Evolution of age at menarche and at onset of regular cycling in a large cohort of French women.

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Evolution of age at menarche and at onset of regular cycling in a large cohort of French women

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Abstract

Background: Early exposure to ovarian hormones is considered to increase breast cancer incidence. The age at which the ovaries become functional is thus important. **Methods**: We explored the evolution of age at first menstruation and at onset of regular cycling on 86,031 women participating in the E3N-EPIC cohort study, part of the European Prospective Investigation into Cancer. **Results**: We observed an increase in mean age at menarche among women born between 1925 and 1930, followed by a steady decrease in the youngest birth cohorts. In contrast, age at onset of regular cycling increased gradually from 1925 onwards. There was thus a steady increase in the interval between age at menarche and at onset of regular cycling, mainly due to an increase in the percentage of women in whom regular cycling started at least 5 years after menarche (from 9.0% among women born in 1925-29 to 20.8% in those born in 1945-50). The increase in the interval between menarche and onset of regular cycling was even greater among women with a late menarche. **Conclusions**: This increase might be due to a change in dietary intake and/or physical exercise aimed at achieving the slim silhouette desired by the younger generations.

Keywords: cohort study/evolution/menarche/menstrual cycle

Introduction

Early exposure to ovarian hormones increases the period during which women are exposed to risk factors for diseases related to oestrogen concentrations, such as breast cancer (Bernstein and Ross, 1993). Age at menarche has long been acknowledged as a risk factor for breast cancer. Convincing evidence exists in the literature showing a reduction in breast cancer risk with increasing age at menarche (Kelsey *et al*., 1993; Butler *et al*., 2000), apparently greater for breast cancers diagnosed early or before menopause rather than when diagnosed after. However, most authors have focused on age at first menstruation, while few studies (Brinton *et al*., 1988; Garland *et al*., 1998; Rockhill *et al*., 1998; Titus-Ernstoff *et al*., 1998; Butler *et al*., 2000) have been concerned with age at onset of regular cycling.

As the evolution of these factors may influence the breast cancer burden, we examined both age at first menstruation and age at onset of regular cycling in a large sample of women participating in the E3N-EPIC cohort study, which is part of the European Prospective Investigation into Cancer (Riboli *et al*, 1992).

Materials and methods

The cohort is composed of women living in France and insured with the Mutuelle Générale de l'Education Nationale, a national health insurance plan covering mostly teachers. They were aged 40-65 years at baseline in 1990. The main objective of the cohort is to identify risk factors for cancer and other diseases (especially cardiovascular diseases, diabetes and osteoporosis) (Clavel-Chapelon, 1997).

For this analysis, we examined answers to the following questions: "How old were you when you had your first menstrual period?" and "How old were you when your periods became regular?". Answers ranged from 7 to 20 years of age for the first question and 7 to 25 for the second question, with additional possibilities for women who had never menstruated or who had never had regular periods.

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Results

A total of 86,031 questionnaires were received. Twenty-three respondents had never menstruated, while 85,683 specified an age at menarche and are considered in the following analysis. The evolution of age at menarche by year of birth is shown in Figure 1. It increased among women born between 1925 and 1930, then decreased among those born between 1930 and 1945, increased again slightly in 1946-47 and subsequently decreased again.
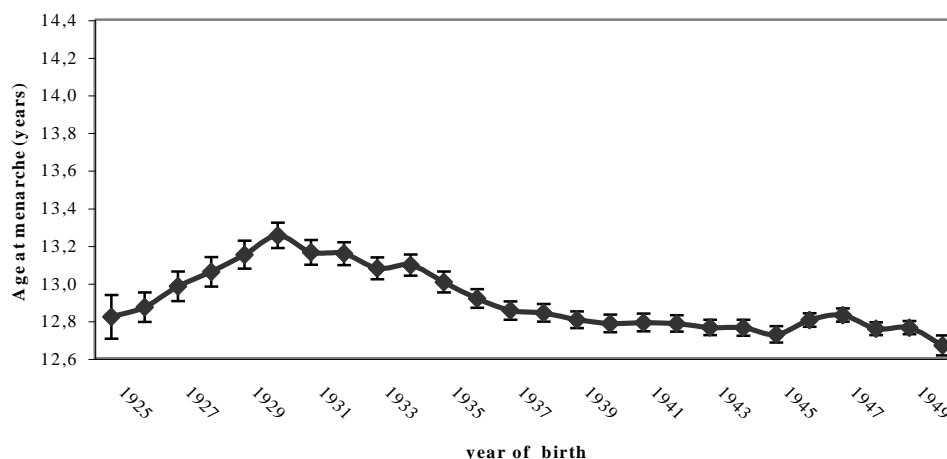

Figure 1. **Evolution of age at menarche by birth cohort in the E3N-EPIC population (*n=85,683*).**

As regards age at onset of regular cycling, 53,272 women gave an age when regular menstruation started, 7,707 reported they had never had regular menses, 1,584 gave incoherent answers (e.g. below age at menarche), 15,515 did not remember and 7,605 did not specify an age. The evolution of age at onset of regular cycling according to year of birth was thus calculated using data from 53,272 women. It increased steadily from 1925 onwards (Figure. 2).
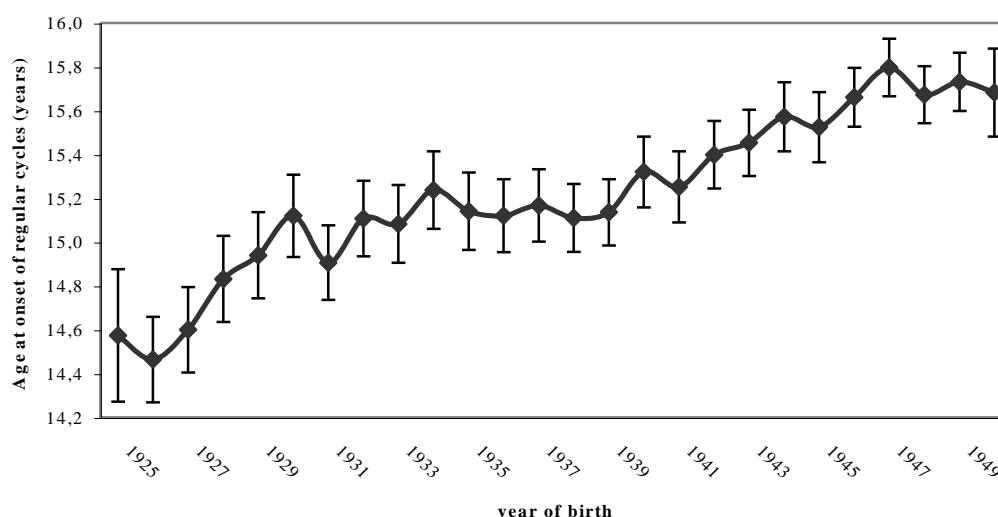

Figure 2. **Evolution of age at onset of regular cycles by birth cohort in the E3N-EPIC population (*n=53,272*).**

The distribution of age at menarche and age at onset of regular cycling in the overall population and by birth cohort is shown in Tables I and II. Among women born between 1925 and 1930, 15.6% experienced menarche at 11 or earlier and 16.4% at 15 or later; among those born between 1946 and 1950, the respective proportions were 17.9% and 9.4%. Likewise, among women born between 1925 and 1930, regular cycling started at 12 or earlier in 17.4% and at 19 or later in 8.4%; among those born between 1946 and 1950, the respective proportions were 17.6% and 18.1%. Indeed, the proportion of women for which menarche and regular cycling occurred late in life is different between older and younger generations, whereas the proportion of women for which these events occurred early is similar between generations.

Table I. **Distribution of age at menarche of regular cycling in the E3N-EPIC population.**

Age at menarche (years)	All women (*n* = 85,706)	Percentage (number) of women born between:				
		1925-1930 (*n* = 8,782)	1931-1935 (*n* = 11,756)	1936-1940 (*n* = 17,295)	1941-1945 (*n* = 20,971)	1946-1950 (*n* = 26,902)
<11	3.4 (2,892)	2.7 (232)	2.4 (277)	3.4 (588)	4.0 (842)	3.5 (953)
11	13.9 (11,907)	12.9 (1,135)	11.1 (1,305)	13.9 (2,397)	15.3 (3,198)	14.4 (3,872)
12	24.6 (21,073)	22.6 (1,987)	21.6 (2,537)	25.2 (4,354)	25.4 (5,326)	25.5 (6,869)
13	26.0 (22,238)	25.0 (2,193)	26.6 (3,131)	25.7 (4,449)	25.1 (5,261)	26.8 (7,204)
14	20.8 (17,846)	20.4 (1,792)	23.3 (2,735)	21.0 (3,640)	20.0 (4,205)	20.4 (5,474)
15	7.7 (6,611)	10.1 (889)	10.0 (1,179)	7.5 (1,297)	7.0 (1,471)	6.6 (1,775)
16	2.5 (2,147)	4.1 (362)	3.3 (386)	2.4 (411)	2.2 (459)	2.0 (529)
>16	1.1 (969)	2.2 (189)	1.7 (201)	0.9 (159)	1.0 (202)	0.8 (218)
Never	0.0 (23)	0.0 (3)	0.0 (5)	0.0 (0)	0.0 (7)	0.0 (8)

Table II. **Distribution of age at onset of regular cycling in the E3N-EPIC population.**

Age at onset of regular cycling (years)	All women (*n* = 60,979)	Percentage (number) of women born between:				
		1925-1930 (*n* = 6,315)	1931-1935 (*n* = 8,509)	1936-1940 (*n* = 12,492)	1941-1945 (*n* = 14,857)	1946-1950 (*n* = 18,806)
<13	17.8 (10,855)	17.4 (1,102)	14.4 (1,220)	18.1 (2,257)	20.0 (2,971)	17.6 (3,305)
13-14	31.0 (18,880)	33.6 (2,121)	33.0 (2,811)	31.5 (3,931)	29.8 (4,428)	29.7 (5,589)
15-16	17.7 (10,795)	20.2 (1,277)	20.5 (1,743)	17.5 (2,189)	16.6 (2,468)	16.6 (3,118)
17-18	6.7 (4,062)	7.3 (460)	7.1 (606)	6.2 (769)	6.4 (951)	6.8 (1,276)
19-20	3.4 (2,084)	2.6 (163)	2.8 (239)	3.1 (392)	3.3 (486)	4.3 (804)
21-22	2.1 (1,275)	1.2 (77)	1.3 (111)	1.4 (172)	2.1 (313)	3.2 (602)
23-24	1.6 (978)	0.9 (54)	1.0 (84)	1.3 (161)	1.8 (261)	2.2 (418)
≥25	7.1 (4,343)	3.7 (236)	5.0 (426)	6.6 (828)	8.5 (1,273)	8.4 (1,580)
Never	12.6 (7,707)	13.1 (825)	14.9 (1,269)	14.3 (1,793)	11.5 (1,706)	11.2 (2,114)

Among women who answered both questions, 25.9% stated that their first period and regular menstruation occurred at the same age, and 31.6% that their periods became regular within a year of first menstruation. For 26.1%, regular cycling started 1 to 5 years after menarche and for 16.4% it started over 5 years later. The distribution of length of time between age at menarche and age at onset of regular menses was analysed by birth cohort (Table III). The percentage of women whose menstrual cycles stabilised rapidly decreased slightly from 64.3% among the older birth cohorts to 52.5% for the younger ones. In contrast, the percentage of women who had to wait 5 years or more before the onset of regular cycling increased from 9.0% for the 1925-1929 birth cohort to 20.8% for the 1945-1950 cohort. The interval between the first period and the onset of regular menstruation increased gradually with year of birth: on average, women born in 1925, 1930, 1935, 1940 and 1950 had regular menstrual cycles 1.87 (SD 2.70), 2.11 (3.05), 2.46 (3.44), 2.80 (3.78) and 3.04 (3.82) years after menarche, respectively.

Table III. **Distribution of time between age at menarche and age at onset of regular menses by birth cohort.**

Birth cohort	Numbers	0-1 year (*n* = 30,631) (%)	1-5 years (*n* = 13,886) (%)	≥5 years (*n* = 8,755) (%)
1925-1930	5,490	64.3	26.7	9.0
1931-1935	7,240	62.4	26.0	11.6
1936-1940	10,699	59.4	25.9	14.7
1941-1945	13,151	56.8	25.2	18.0
1946-1950	16,692	52.5	26.7	20.8

The distribution, by age at menarche, of the length of time between age at menarche and age at onset of regular menses is shown in Table IV. The percentage of women with an interval of 5 years or more between age at menarche and age at onset of regular menses was almost twice as high for those who had had their first menstruation late (at 17 or after) compared with those who had started to menstruate early (before

11) (26.6% versus 13.9%). This increase was more pronounced for the younger cohorts: more than 33% of women born after 1940 and over 17 years of age at menarche waited 5 years or more before experiencing regular cycles, whereas under 20% of women born before 1940 did so (data not shown).

Table IV. **Distribution of time between age at menarche and age at onset of regular menses by age at menarche.**

Age at menarche (years)	Numbers	0-1 year (n = 30,631) (%)	1-5 years (n = 13,886) (%)	≥5 years (n = 8,755) (%)
<11	2,617	59.0	32.1	13.9
11	8,868	59.8	25.8	14.4
12	13,373	58.2	26.2	15.6
13	13,433	57.6	26.6	15.8
14	9,894	57.4	23.5	19.1
15	3,546	54.5	26.7	18.8
16	1,079	51.4	27.3	21.3
>16	459	49.4	24.0	26.6

Discussion

Our large sample of French women born between 1925 and 1950 showed a steadily increasing interval between age at menarche and age at onset of regular cycling. An increase in the mean age at menarche for women born between 1925 and 1930 was apparent, followed by a steady decrease in younger birth cohorts. Conversely, age at onset of regular cycling increased steadily from 1925 onwards. The difference in the shapes of the two graphs is attributable to increases in very long intervals between menarche and regular menstruation.

As with most cohort studies, our study used self-administered questionnaires as the source of information. Information on menstruation is thus potentially prone to recall bias. In one study (Bean *et al*.,1979), 10% of women (n = 160) misclassified age at menarche by over 1 year. Two other studies found that age at menarche was recalled by 62% in the correct annual age group 19 years after the original study (Damon *et al*., 1969) and by 50% 39 years after the study (Damon and Bajema, 1974). Recall of the regularity of menstrual cycles was also analysed by Bean *et al* (Bean *et al*.,1979). Agreement was better for younger than for older women and was very dependent on the definition of regularity. In a subgroup of 549 women who answered the question on menarche twice, with an 18 month interval between replies, we found that 70.7% reported an identical age at first menstruation and 98.5% an age within a year of that initially reported. An increase in the rate of uncertainty about age at menarche with increasing interval since menarche is likely. In our population, the rate of missing answers to age at menarche remained stable across the birth cohorts, whereas the percentage of women who gave no answer to age at onset of regular cycling (which was the question following age at menarche) was, surprisingly, higher in the youngest cohorts. However, errors due to retrospective assessment and to self-reporting would have to be systematically biased to account for the results we observed in the evolution of age at menarche and age at onset of regular cycling.

Ethnic differences may potentially play a role in the characteristics of menstrual bleeding (Harlow and Campbell, 1996; Koprowski *et al.*, 1999). However they cannot account for the changes we observed, as our population was ethnically homogeneous.

A secular trend towards earlier menarche has been clearly identified, with a decrease of ~3-4 months per decade over the past century: 2.1 months for women born between 1840 and 1980 in France (Ducros and Pasquet, 1978), 3.0 for women born between 1840 and 1990 in England (Rees, 1993), 3.4 between women born in 1900 and 1950 in Iceland (Tryggvadottir *et al*., 1994), 2.9 between women born around 1830 and 1960 in Norway (Rosenberg, 1991), 2.8 between women born between 1949 and 1976 in two rural counties in China (Graham *et al*., 1999), 2.0 for Japanese atomic bomb survivors born between 1902 and 1942 (Hoel *et al*., 1983) and 3.2 between women born around 1920 and 1940 in the United States (Wyshak, 1983). Age at menarche was ~15.3 years around 1840 in occidental countries, whereas in the early 1980s it averaged 12.8 (Ducros and Pasquet, 1978). The downward trend seems now to have stopped (Tryggvadottir *et al*., 1994, Rees,1993; Wellens *et al*., 1990) or to have reversed (Dann and Roberts, 1993). Genetic factors as well as external ones such as climate, sunshine and chronic diseases have been put forward as being possibly linked to the evolution of age at menarche. Factors such as unhealthy diet, stress or psychological factors

experienced during World War II might be responsible for the increase in age observed in our population for the 1925-1930 birth cohorts.

Few data are available on the evolution of age at onset of regular cycling. A similar trend towards increasing age at onset of regular cycling can be computed from the data of Rockhill (Rockhill *et al.*, 1998): the percentages of women with an interval of 5 years or more before regular cycling were 8.9, 11.7, 12.2 and 13.6 respectively among controls who had experienced menarche before 11, and at 12, 13 and 14 or over. Absolute values cannot be compared, however, as the study of Rockhill *et al*. concerned women born between 1920 and 1975 (Rockhill *et al.*, 1998). In an other study, time from menarche to the establishment of regular cycles was weakly positively correlated with age at menarche (Garland *et al.*, 1998).

The increase in the length of time before the onset of regular cycles was more apparent among women in younger birth cohorts, in whom menarche occurred late. Use of hormonal treatments cannot account for our findings, as exclusion of ever users of these treatments (treatments to regularize cycles, or oral contraceptives, or both) did not modify our results. It is well documented that excessive leanness before menarche may delay menarche until as late as 19-20 years of age (Frisch, 1990) and that weight loss results in amenorrhea due to hypothalamic dysfunction. A high percentage of body fat (~26-28% of body composition) in mature women is necessary for regular ovulatory cycles (Frisch, 1990). A change in dietary intake and/or in physical activity to achieve the slim figure possibly desired by girls of the youngest cohorts might be responsible for this increase (Stoll, 1998).

The role of early menarche in breast cancer risk is attributed to earlier exposure to circulating ovarian hormones. Few investigations have evaluated the effects of age at onset of regular cycling on breast cancer risk, and their findings are heterogeneous. In an early study (Brinton *et al.*, 1988), there was some evidence of a trend of increasing risk with increasing interval between menarche and onset of regular periods, though no consistent pattern of risk was maintained within age-at-menarche categories. In others studies (Garland *et al.*, 1998; Rockhill *et al.*, 1998; Titus-Ernstoff *et al.*, 1998; Butler *et al.*, 2000), there were very modest variations in risks by length of time before onset of regular cycling overall or across different age-at-menarche strata. After menarche, there is probably a transient period with anovular cycles before cycles are ovulatory. One study (MacMahon *et al.*, 1982) showed an increase in the percentage of anovular cycles with increasing age at menarche. Other cited studies (Harlow and Ephross, 1995) have reported that the probability of anovulation relative to age was ~50-60% for cycles in 10-14-year old girls. Several studies have shown that the prevalence of ovulatory cycles increased with increasing interval since menarche, from 15-44% in the first 2 years to 75-81% after 6 years or more (MacMahon *et al.*, 1982; Apter, 1996). These percentages also depended on age at onset of menarche, earlier menarche being characterised by an earlier onset of ovulatory cycles (Apter and Vihko, 1983; Apter, 1996).

The causes and consequences of the increase in length of time before onset of regular cycling observed in our data have to be considered as well. We suggest that a change in food intake and/or in physical activity to achieve a fashionably slim figure, even more pronounced among members of the youngest cohorts, might be responsible for this increase.

There are various possible reasons for oligomenorrhea in adolescence. An immature hypothalamic-pituitary-ovarian axis may result in oligomenorrhea and anovular cycles. An earlier age at menarche and a later age at onset of regular cycling increase exposure to anovulatory cycles and therefore to hormonal imbalance during adolescence, a period where breast cells have not undergone the maturation process and may thus be initiated under the influence of a carcinogen. Oligomenorrhea may also reflect relative hyperinsulinemia and hyperandrogenism related to obesity or to a polycystic ovary syndrome leading to high LH or androgen concentrations (Stoll, 1998). One study (Van Hoff *et al.*, 2000) found that, compared to girls with regular cycles, oligomenorrheic girls had significantly higher concentrations of LH, androstenedione and testosterone.

Further studies are needed to identify the endocrine characteristics associated with early menarche and with late age at onset of regular cycling, to elucidate whether these characteristics are transitory or are maintained until adulthood and, ultimately, to explore the consequences of our observations on breast cancer incidence.

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