Reduction in incidence and fatality of out-of-hospital cardiac arrest in females of the reproductive age

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Aims
The aim of this study was to determine relative risk (RR) of incidence and fatality of out-of-hospital cardiac arrest (OHCA) by gender and oestrogen status.

Methods and results
In a prospective, population-based observational study from 1998 through 2007, incidence and neurologically intact 1-month survival after OHCA were compared by gender after grouping: 0–12 years, 13–49 years, and ≥50 years according to menarche and menopause age. Among 26 940 cardiac arrests, there were 11 179 females and 15 701 males. Age-adjusted RR of females for OHCA incidence compared with males was 0.72 [95% confidence interval (CI), 0.58–0.91] in age 0–12 years, 0.39 (95% CI, 0.37–0.43) in age 13–49 years, and 0.54 (95% CI, 0.52–0.55) in age ≥50 years. Females aged 13–49 years had a significantly higher good neurological outcome than males [adjusted odds ratio (OR), 2.00 (95% CI 1.21–3.32)]. This sex difference was larger than that in the other age groups [adjusted OR, 0.82 (95% CI, 0.06–12.02) in age 0–12 years and 1.23 (95% CI, 0.98–1.54) in age ≥50 years].

Conclusion
Reproductive females had a lower incidence and a better outcome of OHCA than females of other ages and males, which might be explained by cardioprotective effects of endogenous oestrogen on OHCA.

Keywords
Out-of-hospital cardiac arrest • Sudden death • Cardiopulmonary resuscitation • Epidemiology • Gender • Women

Introduction
Sudden cardiac arrest (SCA) is the leading cause of death in the industrialized world, and approximately 50 000 events occur every year in Japan. Females are generally less likely to die of cardiovascular disease than males, and there are age-related differences in incidence and outcomes of SCA in males and females. But the aetiopathology of gender-related differences in cardiac arrest remains to be determined.

Animal models of cardiac arrest suggest that acute doses of oestrogen are associated with a good prognosis after cardiac arrest. Although some protective effects of oestrogen on the cardiovascular system have been suggested, no clinical studies have assessed the gender differences in incidence and outcomes of SCA by focusing on oestrogen exposure of females.

The Utstein Osaka Project is a large prospective population-based cohort study of out-of-hospital cardiac arrests (OHCA) in Osaka, Japan, which covered about 8.8 million residents and...
was launched in 1998. During the initial 9 years and 8 months, there were 29,192 emergency medical service (EMS)-resuscitated OHCA of presumed cardiac aetiology. Our hypothesis is that endogenous oestrogen has protective effects on OHCA incidence and outcome in this population.

**Methods**

**Study design, setting, and population**
This observational study enrolled all patients who suffered OHCA of presumed cardiac aetiology before EMS arrival, were treated by EMS, and were transported to medical institutions in Osaka Prefecture from 1 May 1998 through 31 December 2007. Osaka is the second largest prefecture in Japan with a population of 8,805,081 inhabitants in an area of 1892 km². The census population included 4,293,763 males and 4,495,591 females, and the proportion of people aged 65 years and over is 14.9% in 2000. Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation. The arrest was presumed to be of cardiac aetiology unless it was caused by trauma, drowning, drug overdose, asphyxia, exsanguinations, or any other non-cardiac causes. These diagnoses were determined by the physician in charge in collaboration with the EMS rescuers.

The research protocol was approved by the institutional review board of Osaka University with the assent of the EMS authorities of the local governments in Osaka Prefecture.

**Emergency medical service systems in Osaka**
In Osaka Prefecture, there are 35 fire stations with emergency dispatch centres. The EMS system is operated by the local fire stations. The free telephone emergency number 119 is used to call for ambulance from anywhere in Japan. Emergency services are provided 24 h each day by them, which are single-tiered in 33 stations and two-tiered in two stations. The latter uses medics followed by physicians. The most highly trained pre-hospital emergency care providers are the emergency life-saving technicians (ELSTs). When called, an ambulance is dispatched from the nearest fire station. Usually, each ambulance has a crew of three emergency providers including at least one ELST. They were allowed to insert an intravenous line and an adjunct airway, and to use a semi-automated defibrillator for OHCA patients during the study period. Specially trained ELSTs were permitted to insert tracheal tubes after July 2004 and administer intravenous epinephrine after April 2006. The use of automated external defibrillators by citizens was legally approved in July 2004. Do-not-resuscitate orders or living wills are not generally accepted in Japan. Emergency medical service providers are not permitted to terminate resuscitation in the field. Therefore, all patients with OHCA who were treated by EMS personnel were transported to hospital and registered in this study. Details of the EMS system in Osaka were described previously.

**Data collection and quality control**
Data were prospectively collected using a form that included all core data recommended in the Utstein-style reporting guidelines for cardiac arrests. Initial rhythm was recorded and diagnosed by the EMS personnel with semi-automated defibrillators on the scene, and confirmed by the physician who was responsible for the on-line medical direction. The time of EMS call receipt and vehicle arrival at the scene was recorded automatically at the dispatch centre. The time of collapse and initiation of bystander CPR was obtained by EMS interview with the bystander before leaving the scene. The time of defibrillation was recorded in the semi-automated defibrillator.

The data form was filled out by the EMS personnel in cooperation with the physicians in charge of the patient, transferred to the Information Center for Emergency Medical Services of Osaka, and then checked by the investigators. If the data sheet was incomplete, the relevant EMS personnel were contacted and questioned, and the data sheet was completed.

All survivors were followed up for up to 1 month after the event by the EMS personnel and investigators with the cooperation of the Osaka Medical Association and medical institutes in this area. Neurological outcome was determined by a follow-up telephone interview 1 month after successful resuscitation, using the cerebral performance category (CPC) scale: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; and category 5, death.

**Key group definition and main outcome measures**
To assess our hypothesis that endogenous oestrogen would influence OHCA incidence and their outcomes, we divided the patients into the following three groups: 0–12 years, 13–49 years, and 50 years and over according to the published data on mean age of menarche (12.2 ± 0.9 years) and menopause (49.5 ± 3.5 years) among Japanese females. According to this criterion, females aged 13–49 years would be considered to be exposed to endogenous oestrogen. The primary outcome measure was annual incidence and neurologically intact 1-month survival. Age-adjusted annual incidence of EMS-treated OHCA of presumed cardiac aetiology by gender were calculated by the direct method using 2000 census data and 1985 Japanese model population. Neurologically intact outcome was defined as CPC category 1 or 2. Secondary outcome measures included return of spontaneous circulation (ROSC), admission to hospital, and 1-month survival.

**Statistical analysis**
Patient characteristics were compared between groups using unpaired t-test for numerical variables, and χ² test or Fisher’s exact test for categorical variables. The relative risk (RR) and its 95% confidence interval (CI) of females against males for the incidence were calculated with the Mantel–Haenszel stratifying by 5-year age stratum. Multiple logistic regression analysis assessed the factors associated with better neurological outcome, and odds ratios (ORs) and their 95% CIs were calculated. As potential confounders, factors that were biologically essential and considered to be associated with clinical outcomes were taken in the multivariable analyses. These variables included age, gender, bystander witnessed status, location of arrest, activity of daily living before arrests, bystander CPR status, first recorded rhythm, time interval from call to the initiation of CPR by EMS personnel, and year of arrest. The interaction between gender and age group on outcomes was also calculated. All of the tests were two-tailed and a P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistical package ver16.0J (SPSS, Inc., Chicago, IL, USA).

**Results**
Figure 1 shows an overview of the study patients based on the Utstein template. A total of 53,526 OHCA were documented during these 9 years and 8 months. Resuscitation was attempted in 50,119, and 29,192 of them were presumed of cardiac aetiology.
Excluding 2166 victims who were witnessed by EMS, 26 940 were eligible for our analyses. Among them, 15 701 (58.3%) were males, 11 179 (41.6%) were females, and the remaining 60 (0.2%) were missed for gender. Of these victims, 10 190 were witnessed by bystanders, and 16 750 were not. Among witnessed cases, 2050 had ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), and 8023 had pulseless electrical activity (PEA) or asystole. Among non-witnessed cases, 845 had VF or pulseless VT and 15 754 PEA or asystole. We could not obtain neurologically intact 1-month survival data for 13 (0.04%) among 26 940 eligible victims. The proportions of neurologically intact 1-month survival among those with VF or pulseless VT and among those with PEA or asystole were 14.8 and 1.4%, respectively, when witnessed, whereas 6.5 and 0.4%, respectively, when not witnessed.

The characteristics of patients who experienced OHCA of presumed cardiac aetiology are shown in Table 1. Females were significantly older than males (mean age, 75.5 ± 16.4 vs. 67.9 ± 16.5 years; P < 0.001). The proportions of females in the 0–12 years group, the 13–49 years group, and the 50 years and over group were 127/311 (40.8%), 612/2120 (28.9%), and 10 440/24 449 (42.7%), respectively (P < 0.001). Females with cardiac arrest were more likely to have their arrests at home than males, and less likely to be witnessed and have VF as initial rhythm, although these differences are statistically insignificant in the age group of 0–12 years. The mean time intervals from call to CPR were similar between genders in each age group.

The incidence of OHCA increased with advancing age group in a non-linear manner in both genders (Table 2). Females had a lower incidence rate than males in every age group. The age-adjusted population-based incidence of OHCA of presumed cardiac aetiology was 32.5 per 100 000 person-years in males and 13.2 in females, and that of witnessed OHCA in males and females was 15.6 and 5.3, respectively. Age-adjusted RR of females for the incidence of OHCA in the group of age 13–49 years was 0.39 (95% CI; 0.37–0.43; P < 0.001), which was smaller than that in the group of age 0–12 years (0.72; 95% CI 0.58–0.91, P = 0.005) and 50 years and over (0.54; 95% CI 0.52–0.55, P < 0.001). In cases of bystander-witnessed OHCA of presumed cardiac aetiology, age-adjusted RRs of females for the incidence in the group of age 0–12 years, 13–49 years, and 50 years and over were 0.67 (95% CI 0.41–1.11, P = 0.092), 0.32 (95% CI 0.27–0.37, P < 0.001), and 0.45 (95% CI 0.43–0.47, P < 0.001), respectively.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age 0–12 years</th>
<th>Age 13–49 years</th>
<th>Age 50 years and over</th>
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<tr>
<td></td>
<td>Female (n = 127)</td>
<td>Male (n = 184)</td>
<td>P</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.7 (3.1)</td>
<td>2.0 (3.2)</td>
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<td>Arrest witnessed by bystanders</td>
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<td>21.2 (39)</td>
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<td>Location of arrest</td>
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<td>Home</td>
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<td>88.6 (163)</td>
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<td>Public space</td>
<td>4.0 (5)</td>
<td>4.9 (9)</td>
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<tr>
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<td>4.4 (8)</td>
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<tr>
<td>Good</td>
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<td>VF or pulseless VT</td>
<td>2.4 (3)</td>
<td>3.9 (7)</td>
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<tr>
<td>PEA</td>
<td>11.4 (14)</td>
<td>14.5 (26)</td>
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<td>Asystole</td>
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<td>81.6 (146)</td>
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<td>Other</td>
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<td>Call to CPR time by EMS personnel (min)</td>
<td>7.5 (2.4)</td>
<td>7.4 (2.6)</td>
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</tr>
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</table>

Data are mean (SD) and % (n).
CPR, cardiopulmonary resuscitation; EMS, emergency medical system; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity.

*Health care facility includes chronic facilities and medical clinics.
Table 3 shows the age-stratified outcomes after OHCA of presumed cardiac aetiology by gender. Among OHCAs of presumed cardiac aetiology, females aged 13–49 years had a significantly higher neurologically intact 1-month survival than males (4.9 vs. 4.4%; adjusted OR, 2.00; 95% CI 1.21–3.32, \( P < 0.001 \)) and 1-month survival (7.4 vs. 7.8%; adjusted OR, 1.57; 95% CI 1.05–2.36, \( P = 0.026 \)) as secondary outcomes. Females aged 13–49 years also showed significantly greater frequencies than males for ROSC (26.3 vs. 20.2%; adjusted OR, 1.90; 95% CI 1.49–2.44, \( P < 0.001 \)), admission (21.6 vs. 15.9%; adjusted OR, 2.09; 95% CI 1.60–2.72, \( P < 0.001 \)), and 1-month survival (7.4 vs. 7.8%; adjusted OR, 1.57; 95% CI 1.05–2.36, \( P = 0.026 \)). In the group aged 0–12 years in which only a few patients survived, frequency of neurologically intact 1-month survival of females was similar to that of males (1.6 vs. 1.6%; adjusted OR, 0.82; 95% CI 0.52–0.55, \( P = 0.86 \)).
group aged 50 years and over, on univariable analysis, females had poorer outcomes than males. However, on multivariable analysis, females had a greater neurologically intact 1-month survival (1.3 vs. 2.2%; adjusted OR, 1.23; 95% CI 0.98–1.54; P = 0.073) and 1-month survival (3.4 vs. 5.2%; adjusted OR, 1.19; 95% CI 1.03–1.37; P = 0.019), though the differences were small.

When limiting witnessed OHCA with presumed cardiac aetiology, findings were almost identical as those in the whole OHCA. Neurologically intact 1-month survival in witnessed OHCA of females and males was 8.0 vs. 7.7%, respectively (adjusted OR, 0.83; 95% CI 0.07–8.60, P = 0.86) in the group aged 0–12 years, 9.7 vs. 8.2%, respectively (adjusted OR, 2.08; 95% CI 1.16–3.73, P = 0.006) in the group aged 13–49 years, and 2.9 vs. 4.2%, respectively (adjusted OR, 1.28; 95% CI 0.98–1.67, P = 0.080) in the group aged 50 years and over.

Discussion

This study showed that females of reproductive age had a lower incidence of OHCA and better outcomes than males in a large population. Although many studies have examined gender- and age-related differences in OHCA occurrence and outcome, the impact of oestrogen status on gender difference was not fully evaluated in the preceding studies.

This study suggests that endogenous oestrogen is protective against the occurrence of OHCA. The mechanism of how oestrogen works protectively against coronary heart disease including SCA is still unclear. It is reported that oestrogen reduces levels of lipoprotein (a), inhibits oxidation of low-density lipoprotein, and improves vascular function. In animal models, oestrogen has cardioprotective effects by binding the oestrogen receptor on vascular cells and producing nitric oxide, which is required for the maintenance and repair of vascular endothelium and dilation of vascular smooth muscle. In autopsies of female SCA victims, vulnerable plaques varied by age, and the association between hypercholesterolaemia and coronary plaque rupture was found only in post-menopausal age. Our data are consistent with these previous studies and strengthen the evidence that endogenous oestrogen has a protective effect against the occurrence of coronary heart disease.

In addition to the protective effect on the occurrence of OHCA, better outcomes after OHCA in females of the reproductive age were demonstrated. Some experimental studies showed that oestrogen might have cardioprotective effects for cardiac arrest. Another report suggested that oestrogen had a possible neuroprotective effect. In an animal experiment, a single low dose of E2, one of the major oestadiols in humans, has neuroprotective effects on CPR after cardiac arrest. These findings suggest the protective effects of endogenous oestrogen against not only the occurrence but also survival after cardiac arrests.

If oestrogen exposure reduces the risk for incidence and fatality of SCA, hormone replacement therapy (HRT) might be effective for reducing the occurrence of OHCA and improving survival after OHCA. Observational studies suggested that post-menopausal HRT reduced CVD and sudden death. However, some randomized controlled trials indicated that HRT rather increased overall coronary heart disease risk, and HRT is not recommended for the prevention of coronary heart disease.

This discrepancy between observational studies and randomized trials is under debate, but it could be partially explained by factors such as the initiation time, dose, and delivery route of HRT, as well as genetics, statin use, and socioeconomic status of the recipients. Further study on the effect of oestrogen as a new therapeutic approach for OHCA would be needed.

This study also showed a lower incidence of OHCA and better outcomes in females compared with males regardless of the age group. There might be other factors than oestrogen which were associated with lower OHCA occurrence and fatality in females. Cardiovascular disease is a major cause of SCA, and representative risk factors for CVD, such as smoking, hypertension, and diabetes mellitus, partially explain these results because CVD risk factors were less likely to occur in females than in males. Some underlying diseases of SCA, such as Brugada syndrome and hypertrophic cardiomyopathy, which are less likely to occur in females, might affect the frequency imbalance of OHCA between genders. A heavy alcohol consumption and physical exercise could also confound the lower incidence of SCA in females because fewer females drink excess alcohol or exercise vigorously. Unfortunately, no information about a history of smoking, drinking, and physical exercise was available in this study. Androgens and testosterone might also be taken into consideration. Although one study suggested that high androgen levels were associated with an increased risk of CVDs, the effects of male sex hormones on CVDs are left unresolved.

Limitations

This study has some limitations. First, we stratified study patients at ages of 12 and 50 years based on the mean age of menarche and menopause in Japanese females. We did not obtain any information on menarche and menopausal status and history of HRT from each female suffering from OHCA. Therefore, we might underestimate the effects of active hormonal status owing to misclassification. However, the prevalence of HRT in Japanese females is <10%, and its influences would be small. Secondly, the presence of CVD and the role of CVD risk factors were not assessed in this study. Thirdly, information about the care after admission was lacking. In-hospital diagnosis (e.g. coronary angiographies) and treatment (e.g. hypothermia) might affect survival after OHCA. Fourthly, data integrity, validity, and ascertainment biases are potential limitations. The data collected by EMS providers included relatively few data points that were easy to attain in an accurate manner at the scene, based on the clear and concise Utstein-style guidelines for reporting cardiac arrest. The uniform data collection, consistent definitions, time synchronization process, and large sample size in the population-based cohort study were intended to minimize these potential sources of bias.

More detailed information about age of menarche and menopause, HRT use, and other potential factors associated with OHCA, including CVD risk factors and in-hospital diagnosis and treatment, and measurement of oestrogen concentration in females suffering from OHCA or interventional trial of HRT, would be needed for better ascertainment of the protective effects of oestrogen on OHCA.
Conclusion
Females in the period between menarche and menopause had a lower incidence and better outcomes of OHCA, which might be explained by cardioprotective effects of endogenous oestrogen on OHCA occurrence and outcome.

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References


