Menopause and risk of non-fatal acute myocardial infarction: an Italian case-control study and a review of the literature

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The relationship between menopause and non-fatal acute myocardial infarction (AMI) was considered by analysing data from a case-control study conducted in Italy between 1983 and 1992. Cases were 429 women, below age 75 years, with a first episode of non-fatal AMI, admitted to 30 coronary care units; controls were 863 women admitted to the same network of hospitals for acute diseases other than cardiovascular, neoplastic, or hormone-related. Post-menopausal women were not at higher risk of AMI than pre/perimenopausal women, after adjustment for age and other selected covariates [multivariate odds ratio (OR) 0.99]. With reference to age at menopause, compared with women reporting menopause when <45 years, the multivariate OR were 1.54 for those aged 45–49 at menopause, 1.36 for those aged 50–52 years, and 0.97 for those aged ≥53, in the absence of any trend in risk. No meaningful relationship emerged with time since menopause (OR 0.85 for <10 years since menopause). The results were similar in women aged <60 and ≥60 years at AMI. Although the present study does not support a substantial relationship between menopause and non-fatal AMI, the overall epidemiological evidence is compatible with a moderate association.

Key words: acute myocardial infarction/case-control study/ menopause/risk factors

Introduction

The hypothesis that menopause and consequent biological modifications are related to the risk of coronary heart disease (CHD) originally derived from the observation that incidence and mortality rates for cardiovascular disease (CVD) in women are substantially lower than in men before menopause, but tend to rise and approach those of men at older ages (Heller and Jacobs, 1978). In the Framingham cohort, the differences in the risk of CHD between men and women progressively diminished with each decade of age and there was a strong inverse association between age at menopause and CHD risk (Gordon et al., 1978; Lloyd-Jones et al., 1999). Most other cohort studies showed some excess CHD risk in women with earlier menopause (Colditz et al., 1987; Jacobsen et al., 1997; Cooper and Sandler, 1998; Cooper et al., 1999; Jacobsen et al., 1999). However, it is difficult to disentangle the simple effect of age from that of menopause on CVD, since the rise of CVD incidence and mortality may simply be due to increasing age, the two variables being strongly related. Further, the results of analytical epidemiological studies on the specific role of menopause are still open to discussion (Barrett-Connor and Bush, 1991; La Vecchia, 1992).

A protective role of female sex hormones on CHD is supported by the observation that hormonal changes related to menopause unfavourably alter the profile of some cardiovascular risk factors (La Vecchia, 1992; Gensini et al., 1998; Greendale et al., 1999). These include increased concentrations of cholesterol, triglycerides, low-density lipoproteins, and apolipoprotein-B, reduced levels of high-density lipoproteins and higher blood pressure (Davis et al., 1994; Schaefer et al., 1994; Dallongeville et al., 1995). Oestrogens have been reported to promote vasodilatation through several biological mechanisms, and to inhibit the development and progression of atherosclerosis (Mendelsohn and Karas, 1999). Moreover, menopausal hormone replacement therapy (HRT) has been associated with a reduction in CHD incidence and mortality in women with no previous cardiovascular events in several observational studies (Stampfer et al., 1991; The Writing Group for the PEPI Trial, 1995; Grodstein et al., 1996; Barrett-Connor, 1998). Conversely, intervention trials on women with previous CHD or at high risk of CHD show no appreciable reduction of risk (Hemminki and McPherson, 1997; Hulley et al., 1998; Petitti, 1998).

To further assess the potential role of menopause on the risk of non-fatal acute myocardial infarction (AMI), we considered data from a case-control study that considered hormonal factors, smoking, and other major AMI risk factors in Italian women (La Vecchia et al., 1987a,b).

Materials and methods

The present study is based on the data of a case-control study on AMI, conducted in Italy between 1983 and 1992, whose general design has already been described (La Vecchia et al., 1987a,b, 1989). Originally, the study focused on oral contraceptives and other hormonal factors, and hence had an upper age limit of 54 years. This limit was raised to 74 years in 1987, and the present analysis is based on data collected until December 1992.

Cases were women with a first episode of non-fatal AMI (International Classification of Disease, ICD-9 410) defined according to the standard World Health Organization criteria (WHO, 1971), admitted
Table I. Distribution of 429 cases of acute myocardial infarction (AMI) and 863 controls in women, according to age and selected covariates. Italy, 1983–1992

<table>
<thead>
<tr>
<th></th>
<th>AMI</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>75</td>
<td>17.5</td>
</tr>
<tr>
<td>45–54</td>
<td>182</td>
<td>42.4</td>
</tr>
<tr>
<td>55–64</td>
<td>98</td>
<td>22.8</td>
</tr>
<tr>
<td>&gt;65</td>
<td>74</td>
<td>17.3</td>
</tr>
<tr>
<td>Education (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>277</td>
<td>64.6</td>
</tr>
<tr>
<td>7–11</td>
<td>110</td>
<td>25.6</td>
</tr>
<tr>
<td>&gt;12</td>
<td>42</td>
<td>9.8</td>
</tr>
<tr>
<td>Body mass indexa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>50</td>
<td>11.7</td>
</tr>
<tr>
<td>20–25</td>
<td>174</td>
<td>40.7</td>
</tr>
<tr>
<td>&gt;25</td>
<td>204</td>
<td>47.7</td>
</tr>
<tr>
<td>Use of hormone replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>388</td>
<td>90.4</td>
</tr>
<tr>
<td>Ever</td>
<td>41</td>
<td>9.6</td>
</tr>
</tbody>
</table>

aThe sum does not add up to the total because of some missing values.

to 30 coronary care units in Italy. A total of 429 patients were interviewed, aged 18–75 years (median age 52 years).

Controls were 863 women, aged 17–79 (median age 52 years), admitted to the same network of hospitals for acute diseases other than cardiovascular, neoplastic, digestive, and hormone-related conditions, or diseases associated with long-term changes in the diet. Of these, 25.3% were admitted for traumatic conditions, 36.4% had non-traumatic orthopaedic disorders (mostly low-back pain and disc disorders); 15.5% had acute surgical conditions; and 22.8% had other illnesses such as acute infections, skin, eye, ear, nose, and throat, or dental disorders. Cases and controls were not singly matched by age, cases and controls. Cases were more frequently overweight than cardiovascular, neoplastic, digestive, and hormone-related conditions, or diseases associated with long-term changes in the diet. Of these, 25.3% were admitted for traumatic conditions, 36.4% had non-traumatic orthopaedic disorders (mostly low-back pain and disc disorders); 15.5% had acute surgical conditions; and 22.8% had other illnesses such as acute infections, skin, eye, ear, nose, and throat, or dental disorders. Cases and controls were not singly matched by age, but the frequency distribution by quinquennia of age was comparable. (47.7% versus 41.1% of controls had a BMI between age at menopause and risk of AMI emerged when menopause was 1.01 (95% CI 0.98–1.04). However, cases were women with AMI diagnosed according to strictly defined criteria (WHO, index, and use of HRT. Educational level was similar in AMI cases and controls. Cases were more frequently overweight (47.7% versus 41.1% of controls had a BMI >25), and reported HRT use (mostly short-term) more often than controls. These factors were consequently allowed for in the multivariate analysis.

Menopausal status and other menopausal characteristics are considered in Table II. The multivariate OR was 0.99 in postmenopausal compared to pre/perimenopausal women. Compared with women reporting menopause at age <45 years, the multivariate OR were 1.54 for those aged 45–49 at menopause, 1.36 for those aged 50–52, and 0.97 for those aged ≥53, in the absence of any trend in risk (P for trend 0.997). The OR for one year of increment in age at menopause was 1.01 (95% CI 0.98–1.04). No relationship between age at menopause and risk of AMI emerged when women aged <60 and ≥60 years at interview were analysed separately. With reference to time since menopause, compared to pre/perimenopausal women the OR was 0.85 for those reporting menopause <10 years earlier, and 0.52 for those whose menopause dated back ≥20 years.

Discussion
This is a hospital-based case-control study with all the inherent strengths and limitations. However, cases were women with AMI diagnosed according to strictly defined criteria (WHO,
### Table III. Relationship between coronary heart disease (CHD) and menopause in selected cohort and case-control studies

<table>
<thead>
<tr>
<th>Reference, country, year</th>
<th>Type of study</th>
<th>Number of cases</th>
<th>Relationship between CHD and menopause</th>
<th>Adjustment/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon et al., 1978, USA</td>
<td>Cohort</td>
<td>43 AMI (fatal and non-fatal)</td>
<td>Premenopause perimenopause postmenopause</td>
<td>Framingham Study, follow-up 24 years. A twofold RR in post-versus premenopausal women was found in 59 cases of CHD at the 20-year follow-up (Kannel et al., 1976).</td>
</tr>
<tr>
<td>Lapidus et al., 1985, Sweden</td>
<td>Cohort</td>
<td>25 AMI (fatal and non-fatal)</td>
<td>Premenopause menopause at age &lt;40 years at age 45 years at age ≤50 years</td>
<td>Follow-up 12 years. Allowance for age.</td>
</tr>
<tr>
<td>Colditz et al., 1987, USA</td>
<td>Cohort</td>
<td>269 CHD (218 non-fatal AMI and 51 CHD death including fatal AMI)</td>
<td>Premenopause natural menopause without HRT use with HRT use surgical menopause without HRT use with HRT use</td>
<td>American Nurses’ Health Study, follow-up 6 years. Allowance for age, smoking and other cardiovascular risk factors. No association with AMI and without HRT use.</td>
</tr>
<tr>
<td>Jacobsen et al., 1997, Norway</td>
<td>Cohort</td>
<td>2767 CHD (fatal)</td>
<td>Natural menopause at age &lt;40 years at age ≥53 years</td>
<td>Tromsø Study, follow-up 29 years. Allowance for age, county and occupation. RR 0.42 (0.25–0.72) for women &lt;70 years old at IHD and with menopause at age ≥53 versus &lt;44 years.</td>
</tr>
<tr>
<td>Cooper and Sandler, 1998, USA</td>
<td>Cohort</td>
<td>84 CHD (fatal)</td>
<td>Natural menopause at age ≥50 years at age &lt;40 years</td>
<td>NHANES I Study. Allowance for age, years of follow-up, race, education, smoking, and HRT.</td>
</tr>
<tr>
<td>Cooper et al., 1999, USA</td>
<td>Cohort</td>
<td>867 CHD (including 45 AMI) (fatal and non-fatal)</td>
<td>Natural menopause at age ≥51 years at age ≥45 years surgical menopause at age ≤45 years</td>
<td>Menstruation and Reproductive History Study. Median follow-up 55 years. Allowance for age; similar RR after further allowance for smoking, diabetes, body mass index and HRT.</td>
</tr>
<tr>
<td>Jacobsen et al., 1999, USA</td>
<td>Cohort</td>
<td>308 CHD (fatal)</td>
<td>Natural menopause all women at age 35–40 years at age 49–51 years at age 56–60 years non HRT users at age 35–40 years at age 49–51 years at age 56–60 years</td>
<td>California Seventh-Day Adventists, follow-up 13 years. Allowance for age, diabetes, hypertension, parity, age at first birth and leisure-time physical activity.</td>
</tr>
<tr>
<td>Rosenberg et al., 1983, USA</td>
<td>Case-control</td>
<td>255 AMI (non-fatal)</td>
<td>Premenopause perimenopause postmenopause</td>
<td>Allowance for age and smoking.</td>
</tr>
<tr>
<td>Palmer et al., 1992, USA</td>
<td>Case-control</td>
<td>858 AMI (non-fatal)</td>
<td>Postmenopause pre-perimenopause menopause at age &gt;50 years menopause at age &lt;45 years natural surgical</td>
<td>Allowance for education, occupation, smoking, hypertension, cholesterol, diabetes, body mass index, family history, physical activity, alcohol, coffee and HRT.</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CHD = coronary heart disease; HRT = hormone replacement therapy; IHD = ischaemic heart disease; OC = oral contraceptives; OR = odds ratio; RR = relative risk; CI = confidence interval.
CI 0.65 – 1997), including 2767 cases of CHD, the RR was 0.84 (95% in primary prevention (Petitti, 1998). Despite a considerable menopause, the RR being 1.50 (95% CI 0.67 – 1998), based on 84 cases of fatal CHD, a moderate, but not significantly increased risks of CHD were found in women with menopause.

In conclusion, this study does not support a substantial association between menopause and AMI risk. An OR of 0.6 (95% CI 0.4–1.0) was found in postmenopausal women compared with premenopausal ones (Rosenberg et al., 1983), and an OR of 0.5 (95% CI 0.2–0.9) was found in pre- and perimenopausal women compared to postmenopausal ones (Palmer et al., 1992), with higher risks in women with menopause at age <45 years than in women with menopause at age ≥50 years.

Thus, there is some suggestion that postmenopausal women may have a higher risk of CHD, although there is substantial heterogeneity in the results across various studies. This is not easily explained by the different types of study (cohort or case-control), the inclusion of fatal or non-fatal diseases, the inclusion of HRT users, the cut-off points selected for age at menopause and other identified factors. Some of these discrepancies may be the result of difficulties in the collection and analysis of epidemiological data on menopause. Besides uncertainties in the definition of the perimenopausal period, age at menopause is difficult to establish in women after hysterectomy and in those using HRT. Moreover, like any other time-related factor, it is important to make an extremely detailed age-adjustment for an unbiased quantification of risk (Pike, 1987).

Some hormonal changes at menopause might influence the risk of CVD. HRT may be protective for atherosclerosis and other cardiovascular risk factors (Writing Group for the PEPI trial, 1995; McCrohon et al., 1996), but may also be thrombogenic, as suggested by the short-term excess risk after starting HRT use in the Heart and Estrogen/Progestin Replacement Study (Daly et al., 1996; Jick et al., 1996; Perez Gutthann et al., 1997). Other potential effects include modifications of plasma lipid profile (Hulley et al., 1998), fibrinolysis (Petitti, 1998) and blood pressure (Hazzard, 1989); however, the potential role of such modifications on the risk of CVD is still undefined.

In conclusion, this study does not support a substantial relationship between age at menopause and non-fatal AMI; the overall epidemiological evidence is compatible with a moderate association between menopausal age and risk of CHD, also supported by the benefit reported for use of HRT in primary prevention (Petitti, 1998). Despite a considerable amount of research, precise epidemiological quantification of that risk is still lacking.

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References
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