Increased mortality among women with Rose angina who have not presented with ischaemic heart disease

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SUMMARY

Background: *Little is known about the clinical importance of disease that is not presented to healthcare services.*

Aim: *To determine the 5-year mortality among those with angina symptoms, known or not known by their general practitioner (GP) to have ischaemic heart disease (IHD).*

Design: *A prospective cohort study.*

Setting: *The study was conducted in the United Kingdom as part of the Royal College of General Practitioners' Oral Contraception Study.*

Method: *In 1994–1995 women (*n *= 11 797) still under GP observation were sent a questionnaire that enquired about their smoking habits, other lifestyle issues, general health, and selected symptoms (including chest pain, assessed using the Rose angina questionnaire). The main outcome measure was the chances (odds) of dying during the next 5 years, among those with and without exertional chest pain, Rose angina or Rose myocardial infarction (MI), stratified by documented history of IHD.*

Results: *Overall, the lifetime prevalence of any exertional chest pain was 10.1% (95% confidence interval [CI] = 9.5 to 10.8); grade I Rose angina was 6.1% (95% CI = 5.6 to 6.6); grade II Rose angina was 1.3% (95% CI = 1.1 to 1.6); and Rose MI was 4.4% (95% CI = 4.0 to 4.9). The prevalence of each condition tended to increase with age, social class, parity, body mass index, and documented history of IHD. The proportion of women documented as having IHD was 23% among those with any exertional chest pain, 21.7% for grade I Rose angina, 37.7% for grade II Rose angina, and 31.4% for Rose MI. Compared to women without Rose angina, significantly higher odds ratios for all-cause mortality were observed among women with grade I Rose angina and no documented history of IHD (adjusted odds ratio [AOR] = 1.71, 95% CI = 1.05 to 2.79); those with grade II Rose angina and documented IHD (AOR = 3.94, 95% CI = 1.58 to 9.83); and women with grade II Rose angina and no documented history of IHD (AOR = 3.35, 95% CI = 1.47 to 7.62).*

Conclusions: *Women with angina symptoms that have not been documented by their GP appear to have an increased risk of future mortality. Research is needed to determine the best way of identifying and managing these individuals.*

Keywords: *angina pectoris; ischaemic heart disease; mortality; health status; community; cohort study.*

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Introduction

THE term 'iceberg phenomenon' describes the observation that symptoms and illness presented to healthcare professionals represent only a proportion of the total occurring within the community.[1] The size of the visible and submerged proportions varies for different conditions. Although sometimes perceived as a phenomenon relating only to mild, self-limiting health problems, accumulating evidence shows that it also occurs with symptoms of serious disease.

Recent examples include a study of Glaswegian residents which found that just over half (58%) of individuals with angina symptoms had presented them to their general practitioner (GP), with men being more likely to do so (66%) than women (53%).[2] A longitudinal study of individuals consulting with low back pain observed that few consulted their GP for this problem after 3 months, yet follow-up in the community at 12 months found that most (75%) still had pain and/or disability.[3] Other researchers found that approximately half of the adults and one-third of the children in a community survey of symptoms suggestive of asthma had no corroborative evidence for this diagnosis in their general practice records.[4,5]

These, and other findings, indicate that a large number of individuals with serious ill-health are hidden in the community. In order to understand the clinical importance of such illness, however, we need to know the clinical impact (i.e. prognostic significance, effect on quality of life, etc.) of illness that is presented to healthcare services and illness that is not. If the non-presented problems are associated with important adverse clinical outcomes, attempts should be made to detect and treat these problems; provided, of course, that adequate resources exist for such actions. On the other hand, if non-presented problems do not have serious adverse outcomes, then arguably, they should be left well alone. Another study[6] found that the short-term outcome for patients in primary care with undetected depression was better than for those with detected depression. The authors concluded that increasing the detection of depression in primary care was unlikely to improve outcomes.

A recent health survey of women remaining in the Royal College of General Practitioners' (RCGP's) Oral Contraception Study offered an opportunity to explore these issues with respect to angina symptoms. Our research question was: do women with angina symptoms, but no previous diagnosis of ischaemic heart disease (IHD), have a different prognosis with respect to mortality than women with angina symptoms and a prior diagnosis?

HOW THIS FITS IN

What do we know?

There has been comparatively little work looking at the clinical importance of symptoms of serious disease that are not presented to healthcare services. If non-presented problems are associated with important adverse clinical outcomes, attempts to detect and treat these problems are required.

What does this paper add?

This study shows that women with angina symptoms that have not been documented by their GP appear to be at increased risk of future mortality. Further work is now needed to determine the best way of identifying and managing these individuals.

Method

Design and sample

This was a prospective cohort study with a 5-year follow-up conducted within the RCGP Oral Contraception Study.[7] Between November 1994 and July 1995 the practices of the 12 303 women (26.5% of the original cohort) still under GP observation in the RCGP Oral Contraception Study were asked to forward a health survey questionnaire to each woman on our behalf.[8] Most agreed to do so, despatching questionnaires to 11 797 women. Recipients of the questionnaire were asked to complete and return it directly to the study. Two reminders were sent to non-respondents. By comparing key information already held on the Oral Contraception Study database with that given in the returned forms we were able to check that the GPs had sent the questionnaires to the correct women (Figure 1).

Health survey questionnaire

The health survey questionnaire enquired about current and past smoking habits, other lifestyle issues, general health, and the occurrence of selected symptoms. Symptoms suggestive of angina or myocardial infarction (MI) were ascertained using the Rose angina questionnaire. This is an epidemiological measure that assesses whether the respondent is likely to have ever experienced angina or MI. Although originally developed in the early 1960s in middle-aged white men,[9] subsequent research has shown that Rose angina in women correlates well with aggregated regional standardised mortality ratios for coronary heart disease[10] and future mortality.[11-13] The questionnaire has proved useful for examining, at the population level, the frequency of angina-like symptoms and factors associated with these symptoms. At the individual patient level, however, the questionnaire has insufficient discriminatory power to enable clinicians to use it for treatment decisions. In order to emphasise this important distinction we have labelled respondents to our survey as having: no exertional chest pain; any exertional chest pain; grade I Rose angina; grade II Rose angina; Rose MI (Box 1).

Rose angina status at 1994–1995

Using data from the health survey we were able to determine whether by 1994–1995 each woman had ever experienced exertional chest pain, Rose angina or Rose MI. The prevalence

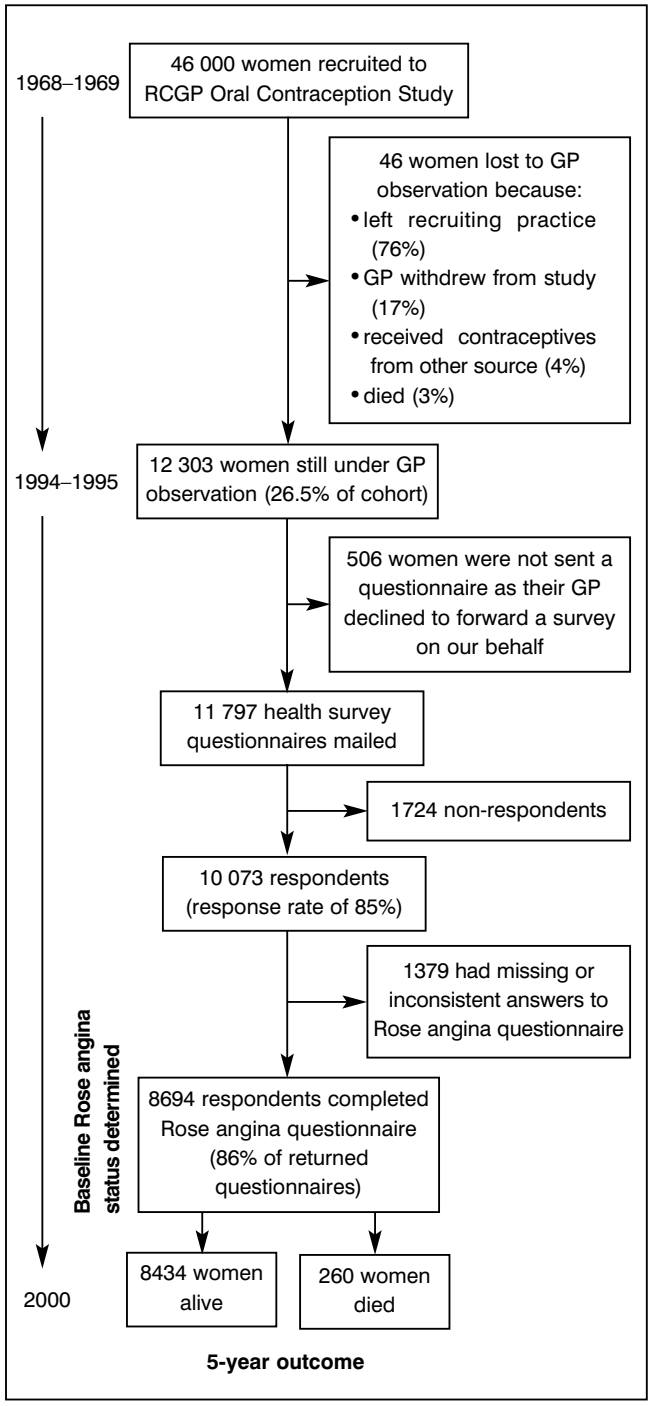

Figure 1. Flow chart of the study.

of each condition among women with different characteristics was examined using the most up-to-date information available. Thus, we calculated the prevalence of each condition by social class (based on partner's occupation) at recruitment in 1968, age, parity, pill status, smoking status, and body mass index (BMI) in 1994.

We then examined the information held on the Oral Contraception Study database to determine whether women reporting chest pain symptoms had IHD (*International Classification of Diseases*[14] codes 410–414) documented during the main study by 1994–1995. By this process we

- No exertional chest pain:
  Respondents reported having never had pain or discomfort in the chest that had occurred when walking uphill or in a hurry.
- Any exertional chest pain:
  Respondents reported that they had (ever) experienced pain or discomfort in the chest, and that the pain or discomfort occurred when walking uphill or in a hurry.
- Rose angina grade I:
  Respondents reported pain that met the criteria for any exertional chest pain and that the pain: caused them to stop or slow down; went away when the respondent stood still; disappeared within 10 minutes or less; occurred in the sternum, left arm and/or left anterior of the chest; did not occur when walking at an ordinary pace on the level.
- Rose angina grade II:
  Respondents reported pain that met the criteria for grade I Rose angina, and reported that the pain occurred when walking at an ordinary pace on the level.
- Rose myocardial infarction (MI):
  Respondents reported that they had (ever) experienced pain or discomfort in the chest and that they had (ever) experienced severe pain across the front of the chest lasting for half an hour or more.

Box 1. Case definitions.

could stratify the women into those with chest pain symptoms and a documented history of IHD and those with symptoms without a history of IHD.

Audit of documented heart disease

Clearly, the stratification relied totally on there being accurate and complete reporting of episodes of IHD during the Oral Contraception Study. In order to assess this, an audit of data relating to 200 questionnaire respondents was undertaken in October 1998. The GPs of 100 women with Rose angina and 100 women without Rose angina were asked to review their medical records for each woman and to indicate whether she had ever been diagnosed as having angina, MI, other IHD, other heart disease or hypertension. They were also asked to indicate whether the woman had ever consulted because of chest pain. The doctors did not know how the women had responded in the postal health survey. Replies were received for 155 women. In most cases (148) there was agreement between the cardiac history reported after reviewing the notes, and the cardiac history held on the Oral Contraception Study database ($\kappa = 0.795$). Two doctors replied that their patient did not have cardiac disease even though they had reported previously such a condition during the Oral Contraception Study follow-up procedures. Five doctors reported cardiac disease in women for whom there was no such history on the Oral Contraception Study database. In three of these cases, however, the diagnosis had been made after the health survey had taken place.

Death outcomes

All of the respondents to the health survey were flagged, so that the study was notified at regular intervals of any deaths and cancer registrations occurring in the women. The notifications included each woman's unique study number, enabling us to link the new information to our existing database, while maintaining confidentiality. Deaths were coded using the *International Classification of Diseases*.[14] Using this information, we were able to determine which women in the postal health survey had died.

Analysis

Lifetime prevalence rates for any exertional chest pain, grade I or II Rose angina, and Rose MI were calculated for different subgroups of respondents and χ^2 statistics were used to look for differences between strata within each characteristic. Deaths occurring in the health survey respondents up to the end of July 2000 were used to calculate unadjusted odds ratios (ORs) for 5-year all-cause mortality among women in each case-definition group known or not known to have IHD, using women not fulfilling the case definition as the reference group. Multiple logistic regression was then used to adjust these ORs for potential confounding variables, which were: age (<50, 50–54, 55–59, 60–64, and 65+ years), social class at recruitment (non-manual, manual), parity at 1994 (0, 1–3, 4+), pill use at 1994 (never, ever), smoking status at 1994 (never, former, current), BMI at 1994 based on self-reported height and weight in the health survey (<25, 25–30, 30+). ORs were calculated, as the outcome (death) was rare. Kaplan-Meier and Cox regression analyses were deemed inappropriate since we had a small number of cases, the time to event was quite short, and we had no censored data owing to all respondents being flagged. The data were analysed using SPSS version 9.1.

Results

Response

After the questionnaire and reminders had been sent out, 10 073 (85.4%) questionnaires were returned. Respondents were of a similar age to non-respondents (mean age at 1994 = 55.9 years versus 55.6 years respectively), but were more likely to be of non-manual social class (32.1% versus 21.2%; $P<0.001$), have a parity of less than 4 in 1994 (83.9% versus 76.4%; $P<0.001$) and be a non-smoker at recruitment (58.9% versus 45.9%; $P<0.001$). Some 8694 (86%) of the returned questionnaires contained complete responses to the Rose angina questionnaire; the rest either had no answer to the core question or inconsistencies with other responses. Women who completed the Rose angina questionnaire were more likely than those with incomplete data to be younger in 1994 (mean age = 56.0 versus 57.1 years), of non-manual social class (32.6% versus 28.7%; $P = 0.002$), and less likely to be a current smoker in 1994 (20.6% versus 23.8%; $P = 0.011$).

Lifetime prevalence of chest pain

Overall, the lifetime prevalence of any exertional chest pain was 10.1% (95% confidence interval [CI] = 9.5 to 10.8); for grade I Rose angina it was 6.1% (95% CI = 5.6 to 6.6); for grade II Rose angina it was 1.3% (95% CI = 1.1 to 1.6); and

Table 1. Lifetime prevalence rates at 1994–1995 of any exertional chest pain, grade I Rose angina (RA), grade II RA and Rose myocardial infarction (MI) for each of the sociodemographic factors examined.

	Sample	Any exertional chest pain		Grade I RA		Grade II RA		Rose MI	
	n	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Age in years (at 1994)									
<50	1506	121	8.0 (6.8 to 9.5)	68	4.5 (3.6 to 5.7)	17	1.1 (0.7 to 1.8)	47	3.1 (2.4 to 4.1)
50–54	2377	194	8.2 (7.1 to 9.3)	116	4.9 (4.1 to 5.8)	16	0.7 (0.4 to 1.1)	86	3.6 (2.9 to 4.4)
55–59	2278	222	9.7 (8.6 to 11.0)	154	6.8 (5.8 to 7.9)	22	1.0 (0.6 to 1.5)	103	4.5 (3.7 to 5.5)
60–64	1555	198	12.7 (11.2 to 14.5)	117	7.5 (6.3 to 8.9)	33	2.1 (1.5 to 3.0)	87	5.6 (4.6 to 6.9)
65+	978	145	14.8 (12.7 to 17.2)	71	7.3 (5.8 to 9.1)	26	2.7 (1.8 to 3.9)	62	6.3 (5.0 to 8.0)
χ^2; *P*-value			53.05; <0.001		22.45; <0.001		31.59; <0.001		23.26; <0.001
Social class (at recruitment)									
Non-manual	2848	201	7.1 (6.2 to 8.1)	140	4.9 (4.2 to 5.8)	19	0.7 (0.4 to 1.0)	99	3.5 (2.9 to 4.2)
Manual	5829	678	11.6 (10.8 to 12.5)	386	6.6 (6.0 to 7.3)	95	1.6 (1.3 to 2.0)	286	4.9 (4.4 to 5.5)
χ^2; *P*-value			43.97; <0.001		9.78; 0.002		13.67; <0.001		9.23; 0.002
Parity (at 1994)									
0	378	36	9.5 (7.0 to 12.9)	18	4.8 (3.0 to 7.4)	7	1.9 (0.9 to 3.8)	15	4.0 (2.4 to 6.4)
1–3	6988	655	9.4 (8.7 to 10.1)	402	5.8 (5.2 to 6.3)	81	1.2 (0.9 to 1.4)	291	4.2 (3.7 to 4.7)
4+	1327	189	14.2 (12.5 to 16.2)	106	8.0 (6.6 to 9.6)	26	2.0 (1.3 to 2.9)	79	6.0 (4.8 to 7.4)
χ^2; *P*-value			29.22; <0.001		10.96; 0.004		6.41; 0.041		8.63; 0.013
Pill status (at 1994)									
Never used	3368	330	9.8 (8.8 to 10.8)	192	5.7 (5.0 to 6.5)	42	1.2 (0.9 to 1.7)	135	4.0 (3.4 to 4.8)
Ever used	5326	550	10.3 (9.5 to 11.2)	334	6.3 (5.7 to 7.0)	72	1.4 (1.1 to 1.7)	250	4.7 (4.2 to 5.4)
χ^2; *P*-value			0.63; 0.426		1.18; 0.277		0.18; 0.676		2.38; 0.123
Smoking status (at 1994)									
Never smoked	4696	413	8.8 (8.0 to 9.6)	263	5.6 (5.0 to 6.3)	52	1.1 (0.8 to 1.4)	178	3.8 (3.3 to 4.4)
Ex-smoker	2041	253	12.4 (11.0 to 13.9)	142	7.0 (5.9 to 8.1)	38	1.9 (1.4 to 2.5)	116	5.7 (4.8 to 6.8)
Smoker	1743	196	11.2 (9.8 to 12.8)	112	6.4 (5.4 to 7.7)	20	1.1 (0.7 to 1.8)	82	4.7 (3.8 to 5.8)
χ^2; *P*-value			23.01; <0.001		4.99; 0.082		6.71; 0.035		12.41; 0.002
Body mass index (at 1994)									
<25	4394	329	7.5 (6.7 to 8.3)	203	4.6 (4.0 to 5.3)	37	0.8 (0.6 to 1.2)	161	3.7 (3.1 to 4.3)
25–30	2947	340	11.5 (10.4 to 12.7)	209	7.1 (6.2 to 8.1)	45	1.5 (1.1 to 2.0)	138	4.7 (4.0 to 5.5)
30+	1231	199	16.2 (14.2 to 18.3)	107	8.7 (7.2 to 10.4)	32	2.6 (1.8 to 3.6)	80	6.5 (5.3 to 8.0)
χ^2; *P*-value			89.40; <0.001		36.53; <0.001		23.96; <0.001		19.01; <0.001
Total	8694	880	10.1 (9.5 to 10.8)	526	6.1 (5.6 to 6.6)	114	1.3 (1.1 to 1.6)	385	4.4 (4.0 to 4.9)

Table 2. Lifetime prevalence rates of any exertional chest pain, grade I Rose angina (RA), grade II RA and Rose myocardial infarction (MI) for those with or without a documented history of ischaemic heart disease (IHD) and hypertension.

	Sample	Any exertional chest pain		Grade I RA		Grade II RA		Rose MI	
	n	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Known previous history of IHD									
No	8408	678	8.1 (7.5 to I8.7)	412	4.9 (4.5 to 5.4)	71	0.8 (0.7 to 1.1)	264	3.1 (2.8 to 3.5)
Yes	286	202	70.6 (65.1 to 75.6)	114	39.9 (34.4 to 45.6)	43	15.0 (11.4 to 19.6)	121	42.3 (36.7 to 8.1)
χ^2; *P*-value			1190.13; <0.001		594.73; <0.001		430.41; <0.001		1002.60; <0.001
Known previous history of hypertension									
No	6957	631	9.1 (8.4 to 9.8)	379	5.4 (4.9 to 6.0)	82	1.2 (1.0 to 1.5)	270	3.9 (3.5 to 4.4)
Yes	1737	249	14.3 (12.8 to 16.1)	147	8.5 (7.2 to 9.9)	32	1.8 (1.3 to 2.6)	115	6.6 (5.5 to 7.9)
χ^2; *P*-value			42.35; <0.001		22.23; <0.001		4.73; 0.030		24.65; <0.001
Total	8694	880	10.1 (9.5 to 10.8)	526	6.1 (5.6 to 6.6)	114	1.3 (1.1 to 1.6)	385	4.4 (4.0 to 4.9)

for Rose MI it was 4.4% (95% CI = 4.0 to 4.9) (Tables 1 and 2). The prevalence of each condition tended to increase with age, manual social class, parity, and BMI (Table 1), and history of IHD and hypertension (Table 2). In each case-definition group, ex-smokers had a higher prevalence of illness than current smokers or those who had never smoked. The prevalence of non-exertional chest pain was 6.0% (95% CI = 5.5 to 6.5) (data not shown).

History of IHD on the Oral Contraception Study database

The proportion of women documented as having IHD on the Oral Contraception Study database was 23% (95% CI = 20.3 to 25.8) among those with any exertional chest pain, 21.7% (95% CI = 18.4 to 25.4) for grade I Rose angina, 37.7% (95% CI = 29.4 to 46.9) for grade II Rose angina and 31.4% (95% CI = 27.0 to 36.2) for Rose MI. Some 96.2%

Table 3. Five-year mortality from all causes for those with or without exertional chest pain, Rose angina and Rose myocardial infarction (MI).

	All women *n*	Deaths *n*	Unadjusted odds ratios (95% CI)	Adjusted[a] odds ratios (95% CI)
Exertional chest pain status				
No exertional chest pain[b]	7814	201	1.00	1.0
Exertional chest pain with a history of IHD	202	17	3.5 (2.1 to 5.8)	2.2 (1.3 to 3.8)
Exertional chest pain without a history of IHD	678	42	2.5 (1.8 to 3.5)	2.1 (1.4 to 3.0)
Rose angina status				
No Rose angina[b]	8054	220	1.00	1.0
Grade I Rose angina with a history of IHD	114	7	2.3 (1.1 to 5.1)	1.5 (0.7 to 3.4)
Grade I Rose angina without a history of IHD	412	19	1.7 (1.1 to 2.8)	1.7 (1.1 to 2.8)
Grade II Rose angina with a history of IHD	43	6	5.8 (2.4 to 13.8)	3.9 (1.6 to 9.8)
Grade II Rose angina without a history of IHD	71	8	4.5 (2.1 to 9.6)	3.4 (1.5 to 7.6)
Rose MI status				
No Rose MI[b]	8309	231	1.00	1.0
Rose MI with a history of IHD	121	10	3.2 (1.6 to 6.1)	2.1 (1.0 to 4.1)
Rose MI without a history of IHD	264	19	2.7 (1.7 to 4.4)	2.3 (1.3 to 3.8)

[a]Adjusted for age in 1994, social class, parity in 1994, smoking status in 1994, and body mass index in 1994; [b]Reference group. IHD = ischaemic heart disease

of women who reported ever having severe chest pain that lasted half an hour or more stated that they had seen a doctor because of the pain. Fifty-three (0.7%) women who denied ever having had any chest pain had a diagnosis of IHD on the Oral Contraception Study database.

Five-year mortality

The risk of dying during the 5 years after completing the questionnaire increased with age, manual social class, and smoking, especially current smoking (data not shown). Looking at the 5-year mortality in each case-definition group, significantly higher ORs tended to be observed among women with any exertional chest pain, Rose angina or Rose MI than for women without these problems, irrespective of whether the woman was known to have IHD (Table 3). Larger ORs were found for those with grade II Rose angina than for those with the less severe grade I angina. The 5-year mortality analyses were based on 260 deaths; 135 from cancer, 37 from IHD, 13 from stroke, 11 from other cardiac problems, 6 from venous thromboembolism, 4 from aneurysms and 54 from other causes. There were, therefore, insufficient data to permit cause-specific analyses. The adjusted OR for non-exertional chest pain in women with a history of IHD was 0.75 (95% CI = 0.10 to 5.58), and among women with no known IHD it was 1.22 (95% CI = 0.71 to 2.09) (data not shown).

Discussion

Summary of findings

Our study has shown that chest pain is common among middle-aged women and that a sizeable proportion of women with these symptoms are not diagnosed as having IHD, with potentially serious consequences.

Strengths and limitations of the study

We were able to examine a large group of women for a relatively long time. Prospectively collected information was available to determine whether a woman had a documented history of IHD. Recall bias, therefore, cannot explain our findings. The small audit of data suggests that the information supplied to the Oral Contraception Study is consistent with that held in the general practice medical records. This rules out incomplete reporting of information to the Oral Contraception Study as a major reason for the large proportion of women reporting angina-related symptoms in the health survey who did not have a documented history of IHD.

We could only investigate women who remained in the Oral Contraception Study and who returned a questionnaire with usable information about angina symptoms. We have shown previously that the large losses to follow-up experienced by the Oral Contraception Study have not biased mortality analyses.[15] Differences in the characteristics of respondents and non-respondents, and between those providing full and incomplete information, could have affected both our estimates of exposure (prevalence of symptoms) and of outcome (mortality). Our high response rate, however, should minimise any distorting effects. We were able to adjust for important potential confounders such as age and smoking history. It is possible, though, that other confounders could explain our observations, at least in part. A further limitation of the study was the small number of outcomes; for example, there were only 14 deaths in women with grade II Rose angina, reflecting the fact that the cohort is still relatively young. The small numbers of deaths also meant that we were unable to include cause-specific analyses. Finally, there may be some reservations about the generalisability of the findings. This study was based on individuals in a unique cohort of middle-aged women originally recruited via their GP for a study of the health effects of oral contraceptives. The experience of these women may not reflect that of other women.

Comparison with other studies

Despite this, our prevalence rates were similar to those found by other studies.[10,16-18] Three-quarters of women in our study with Rose angina did not have a documented history of IHD. The Glasgow study found that 47% of women with Rose angina had not presented these symptoms to their GP.[2] This suggests that a large proportion of the apparent 'unmet need' found by our study is due to the

non-presentation of illness by women, rather than a failure of the GPs to make a diagnosis.

Future implications

Our study is one of the first to extend exploration of the iceberg phenomenon from simple descriptions of the size of the iceberg and the level of the 'waterline', to examinations of the clinical importance of the proportion of illness below the 'waterline'. It disproves the argument that people with symptoms who do not see their doctor are almost surely less severely ill than those who do.[19] Women with diagnosed IHD did not appear to fare any better than those whose IHD was undiagnosed, although direct comparisons were not made and the number of events in each group was small. Important differences between groups may exist but require larger numbers. Even if there are no differences, detecting previously unknown IHD is probably important as it offers the opportunity to provide better symptomatic relief and opportunities to provide new treatments as they become available. Furthermore, when considering importance it is essential that absolute as well as relative measures are considered. The absolute risk of death among women in our study was small, even among those with IHD. Although our data support the notion that angina that is hidden in the community is clinically important, more research is needed to determine the best way of identifying and managing individuals with this condition, especially since the Rose angina questionnaire is not a clinical diagnostic tool.

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