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

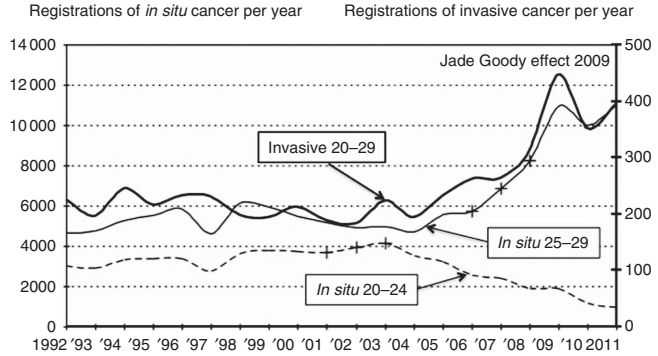

Figure 1. Registrations of *in situ* (CIN3) and invasive carcinoma of the uterine cervix in England: women aged 20–29 years in England 1992–2011 (Office for National Statistics data). '+', Women born 1977–1981, 1978–1982 and 1979–1983.

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).

policy would have taken effect. This could be related to the year on year increase in the percentage of women being sexually active before the age of 16 years: 29.2% according to the latest Natsal survey (Mercer *et al*, 2013). It seems to us feasible that failing to treat several thousand women with CIN3, along with similar numbers with CIN2 (about a third of which progress to CIN3), may have contributed to the increase in invasive cancers seen in women aged 25–29 years.

Castanon *et al* (2013a) cite an article of ours (Herbert *et al*, 2008) that provided preliminary results of a 9-year audit of 133 cervical cancers that was published in 2010 along with concurrent cases of CIN2+ diagnosed at Guy's and St Thomas' (Herbert *et al*, 2010). In that audit we defined screen-detected cancers as cases diagnosed in asymptomatic women investigated for abnormal cytology and found that 15 (83.3%) of 18 cancers in women aged 20–29 years were screen-detected IA or IB1 cancers. The treatment of IA cancer is not the same as that of CIN3 as suggested by Castanon *et al* (2013a), and the effect of a 'cancer diagnosis' on a woman as young as 25–29 years may be devastating. During the period of our audit, only 3 of 41 IA cancers had a single large loop excision of the transformation zone (LLETZ), compared with 85 of 100 cases of CIN3 (Table 1). The most frequent treatment of IA cancer was LLETZ followed by knife cone biopsy, because many of these cancers arise in widespread CIN3 that may be difficult to excise completely on a LLETZ; 5 had trachelectomy and 15 had hysterectomies. Most women with CIN3 had a single LLETZ; those who had further treatment tended to be slightly older. LLETZ is less likely to cause premature rupture of membranes than repeated or larger excisional biopsies (Castanon *et al*, 2013b).

Disallowing screening for women aged 20–24 years, whatever their clinical history of sexual activity, is an experiment that is unfortunately taking place during a period of time when there are birth cohorts at increased risk and screening coverage is falling in younger women.[7] In our opinion, the view that screening women under age 25 years causes 'more harm than good' is letting down a generation of women who are above the ages of those who will benefit from vaccination in the future.

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Response to comment on 'Characteristics and screening history of women diagnosed with cervical cancer aged 20–29'

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Sir,

Dr Herbert *et al* (2014, this issue) suggest that women in England born between 1985 and 1995 have been 'let down' by the National Health Service. It is true that most would neither have been vaccinated against HPV types 16 and 18 nor have been invited to screening between age 20–24. However, we reject the notion that they have been let down. We have estimated elsewhere (Landy *et al*, 2014) that the change in policy (inviting women for screening from age 25 instead of from age 20) will have resulted in about 2800 fewer women per 100 000 being treated for cervical intraepithelial neoplasia and have led to at most 23 extra cancers, of which between 3 and 9 would have been stage 1B or worse. We have seen no new data that would lead us to change these estimates. By way of contrast, we have also estimated that introducing a more sensitive screening test (such as primary HPV testing) in women aged 25–64 could prevent 168 cancers per 100 000 women (even without changing the coverage) (Castanon *et al*, 2013).

We agree with Dr Herbert *et al* that 1A1 cancers may sometimes be treated with a knife cone under a general anaesthetic rather than by loop excision under a local anaesthetic, but we suggest that the audit data they present are out of date and not representative of England today. In our audit, 92% (887 of 965) women aged 20–29 with stage 1A cancer diagnosed since April 2007 had a cone excision. It is difficult to believe that it is desirable to treat over 100 women with high-grade cervical intraepithelial neoplasia by a cone excision in order to prevent one case of 1A cervical cancer that will also be treated by cone excision (albeit possibly a more invasive one).

The decision to only invite women for cervical screening from age 25 is clearly emotive, but it is not helpful to refer to it as an unfortunate experiment. It was based on an independent committee's unanimous view that screening women aged 20–24 was likely to cause more harm than benefit. It was certainly not intended to be an experiment, nor does it constitute a particularly good natural experiment. Taking into account all subsequent evidence, we remain convinced that the combined effect of policies announced in October 2003 (switching from conventional cytology to liquid-based cytology; first invitation at age 25; 3-yearly screening for women aged 25–49 instead of 5-yearly, as was the practice in some parts of England; and 5-yearly screening from age 50 to 64) was for the overall good of women in England.

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