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COMMENTARY

Why are reproductive cancers more common in nulliparous women?

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Abstract It has been known for decades that nulliparity is associated with an increased risk for certain reproductive malignancies, including breast, ovarian and uterine cancers. A recent commentary in *The Lancet* summarized the available evidence based on data in nulliparous women and concluded that the risk of nulliparity was related to the increased number of ovulatory cycles, and so might be preventable by utilization of oral contraceptives. That communication described significant differences in age-dependent cancer mortality in nulliparous nuns, as well as in parous controls, between breast, ovarian and uterine cancers. Moreover, the steep inclines in cancer mortality in nuns are only observed decades after the menopause. Taken together, these observations make it appear unlikely that the number of ovulations is associated aetiologically with increased cancer risks in nulliparous nuns. Here are postulated other possible primary mechanisms that could be responsible for the reported age-related increase in cancer risks in nulliparous women, such as nuns, and conclude that a better understanding of such mechanisms may offer important new insights into tumour initiation in general.

KEYWORDS: breast cancer, breast cancer 1 (BRCA1) mutation, BRCA2 mutation, fragile X mental retardation 1 (FMR1) gene, ovarian cancer, uterine cancer

Nulliparity has for decades been known to be associated with increased reproductive cancer risks. Three recent publications in *The Lancet* offered somewhat contradictory views on the association of nulliparity in nuns and reproductive cancer risks (Britt and Short, 2012; Brosens and Benagiano, 2012; Grant and Price, 2012). The communication initiating the exchange was a commentary by Britt and Short from the Department of Anatomy and Developmental Biology, Monash and the University of Melbourne, respectively (Britt and Short, 2012). It offered a detailed discussion of the association of nulliparity with cancer risks and the potential to reduce such risks through use of oral contraceptive by reducing the number of lifelong ovulations.

The commentary received most of its attention because of the authors' provocative challenge to the Vatican to permit nuns the use of oral contraceptives in attempts to reduce cancer risks. The Vatican had condemned all forms of contraception in the Papal Encyclical *Humanae Vitae* in 1968; but, as Britt and Short (2012) noted, the document also states that '*the Church in no way regards as unlawful therapeutic means considered necessary to cure organic disease, even though they also have a contraceptive effect*'. Two accompanying responses in letter format not only disputed their conclusions but also questioned some of the underlying data that Britt and Short used in support of their arguments (Brosens and Benagiano, 2012; Grant and Price, 2012).

In trying to make sense of these contradictory statements, a figure published in the Britt and Short commentary attracted the current author's attention and is here reproduced with permission in a slightly modified format (**Figure 1**). This figure is based on data on 31,658 Catholic nuns, published in 1969 (Fraumeni et al., 1969), the validity of which has been questioned (Brosens and Benagiano,

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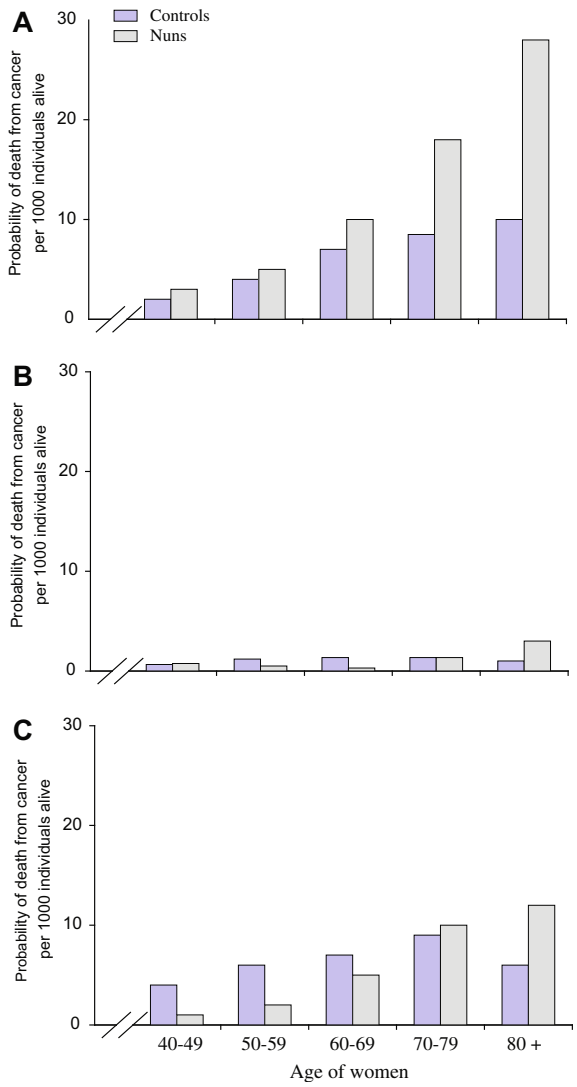

Figure 1 Comparison of three reproductive cancers in nuns and controls: breast cancer (A), ovarian cancer (B) and uterine cancer (C). This figure was modified from Britt and Short, 2012, with permission.

2012). These data do, nonetheless, offer interesting and potentially important additional insights into the association of cancer risks with nulliparity.

Figure 1 indicates significant differences in cancer death risks between nuns and controls. Not mentioned by Britt and Short and the two responses to their commentary, however, is that the age-related death patterns appear to differ greatly for breast, ovarian and uterine cancers. While breast cancer rates increase with advancing female age in controls as well as in nuns (although more markedly in nuns), ovarian and uterine cancer death rates behave distinctively differently. In controls they increase with age — with uterine cancer increasing until age 70—79, but plateauing with ovarian cancer after age 50—59 — and both decline after age 80 years. In contrast, ovarian cancer in nuns appears quite subdued until age 60—69 but then increases, while uterine cancer, similar to breast cancer, steadily increases with advancing age. It thus appears that, in nuns, breast and uterine cancers have similar age-associated mortality patterns, but differ from that of ovarian cancer. Remarkably, in nuns all three cancers demonstrate a sharp increase above age 80 years, when in control populations ovarian and uterine cancers are already again on a decline while breast cancers appear to plateau (**Figure 1**). These age-related differences are of interest because early age at first term birth has been suggested to be protective against late-onset breast cancer, but each pregnancy, in itself, including a first pregnancy, increases the risk of early-onset breast cancer (Kobayashi et al., 2012).

All of these, sometimes apparently contradictory, observations raise the question: why in these three reproductive cancers should nulliparity-associated cancer risks differ so significantly from those of parous women, when all, supposedly as suggested by Britt and Short (2012), should be the consequence of the same excess of ovulatory cycles?

At least a partial explanation may be found in the reported association of these three cancers with mutations in breast cancer 1 and 2 genes (*BRCA1* and *BRCA2*). The association of *BRCA1/2* is, of course, the highest for breast cancer, intermediate for ovarian and by far the lowest for uterine cancer (Altekruse et al., 2007; Campeau et al., 2008; Kadouri et al., 2007; Thompson and Easton, 2002). Differences in the age distribution of cancer mortality, reflected in **Figure 1**, might, therefore, at least in part, be the consequence of the differing prevalence of *BRCA1/2* mutations in these populations.

The matter may, however, be even further complicated by the still unexplained so-called '*BRCA* paradox' (Evers and Jonkers, 2006), characterized by an obvious discrepancy between tumour cells, which rapidly proliferate in the presence of *BRCA* mutations, and embryo cells, which exhibit a proliferative defect in the presence of *BRCA* mutations. The current study group recently reported that the *BRCA1/2* mutations in human embryos appear to be lethal, unless embryos are 'rescued' by presence of a *low FMR1* allele (fragile X mental retardation 1), characterized by $CGG_{n<26}$ triple-nucleotide repeats (Weghofer et al., 2012). This observation raises the possibility that *low FMR1* alleles may not only prevent *BRCA*-associated embryo lethality by countering the suppressive effects of *BRCA1/2* on embryos, but might also have similar effects on tumour cells, and, therefore, provide an explanation for the '*BRCA* paradox' (Weghofer et al., 2012).

Low FMR1 alleles can be found in approximately one-quarter of the female population and appear to be associated with significant adverse effects on female reproduction as well as an increased autoimmune risk (Gleicher et al., 2010a). Albertini in a recent editorial described the ovary astutely as an 'immunological hotspot', pointing out that immune system genes figure prominently in mouse knockout studies of ovulation (Albertini, 2012). *FMR1* genotypes and subgenotypes have recently been demonstrated to define ovarian ageing patterns, as reflected in the rate of follicle recruitment and loss over a woman's reproductive lifespan (Gleicher et al., 2010a,b). They might represent the primary link with ovulatory considerations, implied by Britt and Short to be associated with excessive cancer risk in nuns (2012).

If one assumes that the 'control population' represents the 'natural history' of age-dependent cancer deaths in a general female cohort and that the population of nuns

represents age-dependent cancer deaths in nulliparous women, then discrepancies between these two should point towards the effects of nulliparity on cancer risk at different ages. The age-dependent differences pointed out here strongly suggest that these cancer deaths differ between breast, ovarian and uterine cancers. One, indeed, can conclude from much lower ovarian cancer and uterine cancer rates in nuns up to age 60—69 years that at young ages nulliparity may, indeed, have a protective effect. Indeed, Brosens and Benagiano in their commentary noted that studies have found a general mortality advantage of Catholic nuns of approximately 20—25% over a general population (Brosens and Benagiano, 2012). However, as **Figure 1** shows, breast cancer is obviously different because, in this case, nuns remain at increased risk from a very young age onwards. **Figure 1** also shows that a large majority of cancer mortality from all three of these reproductive malignancies is postmenopausal. In the premenopausal years 40—49, nuns demonstrate mildly increased breast and ovarian cancer rates, while uterine cancers demonstrate significantly higher prevalence in controls. Since uterine cancers probably include endometrial as well as cervical cancers, and the latter's association with promiscuity is well established (Fraumeni et al., 1969; Brosens and Benagiano, 2012), the lower incidence of uterine cancers in younger nuns should not surprise. However, by age 70—79 years, the incidence in nuns is greater than in the control population (Figure IC).

What is it then that, at such very advanced female ages, suddenly there is such a pronounced increase in all three reproductive cancers? I have already postulated above about potential effects due to the interplay of *BRCA1/2* and *FMR1*, which may explain the reported statistical association with ovulatory cycles. Since there is no reason to believe that nuns and controls exhibit different prevalence patterns in *BRCA1/2* and *FMR1* genotype and subgenotype distributions, the genetic predisposition towards all three cancers is likely to be similar in both groups. Nuns, therefore, after age 70, either must be exposed to an environmental promoter or lack exposure to an inhibitor, resulting in greatly increased risks for death from all three cancers. Might the absence of life-long exposure to spermatozoa, consequential on a life of celibacy, be this environmental factor?

Spermatozoa induce distinct adaptive processes in a woman's immune system in preparation for pregnancy (Robertson, 2007). Could a life-long lack of such adaptation, in turn, increase cancer risks on a background of genetic predisposition? The use of oral contraceptives by nuns, under such a hypothesis, would be useless in affecting cancer risks.

Finally, a last rather audacious idea: is it possible that nulliparous women grow older with more remaining stem cells in reproductive organs, which, at more advanced ages, become de-inhibited and start proliferating, leading to the development of cancer? Cancer stem cells are now a widely accepted phenomenon (Castaño and Kim, 2012), and stem cells have been described in breast (Joshi et al., 2012), ovarian (White et al., 2012) and endometrial tissues (Kato, 2012). They might be a source of cancer initiation (Castaño and Kim, 2012; Christgen et al., 2012) and could also be linked to life-long ovulation patterns.

In summary, the patterns of reproductive cancer rates in nulliparous nuns do indeed support an increased lifelong cancer risk in association with nulliparity. The age distribution of these cancer risks, however, makes a direct association with number of lifelong ovulatory cycles, as suggested by Britt and Sort (2012), a rather tenuous hypothesis. A better understanding of reproductive cancer risk in association with nulliparity has the potential of offering significant additional insights into the initiation of cancer risks in general, and, therefore, warrants further investigation.

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Declaration: NG is listed a co-inventor on a number of pending US patent applications, claiming diagnostic and therapeutic benefits from determining FMR1 *genotypes and subgenotypes. He has no other potential conflicts to declare in reference to this submission.*

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