The menopause and breast cancer

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It is usually accepted that an older age of menopause is associated with an increased risk of breast cancer. This is often interpreted as a statement about postmenopausal women; however, some authors, eg ref. 1, explicitly and others, eg ref. 2, implicitly take it as embracing both an increased risk for postmenopausal women who have had a late menopause and an increased risk for older premenopausal women who are still menstruating. We have recently examined the role of menstrual status and age at menopause in a study of risk factors in a population of screened women.³ Our results there and the difficulties we encountered in relating them to the literature have motivated this study.

We begin with a survey of the literature: comparison of reported studies is difficult because of considerable variations in the definitions of menstrual status (as well as absence and vagueness of definitions), the frequent absence of any "menopausal" category, and a lack of age-specific figures. The only clear consensus is that there is a higher risk among women aged 50–54 who are still menstruating than among those who are postmenopausal.

Later we propose a modification of the "two linear component" model for age incidence: this includes increased incidence at the time of the menopause and a subsequent deficit. The intention is to test this model using data from the Edinburgh Breast Screening Trial, and the suitability for this purpose of the data which are being collected is discussed.

Survey of the literature

We have reviewed the literature for information on the following questions:

Question 1. Is there any evidence of an increased risk of breast cancer in postmenopausal women aged 55–65 who have had a late menopause?

Question 2. Is there an increased risk in women who are still menstruating when over 50?

Question 3. Is there any evidence relating to the risk for women aged 45–54 who are currently menopausal?

There is a vast amount of literature relating to questions 1 and 2, but we have tried to include all

reports from screening trials and other key studies which provide figures specific to age-at-diagnosis. The studies from screening projects are particularly relevant to us, as the answers, particularly to questions 2 and 3, might be different from symptomatic women. Three papers^{2 4 5} are from screening trials which are similar to ours in the present context. Reports from the Breast Cancer Detection Demonstration Project (BCDDP) programmes are not so appropriate as they include symptomatic women^{6 7} and in any case lack age specific figures. These two studies provide some evidence of a significant trend of risk with age at menopause, but it is not possible to distinguish "risk" in the perimenopausal period from that in the postmenopausal.

The remaining reports are mostly from case-control studies, which involve symptomatic cases. Some^{8 11} use community controls, but the majority use hospital controls. The previous Edinburgh study¹⁰ uses as controls women cleared on screening in a pilot project in Edinburgh. Except for one study,¹² no additional analysis has been undertaken and the author's own estimates of relative risk and significance levels are quoted.

It is clear that differences in definition of menstrual status will have a crucial effect on these questions. Unfortunately, some authors give no definition while others leave it vague. Where precise definitions are given, the majority use time lapsed from last monthly period as the criterion, but the time lapsed before being deemed to be postmenopausal varies from two months⁴ (alternative definition) to 10 years.¹³ Many of these studies do not allow for any interim category. Details of the definitions are given in table 1. Precise definitions are apparently a difficult problem even for gynaecologists.

QUESTION 1—RISK IN POSTMENOPAUSAL WOMEN AGED 55–65

Full details of reports relevant to this particular question are given in table 2. The Diagnostisch Onderzoek Mammacarcinoom (DOM) report² is not, however, included because its results are presented graphically. This report analyses the effect of age at menopause in two ways; the first is appropriate to

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question 1, and the second to question 2. The first method gives entirely negative results which the authors tend to ascribe to faults in the method; it seems more likely that the two methods are addressing

different questions. This negative result is consistent with our own results³ and with the HIP study.^{4 5}

The most widely quoted references for evidence of increased risk associated with a late menopause are

Table 1 Definitions of menstrual status

Study	Premenopausal	Menopausal	Postmenopausal	Artificial menopause included	Age range (years)
DOM de Waard <i>et al</i> ²	LMP 0-12 mth	Not used	LMP $\geq$ 12 mth	Included	50-64
Edinburgh Alexander <i>et al</i> ³	1st defin. LMP 0-6 mth 2nd defin. LMP 0-2 mth	LMP 6-12 mth LMP 2-12 mth	LMP $\geq$ 12 mth	Excluded	45-65
HIP Shapiro <i>et al</i> ^{4 5}	1st defin. LMP 0-2 mth 2nd defin. Report at first screen that "menopause has not started"	Not used	LMP $\geq$ 2 yr Report at first screen that "menopause has started"	Not stated	40-64
BCDDP Kelsey <i>et al</i> ⁷	LMP 0-3 mth	LMP 3 mth-2 yr	LMP $\geq$ 2 yr	Included	45-74
Adami <i>et al</i> ⁸	Reported postmenopausal at interview or serum FSH $\leq$ 3.0 μ g/l	Not used	Reported postmenopausal at interview and confirmed by serum FSH $>$ 3.0 μ g/l	Not stated	all
Choi <i>et al</i> ⁹	LMP 0-12 wk	LMP 12-1 yr, excluded	LMP $\geq$ 1 yr	Included	35-74
Previous Edinburgh Duffy <i>et al</i> ¹¹	LMP 0-6 mth	Not used	LMP $\geq$ 6 mth	Included	40-60
Wynder <i>et al</i> ¹³	LMP 0-6 mth	LMP 6 mth-10 yr	LMP $\geq$ 10 yr	Not stated	$\geq$ 30
Stavraky <i>et al</i> ¹⁴	Same menstrual pattern as in preceding years	Still menstruating but marked change in pattern—excluded	Menstruation ceased	Excluded if under 50 at time of hysterectomy	all
Helmrich <i>et al</i> ¹⁷	Reported at interview "premenopausal or at the menopause"	Not used	Reported postmenopausal at interview	Included	< 30-70

Notes 1 The first 3 studies use information given at screening, the remainder use information from post-diagnosis (normally post-surgery) interviews
2 References not included here (1, 6, 10, 16, 22) do not state their definitions; however, Trichopoulos *et al* (12) do state that they used hospital records, and Lubin *et al* (16) state that they used a menopausal category which they then excluded from the analysis.
3 The DOM report (2) and Helmrich *et al* (17) essentially keep their menopausal category with the pre-menopausal while the HIP studies (4, 5) tend to keep theirs with the post-menopausal group. However in the latter case it must be noted that the information is taken at first screening and some cancers were detected at later rounds by which time the menopause could have started for some "premenopausal" women.

Table 2 Effect of age of menopause in postmenopausal women aged 55-65 years

Study	Menopausal age (years)					Age at diagnosis (years)
	< 39	40-44	45-49	50-54	> 55	
Edinburgh Alexander <i>et al</i> ³			1.00	0.89	0.89	55-59
HIP Shapiro <i>et al</i> ⁵	1.10	1.00	1.00	1.29	1.29	60-65
Choi <i>et al</i> ⁹	†	1.00	1.00	0.93	0.93	55-59
Previous Edinburgh Duffy <i>et al</i> ¹¹	0.77	0.77	1.00	0.81	0.81	60-64
Trichopoulos <i>et al</i> ¹²			1.00	1.00	1.00	50-69†
Stavraky <i>et al</i> ¹⁴	0.62	1.00	1.00	1.20	1.20	50-50†
Lubin <i>et al</i> ¹⁶	0.54	0.77	1.00	0.95	—*	55-59
	0.60	0.87	1.00	1.40	1.40 *	60-64
		0.54	1.00	1.01	1.55 *	50-69†
		1.00	1.00	2.3	3.2**	55-64

Notes 1 Risks are experiences relative to 1.00 in the smallest age-at-menopause group containing the age range 45-49.
2 All studies which provided relative risk estimates specific to age at diagnosis 55-65 ($\pm$ 5 years) or studies from which this could be calculated have been included here.
3 No age-at-diagnosis specific figures were available for refs 1, 6, 7, 8, 10, 13, 17; of these, 1, 8, 10 report non-significant and 6, 7, 17 report significant trends of risk with age at menopause over their whole age-at-diagnosis range.
* $p < 0.05$; ** $p < 0.01$ (trend tests in each case).
† Because the age-at-diagnosis range overlaps 50-54 these data may be contaminated by information more relevant to question 2.
‡ Figure not supplied because of small numbers.

probably those of Trichopoulos and Stavraký.^{12 14} We have extracted data from the former so as to consider only women who are definitely postmenopausal. This gives the figures quoted in table 2. There is evidence that a menopause at age less than 45 is associated with reduced risk but no further significant evidence of an effect from differences in menopausal age within the range 45–54. A similar situation is noted by Stavraký *et al.*,¹⁴ there is a significant trend of risk with age at menopause across five age categories but this is entirely attributable to low relative risk in the youngest age-at-menopause category and a high relative risk in the oldest age-at-menopause category. For the latter, however, we do not know the ages at diagnosis and so we are not necessarily dealing with postmenopausal cases.

The most positive evidence of a trend of risk in this age range with age at menopause comes from a recent study in Canada.¹⁶ Unfortunately, the authors do not give details of their definitions of menstrual status and there is a large number of women with missing or excluded data. Also the cases were interviewed using a modified questionnaire in the autumn of 1978 to obtain retrospective information of their state in January 1977. In the absence of further information it is not possible to assess the effect of these factors.

We conclude that there is little evidence that the time of the menopause within the age range 45–54 makes a difference to the risk in postmenopausal women aged <65. The relation between age at menopause and age at diagnosis for them is, as stated,⁴ “exceedingly complex”. This must be considered alongside the accepted conclusion that among *all* postmenopausal women without any upper age limit an older age at menopause is associated with increased risk. The refutation of this apparent contradiction must be in terms of either a latent period after the menopause or some other phenomenon applying to women in this age group.

QUESTION 2—PRESENT RISK IN PREMENOPAUSAL WOMEN

The difficulties encountered in comparing studies arising from their use of different menstrual categories has already been mentioned. The problem is particularly important here, and different studies may be reporting apparently conflicting results merely because they are classifying women in the crucial years around the menopause into different menstrual categories. Table 3 gives our own results and shows how differences in definition would have influenced them.

Table 4 gives the results from other studies which are available for this question.

As before, details of the DOM report² are not included in the table; for these questions it is their

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Table 3 *Premenopausal compared with postmenopausal state in women aged 45–54. Details from Edinburgh Study³ showing effect of placement of menopausal group*

Odds ratio (95% confidence interval) for premenopausal women by age at diagnosis (years)		Placement of menopausal group (using 2nd defn)
45–49	50–54	
0.46 (0.18–1.18)	2.56 (1.72–3.85)	With premenopausal
0.36 (0.16–0.80)	1.16 (0.76–1.82)	With postmenopausal

second method of analysis which is appropriate, and they report an increased risk (which is significant using a one-sided test) for their premenopausal as opposed to their postmenopausal state. Their study is, however, restricted to women aged at least 50. By contrast, the HIP study is effectively restricted here to younger women since virtually all women aged 50 or over were postmenopausal. They quote results of higher risks associated with the postmenopausal than with the premenopausal state in this age group. The two screening reports taken together do therefore confirm our own results³ of increased risk for the *premenopausal* state in the age group 50–54 and for the *postmenopausal* state in the age group 45–49.

In the previous Edinburgh Study, however, the premenopausal state was associated with increased risk in both these age groups. The study employs an elegant method for correcting for bias between responses at the screening and diagnostic clinics, which may not, however, be particularly appropriate for this factor. This as well as statistical chance could explain the differences between these results and our current findings for the age range 45–49.

There is a clear consensus that there is a higher risk for women aged 50–54 who are still menstruating than for postmenopausal women of the same age. For the age range 45–49, the conclusions are less uniform; the two screening programmes which include this group (HIP and Edinburgh) report that the premenopausal state is associated with slightly decreased risk. As we have said, these results will depend crucially upon the definitions of menstrual status and upon the status allocated to the perimenopausal category.

QUESTION 3—PRESENT RISK IN MENOPAUSAL WOMEN

Our recent study suggests a hypothesis of increased risk for menopausal women. The relative risk for the “menopausal” state as opposed to all others is 2.98, and this persists after allowing for other risk factors.³

Table 4 Odds ratio for premenopausal compared with postmenopausal status in women diagnosed at ages 45–54 years

Study	Age at diagnosis 45–49 yr			Age at diagnosis 50–54 yr		Comments
	Premenopausal	Postmenopausal		Premenopausal	Postmenopausal	
Ravnihar <i>et al</i> ¹	1.20**	1.00	A	1.20**	1.00	Not known where "menopausal" placed
HIP (Defn 1)	0.64	1.00		Not available		Uses definition at first screening even for later cases. "Post" includes "menopausal"
Shapiro <i>et al</i> ^{4,5} (Defn 2)	0.45	1.00		—all were postmenopausal		Not known where "menopausal" placed
Adami <i>et al</i> ⁸	1.25	1.00	A	1.25	1.00	
Choi <i>et al</i> ⁹	1.76†	1.00	A	1.76†	1.00	Combined figures for all ages in study. Menopausal excluded.
Previous Edinburgh Duffy <i>et al</i> ¹¹	1.56	1.00		2.35**	1.00	See footnote (6) for comments on possible over correction for bias.
Trichopoulos <i>et al</i> ¹²	1.40	1.00		1.38	1.00	From Series A, C; all with a natural menopause included even if date unknown.
Lubin <i>et al</i> ¹⁶	1.80*	1.00	A	1.80*	1.00	Not known where "menopausal" placed
Helmrich <i>et al</i> ¹⁷	2.50*	1.00	A	2.50*	1.00	Combined figures for all ages in study. "Pre" includes "menopausal"

Notes 1 A indicates that the figures quoted for separate age groups are in fact combined figures, normally for ages 45–54.

2 ** $p < 0.01$; * $p < 0.05$; + $p < 0.1$

3 Studies 6, 7, 13, 14 used menstrual status as a stratum, so do not provide data relevant to this question.

4 Wherever possible women who have had an artificial menopause are excluded.

5 Studies 9, 17 which did not provide data specific to this age group have been included because it is likely that their data were concentrated in this age group.

6 Five women interviewed at screening clinic; then within 6 months at the diagnostic clinic reported different menstrual states and for all it was a change from pre- to post-menopausal; this will reflect a genuine change of state as well as reporting bias and so an over-correction may have been made.

There are no studies apart from our own that discuss this question, and so it has to be approached indirectly. Precise definitions are even more important here than they were for question 2, and it is necessary to remember that the gynaecologists warn that the menopause cannot be identified as a present event.²¹

Some evidence can be obtained from comparing those studies which indicate where they have placed their menopausal category. Table 3 shows the effect of this in our study. Those studies which include the menopausal group in their premenopausal category (eg, 17), tend to show a high relative risk for the premenopausal state. The HIP study which tends to over-report the postmenopausal status gives a reduced risk for the premenopausal state.

A further source of indirect evidence is a quite different series of studies which has examined the risk for oral-contraceptive users, including older current users.^{18–21} In these studies, some of the older current users may be incorrectly classified as premenopausal when in fact they are menopausal. Jick *et al*¹⁸ claim that since such women would be at decreased risk these misclassifications would introduce a conservative bias. If, on the other hand, these menopausal women are at increased risk, then the bias would result in inflated relative risks. When we consider that these reports tend to be consistent in showing little evidence of an increased risk associated with use of the pill, and yet two^{18, 21} quote high relative risks for current users aged over 50 (15.5 and 3.8 respectively, which are statistically significant), a hypothesis which explains a systematic bias is very attractive.

An association, whether causal or not, between increased detection of existing tumours and the menopause would lead to a deficit in the few years after the menopause, and this would lead to a positive correlation between age at menopause and age at diagnosis. This has been reported by Chen;²² in our own study there was a statistically significant though small positive correlation between age at menopause and age at diagnosis ($r = 0.1$, $p = 0.012$).

In this review we have found that the increase in risk usually attributed to a late menopause is not particularly apparent in the decade or so after the menopause is completed; on the other hand, we have also found that older women who are still menstruating are at increased risk at the time and that it is possible to interpret this as an increase in risk at the time of the menopause. We now proceed to see whether there is a modification of existing mathematical models which will account for these features.

A modified mathematical model

For female breast cancer it is well known (eg, refs 23–26) that the age-incidence curve breaks between the ages of 45 and 55 with a plateau until it rises again for women over 60. The break occurs at the age of the menopause and is usually attributed to it. The break is not merely an artefact of birth cohort effects²⁵ but if allowance for these effects is made then both Eastern and Western populations have the same basic shape of incidence curve. When the log-incidence rate is plotted

against log age this curve has two linear components with the change from one to the other at the menopausal age (figure).

The premenopausal part of this curve is similar to that of other adult cancers and is consistent with the equation

$$I(t) \propto t^k$$

where $I(t)$ is the age-specific incidence rate at age t and k is between 4 and 5. This in turn is consistent with a biological model of two (or multi-) stage carcinogenesis with approximately constant exposure over each time interval to initiating and promoting factors and with a growth rate for established tumours which is not time or age dependent.^{27 28} Doll *et al*²⁹ modified the equation for lung cancer by replacing the chronological age in years " t " by the time spent as a smoker; and a similar modification for breast cancer replaces " t " by the time from menarche. It is currently believed that the hormone profile during the reproductive period is related to both stages of development: at the first stage either as initiator or providing a suitable environment for some exogenous initiator and then in the second stage as promoter. The particular hormones involved are not known, though it seems likely that oestrogens are involved. A longer reproductive period for women who have an earlier menarche and/or a late menopause will lead to a longer time of "exposure" and hence a longer steep section of the age-incidence path and explain the epidemiological significance of early menarche and late menopause.

Various authors have modified the mathematical or biological models so as to include the second part of the curve. These provide excellent fits to population incidence data over a wide age range and are able to account satisfactorily for known epidemiological risk factors. One would not normally criticise the fit that is achieved in any one instance. In the present context, however, it is interesting that of seven sets of

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population data compared with fitted models,^{27 30} in all but one (Osaka) the pattern of observed rates is flatter around the age of 50 than the fitted model. They also predict that the effect of a late menopause will be seen at all times subsequently and they certainly do not suggest an increased incidence at the time of the menopause.

These extra features can be explained by modifying the basic model to incorporate increased growth of existing tumours at the time of the menopause. This leads to increased incidence at that time and consequently decreased incidence in the short term afterwards. The qualitative effects of superimposing this on the basic model are illustrated in the figure. For the purpose of the model the changes are sharp and immediate but this is certainly an oversimplification.

The modification can be applied to any more detailed models such as those of Moolgavkar *et al* and Pike *et al*^{27 30} and will have the same ability to explain other known epidemiological risk factors as the underlying model. It will also at least qualitatively explain the features that we have been discussing.

Discussion

Evidence has been found in our own study and in the literature that the increased risk associated with an older age of menopause is not very evident until a considerable time has lapsed from the menopause; however, older premenopausal and perimenopausal women are at increased current risk. Current mathematical models give good overall fit to population age-incidence curves but they tend to underestimate the incidence at the younger end of the age range 45–55 and overestimate it at the end of this age range.

A hypothesis has been suggested which explains these features: that there is an increase in growth rate for existing tumours at the time of the menopause. This will lead to an increase in incidence at the time of the menopause and a corresponding deficit shortly afterwards; the effect of super-imposing this on the basic model of uniform increased risk following from a longer length of time spent in the most favourable period for tumour development (menarche-menopause) leads to the confusion in the reported effects of a late menopause in the years shortly after it has taken place and hence in its effect being observed primarily in older women. It also explains the increased current risk for perimenopausal women and provides for the observed flattening of the age incidence curves relative to fitted models at ages 45–55.

Biological support for this modification would ideally come from evidence that human breast

Models for age-incidence (A and B denote younger and older ages at menopause). *—* shows where the effect of an older age at menopause is disguised.

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tumours are indeed growing rapidly or the healthy human breast showing increased mitosis at the time of the menopause. There appears to be little evidence for (or against) either of these: however, it is the clinical experience that tumours detected in perimenopausal women are difficult to treat, and Langlands *et al*³¹ have shown that the prognosis is particularly poor in the first three years; and in their work on cell kinetics Gentili *et al*³² have shown a high labelling index for human breast cancers during the "paramenopausal" period.

From a biochemical point of view the hormone profile of women during the perimenopausal period has been shown to be complex and varied both for the same woman over time and for different women.³³ The normal negative feed-back mechanism between pituitary gonadotropins and ovarian hormones appears to be disturbed so that abnormal combinations of LH, FSH, and oestrogens are commonly observed as well as unusually high or low levels of each individually. Ovulatory cycles normally continue intermittently and can be accompanied by unusually high levels of gonadotropins.^{33 34} It is known that all women experience some anovulatory cycles and therefore may have oestrogen unopposed by progesterone which, as suggested in the oestrogen window hypothesis,³⁵ may favour tumour growth. This is conjecture; what is clear is that there are very decisive changes in the hormone environment and that among these there could well be alterations which could favour tumour growth at least in some cases. Moreover, a casual relation between the menopause and tumour detection need not necessarily be wholly in the one direction: it is conceivable that tumour products could affect the menopause but little is known about these aspects of tumour development.

Our modified model is deliberately qualitative. No precise data are available to test the hypothesis nor to fit parameters to the model. Ideally, prospective data on time of menopause and of breast cancer incidence would be collected for a large cohort. To do this presents obvious practical difficulties.

In the present trial of breast screening,³⁶ data are collected at each of seven annual screening rounds. In particular, each woman is asked to report the date of her last menstrual period. This is obtained at interview before any diagnosis is made. Thus we shall be able to collect a large amount of prospective data on the population as its members move through successive "proxy" menstrual states defined by time lapsed from LMP. For cancer cases this data collection ceases at the last routine interview before diagnosis.

Our intention is that the main analysis to test this hypothesis will be made using a competing risks model at the end of the seven year programme. This will use data on all the women who were deemed free of breast

cancer at the prevalence screen. Approximately 9000 women aged 54 at entry to the programme will be involved. It must be emphasised that this will examine the question in the screening context. Detailed hypotheses of the present type relating time of "diagnosis" fairly precisely to time of menopause will at the least need to use different parameters when modelling screen-detected and symptomatic presentation. The hypothesis also concerns information which is more relevant in the screening context. All women do eventually experience the menopause, and so the information that this may lead to more rapid growth of occult tumours is not perhaps of much practical importance except in the screening context. If, however, our hypothesis is confirmed it will mean that screening schedules could usefully be linked to the onset and termination of the menopause. This would in practice mean more frequent screening for those women over 50 who are still menstruating. will mean that screening schedules could usefully be linked to the onset and termination of the menopause. This would in practice mean more frequent screening for those women over 50 who are still menstruating.

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