RESEARCH COMMUNICATION

Season of Birth and Risk of Endometrial Cancer

Ingrid J Rowlands[1,2*], Philip Weinstein[2,3], Christina M Nagle[1], Amanda B Spurdle[1], Penelope M Webb for the Australian National Endometrial Cancer Study (ANECS)[1] and Australian Ovarian Cancer Study (AOCS)[1]

Abstract

Objectives: Season of birth has been associated with adult morbidity and mortality, but few epidemiological studies have examined whether season of birth contributes to the development of cancer. Using data from the Australian National Endometrial Cancer Study, a population-based case-control study of 1399 cases and 1539 controls, we examined the association between season of birth and risk of endometrial cancer. Methods: Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between season of birth and endometrial cancer. Additional analyses were stratified by state of birth. Results: Season of birth was not associated with endometrial cancer overall, but there was an increased risk among women born in summer in Tasmania, the most southerly state (OR = 4.46, 95% CI: 1.24-16.06) and non-significant increases in the other southern states. Conclusion: Further data are required to confirm these findings, however the observed associations may be due to the longer days and/or greater hours of sunshine in Australia's southerly states in summer, suppressing melatonin levels in summer-born infants and predisposing them to cancer in adulthood.

Keywords: Season of birth - endometrial cancer - latitude - day length - sunshine

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Introduction

Endometrial cancer is the most common malignancy of the female genital tract, and the fourth most common cancer among women in developed countries (Amant et al., 2005). Studies investigating the risk factors for endometrial cancer have focused on reproductive factors (early menarche, late menopause, nulliparity), exogenous hormonal factors (use of hormone replacement therapy [HRT] and oral contraceptives [OC]), physical health (obesity, diabetes) and health behaviours (diet, physical inactivity) (Amant et al., 2005). However, environmental factors have rarely been investigated, despite increasing evidence that environmental factors in early pre- and postnatal life have significant impact on the development of disease in later adulthood (Barker, 2004).

An increasing number of studies suggest that season of birth may be an important environmental predictor of disease. Season of birth has been implicated in the onset of cardiovascular disease (Reffelmann et al., 2011) schizophrenia (Davies et al., 2003), neurological disorders such as epilepsy (Torrey et al., 2000), natural reproductive events such as age at menarche (Matchock et al., 2004) and menopause (Cagnacci et al., 2005). It may also predict a woman's lifetime fecundity (Huber et al., 2008; Kemkes, 2010). Over a decade ago, a Swedish study reported an increased risk of breast cancer among summer-born women (Yuen et al., 1994). Since then, most epidemiological studies have focused on the seasonal variations in cancer survival (Porojnicu et al., 2007). However, more recent evidence suggests that an adult's life expectancy may be influenced by their month of birth, such that individuals born in late spring/early summer may have shorter lifespans than those born in autumn/early winter (Doblhammer and Vaupel 2001; Reffelmann et al., 2011). Thus, season of birth appears to be linked to morbidity and mortality.

Melatonin might be an important mechanism explaining the relationship between season of birth and cancer. Higher levels of this seasonally variable hormone have been associated with a reduced risk of breast cancer (Schernhammer and Hankinson, 2005) suggesting that it may be a potential tumour suppressor (Stevens, 2005). Melatonin is transferred from the mother to the fetus in-utero then, after birth, melatonin secretion begins at 12 weeks of age and is stimulated by darkness (Okatani et al., 1998). Researchers have found that infants' pineal glands are sensitive to light immediately after birth, with infants showing increases in plasma melatonin levels in response to light deprivation at birth (Jaldo-

*[1]Genetics and Population Health, Queensland Institute of Medical Research, [2]School of Population Health, University of Queensland, Brisbane, [3]Barbara Hardy Institute, University of South Australia, Adelaide, Australia *For correspondence: Ingrid.Rowlands@qimr.edu.au*

Alba et al., 1993). Thus, summer-born infants might have lower levels of plasma melatonin as a result of the longer daylight hours in summer, and this may increase their risk of cancer in adulthood. Melatonin may also be particularly relevant to the aetiology of endometrial cancer, as lower concentrations of melatonin are thought to increase oestrogen levels (Stevens, 2005), and unopposed oestrogen is the primary factor involved in the development of endometrial cancer (Amant et al., 2005). Season of birth may also be associated with cancer risk because of its potential effect on onset of reproductive events in women. In light of suggestive evidence in the literature, and a biologically plausible link through melatonin, we examined for the first time whether there was an association between season of birth and risk of endometrial cancer, and whether this association was influenced by reproductive factors.

Materials and Methods

Study participants

The Australian National Endometrial Cancer study (ANECS) was a large Australia-wide, population-based, case-control study of endometrial cancer conducted between July 2005 (May 2005 in Queensland) and December 2007. Women aged 18-79 years, who were diagnosed with incident endometrial cancer during this period were recruited by nurses who liaised with the treatment clinics, physicians and state-based cancer registries across Australia. Of the 2231 eligible women who were invited to participate, 1497 (67%) agreed to take part in the study. Of these, 39 were subsequently excluded (not primary endometrial cancer; diagnosed outside the study period) thus, the final sample comprised 1458 eligible women, 1399 (96%) of whom completed an interview and 1011 of whom were born in Australia. Women in the control group were recruited from the national electoral roll (enrolment to vote in Australia is compulsory). The control women were matched to the state of residence and age distribution (in 5-year bands) of the women with cancer. Half (50%) of the women contacted participated in the study, giving a total of 1539 women in the control group. Of these, 1154 were Australian-born. This study was approved by the Human Research Ethics Committees at the Queensland Institute of Medical Research and all participating hospitals and cancer registries.

Table 1. Latitudes of Australian Capital Cities and the Corresponding Day Length and Hours of Bright Sunshine in Winter and Summer

Capital City and State	Latitude	Day length (winter vs. summer, hours)	Sunshine (winter vs. summer, hours)
Brisbane, Queensland	-27.48	11h30 vs. 13h52	7 vs. 7
Perth, Western Australia	-31.95	11h24 vs. 14h14	5 vs.10
Sydney, New South Wales	-33.87	11h20 vs. 14h24	6 vs. 7
Adelaide, South Australia	-34.93	11h18 vs. 14h30	4 vs. 9
Melbourne, Victoria	-37.82	11h13 vs. 14h47	3 vs. 8
Hobart, Tasmania	-42.88	11h03 vs. 15h21	4 vs. 7

Day Length, Maximum day length; Sunshine, Average daily sunshine hours; Data from the Australian Government Bureau of Meteorology (2010) and Geoscience Australia (2011)

Statistical analysis

We restricted our analyses to women born in Australia and 4 women (3 cases, 1 control) who were born in the Northern Territory were excluded from all analyses. In Australia, the seasons are defined as: summer (December-February), autumn (March-May), winter (June-August) and spring (September-October). It is also important to note that Australia is a large continent, and so day length and hours of sunshine tend to vary across the Australia states, particularly in summer as a result variations in cloud cover (Table 1). In each state the majority of the population live in or around the capital city. Descriptive characteristics of cases and controls were compared using

Table 1. Odd ratios for Season of Birth and Relationship to Endometrial Cancer for Australian-born Women, Stratified by State

		Cases (n=1008)	Controls (n=1153)	OR[a] (95% CI)	OR[b] (95% CI)
Season of birth[c]	Spring	236 (24)	311 (27)	0.86 (0.66-1.12)	0.89 (0.67-1.04)
	Summer	267 (26)	262 (23)	1.13 (0.87-1.48)	1.21 (0.91-1.61)
	Autumn	246 (24)	275 (24)	1	1
	Winter	259 (26)	305 (26)	1.05 (0.81-1.37)	1.12 (0.85-1.48)
State of birth					
QLD	Spr/Aut/Win	184 (76)	202 (75)	1	1
	Summer	55 (23)	67 (25)	0.87 (0.56-1.35)	0.97 (0.61-1.55)
WA	Spr/Aut/Win	43 (61)	71 (81)	1	1
	Summer	27 (39)	17 (19)	1.91 (0.82-4.47)	1.64 (0.62-4.37)
NSW	Spr/Aut/Win	203 (71)	243 (75)	1	1
	Summer	82 (29)	83 (25)	1.09 (0.74-1.62)	1.01 (0.66-1.54)
SA	Spr/Aut/Win	78 (75)	84 (74)	1	1
	Summer	27 (25)	30 (26)	1.24 (0.63-2.43)	1.31 (0.78-2.19)
VIC	Spr/Aut/Win	179 (78)	232 (81)	1	1
	Summer	51 (22)	53 (19)	1.13 (0.71-1.80)	1.30 (0.62-2.72)
TAS	Spr/Aut/Win	37 (65)	46 (88)	1	1
	Summer	20 (35)	6 (12)	4.94 (1.41-17.35)	4.46 (1.24-16.06)

State of birth is ordered by the latitude of each state's capital city; [a]Adjusted for age (years), BMI (kg/m^2), state of residence (QLD, NSW, SA/WA, VIC/TAS); [b]Additionally adjusted for age at menarche (years), age at menopause (Premenopausal, ≤44, 45-54, ≥55), duration of OC use (No, < 60 months; ≥60 months), parous (yes/no), HRT use (≥ 3 months, < 3 months); [c]Additionally adjusted for state of birth (QLD, NSW, VIC, SA,WA, TAS)

$\chi 2$ trend tests for categorical ordinal variables, $\chi 2$ tests for association for categorical nominal variables and t-tests for continuous variables. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between season of birth and endometrial cancer, using autumn as the reference category to be consistent with previous research. We adjusted for age (years), body mass index [BMI (kg/m2)], and state of residence at diagnosis [Queensland (QLD), New South Wales (NSW), South Australia (SA)/Western Australia (WA), Victoria (VIC)/Tasmania (TAS)] and further adjusted for reproductive variables including: age at menarche (in years), age at menopause (≤44, 45-54, ≥55), parity (yes/no), OC duration (never/ < 60 months/ ≥ 60 months), and HRT use (≥ 3 months, < 3 months). Additional analyses were stratified by state of birth (QLD, NSW, SA/WA, VIC/TAS), because seasons differ across the states in Australia. All statistical analyses were performed using SAS version 9·1 (SAS Institute Inc., Cary, NC, USA).

Results

We found no significant variations in BMI, age at menopause or parity by season of birth for women in the control group (results not shown), although spring-born women reported a slightly later age at onset of menarche than autumn-born women (13.15 years vs. 12.75 years, respectively, $p = 0.007$). Overall, season of birth was not significantly associated with risk of endometrial cancer (Table 2). However, there was a non-significant 20% increase in risk for women born in summer compared to autumn (Adjusted OR = 1.21, 95% CI: 0.91-1.61). When we stratified by state of birth we found a significantly increased risk for women born in Tasmania in summer (OR = 4.46, 95% CI: 1.24-16.06) and non-significant increases for women born in WA, VIC and SA. There was no association for women born in QLD or NSW.

Discussion

In this large, Australian case-control study of endometrial cancer, we found no clear association between season of birth and endometrial cancer risk. However, when we stratified by state of birth we found an increased risk of endometrial cancer among women born in summer in Tasmania, the Australian state with the highest latitude (39-43 degrees south). Similarly, women born during summer in other Australian states with higher latitudes (South Australia, Victoria) had a somewhat greater risk of endometrial cancer than women born in the other seasons, however, there was no evidence of an association between season of birth and endometrial cancer for states at lower latitudes (Queensland, New South Wales). Women born in Western Australia (WA) in summer also had a non-significant increased risk of endometrial cancer. Although Perth, the capital city of WA, has a similar latitude to Sydney in New South Wales, Perth has slightly more hours of bright sunshine in summer than the other states because of the reduced cloud cover.

Our findings, and also those from a Swedish study (Yuen et al. 1994), suggest that women born in higher latitudes during summer may have an increased risk of hormonally driven cancers, such as breast and endometrial cancer. The reason for this association is not clear but it may involve a complex interplay between light, neuroendorine hormones (e.g. melatonin) and also an individual's circadian rhythm (Stevens, 2005; Viswanathan et al., 2007). Theoretically, longer day length at higher latitudes in summer would suppress melatonin, which may result in an increased risk of reproductive cancers. Alternatively, the season of conception may be more important than the season of birth. Specifically, women born in Australia in summer would have been conceived in the darker months and environmentally driven factors (e.g. maternal vitamin D, infection) during this early in-utero period may be more critical to adult health outcomes (Barker, 2004; Finch and Crimmins, 2004). It is also possible that our results are due to chance given the small numbers of women born in summer in Tasmania, however, it is interesting that we do see a similar trend in the other southerly states. Longitudinal research that is able to reliably measure in-utero exposures (e.g. maternal nutrition and disease), in addition to infant and adult environmental exposures (including both day length, hours of sunshine), will be important for understanding the individual variability in the onset of cancer and other diseases.

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