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REVIEW

The secondary Müllerian system, field effect, BRCA, and tubal fimbria: our evolving understanding of the origin of tubo-ovarian high-grade serous carcinoma and why assignment of primary site matters

Naveena Singh[1], C. Blake Gilks[2], Nafisa Wilkinson[3] and W. Glenn McCluggage[4]

Departments of Pathology, [1]Barts Health NHS Trust, London, United Kingdom, [2]Vancouver General Hospital and University of British Columbia, Vancouver, Canada, [3]St James' Hospital, Leeds, and [4]Royals Hospitals Trust, Belfast, United Kingdom

Summary

It has long been held that most epithelial ovarian carcinomas arise from the ovarian surface epithelium. Theories on origin were based on the assumption that there was a common cell of origin for all ovarian carcinoma histotypes, and that these histotypes were closely related and frequently admixed. It is now recognised that the histotypes are distinct diseases. Recent studies on early, organ-confined, non-uterine high-grade serous carcinoma (HGSC) have led to a change in our understanding of their anatomical site of origin. These studies were initially on patients at high risk of developing HGSC but more recently have been extended to cases without family history or genetic markers of increased risk. These have shown that incidental HGSC, when detected before dissemination, is most commonly identified in the tubal fimbria. As a result, we have had to revisit theories on the cell and site of origin of HGSC. This progress in our understanding has necessitated a change in how we handle cases in clinical practice, as it impacts on primary site assignment, which in turn has implications for staging. In this review we will discuss the evolution of our understanding of the cell of origin of HGSC, the evidence for the tubal fimbria as the anatomical site of origin of most non-uterine HGSC, and the clinical implications of these recent developments.

Key words: Fallopian tube, HGSC, high-grade serous carcinoma, origin, ovary, primary peritoneal carcinoma, site assignment, staging, STIC.

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INTRODUCTION

In 2001, dysplastic changes were reported within the tubal fimbria in risk-reducing salpingo-oophorectomy (RRSO) specimens, suggesting the possibility that these represented the long sought precursor of non-uterine high grade serous carcinoma (HGSC).[1] Evidence supporting tubal origin in both hereditary and sporadic cases of HGSC has since accumulated over the ensuing years. This view has not been universally accepted, primarily as it conflicts with traditional theories on the origins of ovarian carcinoma, and secondarily owing to variation in the detection of tubal lesions in association with HGSC, which may in turn be due to differences in sampling or difficulties in diagnostic interpretation. Despite therapeutic advances together with the emerging effects of 'personalised medicine', HGSC continues to have an abysmal prognosis with approximately 150,000 deaths annually worldwide.[2]

Understanding the origins of this aggressive disease is imperative and adopting a uniform approach to classification and staging is essential to underscore the fundamental differences between different ovarian carcinoma histotypes, with profound implications for treatment and genetic counselling. Wider acceptance of a uniform approach will allow accrual of better prospective data to inform optimal risk reducing/preventative strategies. This review critically examines prevailing views on the origins of non-uterine HGSC and the evidence supporting these, and provides guidelines for assignment of primary site of HGSC in practice. It is stressed that this review only deals with HGSC, the other histotypes of ovarian carcinoma (clear cell, endometrioid, low-grade serous and mucinous) arising in the ovary from borderline tumours or other precursor lesions such as endometriosis.

THEORIES OF ORIGIN

A number of theories have been proposed over the years regarding the cell of origin of ovarian cancer. The early theories were encumbered by two assumptions: (1) that ovarian carcinoma is a single disease, albeit one that can exhibit a range of Müllerian cell types (including mixed tumours in which there are admixtures of different cell types), and (2) that ovarian carcinomas arise in the ovary, because that is where the dominant mass is found. With regards to the second point, it is important to make the distinction between cell of origin and site of origin. As noted previously and discussed later, recent data support HGSC as arising in the fallopian tube in most cases; this has, in turn, impacted on the discussion about cell of origin. Early theories on cell of origin can be seen, in retrospect, as a struggle to reconcile the fact that the ovary is not derived from the Müllerian system, but is covered by mesothelium, and does not normally contain Müllerian-type epithelium (with the exception of the tubal type epithelium within cortical inclusion cysts), with the overtly Müllerian nature of most ovarian carcinomas and borderline tumours. With the recognition that ovarian carcinoma is not a single disease but five distinct diseases (HGSC, clear cell, endometrioid, low-grade serous and mucinous),[3] and that true 'mixed' carcinomas are exceedingly rare,[4] the discussion of cell of origin has been freed from the need to find a single cell type that can give rise to all ovarian carcinoma histotypes.

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Although the dominant mass in most cases of HGSC, whether sporadic or associated with germline BRCA1/2 mutation, is within the ovary, it is now appreciated that the ovaries are highly suitable sites for metastasis, and a dominant ovarian mass cannot be equated with an ovarian primary site. For example, patients with primary gastric, colorectal, appendiceal, and endocervical carcinomas may have a dominant ovarian mass at presentation.[5,6]

In this review we focus specifically on HGSC, and briefly discuss the following four theories of cell of origin: ovarian surface epithelium, secondary Müllerian system/extra-uterine Müllerian epithelium, tubal-peritoneal junction, and tubal fimbria. These theories have significant overlap and therefore are not mutually exclusive.

OVARIAN SURFACE EPITHELIUM AS ORIGIN OF OVARIAN CARCINOMA

Until 10 years ago, the dominant theory regarding the cell of origin of ovarian carcinoma proposed that most arise from the ovarian surface epithelium (OSE), the mesothelium covering the ovary, as reviewed elsewhere.[7] An extension of this theory, based on the belief that ovarian cortical inclusion cyst epithelium (CICE) is derived from OSE, suggested that most ovarian carcinomas arose from CICE. This theory satisfied the assumption that ovarian carcinomas arise in the ovary, attributing the cell of origin to the only epithelial cell population normally found in the ovary, and it was also able to account for the Müllerian nature of ovarian carcinomas, given the presence of tubal-type cells in CICE. The evidence in support of this hypothesis was minimal; rare cases of apparently early or *in situ* lesions involving the OSE or CICE were described[8,9] and experimental models of transformation of OSE gave rise to tumours that resemble ovarian carcinoma in humans.[10–12]

However, the scarcity of early or *in situ* lesions involving the OSE or CICE was a major weakness of the theory. This theory, although poorly supported by data, served well and was widely accepted until evidence began to emerge that the site of origin of HGSC was the tubal fimbria in most cases, and such cases clearly do not arise from OSE/CICE. At this time there remains very scant data supporting OSE as the cell of origin of HGSC, and it has even been suggested recently that CICE is truly of Müllerian origin, having arisen through implantation of fallopian tube epithelium within cortical inclusion cysts lined by mesothelial cells.[13] This latter view is controversial, and it is uncertain at present whether the tubal-type CICE arises through metaplasia of OSE (mesothelium) entrapped in cortical inclusion cysts or is a result of detached fallopian tube epithelial cells colonising cysts.

In summary, the theory of OSE/ICE as the cell of origin of most ovarian carcinomas, including HGSC, is no longer tenable in the face of mounting evidence supporting origin in the fimbrial end of the fallopian tube. Some HGSC may indeed arise from OSE or ICE but these would account for a minority of cases. The best hope of resolving the question of what percentage of HGSC arise in the ovary versus fallopian tube will come from follow-up of patients who undergo salpingectomy without oophorectomy. This is an increasingly common procedure referred to as 'opportunistic salpingectomy', whereby fallopian tubes are removed at the time of gynecological surgery for other indications as a way of potentially reducing the risk of developing HGSC, if child bearing is no longer a consideration.[14]

SECONDARY MÜLLERIAN SYSTEM/ EXTRA-UTERINE MÜLLERIAN SYSTEM AS ORIGIN OF OVARIAN CARCINOMA

HGSC is one of a number of carcinomas of the female reproductive organs that are of Müllerian type; the designation 'Müllerian' refers to those epithelia that are found in structures derived from the Müllerian ducts. The ducts arise through invagination of the coelomic epithelium overlying the mesonephros during embyonic development, giving rise to the fallopian tube and uterus, with serous (or tubal), endometrial and endocervical-type lining cells.[15] These epithelia are in continuity with the OSE, a specialised mesothelium covering the ovary.[16] While the fallopian tube and uterus constitute the primary Müllerian system, the designation 'secondary Müllerian system' was proposed by Lauchlan in reference to the pelvic and lower abdominal mesothelium and subjacent mesenchyme with its potential to differentiate into Müllerian type epithelium and stroma.[17] This theoretical potential for Müllerian differentiation was proposed as an explanation for Müllerianosis, i.e., endometriosis, endosalpingiosis, and endocervicosis. The assumption was that endometriosis (as well as endosalpingiosis and endocervicosis) arises *in situ* in the pelvic peritoneum and ovary as a metaplastic phenomenon from the secondary Müllerian system. Lauchlan noted that 'It has not been seriously suggested...that an ovarian focus of, say, endometriosis, acts as a kind of Tinkerbell sprinkling replicas of itself, like stardust, throughout the peritoneum',[18] thus rejecting the possibility of endometriosis at different sites being clonally related. In fact, we have recently shown a clonal relationship between physically separate foci of endometriosis,[19] and the pathogenesis of endometriosis remains controversial; it is not definitively known whether it arises *in situ* through metaplastic change in the secondary Müllerian system, or through 'metastasis' (retrograde spread) from the endometrium. While the latter is likely to account for most cases of endometriosis, both mechanisms may apply.

The proposal of a secondary Müllerian system, based on the close embryological relationship between the pelvic peritoneum and the epithelium of the fallopian tube and uterus, formed the basis for a second theory of origin of HGSC, and the concept of primary peritoneal carcinoma (PPC). This entity was first described in 1959[20] and believed to arise from totipotential pelvic peritoneum, capable of differentiating into any of the derivatives of the Müllerian ducts. PPC was subsequently defined as high-grade serous carcinoma involving the peritoneum in the absence of an ovarian mass[21–23] and, in order to promote uniformity in diagnosis, strict criteria were proposed,[24] which have been adhered to until recently (see 'Proposal for site assignment in HGSC' section below). Additional support for the existence of PPC came from its rare but well documented occurrence many years after prophylactic oophorectomy in BRCA mutation carriers.[25–27] PPC was held forth as evidence of origin of HGSC from the secondary Müllerian system, but in practice, with meticulous examination of the tubes and ovaries, this is a rare diagnosis as the majority of these cases demonstrate tubo-ovarian involvement.[28]

It was also suggested that epithelial ovarian neoplasms arise synchronously and independently at multiple sites within the field defined by the hypothetical secondary Müllerian system i.e., a 'field effect',[18] in response to a common carcinogenic