publications, topical reviews, and book chapters.

Data Synthesis: Articles specific to ovarian cancer were reviewed to examine whether the six rules from the Hanahan and Weinberg conceptual framework were applicable to biomarkers of ovarian cancer. This approach allows for the application of a general framework for the development of solid tumors to the development of ovarian cancer.

Conclusions: The six rules for tumor cell development outlined in the Hanahan and Weinberg conceptual framework are applicable to biomarkers expressed or observed in patients with ovarian cancer.

Implications for Nursing: Oncology nurses can enhance their clinical teaching by integrating this information into their practice. Nurses who conduct research on ovarian cancer can use this framework to guide the selection of biomarker(s) for these studies. Finally, nurse educators can use this framework when teaching students key concepts in the care of patients with cancer.

Inherent biologic differences exist among and within various types of human cancer. Although tumors arise and proliferate from a single abnormal cell, they quickly become heterogeneous in their cellular composition, with some more differentiated than others. Historically, experimental work in histology (the microscopic structure of tissues), cytology (structure and function of cells), morphology (form and structure of living organisms), and epidemiology (incidence and prevalence of disease) has provided diverse phenotypes for various cancers. However, as molecular methods improve, synthesizing experimental evidence and thinking conceptually about the underlying rules that govern tumor development have become possible (Hanahan & Weinberg, 2000).

The purpose of this article is to apply the Hanahan and Weinberg (2000) conceptual framework for the development of cancer cells to biomarkers observed or expressed in ovarian cancer. Ovarian cancer was chosen as the tumor type because this framework has not been applied to it and knowledge of biomarkers for ovarian cancer has increased in recent years.

The Rules for Making Tumor Cells and Biomarkers of Ovarian Cancer

The Hanahan and Weinberg conceptual framework attempts to synthesize existing knowledge about tumors and the rules

Key Points . . .

- The Hanahan and Weinberg conceptual framework is applicable to biomarkers of ovarian cancer.
- The hallmarks of cancer can be distilled to six rules that also apply to biomarkers of ovarian cancer.
- Information about biomarkers of ovarian cancer has increased during recent years, and nurses should integrate this knowledge into their clinical practice.

required for malignant transformation. After a rewview of years of literature in cell biology, biochemistry, genetics, and clinical oncology, six rules were distilled regarding the development of tumor cells (Hahn & Weinberg, 2002; Hanahan & Weinberg, 2000). Hanahan and Weinberg stated that "we foresee cancer research developing into a logical science, where the complexities of the disease, described in the laboratory and clinic, will become understandable in terms of a small number of underlying principles" (p. 57). The six rules are: (a) self-sufficiency in growth signals, (b) insensitivity to growth-inhibitory signals, (c) evasion of programmed cell death (apoptosis), (d) limitless replicative potential, (e) sustained angiogenesis, and (f) tissue invasion and metastasis (Hanahan & Weinberg). Detailed information about each rule

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Rule	Evidence (Exemplar)	Other Names	Other Family Members and Homologues	Loci	Characteristics of the Exemplar	
Self-sufficiency	EGFR	HER2/neu	EGFR (erbB1) HER2/neu (c-erbB-2) HER3 (erbB-3) HER4 (erbB-4)	17q21–22	Cell proliferation Differentiation Activation of key transcription factors	
Insensitivity to growth-inhibitory signals	TGF	TGF-α or EGF	TGF-α TGF-β	19q	Anti-growth factor Prevention of phosphorylation of retinoblastoma protein Prevent cell cycle at G ₁	
	c-myc	p64 p67	тус	8p24	DNA-binding proteins Cell proliferation Activate and inactivate cyclins family and p53	
Apoptosis	p53	Тр53	N/A	17p13.1	DNA-binding protein Sequence-specific transcription factor Growth arrest Apoptosis Metabolite deprivation, physical damage DNA damage, heat shock, hypoxia Oncogene expression	
Immortality (limitless repli- cative potential)	Telomerase	N/A	N/A	Adds hexanucleotide repeats to ends of telomeric DNA	Large ribonucleoprotein complex Expressed only in embryonic cells and gametocytes	
Sustained angiogenesis	VEGF	PDGF-β PIGF	VEGFA VEGFB VEGFC VEGFD VEGFE	VEGFA 6p21.3	Embryonic vasculogenesis and angiogenesis Proliferation Sprouting, migration, tube formation of endothelial cells	
Metastasis (tissue invasion)	E-cadherin	N/A	N-cadherin P-cadherin VE-cadherin	16q22.1	Highly conserved cytoplasmic tail complexes with catenins family Cellular cohesion and detachment	
	Interleukin-6	IL-6	Cytokine	Unknown	B-cell differentiation Immunoglobulin production Megakaryopoiesis (generation of platelet precursors)	
	CA125	MUC16 (gene)	N/A	19p13.2	Ligand for galectin-1 Ligand for mesothelin	

Table 1. Rules From the Hanahan and Weinberg Conceptual Framework

EGF—epidermal growth factor; EGFR—epidermal growth factor receptor; N/A—not applicable; PDGF—platelet-derived growth factor; PIGF—placental growth factor; TGF—transforming growth factor; VEGF—vascular endothelial growth factor

Note. Based on information from Hanahan & Weinberg, 2000.

and the exemplars provided in the original article are summarized in Table 1.

All of the rules that govern malignant transformation are grounded in the cell cycle and the proteins involved in the regulation of cellular proliferation. The six rules for malignant transformation are described in the context of the cell cycle; however, the rules do not need to occur in a specific order, and all of the rules of tumorigenesis do not necessarily have to occur in all types of human cancer. Figure 1 provides a glossary of terms that are used throughout this article.

Self-Sufficiency

Normal cells depend on external signals to grow and divide in the context of their neighbors. Tumor cells acquire the ability to replicate, divide, and grow without exogenous growth signals. In addition, tumor cells acquire the ability to alter or generate their own growth signals, rendering them independent from their microenvironment (Hanahan & Weinberg, 2000). Tumor cells also develop alterations in signal transduction that allow them to overexpress growth factors, receptors, and other domains on their cellular surfaces.

The biomarker that best illustrates the self-sufficiency rule is the epidermal growth factor receptor (EGFR). EGFR is part of a large superfamily with many members, including HER2/neu (c-erbB-2), HER3 (erbB-3), and HER4 (erbB-4). Overexpression of EGFR is observed in a large number of epithelial human tumors, where it initiates a phosphorylation cascade that is responsible for cell proliferation, differentiation, and activation of other signaling pathways that lead to the activation of key transcription factors (Aunoble, Sanches, Didier, & Bignon, 2000).

HER2/neu in ovarian cancer: Amplification of HER2/ neu is found in 19%–59% of ovarian tumors (Aunoble et al., 2000). No correlation has been found among HER2/neu expression and tumor stage, tumor grade, or histologic tumor **Amplification:** chromosomal changes in tumor cells that allow for more than one copy of a gene to be present; amplification is sometimes referred to as a copy number alteration or aneuploidy (Alberts et al., 2002).

Confluency rule: Cells grown in culture grow exponentially until confluency is reached. Once plated cells have occupied the surface space, they will no longer divide until additional resources and space are provided (King & Stansfield, 2002).

Glycoprotein: a protein containing a small amount of carbohydrate (< 4%), also known as a membrane protein (Alberts et al., 2002; King & Stansfield, 2002)

Immunoglobulins: antibodies secreted by mature lymphoid cells; immunoglobulins (lgs) are y-shaped tetrameric molecules with five known chain classes: IgA (epithelial tissues of respiratory and digestive tracts), IgE (allergies), IgD (unknown function), IgG (most common and responsible for immunologic memory), and IgM (early response to initial antigen exposure) (King & Stansfield, 2002).

Interleukins (cytokines): a group of at least 15 soluble proteins secreted by leukocytes that promote growth and differentiation of immune cells

Mesenchyme: embryonic type of connective tissue, consisting of amoeboid cells with many processes; these cells form loose networks and produce the connective tissue and circulatory system during development of vertebrates (King & Stansfield, 2002).

Mitogen: a compound that stimulates cells to undergo mitosis (King & Stansfield, 2002)

Signal transduction: pathways through which cells receive external signals and transmit, amplify, and direct them internally (King & Stansfield, 2002)

Tumor suppressor genes: antioncogenes (King & Stanford, 2002) that suggest the production of too little gene product through loss of function mutations or allelic loss (Nussbaum et al., 2001) or result in tumorigenesis

Figure 1. Definitions

type. However, overexpression of HER-2/neu in ovarian cancer predicts platinum therapy chemotherapy resistance in 75% of patients (Aunoble et al.).

Insensitivity to Antigrowth Signals

The role of most normal cells in human tissues is to maintain organ homeostasis. Inter- and intracellular signaling helps to maintain the balance among various cells within tissues. Healthy cells use signaling pathways to monitor the external environment in which they find themselves. This monitoring role allows cells to decide to proliferate, remain senescent, or initiate apoptosis (Evan & Littlewood, 1998). Abnormal cells acquire the ability to override external signals and proliferate independent of their environment.

The best characterized biomarker that illustrates the insensitivity rule is tumor growth factor- β (TGF- β). The TGF- β superfamily includes bone morphogenic proteins, growth and differentiation factors, activins, inhibins, and Mullerian inhibitory factors (Chin, Boyle, Parsons, & Coman, 2004). TGF- β functions as a cytokine in the human ovaries, acting as a regulator of epithelial cell growth, differentiation, motility, organization, and apoptosis (Chin et al.). The inhibins are the best understood member of the TGF- β family in ovarian cancer.

Inhibins and ovarian cancer: Inhibins are produced and secreted by normal ovarian tissue and ovarian tumors; however, increased production and secretion of inhibins are more common with mucinous ovarian tumors. Two heterologous subunits of inhibins exist, namely βA or βB , that form dimers called activins. These subunits are responsible for tissue development, immunosuppression, and proliferative and antiproliferative activity (Robertson et al., 2004; Tong, Wallace, & Burger, 2003).

Inhibins regulate pituitary follicle-stimulating hormone secretion using a negative feedback loop (Robertson et al., 2004). The primary mode of action of inhibins is to antagonize the activins (in dimer configuration), which renders the inhibins as indicators of ovarian cancer recurrence. Inhibins are measured as biomarkers in conjunction with CA125 levels. Inhibin A (α - β A) and inhibin B (α - β B) are serum biomarkers drawn in conjunction with CA125 to monitor granulosa cell ovarian cancer after surgical debulking. The inhibins are markers of altered circulation and considered a characteristic of mucinous ovarian cancer; however, their utility in epithelial ovarian cancer is unknown.

Evading Apoptosis

Apoptosis controls cellular proliferation and attrition in normal cells. Apoptosis occurs in response to DNA damage, during conditions of extreme cellular stress (e.g., heat shock, lack of nutrients), and in response to external injury or damage (Hanahan & Weinberg, 2000). The process of apoptosis can last 30–120 minutes and follows a distinct pattern, beginning with cellular membrane disruption. The cytoplasmic and nuclear skeletons break down, the cytosol is extruded, the chromosomes is degraded, and nuclear fragmentation occurs (Hanahan & Weinberg). The degraded cell is engulfed by a leukocyte and metabolized within 24 hours.

Tumor cells can evade apoptosis and gain the ability to proliferate indefinitely (Evan & Littlewood, 1998; Hahn & Weinberg, 2002). Two well-characterized pathways of apoptosis exist, one that includes the mitochondrial caspases and one that uses the p53 transcription factor to activate the ubiquitin pathways of cellular death. A multitude of biomarkers are associated with both apoptotic pathways, but the best characterized biomarker that illustrates the evading apoptosis rule is p53.

p53 in ovarian cancer: The loss of the tumor-suppressor gene Tp53, which leads to overexpression of the p53 protein, occurs in 30%-50% of ovarian cancers and is specific for serous carcinomas (Aunoble et al., 2000; Fujita, Enomoto, & Murata, 2003). In addition, overexpression of the p53 protein is observed in 26%–62% of ovarian tumors (Aunoble et al.). Loss of the p53 gene occurs through a variety of mutations (e.g., missense, frameshift, splice-site). Patients with ovarian tumors associated with the loss of p53 have a poorer survival when considered with a variety of other characteristics, including International Federation of Obstetrics and Gynecology stage, tumor grade, and histologic type (Aunoble et al.; Wenham, Lancaster, & Berchuck, 2002). The p53 gene is unlike c-myc, k-ras, and HER2/neu. When the p53 gene is lost, the p53 protein is overexpressed but its function may be altered (Hanahan & Weinberg, 2000).

The ability of cancer cells to respond to chemotherapeutic agents has been shown to depend on functional apoptotic pathways (Fraser et al., 2003). In ovarian cancer, drug-induced apoptosis is governed by the up-regulation of proapoptotic factors, including p53, and modulation of cell survival factors (Fraser et al.). The loss of p53 initiates several cascades that render ovarian cancer cells resistant to cisplatin and paclitaxel (Fraser et al.).

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Limitless Replicative Potential (Immortality Rule)

Normal cells, during each replication, lose 50–100 base pairs of DNA at the ends of every chromosome. Telomeres function as specialized DNA that create protective caps on the ends of chromosomes (Hanahan & Weinberg, 2000). Once the telomeres have eroded completely, the chromosomes become susceptible to end-to-end fusion and karyotypic disarray and the cell is marked for death (Hanahan & Weinberg; Matias-Guiu & Prat 1998).

In culture, cells grow until they reach confluency, usually after 60–80 cell generations, at which point they enter a nongrowing yet viable state called senescence (Hahn & Weinberg, 2002). The replicative capacity of a cell directly correlates with telomere length, thus creating a mitotic clock that signals when a cell should enter senescence (Villa et al., 2000). Tumor cells that express telomerase gain the capacity to replicate without limit and can become immortal (Hanahan & Weinberg, 2000). The biomarker that best illustrates the immortality rule is telomerase. Telomerase is a large ribonucleoprotein complex that is expressed only in normal embryonic cells and gametocytes (King & Stansfield, 2002).

Telomere maintenance and telomerase activity in ovarian cancer: Normal adult cells do not express telomerase. Ninety-two percent of ovarian tumors express telomerase (Matias-Guiu & Prat, 1998). Expression of telomerase is equivalent to cellular resistance to apoptosis (Villa et al., 2000). Increased telomerase expression has been associated with a poorer prognosis in all ovarian tumor types (Wenham et al., 2002). Ovarian cancer cells in culture have been shown to use telomerase to catalyze the synthesis of new repeats during DNA replication (Wenham et al., 2002). Telomere length is related inversely to the degree of chromosomal abnormality in ovarian cancer; however, whether telomerase is activated as a part of tumorigenesis or is a result of subsequent chromosomal instability remains to be determined (Counter, Hirte, Bacchetti, & Harley, 1994).

Sustained Angiogenesis

Angiogenesis is a normal process by which capillaries are formed and blood is supplied to tissues. This process is tightly controlled by a net balance between positive and negative regulators (Mukhopadhyay & Datta, 2004; Ribatti, 2005). Solid tumors are confined within the organ space and cannot grow beyond 2 mm unless they acquire access to the circulatory system. Without access to a blood supply, tumor cells are subject to necrosis and apoptosis (Hanahan & Weinberg, 2000; Mukhopadhyay & Datta). Several factors are involved with angiogenesis; however, the biomarker that best illustrates the sustained angiogenesis rule is the vascular endothelial growth factor (VEGF) family (Ribatti).

VEGF is classified as an endothelial cell-specific mitogen with five known isoforms of the gene named VEGFA, VEGFB, VEGFC, VEGFD, and VEGFE (Ribatti, 2005). VEGF has preferential and specific binding to VEGF receptors (VEGFR), of which three forms are known to exist: VEGF R1 and VEGFR2, which are restricted to endothelium, and VEGFR3, which has preferential binding with lymphatic endothelium (Ribatti). The VEGF gene is homologous with the platelet-derived and placental growth factor family of genes (Ribatti).

VEGF is responsible for embryonic vasculogenesis and angiogenesis and rarely is expressed in normal adult tissues.



Figure 2. Hanahan and Weinberg Conceptual Framework Note. From "The Hallmarks of Cancer," by D. Hanahan and R.A. Weinberg, 2000, Cell, 100(1), p. 58. Copyright 2000 by Elsevier. Reprinted with permission.

When expressed in normal adult tissues, VEGF induces proliferation, sprouting, migration, and tube formation of endothelial cells (Tammela, Enholm, Alitalo, & Paavonen, 2005). Endothelial cells are quiescent except in human ovaries, the uterus, and skin cells (Ribatti, 2005). In normal ovarian tissue, VEGF is responsible for neovascular formation within the corpus luteum and for growth of the ovarian follicle (Sonmezer, Gungor, Ensari, & Ortac, 2004). Within the uterus, VEGF supports the growth of the endometrial vessels during embryo implantation (Ribatti).

Vascular endothelial growth factor in ovarian cancer: High degrees of tumor angiogenesis and VEGF expression have been shown to correlate with poorer survival in patients with ovarian cancer (Alvarez-Secord et al., 2004). Although increased serum VEGF levels alone do not provide a clear indication of angiogenesis in ovarian cancer, high levels of VEGF in ascitic fluid are a more accurate predictor of tumor growth and spread (Hsieh et al., 2004).

Ascites is the collection of fluid within the pelvis of patients with ovarian cancer that supports the growth of tumor cells in vitro and in vivo (Hsieh et al., 2004). The production of ascites follows impaired lymphatic drainage in a feedback loop that increases the rate of lymph production because of the lack of drainage (Hsieh et al.). VEGF has been implicated as an important mediator of ascites formation. VEGF is an upstream regulator of PI3KCA, a known oncogene in ovarian cancer, and is associated with ascites formation as an early event in malignant transformation (Shayesteh et al., 1999; Sonmezer et al., 2004; Zhang et al., 2003).

Tissue Invasion and Metastasis

Although immune cells can travel and invade under normal circumstances, tissue invasion and metastasis generally are observed only in tumors. The extracellular matrix is an important component of the process of metastasis because of its role in cellular adhesion. Cellular adhesion involves zonula occludens (tight junctions), zonula adherens (adherens junctions), and macula adherens (desmosomes) (Sundfeldt, 2003). The adherens and tight junctions polarize the cells and participate in condensation during tissue development, compaction during embryogenesis, contact inhibition, wound healing, and tumorigenesis (Sundfeldt).

Crucial to cellular adhesion processes are five classes of molecules: interleukins, immunoglobulins, cadherins, integrins, and extracellular proteases (King & Stansfield, 2002). Cell-to-cell adhesion requires cadherins, selectins, and integrins; cell-to-matrix adhesion requires integrins and transmembrane proteoglycans (Alberts et al., 2002). The best characterized biomarkers that illustrate the tissue invasion and metastasis rule are E-cadherin and CA125.

E-cadherin is a member of the cadherins family, also known as cell adhesion molecules, which are dependent on calcium or magnesium to function (Alberts et al., 2002). Cadherins are glycoproteins that facilitate cell-to-cell adhesion, which creates an integral part of the cell membrane (Alberts et al.). Four members of the family exist, including E-cadherin (the best described, specific to epithelial cells), N-cadherin (found in neurons, heart, skeletal muscle, lens, and fibroblasts), P-cadherin (found in placenta, epidermis, and breast epithelium), and VE-cadherin (specific to endothelial cells) (Alberts et al.).

CA125 is expressed as part of normal ovarian function the first trimester of pregnancy and during the menstrual cycle (Kafali, Artunc, & Erdem, 2007; Kan, Yeh, Ng, & Lou, 1992; Kenemans, van Kamp, Oehr, & Verstraeten, 1993; Verheijen, van Mensdorff-Pouilly, van Kamp, & Kenemans, 1999). In addition, CA125 is known to be elevated in benign conditions, such as pelvic inflammatory disease, endometriosis, and ovarian cysts (Jacobs & Bast, 1989; Rubin & Sutton, 2004). CA125 may participate in the mechanisms of tissue renewal of the reproductive tract during ovulation (Nustad, Onsrud, Jannson, & Warren, 1998). CA125 is hypothesized to lubricate surrounding tissues and decrease the immune responses to exposed tissue until repair is complete (Auersperg, Ota, & Mitchelle, 2002; Nustad et al.). During normal ovulation, the ovarian surface epithelium must quickly repair the postovulatory wound created by follicular rupture. This process requires the migration of ovarian surface epithelium stem cells to maintain the tissue until the outcome of fertilization is known (Roskelley & Bissell, 2002). E-cadherin is not expressed in those cells because they do not require adhesion properties. The ovarian surface has an epithelial-mesenchymal phenotype, meaning it has characteristics of epithelial and mesenchymal tissues and is not fully committed to becoming epithelium (Auersperg et al., 2002). Mesenchymal cells are inherently migratory given their cellular function in wound healing. These cells undergo an epithelialto-mesenchymal transformation that maintains tissue integrity (Roskelley & Bissell). However, the epithelial and stromal cells of the ovary express E-cadherin to maintain adhesion.

E-cadherin in ovarian cancer: Approximately 64% of ovarian tumors show a loss of E-cadherin expression (Faleiro-Rodrigues, Macedo-Pinto, Pereira, Ferreira, & Lopes, 2004). In ovarian cancer, decreased expression of E-cadherin is associated with a poorer stage and histologic type and peritoneal metastasis (Faleiro-Rodrigues et al.; Roskelley & Bissell, 2002). In addition, epithelial-to-mesenchymal transformation is strongly associated with a more metastatic phenotype in patients with ovarian cancer (Roskelley & Bissell). Loss of E-cadherin expression is associated with tumor progression.

CA125 in ovarian cancer: CA125 is elevated in 95% of women with serous ovarian tumors and adenocarcinomas (Verheijen et al., 1999). Generally, it is not elevated in women with tumors of mucinous or germ cell origin (Rubin & Sutton, 2004). Elevations in CA125 following total abdominal hysterectomy and bilateral salpingo-oophorectomy or first-line chemotherapy for ovarian cancer suggest disease recurrence or treatment failure. In addition, increases in CA125 are associated with progression from benign to malignant states in cultured cells (Kui Wong et al., 2003; Seelenmeyer, Wegehingel, Lechner, & Nickel, 2003). The acquired function of CA125 in ovarian tumors is to protect

Biomarker	Normal Ranges	Ranges in Samples of Patients With Ovarian Cancer	Platform and Assay Manufacturer	References
HER2/neuª	Range = 595–1,947 HNU/ml Mean = 1,203 HNU/ml <u>+</u> 279 HNU/ ml	Range = 526–16,332 HNU/ml; 1,761 was cho- sen as the cutoff for an elevated level (i.e., two standard deviations above the mean).	ELISA	Cirisano & Karlan, 1996; Meden et al., 1994; Meden & Kuhn, 1997
р53ª	Range = 0–0.50 U/ml	Median = 0.69 U/ml (benign tumor median = 0.32 U/ml)	ELISA	Sorak et al., 2007
Telomerase	Value < 0.2 $A_{450-665}$ nm	Mean = 0.795 (\pm 0.168) $A_{450-665}$ nm	PCR, ELISA/ Roche	Sun et al., 2007
VEGF	Range = 10.0–778.8 pg/ml Value = < 300.0 pg/ml	Median = 220.0 pg/ml; range = 134.7–671.2 pg/ml)	ELISA/Quantikine Hu- man VEGF Kit, R & D Systems	Candido Dos Reis et al., 2002; Hazelton et al., 1999
CA125	Value = < 35 U/ml (although some assays report < 21 U/ml)	20–10,000 U/ml (not all ovarian tumors secrete CA125)	ELISA/Centocor Roche, Boehringer	Jacobs & Bast, 1989; Verheijen et al., 1999

Table 2. Normal Ranges for Biomarkers of Ovarian Cancer

^a Commercial assays for this biomarker do not exist.

ELISA—enzyme-linked immunosorbent assay; PCR—polymerase chain reaction; VEGF—vascular endothelial growth factor

ovarian tumor cells from immune system surveillance (Kabawat, Bast, Welch, Knapp, & Colvin, 1983; Tannock, Hill, Bristow, & Harrington, 2005).

Discussion

Although the Hanahan and Weinberg conceptual framework provides a useful model to understand some of the biomarkers for ovarian cancer, it has limitations. First, the visual representation of the original framework appears in Figure 2 as a circular model with interchangeable parts; however, the exact sequence of events that leads to the expression of various biomarkers for ovarian cancer or other cancers has not been established at the present time. In addition, the framework makes no distinction among which phenomena were observed exclusively in human, animal, or cellular models. Based on available data, knowing which rules are directly applicable to individual patients is not possible.

Even so, understanding the biomarkers for ovarian cancer in the context of these rules provides justification for their use in clinical studies and a useful framework for teaching students about the mechanisms of tumorigenesis. Table 2 lists normal ranges for the various biomarkers highlighted in this article. VEGF, CA125, and inhibin A and B are the only biomarkers that have commercially available clinical assays. The other biomarkers are used in clinical trials and not approved by the U.S. Food and Drug Administration for clinical use. All of the biomarkers highlighted in this article are produced in varying quantities in normal and cancerous cells. How these biomarkers differ in women with and without ovarian cancer needs to be determined.

The application of this framework to the various biomarkers that are expressed or observed in patients with ovarian cancer provides oncology nurses with information that can be used for patient education about the rationale for various diagnostic tests and therapeutic interventions. In addition, nurses who conduct research on ovarian cancer can use this framework to guide the selection of biomarkers for studies. More research is needed on changes in and interactions among these biomarkers throughout the trajectory of ovarian cancer.

Conclusion

The six rules for tumor development outlined in the Hanahan and Weinberg conceptual framework are applicable to biomarkers associated with ovarian cancer. Understanding these biomarkers within the context of the rules provides justification for their use in clinical research and an informative framework for clinician and patient education and begins to integrate biomarkers for ovarian cancer into the broader framework of tumor cell biology.

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