EDITORIAL

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Reproductive factors, hormones and colorectal cancer—still unresolved

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Differences in morbidity rates between males and females have been reported for many cancer sites. Specifically, in the colon, cancers in females are more commonly detected in the right colon, are more often microsatellite instable (MSI-H) and differ in clinical behaviour (Meza *et al*, 2010; Arnold *et al*, 2016). While differences in lifestyle such as smoking, alcohol consumption, occupational exposures can partly explain some of the gender difference, reproductive and hormonal factors are additional highly plausible explanatory factors. Exposure to female sex hormones was shown to be associated with cancer promotion in many leading tumour sites such as the breast, ovary, endometrium and thyroid (Santen *et al*, 2010; Xhaard *et al*, 2014; Chlebowski *et al*, 2015). The use of postmenopausal hormone replacement therapy (HRT) has been shown to increase the risk of these cancers, but not the risk of colorectal, stomach or lung cancers (Rennert *et al*, 2009; Camargo *et al*, 2012; Clague *et al*, 2014; Wang *et al*, 2016) where oestrogen exposure was associated with reduced, rather than increased, risk.

The study of the effect of hormonal and reproductive factors on cancer occurrence usually involves evaluation of reproductive characteristics of a woman, representing mostly exposure patterns to endogenous sex hormones (age at menarche and menopause, years of periods/fertility, number of pregnancies, number of births, number of children born, age at first birth, duration of breast feeding) (Peters *et al*, 1990; Kvåle and Heuch 1991; Zervoudakis *et al*, 2011; Lu *et al*, 2014), and evaluation of exposure to exogenous hormones delivered in shape of oral contraceptives, HRT or fertility-related treatments (Kampman *et al*, 1997; Martínez *et al*, 1997; Nichols *et al*, 2005; Lin *et al*, 2007; Kabat *et al*, 2008; Bosetti *et al*, 2009; Tsilidis *et al*, 2010; Li *et al*, 2013). Many methodological traps lay in the way of a scientist trying to quantitate the total hormonal exposure of an individual, and even more so if trying to compare effects between women. Some of the difficulty is the result of changes over time in the reproductive behaviour (fewer children, later age at first birth), and some are the result of change in use and content of OC and HRT (minimization of ingredient concentration, change in oestrogen/progesterone type and combination ratio). A further complication is the notion that sex hormones in the body interact with other endocrinological systems to produce a combined effect that is hard to measure.

The publication by Murphy *et al* (2017), in the current issue of BJC, is the most recent of a line of manuscripts evaluating the question at stake, using the data from the reputable observational arm of the Women's Health Initiative study. The study of a cohort of close to 100 000 women followed for more than 11 years and with >1100 colorectal cancers did not show meaningful associations between any of the studied parameters, beyond any parity, and colorectal cancer risk. It is worthwhile noticing that the studied cohort includes mostly highly educated, non-obese, white women with low smoking and alcohol consumption, and a high rate of use of HRT or hysterectomies. Surprisingly to this population prototype, more than half the women had three or more children and yet 50% of them never breastfed. Half the participants had their (natural or artificial) menopause before age 50. We are thus currently in a situation where reproductive factors representing endogenous exposures to sex hormones do not seem to show meaningful association with CRC risk. In contrast, the former data as well as the data from the WHI study (Chlebowski and Anderson, 2014) show repeatedly that use of external hormones, especially HRT, but also use of oral contraceptives, is associated with significant reduction in CRC risk.

A plausible explanation for the conflict between the lower CRC incidence following exposure to exogenous hormones, known to be carcinogenic and to increase incidence of other tumours seems to lay in a tissue-specific difference where colonic or gastrointestinal tract tissue differs from other tissues in its handling of exposure to hormones. As hormone effects on the cell are delivered through attachment to receptors, the immediate suspect is the oestrogen receptor (ER). Early studies have demonstrated the existence of both ERs and progesterone receptors in unaffected colorectal mucosa (Hendrickse *et al*, 1993; Oshima *et al*, 1999). The ERs were shown to respond to oestrogen challenge and to synthesize progesterone in tumour cells (Hendrickse *et al*, 1993). The discovery in 1996 (Mosselman *et al*, 1996) that there are actually two types of ER, alpha (Erα) and beta (ERβ), controlled by two

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different genes (*ESR1*, *ESR2*; Younes and Honma, 2011), and that ERβ is overexpressed in healthy human colon tissue (Witte *et al*, 2001) (and in oesophagus, stomach, pancreas, lung and brain; Iwao *et al*, 2001; Matsuyama *et al*, 2002; Batistatou *et al*, 2004; Liu *et al*, 2004; Abe *et al*, 2010) and has reduced expression in malignant colon tissue, suggesting that this receptor could be of importance (Kennelly *et al*, 2008; Rudolph *et al*, 2013). ER*β* is the predominant receptor expressed in both normal and malignant colonic tissue with little ER*β* expression (Elbanna *et al*, 2012). ER*β* expression is reduced during the colonic carcinogenic process (Foley *et al*, 2000, Konstantinopoulos *et al*, 2003; Thomas and Gustafsson, 2011). Thus, oestrogen signalling has an antitumourigenic role in the colonic mucosa through selective activation of proapoptotic signalling mediated by ER*β*, inhibition of inflammatory signals, and modulation of the tumour microenvironment and immune surveillance mechanisms (Caiazza *et al*, 2015). The existence of ER*β*, shown to have unique mechanisms of handling oestrogen, producing signals which lead to reduced tumourigenesis can explain the differential handling of oestrogen by different body tissues.

But if this is the case, why do we see effects with exogenous exposures but almost none with endogenous exposures? Endogenous exposures, in currently studied populations, may be of relatively low level due to low number of pregnancies in western populations. Alternatively, the endogenous effect could not be demonstrated because the studied populations were too homogeneous to allow for comparison of very high exposures with very low exposures. Or could it all be related to the activity level of progesterone depressed by the ER*β* (Sá *et al*, 2015)? Could other pregnancy-related hormones such as human chorionic gonadotropin be an important mediator of risk? If in breast cancer, the risk of exogenous exposures, by HRT, is mostly mediated through the progesterone component of the combination, could this same progesterone, and not the oestrogen, be the agent that acts inversely in the ER*β*-rich colon tissue? If this is the case, could ER*β* agonists serve as modulators of progesterone levels and serve as preventative agents in the colon?

With dozens of manuscripts on the subject and ever increasing knowledge about mechanisms of hormonal activity, the question of lower CRC risk in females and its unique presentation is still unresolved.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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