NASEM Consensus Committee: Assessment of NIH Research on Women's Health

Ovarian Cancer 2024: Knowledge gaps and barriers to improving outcomes

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Disclosures

- I am employed by the University of California, Los Angeles.

- I have no specific financial relationships to disclose.

Ovarian cancer statistics 2024

Incidence and Prevalence in US Women

- 19,680 new cases in 2024 (1.1% of new cancer cases)
- 236,511 women living with ovarian cancer

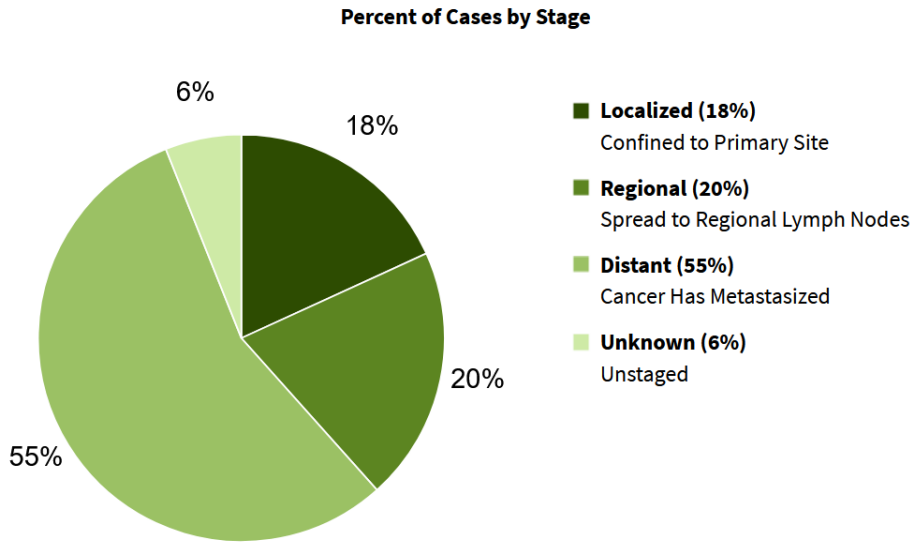
Mortality in US Women

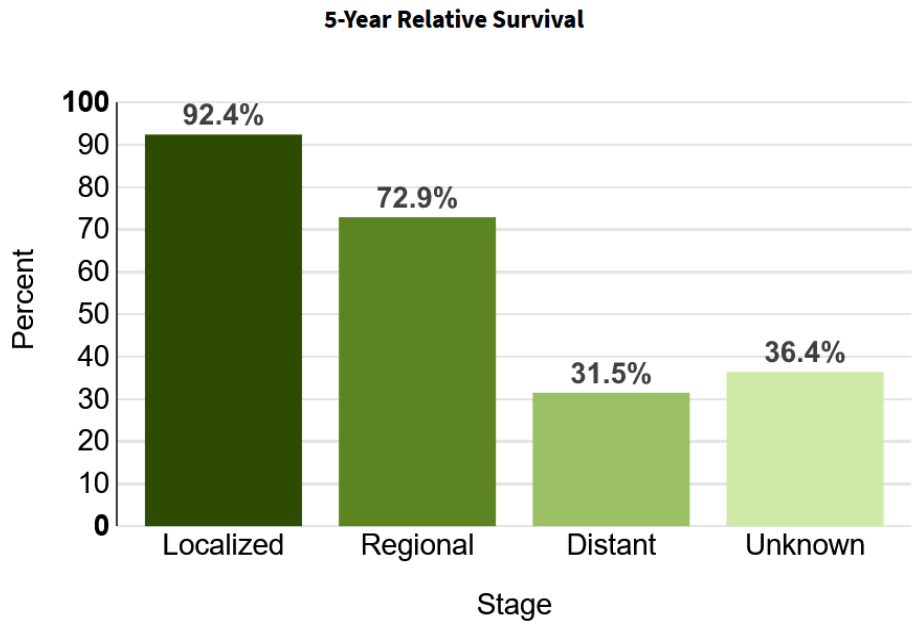
- 12,740 women will die in 2024 (2.2% of cancer deaths)
- High mortality cancer: Death to incidence ratio more than 3X that for breast cancer
- 5-year survival remains ~50%

Strongest risk factors

- Family history/Genetic risk:
- 25% associated with inherited mutation
- Age (Median 63 yo)

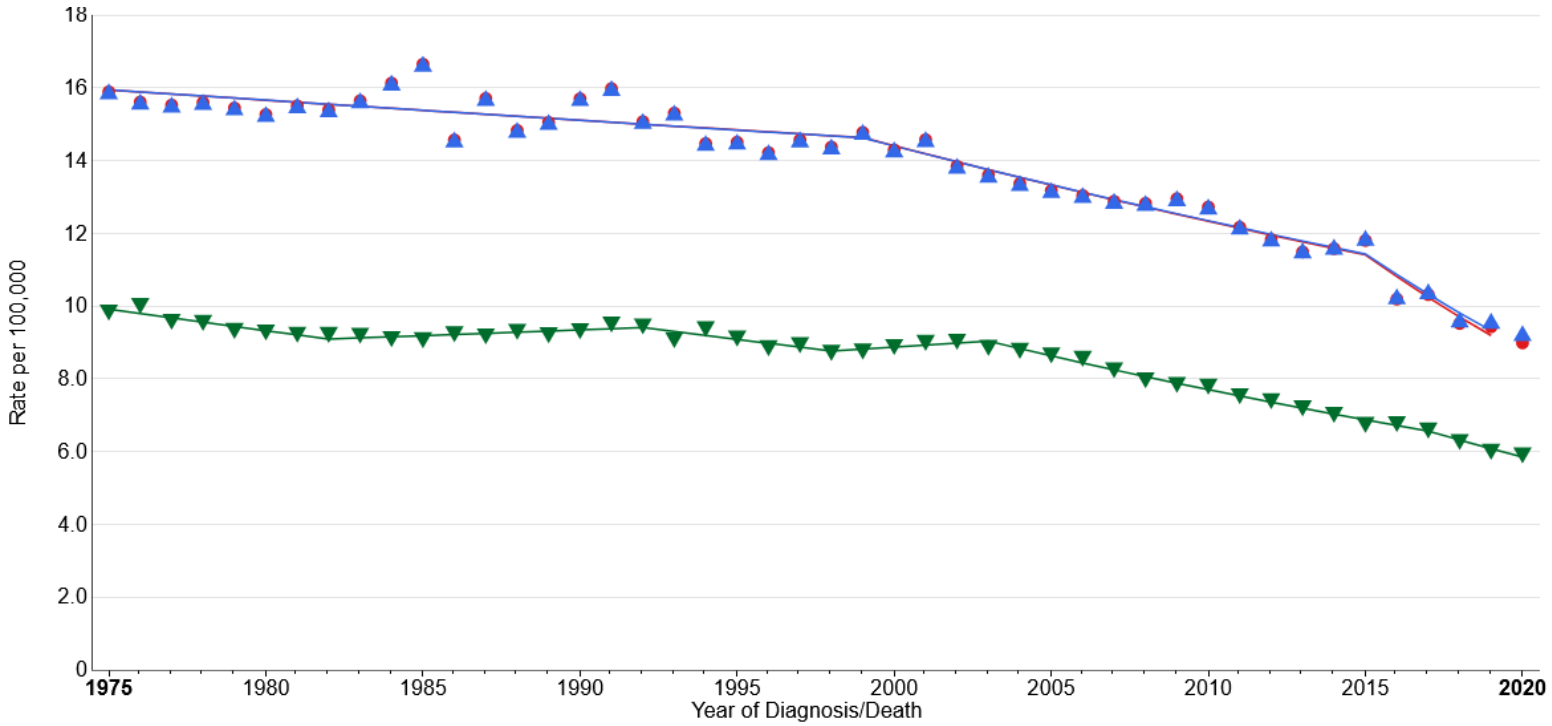
https://seer.cancer.gov/statistics-network/explorer/





The good news: Incidence and Mortality Decreasing

Long-term trends in SEER incidence and mortality



SEER Incidence Data, November 2022 Submission (1975-2020).
U.S. Mortality Data (1969-2020), National Center for Health Statistics, CDC.

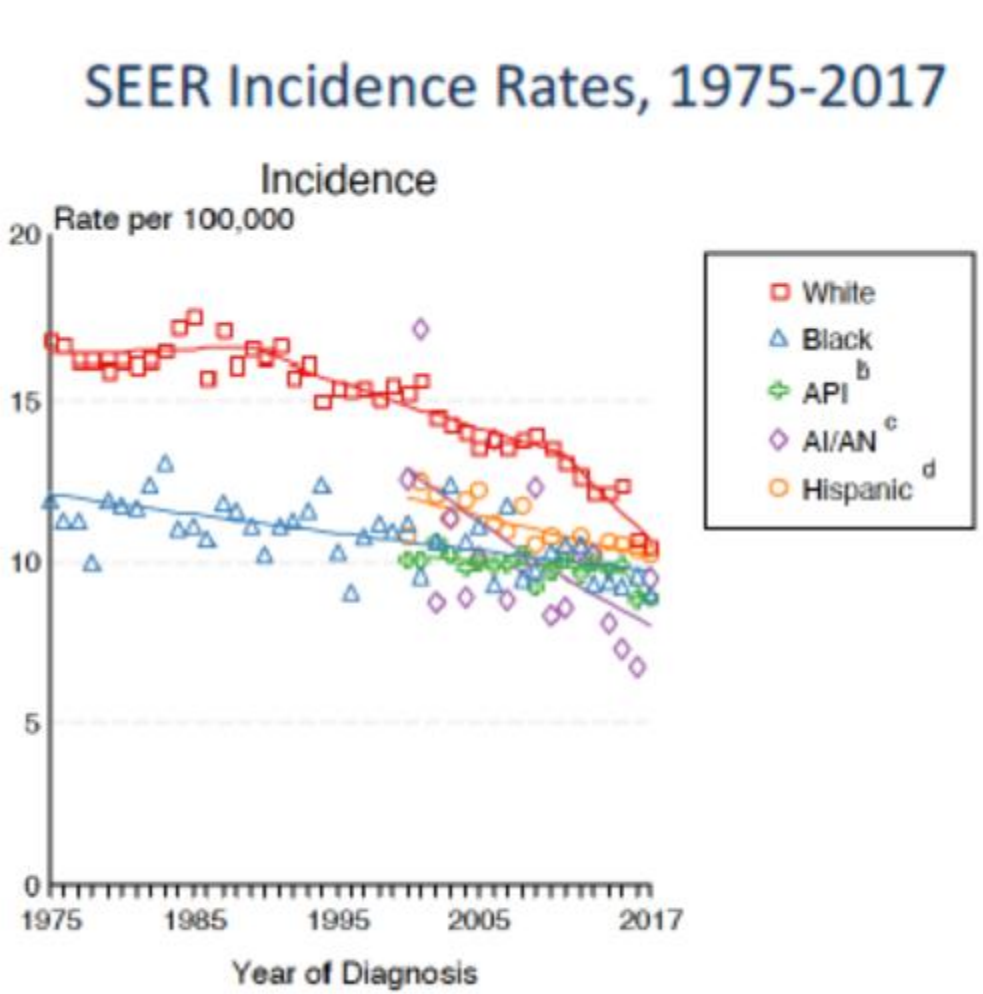
Incidence down due to:

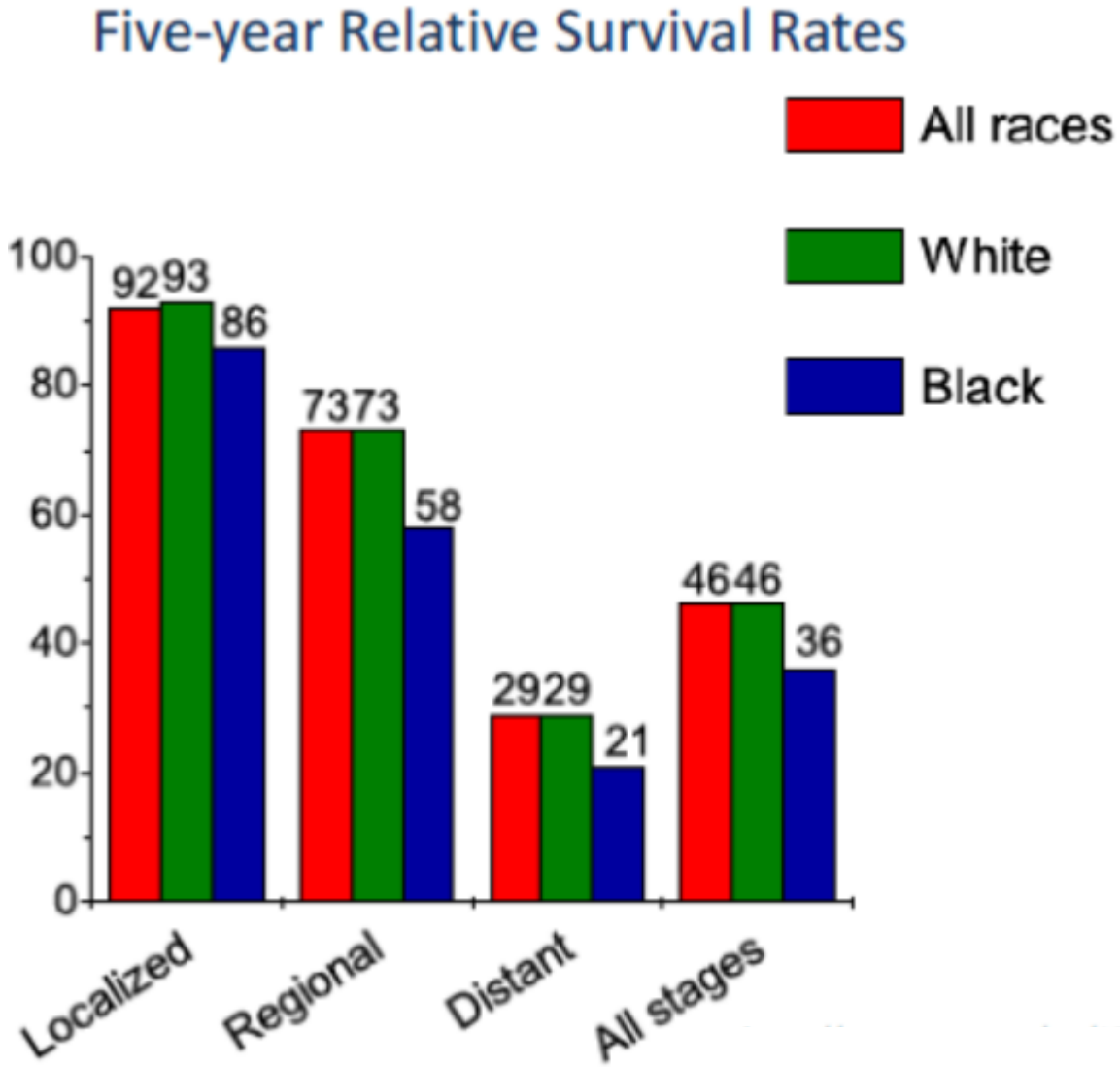
- OCP use increased in 1970s/80s
- 2015 ACOG recommends opportunistic salpingectomy.
- 2013 Supreme Court rules that genes are not patentable led to increase cancer genetic testing

Mortality down due to:

- Better cytotoxics (Paclitaxel 1992)
- Better targeted agents (BEV, PARPs, PEMBRO all since 2014)
- More guideline concordant care and medical/surgical support (growth factors, antibiotics, thrombolytics)

Ovarian cancer: Incidence and mortality by race/ethnicity





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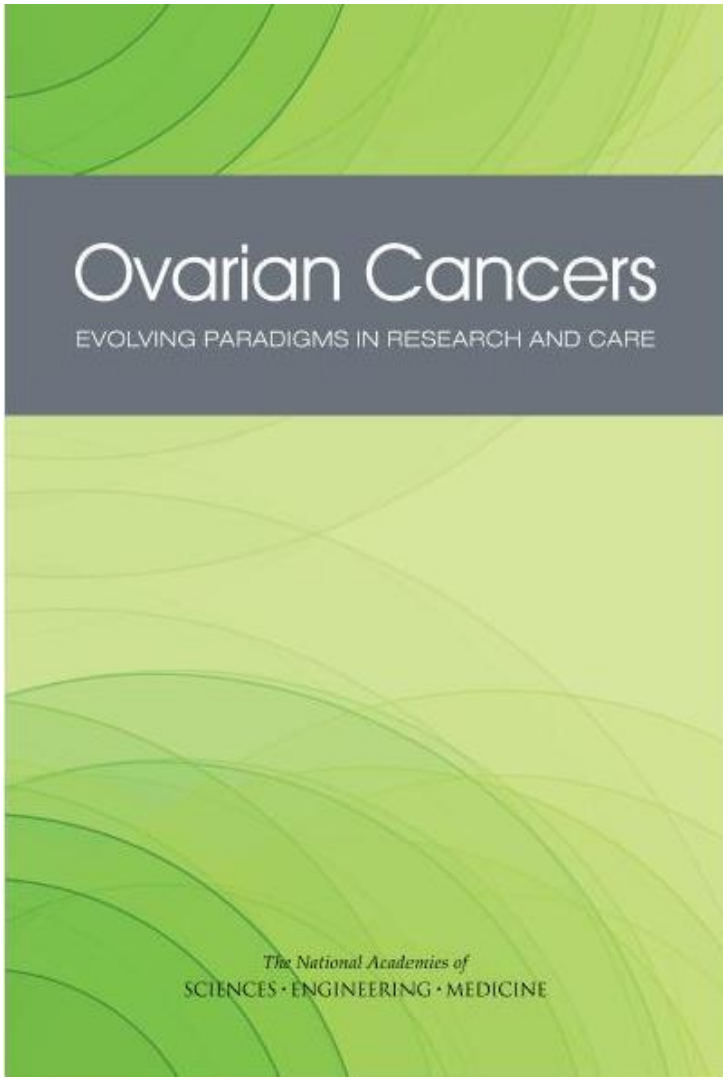
Ovarian Cancers:
Evolving Paradigms in Research and Care

Ad hoc committee assessed the state of the science in ovarian cancer to identify key gaps and research opportunities to reduce the incidence and mortality

#Ovarian Cancers
www.nas.edu/OvarianCancers
2016

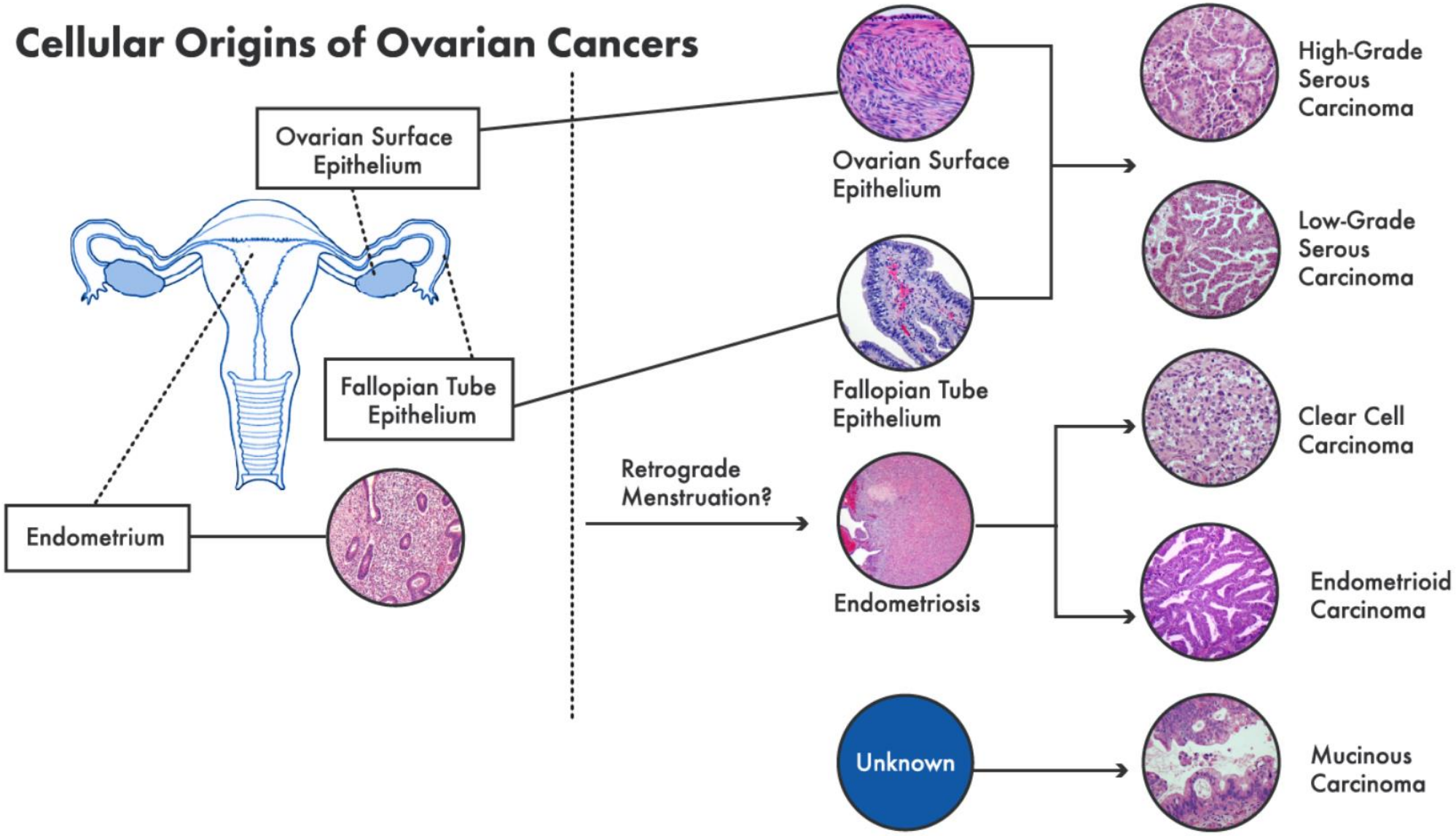


NASEM: State of the Science of Ovarian Cancer Research

Areas of Recommended Research:

- **Histotype specific research (High grade serous, Low grade serous, Clear cell, Endometrioid, Mucinous)**
  - As the most common and lethal subtype, HGSC should be prioritized
- Better define subtype characteristics: differences in risk factors, genetics, cell of origin, biology, early detection, biomarkers, molecular targets, etc
- Precision approaches to heterogenous group of cancers: Chemotherapy, molecularly-targeted and immunologic treatments that are subtype specific

Ovarian cancer is not one disease



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NASEM: State of the Science of Ovarian Cancer Research

- Develop strategies to increase genetic testing and cascade testing
- Deploy surgical and non-surgical prevention strategies for specific subtypes and at-risk populations
- Need subtype specific early detection strategies
- Improve standardization in ovarian cancer care: reduce disparities in health care delivery and outcomes
- Survivorship and long-term disease management
- New approaches to more rapid dissemination and implementation of new knowledge and evidence-based practices

Genetic testing can improve survival and save lives

- NCCN guidelines have recommended universal genetic testing of ovarian cancer patients since 2010, yet only **about a third are being tested**
- ~25% of EOC patients will carry an inherited pathogenic variant Up to 5000 EOC cases could potentially be prevented each year
  - 65-85% are due to BRCA1/2, 15-35% due to RAD51C/D, BRIP1, PALB2 and MMR
- For patients: Lack of testing leads to missed opportunities for targeted therapies and prevention of second cancers.
  - PARPi use significantly improves overall survival in BRCA1/2 carriers
- Missed opportunity for cascade testing and primary prevention for families.
- Need better implementation of genetics into clinical workflow (and better insurance coverage for testing)
- More research into disease penetrance and novel prevention approaches

Salpingectomy as primary prevention in general population

- Screening/early detection efforts have been unsuccessful
  - Future/ongoing efforts should be subtype specific
- Risk-reducing salpingectomy (RRS) recommended for over a decade
- Retrospective and prospective evidence support RRS as effective in significantly reducing HGSC in general population
- Universal uptake of salpingectomy during hysterectomy and in lieu of tubal ligation could prevent ~2000 deaths/yr in U.S. and save ~$500M U.S. health care dollars annually.
- Low uptake at the current time. Need improved awareness among women of all backgrounds, as well as reducing knowledge gaps among medical professionals—beyond OB/GYNs

Ovarian cancers' clinical course—and "pain points" to address

- Late stage at diagnosis remains most common presentation
  - Hampers early detection/etiology investigations
  - Polyclonality of disease sets stage future drug resistance
  - Better research models
- Majority of patients initially respond to platinum-based chemotherapy but majority experience recurrence
  - Need better biomarkers to identify/predict response or resistance
  - Urgent need for more effective and targeted treatments for PROC
  - Need to better understand intrinsic immune resistance mechanisms
- Patients typically undergo multiple courses of treatment. Remissions progressively get shorter with each subsequent therapy
  - Need better ways to assess response/progression (liquid biopsy, biomarkers, ctDNA, etc) to improve outcomes

Ovarian cancers' clinical course—and "pain points" to address

- Unique survivorship needs related to
  - Significant anxiety/fear due to risks of repeated recurrences
  - Multiple lines of treatment with cumulative toxicities over years
  - Additional burdens due to caregiver responsibilities
  - Financial toxicities impact quality of life
- Disparities in care delivery: Majority of patients receive care that deviates from national guidelines
  - Negatively impacts patient survival
  - Race, poverty level, insurance status impact access to care
- Innovative clinical trial designs
  - Relatively small numbers of patients, especially for target-selective trials
  - Close collaboration with regulators to agree upon pathway to drug approvals
  - Support for consortia to be able to meet trial endpoints

Therapeutic challenge: Overcoming resistance

- Platinum resistance will ultimately develop in nearly all patients
- **Urgently** need research on mechanisms of resistance and new approaches that can restore sensitivity and/or target new pathways
- PARPi have significantly improved outcomes. But only useful in about half of patients. Need novel therapeutic approaches for the other half of patients.
  - Need Research to unravel and overcome multiple mechanisms of PARPi resistance
- Immunotherapeutic approaches have been disappointing for most ovarian cancer patients.
  - Trials are ongoing, but need research to understand ovarian cancer microenvironment. Why are they immunologically “cold” and harness new information for new therapies
- Antibody-drug conjugates (e.g. mirvatuximab soravtansine, trastuzumab-deruxtecan) improving progression free survival, but resistance occurs

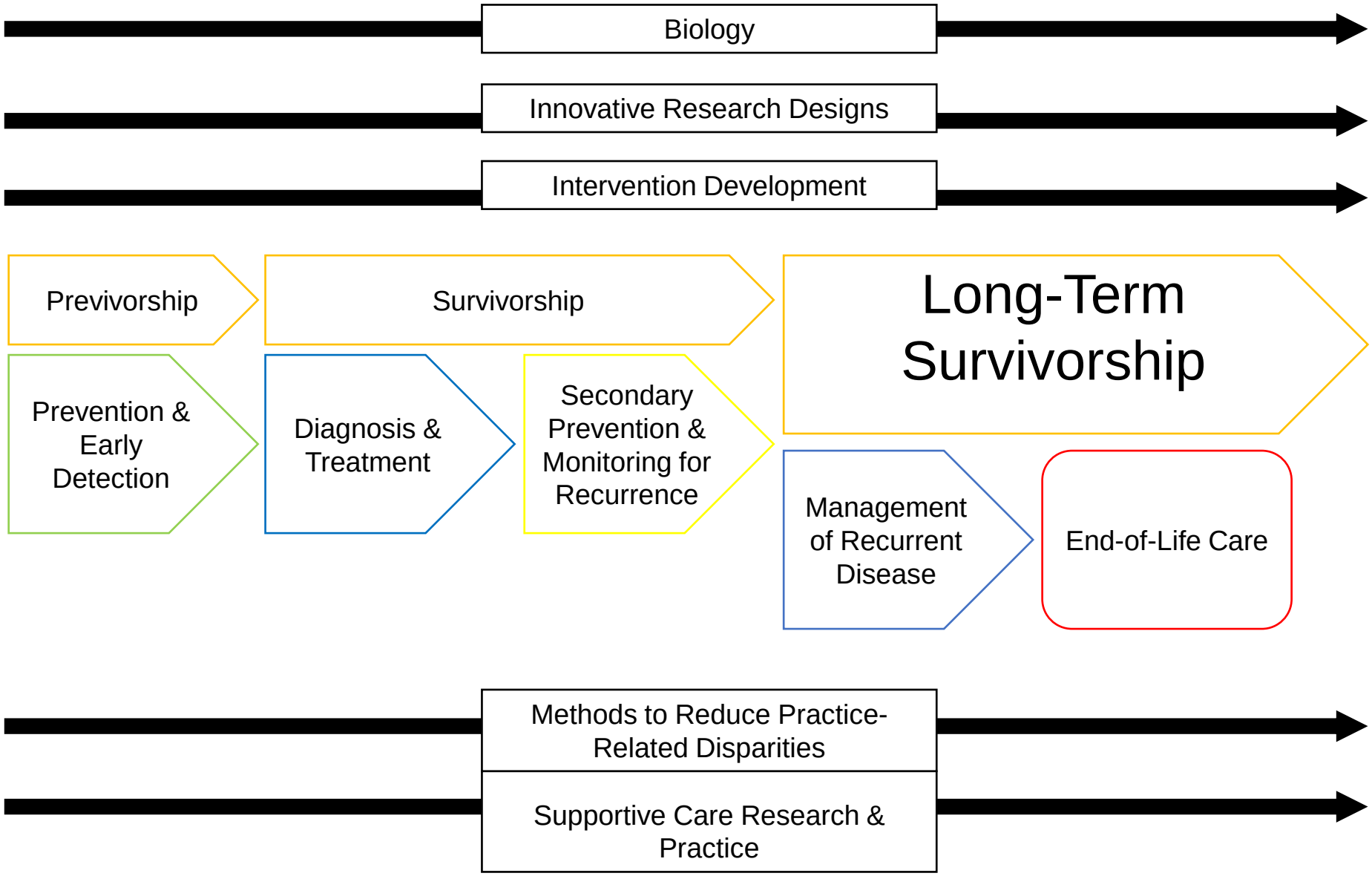
Part of the problem: Gynecologic cancers are underfunded

- Funding disparity compared to other tumor sites
  - Using funding-to-lethality scores, there is an 18-fold difference in ovarian cancer funding relative to breast cancer
  - (And a 30-fold difference in uterine cancer funding compared to breast cancer)
- Real-life implications for patients:
  - Less support for investigator-initiated grants and fewer breakthrough discoveries
  - Fewer clinical trails available for ovarian cancer patients which has resulted in fewer new treatment advances
  - More difficulty in access to trial further exacerbates disease burden on historically disadvantaged groups
- Implications for the future:
  - Fewer young investigators/trainees focusing on gyn malignancies
  - Fewer thought leaders/advocates at the table making decisions

Opportunities to improve ovarian cancer outcomes now

- Implementation efforts to broaden genetic testing, cascade testing, and primary prevention
- We've pushed the survival curve rightward, but almost all patients experience multiple recurrences and better survivorship care plans are needed
- Tumors are platinum sensitive at diagnosis, but emergence of resistance is almost universal and new treatments are urgently needed
- New drug approvals are great, but better insurance coverage needed
- Improve access and number of clinical trials as well as innovative designs
- Facilitate pathways to guideline concordant care to help eliminate inequities
- Increase funding to ensure pipeline of clinical trialists, scientists, and new discoveries

Continuum of Ovarian Cancer Research



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Thank you for your attention