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Original Article

Oncology Section

Age at Menarche as a Navigator of Gallbladder Cancer: A Case-control Study

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ABSTRACT

Introduction: Age at menarche is said to be a risk factor for Gallbladder Cancer (GBC). The available research about the association of age at menarche with GBC, by taking a cut-off age of 13 years, is neither uniform nor consistent and at best inconclusive.

Aim: To evaluate the association between age at menarche and the risk of GBC, based on cut-off age of 13 years and treating age at menarche as a continuous variable.

Materials and Methods: A hospital based case-control study was conducted on 92 female patients and 92 female controls. The data was collected from the Department of Surgical Oncology, Sir Sunderlal (SS) Hospital, Banaras Hindu University, Varanasi, Uttar Pradesh, India during the period of October 2018 to June 2019. Logistic regression analysis was performed and Adjusted Odds Ratio (AOR) with its 95% CI (Confidence Interval) was obtained.

Results: In the present study, the mean age of GBC cases and control were 56.84±8.74 years and 51.21±6.37 years, respectively. With the reference category of menarche age, the females with menarche age >13 years were insignificantly at lower risk of incidence of GBC (AOR=0.569; 95% CI: 0.263-1.233). But when age at menarche was considered as a continuous variable; the AOR was significantly lower among females found decreasing with increasing age at menarche (AOR=0.798; 95% CI: 0.666-0.955).

Conclusion: This exercise indicates, using a reference category of continuous measurements obtained result may be inconclusive with an influence of subjective decision making so it is suggested to prefer the recorded discrete continuous value for the analysis procedure.

Keywords: Reference category, Reproductive duration, Risk

INTRODUCTION

The GBC is a biliary tract malignancy with poor prognosis and is diagnosed at later stage. The incidence is much higher among females and in India it is comparatively higher in the northern states [1,2]. The development of GBC is a multifactorial process, associated with a variety of risk factors in females e.g., age at menarche, age at first birth, age at last birth, age at menopause, abortions and parity [3-6]. GBC is associated with repeated exposure of female sex hormones and among these, age at menarche has been identified as an important risk factor which is the marker of change in hormonal status. The identified associated risk factor of GBC was pointed towards imbalance of hormones e.g., endogenous oestrogen and progesterone [7].

Menarche is the most commonly remembered milestone of puberty and a signal of reproduction process [8-10]. Earlier the age at menarche, earlier may be the entry in reproduction process [11] which may lead to the higher reproductive span of life resulting to producing more children [12]. Some studies reported higher age at menarche (>13 years) as a risk factor [3,4] while some others reported a lower age at menarche (<13 years) as responsible for increased risk of GBC [5,6]. Andreotti G et al., found 1.82, 1.80 and 1.75 folds of higher risk for GBC among those who had menarche at age ≥17 years, between 16-17 years and between 14-15 years, respectively, when compared with those of menarche age at ≤13 years [13]. While Tyagi B et al., reported increase in risk of GBC with the increase in the age at menarche but the association was not statistically significant [4].

These varied findings do not enable the researchers to make a decision whether age at menarche is a risk factor or not. The studies evaluated the risk of GBC considering an age as the reference category [3-6]. Since, the period of recall to respond age at menarche is very high, so the collection of data on discrete value of age at menarche is more appropriate to consider in the analysis. Therefore, the present study was undertaken to compare the decision emerging by choosing the reference category and by using the usual recorded data as the continuous variable to guard the researchers for making a decision on whether age at menarche could be a risk factor of GBC or not. The following two approaches were used:

1. By taking a reference category of age at menarche.
2. By taking age at menarche as the continuous variable.

The aim of the present study was to identify the association of age at menarche with GBC.

MATERIALS AND METHODS

The present study was a hospital based case-control study conducted in the Department of Surgical Oncology at the tertiary care university hospital of Banaras Hindu University, Varanasi, Uttar Pradesh, India, during the period of October 2018 to June 2019. The study was ethically approved by the Ethics Committee of the Institute of Medical Sciences, BHU, Varanasi, Uttar Pradesh, India. (Letter number: No. Dean/2018/EC/910).

Sample size calculation: The sample size was obtained by using the formula for cases control studies with equal number of cases and controls i.e., control to cases ratio (r) was 1. At level of significance 5% (i.e., α=0.05) and power (1-β)=0.90, Using 42% females with their menarche age ≤13 years and anticipated odds ratio=2.64 [6], p1 was calculated as 66%. So; the sample sizes of cases and controls computed were 92 each. Sample size was calculated using the formula [14]:

$$n=\frac{(r+1)}{r}\times\frac{\{p(1-p)\}\ (Z_{\alpha/2}+Z_{1-\beta})^2}{(p1-p2)^2}$$

Inclusion criteria: Ninety-two consecutive incident GBC cases were taken from the Outpatient Department (OPD) of Surgical Oncology and 92 female controls taken who were either female attendant of the patient or the females of other OPD suffering with some minor illnesses. The criterion for the selection of cases was

that she was a proven GBC case by histopathology/cytopathology. Both cases and control having age more than 40 years were included in the study.

Exclusion criteria: Patients who had undergone any GBC specific treatment or suffered from any major chronic illness in the past or those who had not given informed consent to participate in study were excluded from the study.

Before collecting the information, an informed consent was obtained from each participant after explaining the objective of the present study. A semi-structured questionnaire was administered to each individual to collect all the required information related to demographic and reproductive history such as present age, age at menarche, age at first birth, menopausal age, number of live births and foetal loss. The primary interest of the present study was to establish the association of GBC with age at menarche, hence other variables e.g., reproductive duration, duration between age at menarche and age at first birth, foetal loss and menopausal status were considered as the confounding variables. These confounders were directly linked with number of pregnancies subsequently to the hormonal changes.

STATISTICAL ANALYSIS

The logistic regression analysis was performed with the two approaches; first in which age at menarche was considered with a reference category and second by considering age at menarche as the continuous variable. Finally, the AOR with 95% CI was obtained. Statistical tests were performed using Statistical Package for the Social Sciences (SPSS) version 20.0 software.

RESULTS

In the present study, the mean age of GBC cases was significantly higher (56.84±8.74 years) than the controls (51.21±6.37years); while mean menarche age was significantly lower in cases (13.65±2.11 years) than the controls (14.63 ±2.15 years). The mean age at first birth among cases was also significantly lower (19.08±2.24 years) than the controls (20.48±3.38 years). Mean age at last birth among cases and controls were 31.88±5.37 years and 28.09±4.10 years. The mean live births were significantly higher in cases (5.15±1.63 years) than the controls (3.21±1.38 years).

The mean reproductive duration was significantly higher in cases (12.80±5.00) years as controls (7.61±4.37 years). Average duration between age at menarche and the first birth was lower (5.43±2.35 years) among the cases than the controls (5.85±3.33) years [Table/Fig-1]. The proportion of women with the incidence of foetal losses (either abortions or still birth) was 32.6% among cases which was lower than the controls (43.5%) but not statistically significant. Menopausal females were significantly higher in cases (95.7%) as compared with controls (84.8%).

Variables	Cases Mean±SD	Control Mean±SD	Independent t-test p-value (t-value)
Present age (years)	56.84±8.74	51.21±6.37	0.0001 (4.99)
Age at menarche (years)	13.65±2.11	14.63±2.15	0.002 (-3.11)
Age at first birth (years)	19.08±2.24	20.48±3.38	0.001 (-3.31)
Age at last birth (years)	31.88±5.37	28.09±4.10	0.0001 (5.38)
Age at menopause** (years)	45.46±3.55	45.86±3.51	0.469 (-0.73)
Reproductive duration (years)	12.80±5.00	7.61±4.37	0.0001 (7.49)
Duration from menarche age to first birth (years)	5.43±2.35	5.85±3.33	0.323 (-0.99)

[Table/Fig-1]: Descriptive statistics of menstrual and reproductive variables of cases and controls.
**Among the total sample; 88 GBC cases and 78 controls were menopausal

The adjusted OR when age at menarche was used with its reference category as ≤13 years and >13 years; the risk of GBC, though lesser by 43.1% among females with age at menarche >13 years (OR=0.569) compared to <13 years; but statistically it was insignificant (95% CI: 0.263-1.233). While, increasing age at menarche indicated the protective effect when considered as a continuous variable (AOR=0.798; 95% CI: 0.666-0.955). This explains that for each unit increase of age at menarche, the risk of occurrence of GBC will reduce by 20% [Table/Fig-2].

Variables		AOR (CI)*	AOR (CI)**
Age at menarche	>13 years	0.569 (0.263-1.233)	0.798 (0.666-0.955)
	≤13 years	1	
Reproductive duration#		1.275 (1.166-1.394)	1.271 (1.163-1.389)
Duration from menarche age to first birth		1.033 (0.904-1.181)	0.995 (0.866-1.144)
Foetal loss (abortion or still birth)	Occurred	0.501 (0.246-1.018)	0.480 (0.234-0.985)
	Did not occur	1	1
Menopausal status	Occurred	3.484 (0.908-13.374)	3.627 (0.934-14.083)
	Still menstruating	1	1

[Table/Fig-2]: Association of GBC with age at menarche.
#Duration between age at last birth and age at first birth; *Menarche age with a reference category; **Menarche age treated as a continuous variable

DISCUSSION

Menarche is considered to be the milestone of ovulation initiation which is the result of hormonal changes [15]. The association between hormonal risk factors and GBC could be partly attributed to the oestrogen in absence of sufficient progestin [16-18]. Puberty and menarche result from the changes in the hormone levels of oestrogens, androgens and progesterone which secret in increasing amounts from the ovaries and adrenal glands [19]. In the present study, the role of age at menarche to GBC was investigated because of two reasons; first the contrasting findings in the studies for the same reference category of age at menarche in the same region [3,5] and secondly since reference category suffer with loss of information when a continuous variable is recorded as a discrete variable and reference category is defined. For example, age at menarche which was collected as the integral values, we cannot choose the reference category in fraction, though it must be in fraction for valid risk assessment. The present study compared the decisions emerging when the data was analysed using reference category of age at menarche and when treated as the continuous variable adjusted for confounding variables. The mean age at menarche among GBC females was lower (13.65±2.11) years than the controls (14.63±2.15) years; similar to other studies [3,5]. The lower age at menarche among GBC cases signify that early age at menarche could be a risk for GBC.

Following the same reference category of age at menarche (≤13 years and >13 years) the present study, indicated (statistically) no role of age at menarche on the incidence of GBC, though AOR was nearly half (0.569); but when age at menarche was treated as the continuous variable, significant contribution to the incidence of GBC was found. As the age at menarche increased, the risk of occurrence of GBC decreased; for each unit increase of age at menarche, a reduction of 20% in the occurrence of GBC was found (AOR=0.798; 95% CI: 0.666-0.955). Shukla VK et al., and Tamrakar D et al., reported females with age at menarche <13 years were at higher risk of GBC [5,6]; while Pandey M reported females of age at menarche >13 years were at higher risk of GBC [3]. The contrasting findings are perhaps due categorisation with invalid choice of reference category.

Limitation(s)

Measuring age at menarche using recall method is said to be influenced by error of poor memory. However, the error may be minimum as menarche is one of the important events in female's life cycle.

CONCLUSION(S)

The present study indicates that, using a reference category of continuous measurements, which is likely to suffer from the information loss, may not be robust. Instead, one should treat the continuous measurements as the continuous variable in the analysis. In the present study, it was observed that the age at menarche was lower among GBC cases showing that early age at menarche could be a risk for GBC.

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