AGC Subclasses and Risk of Invasive Cancers

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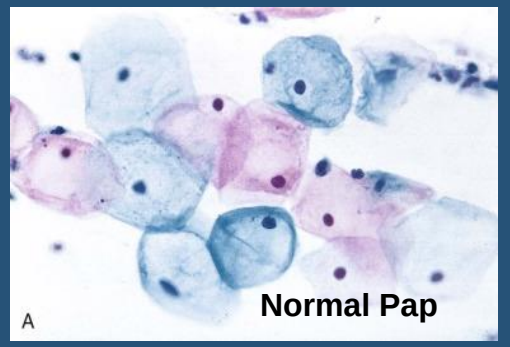
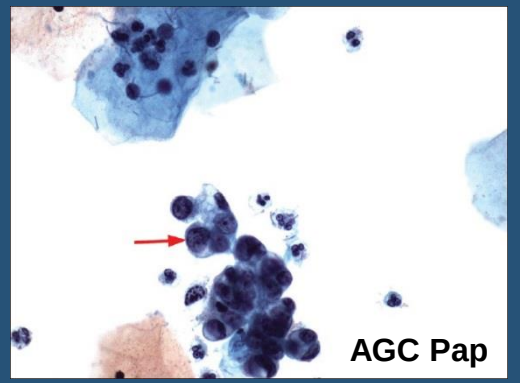
Introduction

Glandular cell abnormalities on cervical cytology include[1]:

- **AGC (Atypical Glandular Cells)**
- AGC favor neoplasia
- Endocervical AIS
- Adenocarcinoma





1. Solomon D, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287(16):2114-9.

Introduction

AGC is further categorized based on the origin of the glandular cells as:

- Endocervical (AGC-EC)
- Endometrial (AGC-EM)
- Not otherwise specified (AGC-NOS)

Introduction

- AGCs are found in <0.5% of all cervical cytology reports
- Previous research recognized an association between AGC and premalignant/malignant disease, primarily endometrial cancer [2]
- Whether each AGC-subclass (EC, EM, or NOS) carries a similar risk of post-AGC invasive cancers has not been assessed

2. Schnatz PF, Guile M, et al. Clinical Significance of AGC on Cervical Cytology; Obstet & Gynecology 2006,107(3):701-708.

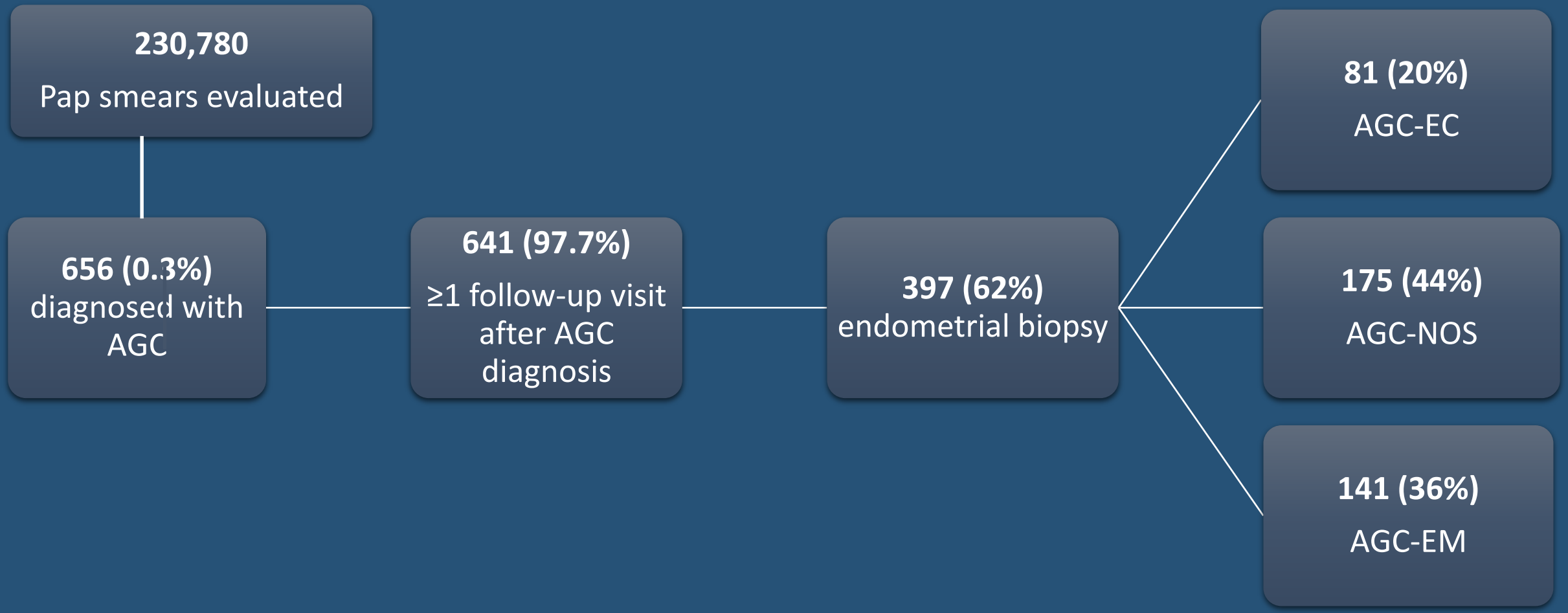
Objective

- to assess the risk of invasive cancers associated with AGC subclasses

Methods

- Approved by The Reading Hospital (TRH) IRB.
- All cases of AGC were diagnosed between 1/1/2005 and 6/1/2017.
- Demographics, cytology, histologic findings, and the final diagnosis of invasive cancers after the initial AGC finding were recorded.
- A multivariate survival analysis was conducted using SAS v. 9.3.
- Covariates adjusted in the survival analysis include Age, BMI, HTN, DM, Smoking, Dyslipidemia, PCOS, OCP use, IUD use.

Results


230,780
Pap smears evaluated
656 (0.3%)
diagnosed with AGC
641 (97.7%)
≥1 follow-up visit after AGC diagnosis
397 (62%)
endometrial biopsy
81 (20%)
AGC-EC
175 (44%)
AGC-NOS
141 (36%)
AGC-EM

Results

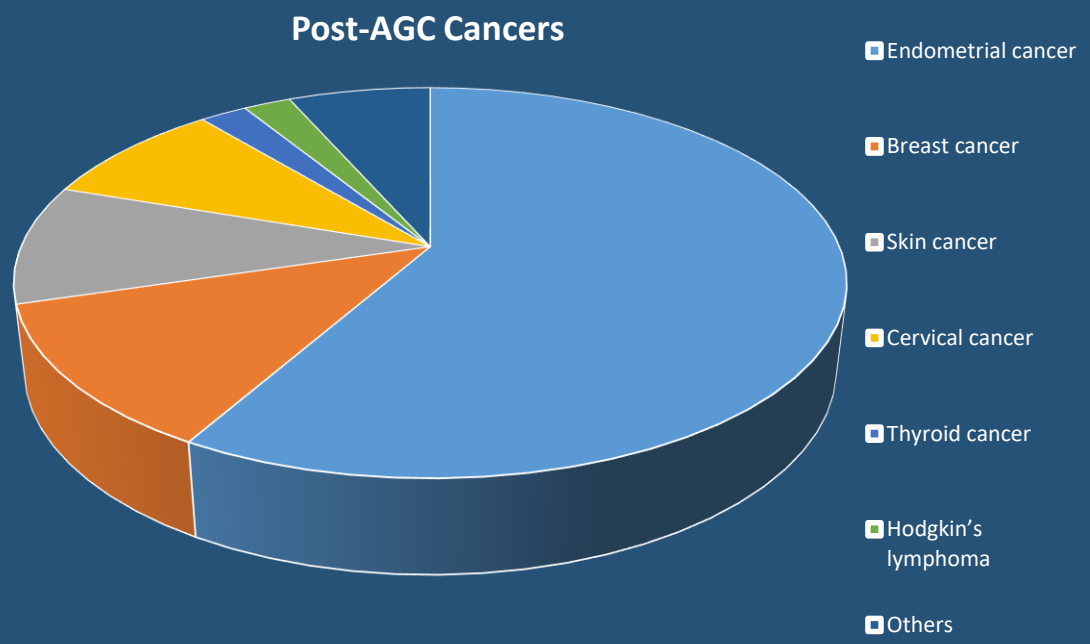
Follow up time after AGC Diagnosis:

- Mean (SD) = 4.7 (3.2) years
- Median 5.2 years
- Min-Max 0.01-10.4 years

Results

A total of 91(14%) had at least one invasive cancer diagnosed after AGC:

- Endometrial cancer = 53
- Breast cancer = 11
- Skin cancer = 9
- Cervical cancer = 8
- Thyroid cancer = 2
- Hodgkin's lymphoma = 2
- Others = 6

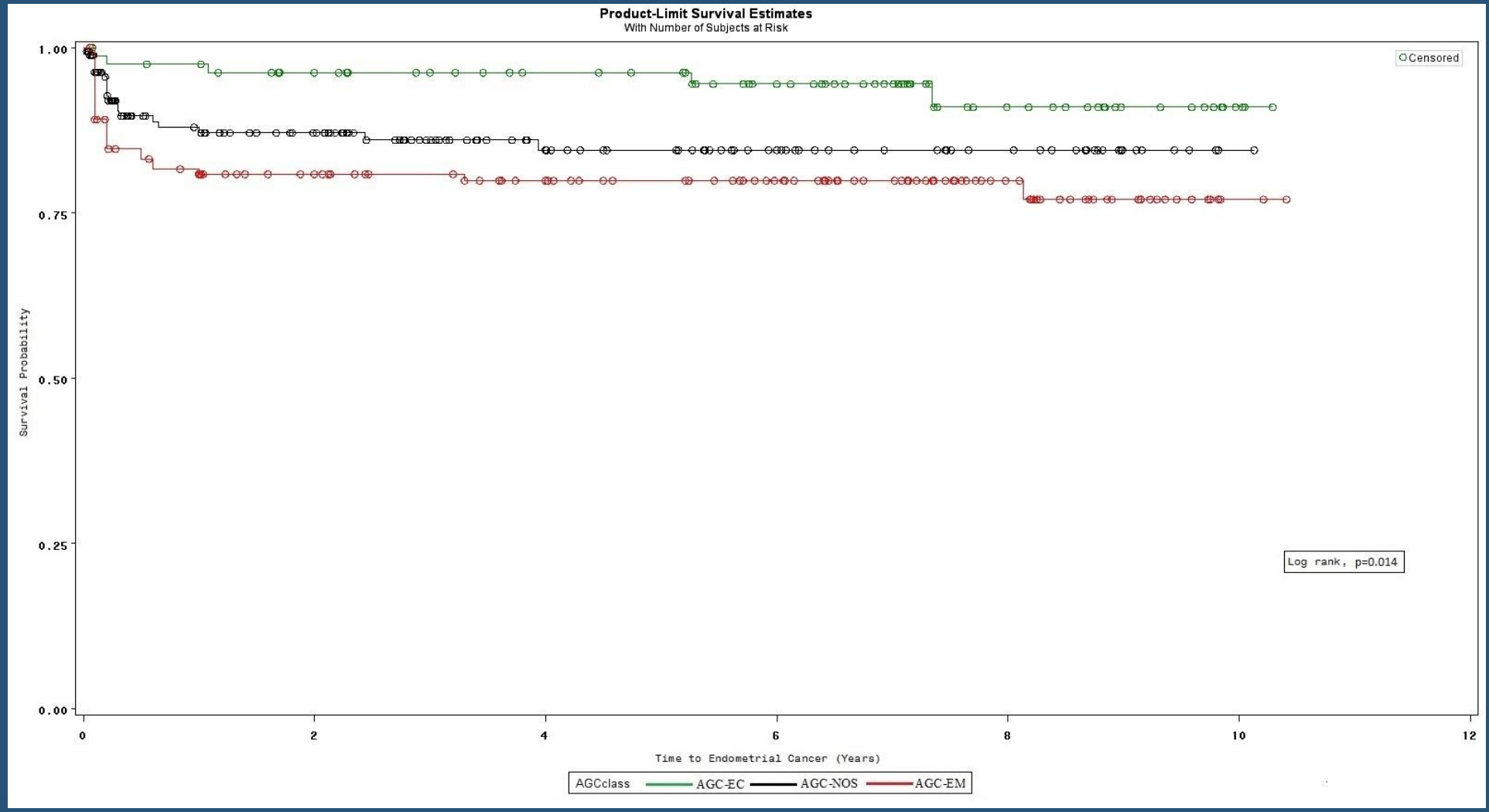


Results

Of the 397 who had endometrial biopsy, the incidence of endometrial cancer increases in a stepwise manner across AGC subclasses from AGC-EC, AGC-NOS, to AGC-EM (Cochran-Armitage trend test, p=0.0025)

Endometrial Cancers	**AGC-EC**	**AGC-NOS**	**AGC-EM**	**P value***
Yes (n=53)	5 (6.2%)	20 (11.4%)	28 (19.9%)	**0.0025**
No (n=344)	76 (93.8%)	155 (88.6%)	113 (80.1%)	

Fig.1 Multivariate adjusted survival curves for three AGC subclasses on the Time-to-Endometrial cancers



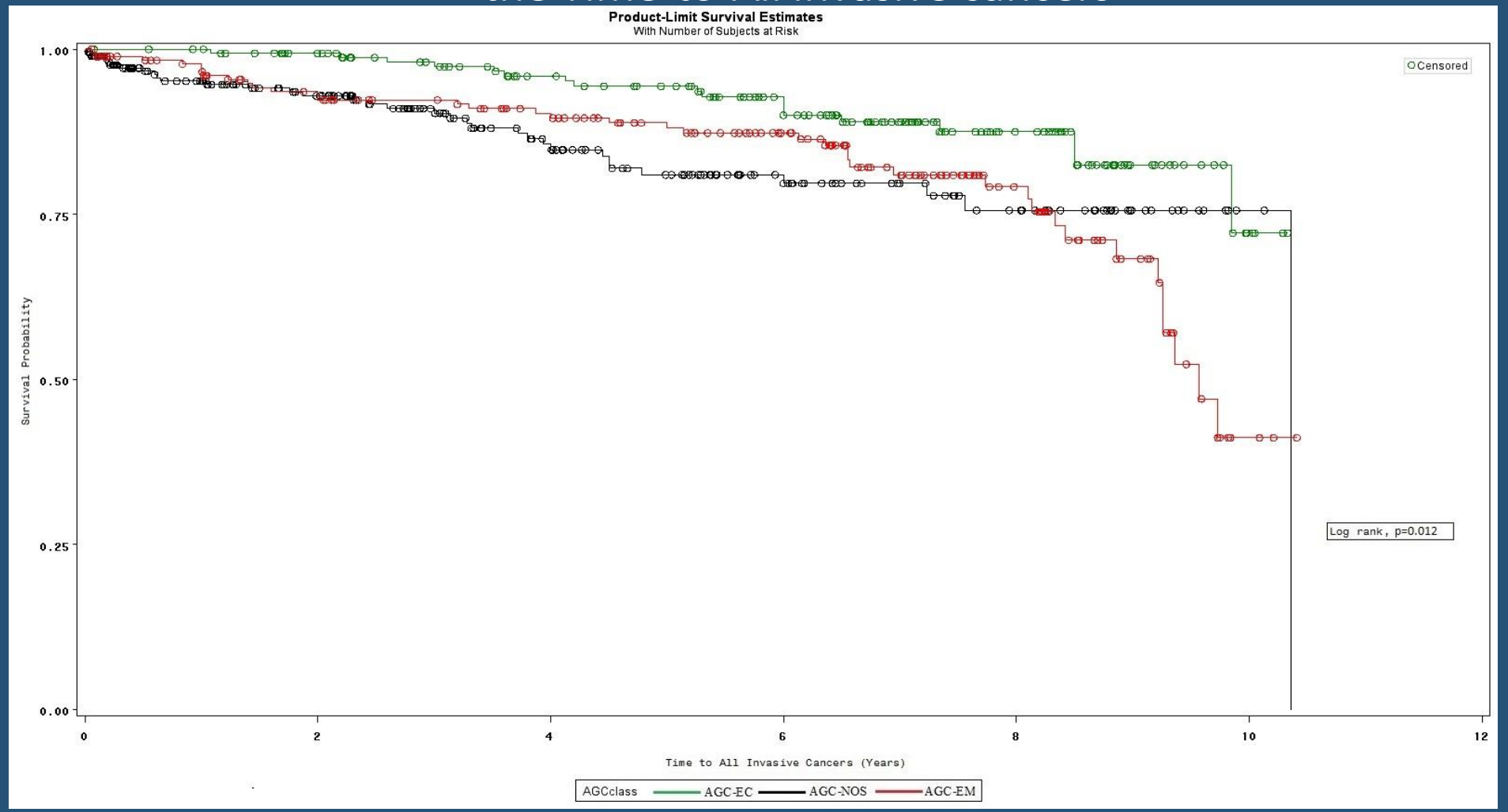
While analyzing Time-to-Endometrial cancer, the survival curve of AGC-EC is clearly distinct from AGC-NOS and AGC-EM (log rank test, p=0.014, Fig. 1).

Results

The incidence of invasive cancer increases in a stepwise manner across AGC subclasses from AGC-EC, AGC-NOS, to AGC-EM (Cochran-Armitage trend test, p=0.005)

All Cancers	AGC-EC	AGC-NOS	AGC-EM	P value
Yes (n=91)	18 (10.5%)	35 (12.2%)	38 (20.8%)	**0.005**
No (n=550)	154 (89.5%)	251 (87.8%)	145 (79.2%)	

Fig. 2 Multivariate adjusted survival curves for three AGC subclasses on the Time-to-All invasive cancers



While analyzing Time-to-All invasive cancers, the survival curve of AGC-EC is clearly distinct from AGC-NOS and AGC-EM (log rank test, p=0.012, Fig. 2).

Discussion

- The incidence of AGC (0.3%) in our institution was similar to the incidence in previous reports
- Each of the AGC subclasses may carry a different risk for post-AGC endometrial cancers and all cancers
- The risk profile of AGC-EC for developing and time-to-developing, post-AGC cancers is distinctly less severe than AGC-NOS and AGC-EM

Discussion

Strength of Study

A longitudinal study design, multivariate survival analysis with time-to-event considered and covariates (other risk factors of endometrial cancers) adjusted.

Limitation

A small incidence of extra-uterine cancers due to relatively small sample size, inadequate power to detect significance of association between AGC and post-AGC extra-uterine cancers.

Implication

The risk of AGC-NOS should not be underrated and may warrant similar close workup as AGC-EM, which is endometrial and endocervical sampling regardless of age.

Conclusion

- The three AGC subclasses may carry different risk profiles for developing, and time to develop, post-AGC invasive cancers, including but not limited to endometrial cancer.

- There may be a stepwise increase in the risk of post-AGC malignancies across AGC subclasses from AGC-EC to AGC-NOS to AGC-EM.

Conclusion

- The risk profiles of AGC-NOS may be similar to AGC-EM, thus AGC-NOS may warrant the similar initial workup as AGC-EM.

- Further large population based prospective studies are needed to confirm the study findings.