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# Comment on 'Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis'

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**Sir,**

We read with interest the recent meta-analysis by Mei *et al* (2014). In this study, Mei *et al* examined the prognostic value of the local inflammatory infiltrate in colorectal cancer as measured by both the generalised inflammatory infiltrate and by immunohistochemical analysis of T-lymphocytic subsets. The authors concluded that, in comparison with assessment of T-cell subset density, semiquantitative assessment of the generalised inflammatory infiltrate at the invasive margin, utilising the Jass score or Klintrup–Mäkinen grade (Jass *et al*, 1987; Klintrup *et al*, 2005), was a more robust prognostic marker of cancer-specific, overall and disease-recurrence-free survival. Indeed, in patients undergoing resection for Stage I–III disease, a high-density generalised inflammatory infiltrate was associated with an almost 60% increase in overall survival.

The present study mirrors recent results from both our group and others (Vayrynen *et al*, 2013; Richards *et al*, 2014). In 365 patients undergoing potentially curative resection for Stage I–III colorectal cancer, Klintrup–Mäkinen grade strongly correlated with T-cell subtype density in the invasive margin, tumour stroma and cancer cell nests (Richards *et al*, 2014). Furthermore, on univariate analysis, a strong Klintrup–Mäkinen grade was associated with improved cancer-specific survival (hazard ratio 0.54, 95% confidence interval 0.43–0.68); indeed this was comparable if not superior to the prognostic utility of measuring T-cell subtype density or the use of a composite score, such as the Galon Immune Score. Similarly, in a cohort of 117 patients with Stage I–IV colorectal cancer undergoing resection, Vayrynen *et al* (2013) found that Klintrup–Mäkinen grade closely correlated with not only T-cell density, but also macrophage, neutrophil and dendritic cell density at both the invasive margin and within the intratumoural compartment. In addition, Klintrup–Mäkinen score was associated with recurrence-free survival.

Therefore, taken together, these results are consistent with the concept that increased density of an inflammatory cell infiltrate in the tumour microenvironment represents a coordinated effective immune response and that individual inflammatory cell types offer little additional prognostic value. If this proves to be the case, then it may be that the conspicuous inflammatory cell infiltrate, long recognised by investigators to be associated with good outcome, is the normal immune response to a colorectal cancer and that the abnormal response is a scarce or absent inflammatory cell infiltrate, representing an uncoordinated immune response. The implications of such a hypothesis are several and profound. First, the immune context in which an inflammatory cell is found in the tumour microenvironment would become of paramount importance. Second, it would move the focus of investigations from the nature of the inflammatory cell infiltrate in those with a conspicuous inflammatory cell infiltrate to those with a scarce or absent inflammatory cell infiltrate (eg, see Mohammed *et al*, 2012; Richards *et al*, 2012). Third, it would become a pre-requisite of all investigations that the density of the tumour inflammatory cell infiltrate in the tumour microenvironment is defined.

With this in mind we have recently validated an automated, computer-based scoring method with similar prognostic value to the Klintrup–Mäkinen grade (Forrest *et al*, 2014). It is hoped that introduction of such a tool will facilitate the incorporation of such an assessment of the generalised inflammatory cell infiltrate into routine clinical practice and provide a solid platform for the further investigation of the importance of inflammatory cell infiltrate (absent–scarce/conspicuous) in determining outcome in patients with colorectal cancer.

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# Response to comment on 'Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis'

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**Sir,**

We are most grateful to Professor Park, McMillan and Roxburgh (2014) for their interest and valuable comments on our manuscript titled 'Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis' (Mei *et al*, 2014). They cited several recently published studies with consistent results, pointing out some other important relationships among inflammatory cell infiltrate, the tumour microenvironment and immune response in colorectal cancer (CRC), which were not discussed in detail in our original publication because of the length of the publication. Therefore, some major concerns, such as the following, must be addressed.

First, the analytical methods used in our publication for the generalised tumour inflammatory infiltrate were relatively standardised ones and included the Jass classification, the Klintrup—Makinen (K–M) criteria and Crohn's-like reaction criteria. The pooled hazard ratios and 95% CIs for overall survival, cancer-specific survival and disease/recurrence-free survival in a subset of highly generalised tumour inflammatory infiltrate were $<1$, indicating a robust survival marker for CRC. However, conflicting results (with HRs and 95% CI across 1) were noted among individual studies as heterogeneity originated from local inflammatory reaction grading systems, patient characteristics, follow-up schemes and some other factors, which was especially evident among individual T-cell subtypes. More detailed

stratifications by tumour location, stage, grade and other microenvironmental components should be proposed.

Second, there have been conflicting reports regarding the relationship between inflammatory cell infiltrate and local inflammatory response for CRC prognosis, justifying the need for further analyses. In our meta-analysis, we did not include some of the mentioned studies because of the following reasons.

(1) absence of time-to-event (survival) data for high-grade over low-grade immune cell inflammation (Klintrup *et al*, 2005);
(2) sharing of the same cohort (Richards *et al*, 2012a, b);
(3) investigating the outcome of tumour inflammatory cell infiltrate in primary operable invasive ductal breast cancer (Mohammed *et al*, 2012);
(4) study publication after the deadline of August 2013 (Vayrynen *et al*, 2013; Richards *et al*, 2014).

To minimise variation between studies, currently, standardised and robust methods for assessment of the generalised inflammatory cell infiltrate used in clinical practice are urgently needed. Forrest *et al* (2014) developed an automated, computer-aided scoring method that proved to be more facilitated, objective, accurate, reproducible and cost-effective than the manual method. We assumed that some larger prospective studies could be proposed to validate the robustness of association between not only the generalised inflammatory cell infiltrate but also the subsets of T lymphocytes as well and CRC survival.

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# Comment on 'Characteristics and screening history of women diagnosed with cervical cancer aged 20–29'

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**Sir,**

We agree with Castanon and her colleagues (Castanon *et al*, 2013a) that the more than two-fold increase in cervical cancers registered in women aged 25–29 years in England in the last decade cannot entirely be explained by the cessation of screening women aged 20–24 years, which was first recommended in 2003. Nevertheless, we cannot believe that policy has not had some effect on the increase. Incidence of invasive cervical cancer per 100 000 women aged 25–29 years was higher in 2011 than the previous highest level in that age group: 19.3 compared with 14.8 in 1986 (Office for National Statistics).

Since 1992, registrations in England as a whole of invasive carcinoma of the uterine cervix in women aged 25–29 years have consistently represented 3% of total registrations of invasive and *in situ* cancer combined (cervical intraepithelial neoplasia grade 3, CIN3, is registered as carcinoma *in situ*), and the two diagnoses have increased in parallel, including during the so-called 'Jade Goody effect' in 2009, which is consistent with most of these cancers being screen-detected (Figure 1). The number of increased registrations of CIN3 since 2004 in women aged 25–29 years (the peak age group for CIN3 since the late 1980s) is greater than the simultaneous decrease in women aged 20–24 years, suggesting an increased risk in women born between about 1977 and 1983 (marked '+' in Figure 1), which was before the effect of the new

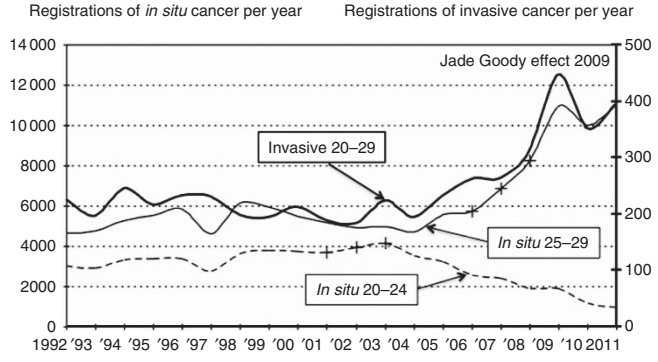


Figure 1. Registrations of *in situ* (CIN3) and invasive carcinoma of the uterine cervix in England: women aged 20–29 years in England 1992–2011 (Office for National Statistics data). '+', Women born 1977–1981, 1978–1982 and 1979–1983.

**Table 1. Treatment of stage IA cervical carcinoma compared with CIN3**

| | IA cancer (1999–2007) | | CIN3[a] (2002–2004) | |
|---|---|---|---|---|
| **Age band (years)** | | | | |
| (<25) | (3) | | (11) | |
| 20–34 | 22 | | 74 | |
| 35–49 | 16 | | 22 | |
| 50–64 | 3 | | 4 | |
| Total | 41 | | 100 | |
| **Treatment** | | **Aged 35+** | | **Aged 35+** |
| Single LLETZ | 3 | 1 | 85 | 17 |
| Two LLETZ | 0 | 0 | 7 | 3 |
| Knife cone | 18 | 6 | 2 | 1 |
| Trachelectomy | 5 | 0 | 0 | 0 |
| Hysterectomy | 15 | 12 | 6[b] | 5 |
| Total | 41 | 19 | 100 | 26 |

Invasive carcinoma diagnosed only by microscopy: maximum invasion 5.0 mm depth × 7.00 mm width.

[a]Hundred cases were selected randomly from alphabetical list of cervical intraepithelial neoplasia grade 3 (CIN3) cases treated at Guy's and St Thomas' during the middle 3-year period of our published 9-year cancer audit (Herbert *et al*, 2010).

[b]One hysterectomy was carried out for uterine fibroids in a 33-year-old woman who would otherwise have had a single large loop excision of the transformation zone (LLETZ).