

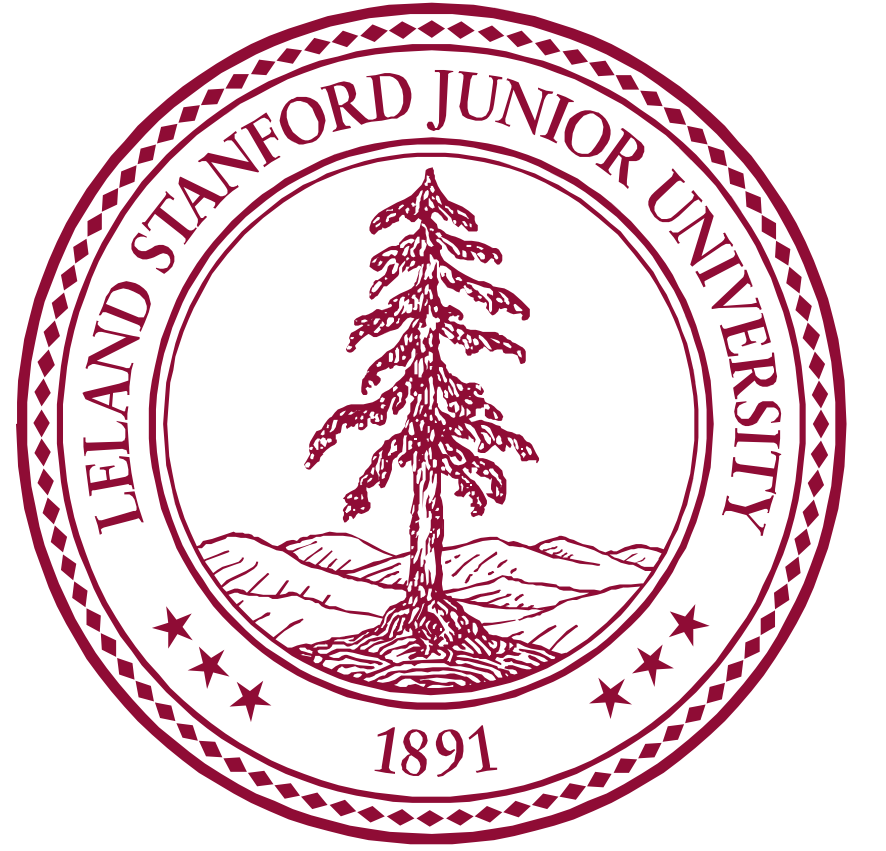


Avian Ovarian Cancer – A Model for Human Ovarian Cancers

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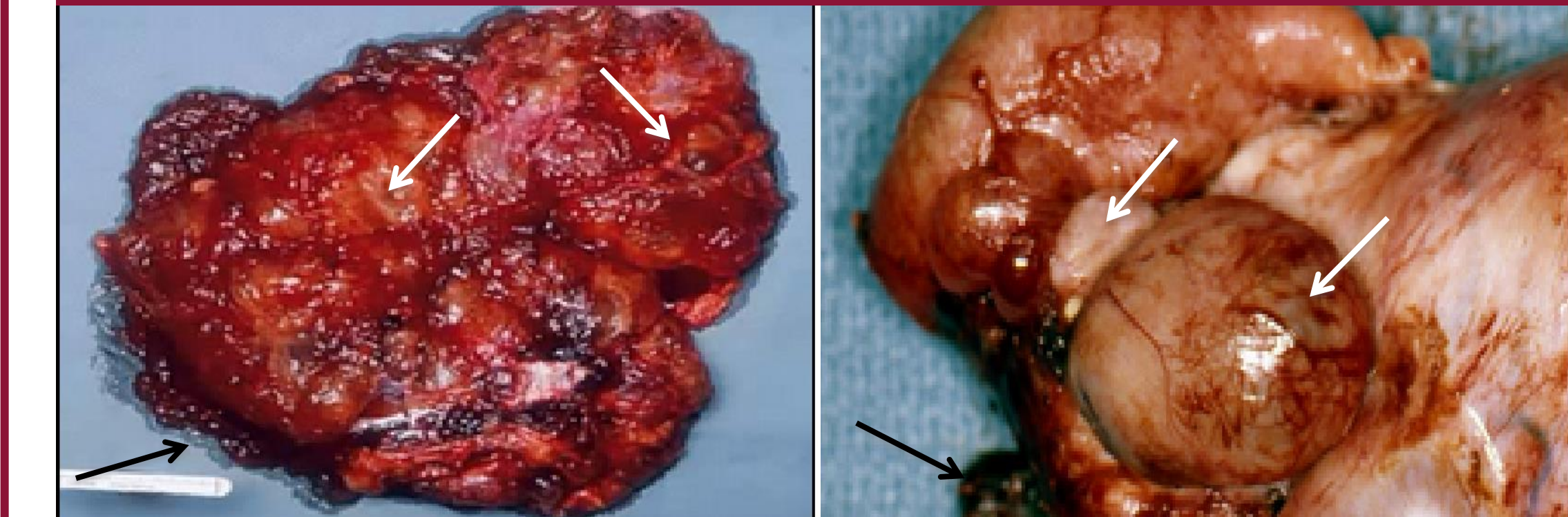
In Humans

- A leading cause of death among women in US: the eighth most common cancer and the fifth leading cause of cancer deaths¹
- High mortality due to lack of effective early detection: 80% of women diagnosed at late stages when tumors have metastasized²
- Barriers for early detection: non specific symptoms and lack of bio markers

In Avian Species

- High rate of spontaneous cancers in chickens: 35 %³
- High incidence in psittacines with a history of over production of eggs⁴
- Incidence increases with age
- Not clinically detected until quite advanced

Human Ovarian Cancer



White arrow: tumor nodules
Black arrow: endometriosis

White arrow: tumor nodules
Black arrow: endometriosis

(Amortegui, et al, Global Libr Womens' Med)

Disease Similarities

- 4 types of carcinomas observed:
 - serous, endometrioid, mucinous & clear cell⁵
- Preceded by putative precursor neoplastic lesions
- Similarities in histology, metastasis, and stages of cancer⁵
- Gene expression patterns (p53, HER-2⁶)
- Risk factors:
 - incessant ovulation, excessive gonadotropin stimulation
- Overexpression of COX-1 and COX-2 in ovarian cancers⁷

Disease Differences

- Chickens lack lymph nodes: leads to difference in nodal involvement in metastasis⁸
- Unilateral (chickens) vs bilateral (humans) ovary: leads to difference in sub-staging
- Chicken luteal phase different from humans
- Immunoglobulin system: Classes in chicken IgA, IgM, IgG/IgY⁹. Classes in humans: IgA, IgM, IgG, IgD, IgE
- Chicken MHC (B complex) genes smaller in size and simpler¹⁰ than human MHC genes

Chicken Ovarian Cancer



White arrow: tumor lesions
Black arrow: atretic follicles

White arrow: Follicular cysts associated with malignancy

(Ansenberger 2009)

(For the Birds, San Jose, CA)

Chickens Can Be Great Models

- Develop spontaneous cancers between 2-7 years of age
- Ovulatory cycle every 24-26 hours
- Rapid disease progression
- Chicken genome sequenced, aligned and well-studied
- Chicken models are widely available
- Prevention and treatment trials on chicken models can save time and reduce expense and failure risk in human clinical trials

Ongoing Research on Chicken Models

- Biomarkers for early detection (eg: analysis of plasma proteome³)
- Agents (eg: oral contraceptives like progestin¹¹) and lifestyle (eg: calorie restriction¹², diet with flaxseed¹³) for tumor prevention
- Study ovulation induced genetic damage to ovarian epithelial cells
- Insight into mechanisms involved in cancer development (eg: cathepsins¹⁴, E-cadherin¹⁵)
- Understand the antitumor humoral immune response; presence of anti-tumor and anti-ovarian antibodies could be a potential diagnostic marker for ovarian carcinoma¹⁶

References

1. Ovarian Cancer, <http://www.edc.gov/cancer/ovarian>
2. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, et al. (editors). SEER Cancer Statistics Review, 1975-2008. National Cancer Institute, Bethesda, MD. Available from: http://seer.cancer.gov/csr/1975_2008/ based on November 2010 SEER data submission, posted to the SEER web site, 2011
3. Hawkrigde, et al. Measuring the Intra-individual Variability of the Plasma Proteome in the Chicken Model of Spontaneous Ovarian Adenocarcinoma. *Anal Bioanal Chem*. 2010
4. Reavill D, Schmidt R. Tumors of the psittacine ovary and oviduct: 37 cases. *Proc Annu Conf Assoc Avian Vet*. 2003;67-69
5. Barua, et al. Histopathology of Ovarian Tumors in Laying Hens: A preclinical model of human ovarian cancer. *Int J Gynecol Cancer*. 2009
6. Hakim AA, Barry CP, Barnes J, et al. Ovarian adenocarcinomas in the laying hen and women share similar alterations in p53, ras and HER-2/neu. *Cancer Prev Res*
7. Rask K, Zhu Y, Wang W, Hedin L, Sundfeldt K (2006) Ovarian epithelial cancer: a role for PGE2-synthesis and signalling in malignant transformation and progression. *Mol Cancer* 5: 62
8. Nagy, Z.A. & Horvath, E. & Urbán, Z. (1973). Antigen capture in chicken spleen during the primary immune response and relationship to phagocytic activity. *Nature: New biology*, 242, 9. Davison, et al. *Avian Immunology*. Elsevier/Academic Press, 2008
9. Lebaeq-Verheyden, Vaerman, J.P., and J. F. Heremans (1974). Quantification and Distribution of Chicken Immunoglobulins IgA, IgM, and IgG in Serum and Secretions. *Immunology* 27: 683
10. Kaufman, et al. The chicken B locus is a minimal essential major histocompatibility complex. *Nature*. 1999 Oct 28;401(6756):923-5
11. Treviño LS, Buckles EL, Johnson PA. Oral contraceptives decrease the prevalence of ovarian cancer in the hen. *Cancer Prev Res (Phila)*. 2012 Feb;5(2):343-9. doi: 10.1158/1940-6207.CCR-11-0344. Epub 2011 Dec 1
12. Carver DK, Barnes HJ, Anderson KE, Pettite JN, Whitaker R, Berchuck A, et al. Reduction of ovarian and oviductal cancer in calorie-restricted laying chickens. *Cancer Prev Res* 2011;4:562-7
13. Ansenberger K, Richards C, Zhuge Y, Barua A, Bahr JM, Luborsky JL, Hales DB. Decreased severity of ovarian cancer and increased survival in hens fed a flaxseed-enriched diet for 1 year. *Gynecol Oncol*. 2010 May;117(2):341-7. doi: 10.1016/j.ygyno.2010.01.021. Epub 2010 Feb 13
14. Ahn SE, Choi JW, Rengaraj D, Seo HW, Lim W, Han JY, Song G. Increased expression of cysteine cathepsins in ovarian tissue from chickens with ovarian cancer. *Reprod Biol Endocrinol* 2010, 8:100
15. Ansenberger, et al. E-cadherin expression in ovarian cancer in the laying hen, *Gallus domesticus*, compared to human ovarian cancer. *Gynecologic Oncology*. 2009, 113: 362-369
16. Barua A, Edassery SL, Bitterman P, Abramowicz JS, Dirks AL, et al. (2009) Prevalence of antitumor antibodies in laying hen model of human ovarian cancer. *Int J Gynecol Cancer* 19: 500-507. doi: 10.1111/IGC.0b013e3181a39db1