Journal of Carcinogenesis & Mutagenesis

Olsson, J Carcinog Mutagen 2019, 10:4

Mini Review Open Access

Is Cyclic Stimulation of the Breast Epithelium the Key Hormonal Factor Behind Breast Cancer?

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Received Date: September 20, 2019; **Accepted Date:** October 07, 2019; **Published Date:** October 15, 2019

Abstract

Exposure to many regular menstrual cycles during a life time or many cycles before first full term pregnancy may be a key factor behind the hormonal stimulation of the breast epithelium and the hormonal carcinogenesis. Most of the risk factor studies on the breast cancer and cycle characteristics were done before 2010. A consistent picture emerges that many regular cycles is an important risk factor and that early age at menarche, late menopause, few children, and late age at first full term pregnancy, short nursing and a short interval between onset of menses and establishment of regular menses may be surrogates for this risk. A majority of studies have been retrospective often using for cycles average cycle length recorded at one occasion. There is a great need to do large prospective studies following women for a life time. Valid data on menstrual cycle characteristics is needed for creating optimal risk factor models.

Keywords: Menstrual cycle; Menopause; Progestins; Luteal phase

Introduction

Proliferation in a tissue is strongly related to the cancer risk of an organ. Proliferation of the breast mainly takes part in the luteal phase of the menstrual cycle. During the luteal phase the progesterone exposure is highest and studies have implicated progesterone/progestins to be of great importance for breast carcinogenesis in relation to OC use, HRT use, and BRCA1 carcinogenesis [1-12].

The menstrual cycle varies mainly in different length of the follicular phase, while the luteal phase is rather constant. Therefore women with short cycles go through more time in the luteal phase and are exposed to a higher epithelial proliferation with more cells entering and going through the cell cycle than in women with longer cycle length.

Review and Discussion

Studies on direct menstrual cycle characteristics are few and mainly done before 2010. We pioneered the research 1983 by showing that the risk of breast cancer was associated with regular and short menstrual cycles [13]. In a later study we found that the number of cycles before first full term pregnancy was a very important risk factor [14].

Being retrospective and using average menstrual cycle length a consistent picture emerges that many regular cycles either before first full term pregnancy or during life time are associated with a higher risk for breast cancer [13-26]. Surprisingly only studies of surrogates of the menstrual cycle have been done during recent years.

In Table 1 factors directly or indirectly affecting the menstrual cycle in relation to breast cancer risk are presented. Do these indirect risk factors (probably surrogates of cycle activity) fit into the picture? An increased risk of breast cancer with OC use has been found both for a combination of estrogen/progestin or progestin only administration [12]. It will be of importance to elucidate if this risk mainly operates in women with natural long cycles and who, when taking hormones, shorten their cycle length or continuously is exposed to progestins.

Further HRT given at menopause expands the menstrual span and the breast cancer risk is higher for HRTs combining estrogen and progestins compared with estrogen only drugs [8-11]. An early age at menarche expands and a late menopause expands the menstrual span with exposure to more cycles. This is also true for a short interval between onset of menses during puberty and establishment of regular menses. Also women being nulliparous, having few children or a late age a first full term pregnancy are exposed to more cycles life time or early in life.

During nursing especially when complete both during day and night time menstrual cycle activity is suppressed and resumes when nursing ends. Protective factors of breast cancer also fit into cycle picture. Castration ends cyclic activity from the ovaries [27]. A high physical activity is associated with irregular or no menses [28]. A low BMI are associated with irregular or no menses [29]. Cystic ovarian and breast disease often linked to irregular cycles are both protective for breast cancer [30].

Also reducing the menstrual span by early, late menarche and early menopause, and long nursing show protection [31-34]. Avoiding hormonal exposures with progestins may be very fruitful ways to prevent breast cancer except in women with normally short cycles where OCs should be used to prolong cycles.

Concern has been raised about different bias operating when recording cycle characteristics retrospectively [35,36].

Increased risk of breast cancer	Decreased risk of breast cancer
Short cycle length	Long cycle length
Regular cycles	Few life time cycles or few cycles before first full term pregnancy
Many cycles during life time or before first full term pregnancy	Oral contraceptive use in women with short cycles giving a woman longer artificial cycles
Expanding menstrual span by HRT use peri- and postmenopausally	Surrogates:
Oral contraceptive use in women with long cycles giving a woman shorter artificial cycles	Late age at menarche
Surrogates:	Early menopause
Early age at menarche	Castration
Late menopause	Many children, early age at first full term pregnancy
Few children, late age at first full term pregnancy	Long nursing
Short nursing	Long interval between onset of menses and establishment of regular menses
Short interval between onset of menses and establishment of regular menses	Physical activity associated with irregular or no menses
Hormonal measurement at one occasion.	A low BMI associated with irregular or no menses
	Cystic ovarian and breast disease often linked to irregular cycles

Table 1: Factors directly or indirectly affecting the menstrual cycle in relation to breast cancer risk.

Conclusion

It is therefore of outmost importance to design prospective studies where data is collected yearly during a life time. It is conceivable that the risk of menstrual cycle activity in relation to breast cancer risk is underestimated due to imprecise measurements and mainly retrospective assessment at one occasion. The risk factor information is needed for creating optimal risk factor models. Hormonal intervention in a woman to prevent breast cancer also needs to take her normal hormonal status into account.

Acknowledgement

Supported by grants from the Swedish Cancer Society, The Berta Kamprad Foundation and local hospital funds.

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