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Bioengineering approaches to improve gynecological cancer outcomes

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Abstract

Gynecological cancers are diagnosed in over a million females worldwide, with ovarian, endometrial (uterine), and cervical the most common. Here, we highlight recent progress by bioengineers to improve screening and diagnosis for these diseases, including potential point-of-care approaches. We provide particular attention to the use of tissue engineering, biomaterials, microfluidics, and organoids to identify mechanisms regulating disease progression and predict therapeutic responses. We also highlight opportunities for engineers to address the racial/ethnic/geographic disparities that continue to impact gynecological cancer outcomes. A challenge to improve outcomes for all gynecological cancers will be to expand the diversity of patients included in basic/clinical research to better capture the confounding effects of social/economic variables on disease progression.

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Introduction

Cancers of the female reproductive tract, referred to as gynecological cancers, are diagnosed in nearly 1.4 million worldwide and lead to 15% of all female cancer deaths [1]. The three most common gynecological malignancies are cervical, endometrial (uterine), and ovarian (Figure 1). The underlying causes of these cancers vary and include viral oncogenesis (*e.g.*, human papillomavirus (HPV) in cervical cancer), genomic risk factors (*e.g.*, Lynch syndrome for endometrial cancer, *BRCA1/2* mutations for ovarian cancer) and the patient's lived experience (*e.g.*, reproductive history, obesity). Hidden within these general observations are important disparities that require acknowledgement and focused efforts to address. For example, African-American/Black patients in the United States have an increased risk of dying from gynecological cancers: 27% in ovarian [2], 50% in endometrial [3], and 114% in cervical cancer [4]. For cervical cancer there are also global disparities, with over 85% of females in high-income countries vaccinated against HPV compared to 40% in low- and middle-income countries [5]. These averages also vary within countries with African-American/Black and Hispanic/Latinx teens having higher vaccination rates compared to white teenagers in the United States [6]. Here, we highlight recent efforts and offer suggestions for how biomedical engineers can improve screening and diagnosis, develop models of early disease to understand disease progression, reconstruct the tumor microenvironment of advanced disease to identify new therapies, and address the inter-patient heterogeneity and disparities that remain a challenge.

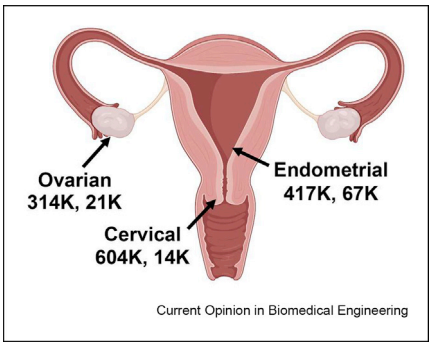
Screening and diagnosis

As tumor stage at the time of clinical presentation consistently predicts survival, improving our ability to detect and diagnose these malignancies at an earlier stage will undoubtedly improve patient outcomes. Here, we describe the standard of care for screening and diagnosis for each of the three most common gynecological cancers and discuss engineering approaches to move the field toward earlier diagnoses.

Ovarian cancer

Ovarian cancer outcomes are particularly grim due to frequent diagnosis at late stage stemming from a combination of vague symptoms that can easily be attributed to other causes and a lack of effective screening modalities. Routine screening for ovarian cancer remains the pelvic exam, which has a positive-predictive value of <4% in asymptomatic females [7]. Serum carbohydrate

Figure 1



Schematic of origin sites for gynecological cancer. Prevalence is provided for patients worldwide and in the United States as (world, US), rounded to the nearest thousand. Note the disparity in cervical cancer prevalence between the two estimates. Created with BioRender.com.

antigen 125 (CA125) is elevated in most ovarian cancers and has been the subject of extensive study, but it is elevated in too many other conditions to be accurate enough for routine screening [8]. Moreover, CA125 levels vary between racial groups and are a particularly poor predictor for Black/African-American patients [9]. To improve sensitivity and specificity, extensive research has been devoted to developing algorithms that couple CA125 with additional biomarkers [10], clinical characteristics, and imaging findings, but to date none are validated for routine use in the general population. Informatics-based approaches of longitudinal surveys about urinary/digestive habits collected from patients might prove useful to design a future screening tool, particularly if they could be paired with subtle changes in biomarkers.

Patients with a strong family history of ovarian cancer and/or a known genetic risk factor (*e.g.*, *BRCA1/2* mutation) would benefit the most from improved screening options. In many cases these patients opt for prophylactic salpingo-oophorectomy, which reduces the risk of ovarian cancer by 80–90%. As this results in infertility and menopause, an alternative approach could be to pursue surgery at the first sign of disease if screening was reliable. Toward that end, endoscopic imaging of the fallopian tube has been proposed, because most ovarian cancers are thought to originate within the fallopian tube as serous tubal intraepithelial carcinomas (STICs) [11]. A sub-millimeter endoscope was able to capture multispectral fluorescent images of STICs and collect cells for downstream molecular analysis [12]; further testing is needed to determine the clinical utility of this technology.

As a result of the limited screening options, most ovarian cancers are diagnosed when patients with concerning symptoms undergo bloodwork and CT/ultrasound imaging. This leads to surgery and pathological examination of tissue for definitive diagnosis. The need for tissue examination is particularly limiting with ovarian tumors, which are rarely biopsied to prevent malignant cell dissemination throughout the peritoneal cavity. Instead, intraoperative examination of tissue frozen sections is used to determine the need for surgical staging in most patients. Imaging approaches that could facilitate tissue-independent diagnoses would facilitate better therapeutic planning, potentially reducing the need for multiple surgeries or permitting neoadjuvant chemotherapy in patients without disseminated disease. This approach could also reduce time spent in medical centers, particularly for patients that must travel for access to specialty care.

Endometrial cancer

There are no screening modalities directed toward detecting endometrial cancer in current practice. Most patients with endometrial cancer are identified when they report abnormal vaginal bleeding to a physician; standard of care evaluation includes transvaginal ultrasound (TVUS) and/or endometrial biopsy for pathological examination. Despite more specific symptoms, patients and doctors can overlook the potential danger; in particular, African-American/Black patients are less likely to have standard diagnostic procedures performed [3]. TVUS measures the thickness of the endometrium to distinguish malignant lesions and has a high false-positive rate. However, TVUS missed five times more cases of endometrial cancer amongst African-American/Black as compared to white patients, potentially due to differences in fibroid prevalence [13]. This disparity in diagnosis points to the need for more accurate screening tools. One such development is the PapSEEK test, which uses fluids routinely obtained during a Pap test to assay for 18 common mutations and aneuploidy [14]. Using endocervical sampling, 81% of endometrial cancer cases were correctly identified, with a false-positive rate of only 1.4%. Moreover, there is potential for engineering approaches such as this to reinvent the process of diagnosis. The seemingly simple requirement for an in-person visit can be limiting as the need to make special arrangements for work or childcare may cause patients to defer seeking care until symptoms are prohibitive for living normal life. Other deterrents to seeking medical care include physical and emotional discomfort associated with receiving a pelvic exam. One could imagine adaptation of tests such as PapSEEK to using an at home collection device similar to a tampon that is mailed in for analysis. Furthermore, this approach could potentially be expanded to a screening approach for high-risk patients, which could be identified using an informatics-based approach that employs clinical variables, such as age, body mass index, and family history.

Cervical cancer

The dramatic reduction in cervical cancer stemming from widespread screening is perhaps the most salient

example of the success that early intervention can have in improving patient outcomes. The Pap test effectively revolutionized our approach to detecting cervical cancer by taking advantage of characteristic changes in cellular appearance following HPV infection, which is the initiating event in nearly all cervical cancers, and importantly, visible well before cancer has developed. Indeed, after introduction of the Pap test in the United States, cervical cancer rates fell by approximately 75%, while in areas where it is less widely used, similar reductions have not been observed. Since that time, early intervention for cervical cancers has been further refined in high-income countries by effective HPV vaccination and the addition of molecular assays for those with false negatives by screening cytology [15]. Either an abnormal Pap test or molecular detection of high-risk HPV prompts colposcopic examination by a medical professional, which involves application of acetic acid to the cervix to locate the abnormality and facilitate targeted biopsy. The sampled tissue is then processed within a laboratory so that slides can be prepared and examined by a pathologist, who will render a formal diagnosis. While effective, this test can cause significant discomfort and the development of imaging approaches that do not require tissue biopsy would benefit patients.

Despite the dramatic reductions in cervical cancer incidence brought about by the Pap test and our ability to use it even in low-resource settings, cervical cancer continues to have a strong worldwide disparity, with incidence rates nearly three times larger in low- and middle-income countries [16]. Pap tests require relatively little technical preparation, but they require pelvic exam for collection, which can be uncomfortable and anxiety-provoking, as well as pathologic expertise for interpretation, particularly if the results are to be actionable without confirmation by tissue biopsy. Future engineering solutions will be vital to provide low-cost point-of-care screening tools to detect and reliably diagnose early lesions. As an example, automated imaging systems to visualize and classify lesions without the need for on-site pathologists have been developed [17]. To enable onsite detection of HPV DNA, a disposable microfluidic chip was developed that is capable of colorimetric loop-mediated isothermal amplification (LAMP) detection in combination with a smartphone [18]. Through the testing and implementation of these point-of-care technologies in low-resource settings, the global burden of cervical cancer can be mitigated as HPV vaccination campaigns continue.

Modeling early tumor development

As prevention and early detection are essential to improve gynecological cancer outcomes, an important role for biomedical engineers is to develop model systems to better understand these early stages of disease. Such systems can provide insight to enable chemoprevention as well as identify biomarkers for early detection. To have more precise control and increase throughput to examine multiple variables, engineers have increasingly turned to *in vitro* models.

Ovarian cancer

In vitro models of the precursor site for ovarian cancer, the fallopian tube, have been primarily developed to focus on the reproductive cycle and fertility. For example, a microfluidic model using human fallopian tube tissue was able to maintain ciliary beating after being cultured for 21 days [19]. Sourcing human tissue for such models is a substantial challenge if they are to be used for broad testing of genetic, hormonal, and extracellular matrix (ECM) alterations behind STIC development and progression to the ovary. Recently, readily-accessible canine oviducts, CRISPR editing to mutate *TP53*, and a microfluidic device with an air-liquid interface were used to recapitulate the morphology of STIC progression [20]. With additional modifications, the microfluidic platform could potentially be utilized for studies of temporal and/or spatial effects of hormonal changes associated with the reproductive cycle and menopause. *In vitro* systems have also been developed that model STIC growth as cells exfoliate and metastasize to the ovary. Loss of PTEN in mouse oviductal epithelial (mOE) cells increased multicellular spheroid formation, cell survival and adherence to the stroma of *ex vivo* cultured ovaries [21]. One theory for how cells from STICs metastasize to the ovary is that they integrate into cortical inclusion cysts that likely form following ovulation wounding of the ovarian surface. To model cortical inclusion cysts, we developed a 3D curved lumen made of collagen I/III and seeded with mOE and mouse ovarian surface epithelium cells, the two cell types that line inclusion cysts. mOE cells were invasive whereas the ovarian surface epithelial were not [22]. In addition, we determined that decreased collagen I, increased collagen III, and increased curvature increased mOE invasion [22,23].

Endometrial cancer

Efforts to develop models to investigate the genesis of endometrial cancer can build from models used to study the healthy endometrium, which mimic the complex remodeling that the endometrium undergoes in response to cyclic hormonal changes. For example, using a PEG hydrogel modified with synthetic adhesion sequences, a layered endometrium with stromal cells in the gel and epithelial cells on the surface was generated and demonstrated decidualization, accumulation of basement membrane, and collagen reorganization [24]. The same group then established co-cultures of human endometrial adenocarcinoma cells and endometrial stromal cells within a PEG construct that was selectively dissolved with SrtA to study temporal cytokine changes in response to inflammatory stimuli [25]. Another hydrogel model of the

endometrium used gelatin-methacrylate to recapitulate features of the endometrial microenvironment including physiologically-relevant stiffness, formation of endothelial networks, and responsiveness to hormonal cues [26]. Of course, synthetic materials may not fully recapitulate the native ECM. Isolated cells and decellularized matrix were used to generate a 3D model of the endometrium that maintained the native ECM and was responsive to hormones over a 28-day period [27]. While these hydrogel models provide dynamic and novel approaches to model the healthy endometrium, they could be used to examine the effect of common mutations to better understand the early development of endometrial cancer.

Cervical cancer

The development of models for the early stages of cervical cancer has been more limited. One model utilized de-epidermised skin to model the underlying stroma; cervical cancer cells (C33A) cultured on top formed stratified epithelial layers and recapitulated cervical differentiation markers seen *in vivo* [28]. Of course, the connective tissue of the cervix may differ substantially from skin due to its need to remodel in support of pregnancy. A model of cervical thinning at delivery used porous silk protein scaffolds along with human cervical fibroblasts to create engineered constructs that could be monitored for changes in collagen density/cross-linking and mechanical properties in response to hormones [29]. Combining models such as this with the epithelial component would be useful to examine the biochemical and mechanical alterations that occur in early tumorigenesis. Additionally, they could be used to model HPV infection, clearance, and transition to cancer.

Recapitulating the tumor microenvironment *in vitro*

As tumors establish in the primary site and metastasize, there are notable changes to the cells and ECM that surround the tumor cells — the tumor microenvironment. The first step to modeling the tumor microenvironment is to define the components that are in it. One method that can help define the candidate stromal/immune cells is mass cytometry, which detects metal-labeled antibodies bound to single cells. A recent paper used 17 human ovarian tumor cell samples to identify cell types associated with poor outcomes [30]. This type of investigation should be applied to the other gynecological cancers. A detailed matrisome analysis conducted for ovarian cancer provides a blueprint to study ECM changes in other gynecological cancers [31].

Ovarian cancer

The majority of ovarian cancer patients develop metastases to the omentum; therefore, modeling this organ has received extensive attention. We recently modeled the metastatic omentum used pathologically-relevant collagen I concentrations to examine how sensitivity to growth factors found in ascites was impacted by changes to collagen during metastasis [32]. This study observed increased collagen I both in/near the tumor, but also at sites distal from the tumor. Future work should examine the effect of tumor microenvironment modifications such as this which precede colonization by additional tumors. Another recent model of the metastatic omentum used PEG hydrogels modified with adhesion peptides inspired by the omental ECM and found that this system mimicked drug response better than tissue culture plastic [33]. This suggests future drug studies may be more useful when conducted with physiologically-relevant culture models.

The omentum is home to many different cell types and inclusion of those cells into *in vitro* models could provide insight into the metastatic process. For example, we developed a co-culture device that incorporated the mesothelial cells that line the outside of the omentum and the alternatively-activated macrophages (AAMs) commonly found in the disease. Through a combination of experimental perturbations and computational analysis, this identified a role for AAMs in supporting metastasis to the omentum through upregulation of P-selectin on the mesothelial cells [34]. Using a modification of this culture system, additional AAM-secreted factors were found to stimulate spreading from tumor aggregates [35]. Of course, additional organs are impacted by ovarian cancer metastasis; techniques developed in these studies could be applied to understand those microenvironments.

Endometrial cancer

Recent studies of endometrial cancer have also benefited from multi-cellular systems and biomaterials-based approaches. For example, co-cultures revealed that an environmental toxin can enhance cancer cell migration/invasion, but only in the presence of AAMs [36]. Future studies of endometrial cancer should consider how other stromal/immune cells impact the effects of external stimuli. To investigate the tumor cell/macrophage interactions in endometrial cancer, co-cultures of tumor cells and various types of macrophages were conducted in a reversibly cross-linked gelatin hydrogel [37]. Consistent with other tumor models, this demonstrated that AAMs induced tumorigenic activities such as invasion. This hydrogel method can be adapted to other stromal cells to tease out the complex interactions at play.

Cervical cancer

It is well established that persistent, rather than intermittent, HPV viral infections are responsible for cervical carcinogenesis; however, modeling this phenomenon has been a challenge. A recent study used murine papillomavirus to mimic persistent HPV infection and induced progressive, neoplastic disease in an immunocompetent

mouse [38]. This model has since been extended to demonstrate successful sexual transmission [39]. Future studies with this model could isolate cells along disease progression to use in combination with *in vitro* models of the cervix [28,29]. Additionally, these systems could be used to study the role of the microbiome in HPV clearance, as the microbiome of the genital tract varies across populations [40]. However, the high HPV + population relative to patients that develop cervical cancer suggests that additional mechanisms support tumor progression. Hyperactivation of YAP1 has been shown to be sufficient to cause cervical cancer, and to support HPV + mechanisms of carcinogenesis [41]. Because YAP1 is a mechano-sensor, future *in vitro* systems should examine the role of mechano-stimuli in cervical cancer progression.

Improving the physiological relevance of engineered models

To date most gynecological cancer studies have relied on a relatively small number of immortalized cell lines that have been cultured for decades in non-physiological conditions. Recent evidence has demonstrated that this culture setup may limit the ability of these cells to recapitulate tumor behaviors. For example, a recent study with serially passaged non-adherent spheroids demonstrated that long-term non-adherence was sufficient to cause chemoresistance, a mechanism that would have been missed with traditional cell culture [42]. This is particularly important for ovarian cancer as metastasis often includes a period where the cells are in suspension in the ascites. In addition to adhesion, stiffness of standard culture substrates has been shown to impart phenotypic changes to breast cancer cells [43]; whether this occurs with gynecological tumor cells has not been determined.

Therefore, an important step to model these tumors and address patient heterogeneity will be to utilize primary cells. Organoids are three-dimensional *in vitro* models isolated from tumors that maintain the unique genetic and disease hallmarks of their *in vivo* counterparts and are particularly suited for therapeutic screening or personalized medicine predictions. For ovarian cancer, an organoid biobank has been established with 56 lines from 32 patients [44]. The organoids captured the heterogeneity of the different histological subtypes of ovarian cancer from which they were derived and retained subtype-associated differences in sensitivity to carboplatin/paclitaxel. A similar study with a *BRCA1*-mutated ovarian cancer organoid demonstrated the expected sensitivity to PARP inhibitors [45]. While still early stage, some studies have begun to compare ovarian cancer organoid drug response to patient clinical outcomes and see a significant correlation [46]. An endometrial organoid biobank was also recently established from tissue biopsies ranging from precancerous lesions to late-stage tumors, recapitulating appropriate histology and maintaining genetic variations [47]. Organoids were tested with standard chemotherapeutics and a mTOR inhibitor, demonstrating patient-specific responses including sensitivity to the mTOR inhibitor in a line with mutations in the PI3K-AKT pathways. The first cervical cancer organoids were recently developed using material gathered from Pap smears. The organoids retained the HPV genome, suggesting that this approach could be used to model the early stages of cervical cancer from easily-obtained material [48].

Of course, simply generating more cell lines or using organoids does not guarantee inclusion of patients subject to disparities; analysis of 1393 established cell lines identified only 6% as having African/African-American ancestry and just under 2% as Hispanic/Latinx [49]. In addition to increased racial/ethnic diversity, more effort is needed to incorporate the impacts of poverty, diet, stress, and reproductive history into engineered models — and to report this information [50] — in order to identify cellular mechanisms that manifest in disparate outcomes.

Author contributions

A.A., A.L.C., S.M., and P.K.K. conceptualized this piece, A.A., A.L.C., and P.K.K. curated the papers analyzed, A.A., A.L.C., S.M., and P.K.K. wrote the manuscript, and P.K.K. edited the manuscript.

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