New Biomarkers For Early Detection Of Ovarian Cancer

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INTRODUCTION

Ovarian cancer is the fifth most common malignancy among women worldwide and the most lethal of all gynecological cancers. With a lack of early warning symptoms or reliable screening methods, the majority of patients are diagnosed at advanced stages (III or IV), when 5-year survival rates are only 20%. However, this rate increases up to 80% when tumors are detected at stages I or II but, regrettably, only the 20% of the cases are detected in these early stages. Given these significant differences between the survival rates in difference stages, the stage at diagnosis represents the major prognostic factor in ovarian cancer and the best way to improve the survival is to develop tumor markers that could be used to detect the early stages of the disease.

Owing to the lack of sensibility and specificity of the current diagnostic, the aim of this review is to describe some of the future biomarkers that could increase cases of ovarian cancer detected in early stages.

MATERIALS & METHODS

The studies in this review were identified through systematic searches of PubMed with the English terms "diagnostic ovarian cancer" "ovarian cancer biomarkers", "kallikreins ovarian cancer", "CA-125 ovarian cancer", "HE4" B7-H4", or "kallikreins ovarian cancer", mainly from 2000 to 2013 and including some of the most innovative paper of 2014. Initially, a total of 50 article were selected but after reading each one, only among 20 articles were included in the final review.

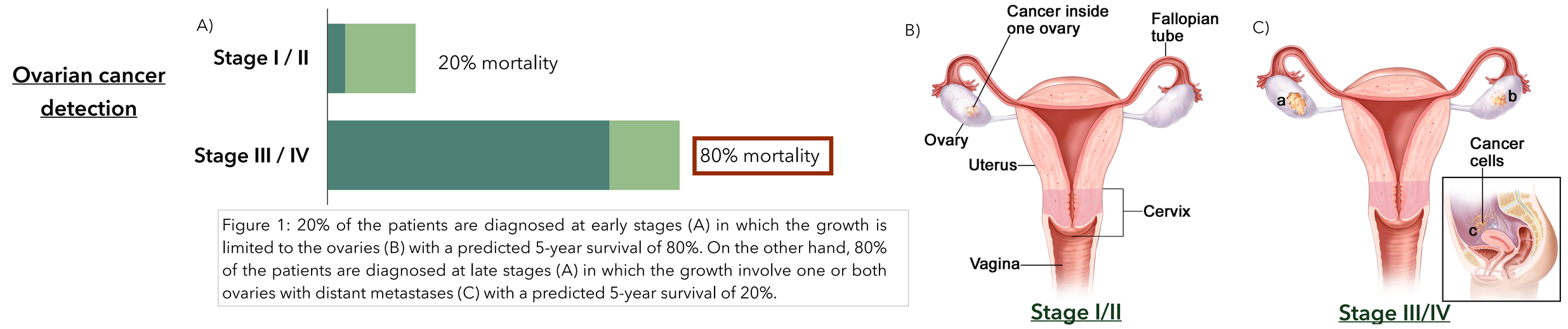
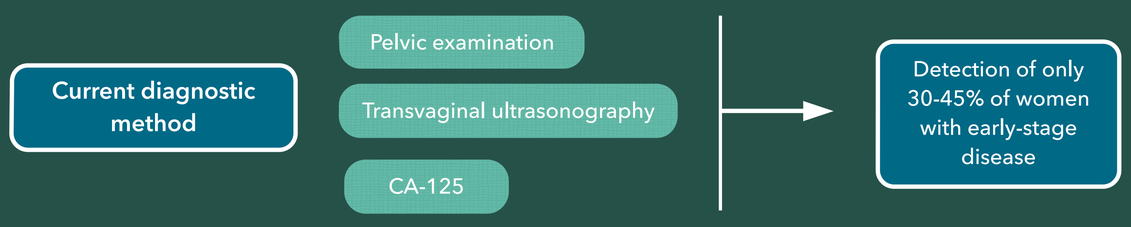


Figure 1: 20% of the patients are diagnosed at early stages (A) in which the growth is limited to the ovaries (B) with a predicted 5-year survival of 80%. On the other hand, 80% of the patients are diagnosed at late stages (A) in which the growth involve one or both ovaries with distant metastases (C) with a predicted 5-year survival of 20%.

RESULTS

Available tools for early ovarian cancer detection

Owing to the low prevalence of ovarian cancer, an effective screening method for detection of early-stage disease requires a specificity of at least 99'6% and a sensitivity of at least 75% to be considered an effective tool.



Because of the lack of efficacy of the current diagnostic method, the challenge continues being to find a better tool or strategy to detect early-stage ovarian cancer in order to increase the survival.

HE4

HE4 has been reported as the most promising marker to aid in OC diagnosis. Recent studies have shown elevated HE4 protein levels in serum from patients with ovarian tumors, demonstrating a similar sensitivity to CA125, but increased specificity for malignant tumors as compared to benign disease.

Most of results provide evidence of the cellular and molecular mechanisms that may underlie the motility-promoting role of HE4 in ovarian cancer progression although the precise mechanism by which HE4 promotes ovarian disperse occurrence and dispersion has remained elusive.

Kallikreins

The kallikrein locus spans approximately 265 kb on chromosome 19q13.3-13.4 and codify for 15 serine proteases, hK proteins, that have been confirmed in various biological fluids lending proof to the secreted nature of these proteins.
KLKs are expressed in diverse human tissues and are involved in various patho-physiological processes. However, numerous studies have determined the aberrant expression of members of the KLK family in ovarian cancer tissue, serum from women with ovarian cancer and ovarian cancer cell lines at either the mRNA or protein level or both (Figure 2). Interestingly, KLK6 and KLK10 have shown a strong potential as clinical serum biomarkers for this cancer.

Aberrant expression of KLKs in ovarian cancer

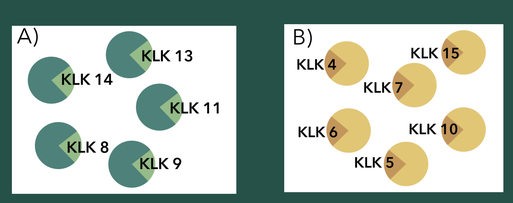


Figure 2: A) The levels of **KLK8**, **KLK9**, **KLK11**, **KLK13** and **KLK14** in tumor tissues are higher in early stage disease, when optimal debulking surgery has been performed and in those patients who responded to chemotherapy and have a long survival time. B) The high mRNA and/or protein levels of **KLK4**, **KLK5**, **KLK6**, **KLK7**, **KLK10** and **KLK15** are associated with shorter progression-free and overall survival time of patients and their up-regulated expression is associated with high rade and late stage disease, belonging to the more aggressive type-II tumors.

B7-H4

B7-H4 (B7x or B7S1) is a member of the B7 family and it is known to be critically involved in the down-regulation of antigen-specific immune response by inhibiting proliferation, cell-cycle progression and cytokine productions of CD4+ and CD8+ T cells.

B7-H4, overexpressed in ovarian cancers (Figure 3), binds to an unknown putative receptor expressed on activated but not naive T cells. Consequently, they lead the inhibition of T cells activation and IL-2 production suggesting that B7-H4 could be implicated in a mechanism of down-regulating antitumor T cell responses at the level of the effector cell.

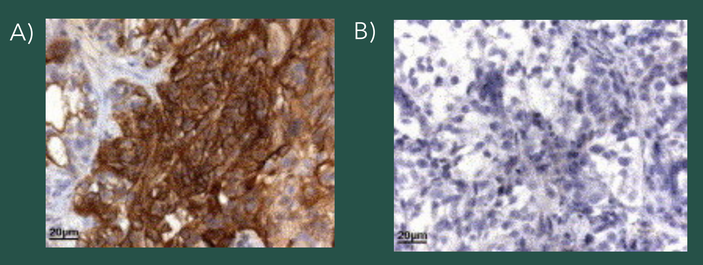


Figure 3: Immunohistochemical staining of tumor sections with an antibody against B7-H4 (A57.1 antibody) show strong cell surface staining of a majority of the tumor cells (A) whereas no B7-H4 protein is detected in the control tumors (B).

The results of numerous studies have shown that B7-H4 is detectable in elevated levels in serum of ovarian cancer patients but is not typically elevated in patients with benign diseases thereby it could be a good serum biomarker. Furthermore, it has been shown that the multivariate analysis of CA-125 and B7-H4 increased the sensitivity and specificity when compared with the analysis of each marker alone so it could be a possible choice to increase the efficacy of the tools detection. Finally. blocking B7-H4 could be a important target for novel antibody-specific therapeutic strategies in patients with ovarian cancer.

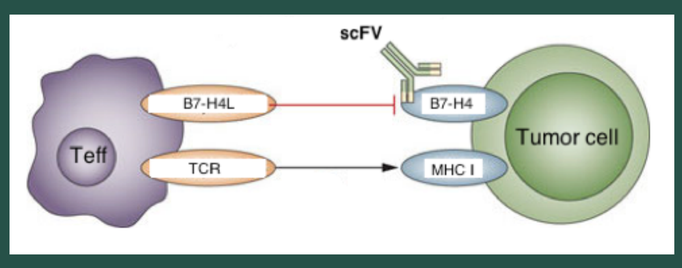


Figure 4: The binding of B7-H4 expressed by malignant cells to a putative ligand (B7-H4L) on the surface of T cells significantly impairs the activation of the latter within the tumor microenvironment so the antibody can revert T-cell inhibition and hence favor the elicitation of T cell- mediated antitumor responses .

CONCLUSIONS

- Ovarian cancer is the most lethal of all ginnecological cancers and requires an effective method of diagnosis in order to increase the cases detected at early stages.
- HE4 has been describe as a promising biomarker with a similar sensitivity to CA-125 but increased specificity.
- Some KLKs are aberrantly expressed in ovarian cancer suggesting that could play significant roles in tumor and could be a possible screening and diagnostic ovarian cancer biomarker
- B7-H4, a down-regulator of antigen-specific immune response, is overexpressed in ovarian cancer. It coul be a poossible biomarkers for ovarian cancer and a possible target for therapeutic strategies