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Ricci S, Capocaccia R, Manna P, Piscicelli C, Serra GB
Trimboli A

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

ORIGINAL PAPERS, CLINICAL CARDIOLOGY

Hormone Replacement Therapy and Mortality for Ischaemic Heart Disease, Cerebrovascular Diseases and Breast Cancer in Italy and the U.S.A.

S. Ricci, G. B. Serra, C. Piscicelli, P. Manna, A. Trimboli, R. Capocaccia[1]

Observational studies indicate that hormone replacement therapy (HRT) reduces ischaemic heart disease (IHD) mortality, but not stroke mortality; on the other hand a slight increase in breast cancer (BC) after 5 years of HRT treatment is widely recognised. Prescription of HRT in countries with a generally low IHD incidence rate may thus lead to a different risk/benefit balance for long-term HRT users. In this study we considered female mortality due to IHD, cerebrovascular diseases (CeVD), all malignant neoplasms (MN) and BC in Italy and in the U.S.A. to detect any possible differences that could alter the HRT risk/benefit assessment. In 1997, in Italy as well as in the U.S.A., cardiovascular diseases were the leading cause of death in women aged 50 or over, but with some differences in IHD and CeVD mortality in particular. In Italy, in women aged 50 and over, 12.6 % of all female deaths were attributed to IHD and 14.6 % to CeVD, whereas in the U.S.A. 19.4 % were due to IHD and 8.1 % to CeVD. In the U.S.A., IHD mortality remained constantly higher than CeVD mortality throughout all age decades whereas in Italy this was only the case in the 50–79 age group. The proportion of deaths due to IHD was always higher in the U.S.A. than in Italy. On the other hand, BC mortality is quite similar in the two countries: 3.6 % and 3.0 % of all deaths in women aged 50 or over, in Italy and in the U.S.A, respectively. IHD mortality is higher than BC mortality among American women, and their ratio by age decades is almost twice as high as the one observed in Italy for each decade. In the U.S.A., among women aged 40–49, 50–59, 60–69, 70–79 and ≥ 80 years, the IHD/BC ratios were 0.5, 1.0, 2.5, 5.2 and 14.6 respectively vs 0.2, 0.3, 1.0, 3.0 and 8.5 in Italy. In the light of these mortality differences, if ongoing randomised clinical trials confirm the use of HRT as primary, or secondary prevention in heart disease, it will still be important to take into account a different risk/benefit ratio for long-term HRT users in countries with an IHD incidence lower than that registered in the U.S.A. *J Clin Basic Cardiol 2002; 5: 105–108.*

Key words: hormone replacement therapy, ischaemic heart disease, cerebrovascular disease, breast cancer, mortality, Italy, USA

Menopause affects lipid profile, vascular functions and metabolism of carbohydrates resulting in an increased cardiovascular risk. It was widely recognised that many of these changes can be reversed by hormone replacement therapy (HRT) [1, 2]. Moreover, a great number of epidemiological studies have shown a reduced cardiovascular morbidity and mortality in HRT users. In the light of these findings cardiovascular diseases (CVD) were regarded also as a long-term effect of ovarian failure so that in the early nineties HRT was recommended as an adequate prevention measure [3, 4].

However, a great number of pathologies fall into CVD category. Among these, ischaemic heart disease (IHD) and cerebrovascular diseases (CeVD) – especially stroke – are the most frequent. The protective effect of HRT has been observed only for IHD, whilst data on its effect on stroke are contradictory and at present inconclusive [5–9].

The different effects of HRT on IHD and stroke implies that the risk-benefit balance is related to IHD and CeVD (stroke) incidence. Therefore considering data from international studies – mostly U.S.A. studies – it might be important to take into account IHD and stroke mortality data from each country to assess possible similarities or differences with those reported in the U.S.A.

Methods

This study analysed 1997 mortality data from Italy and the United States. For Italy, the analysed data were those provided by the National Statistical Institute (ISTAT), divided by causes of death, sex and age decades. For the United States statistical information is compiled into a national database through the Vital Statistics Cooperative Program of the National Center for Health Statistics (NCHS), Center for Disease Control and Prevention. We have used data based on unpublished worktables available on the NCHS Web page, at www.cdc.gov/nchs/datawh/statab/upubd/mortabs/gmwk291.htm, divided by causes of death, sex, race and age decades.

Cause-of-death statistics are classified in accordance with the Ninth Revision, International Classification of Diseases (ICD-9). According to this classification, the Italian and U.S.A. numbers of deaths reported in this study, correspond to code numbers 410–414 for IHD, 430–438 for CeVD, 174 for breast cancer (BC), and 140–208 for all malignant neoplasms (MN). A slight discrepancy in data available for the two countries concerns CVD as a whole, since Italian data referred to deaths caused by all CVD – codes 380–459 – and U.S.A. data referred only to deaths caused by major CVD – codes 390–448. For all female deaths in the two countries, we calculated the percent mortality due to CVD, IHD, CeVD, all MN and BC in women aged 50 and over and by age decades from 40 upwards. We also calculated the ratio between IHD and BC numbers of deaths over the above age decades.

Results

In 1997, total female mortality in Italy was 274,814 (0.93 %) deaths, out of a female population of 29,590,246, while mortality in the U.S.A. was 1,160,206 (0.85 %) out of a total female population of 136,618,400. Among all women who died in that year, those aged fifty and over accounted for 95.9 % in Italy, and for 91.8 % in the U.S.A. Among women aged fifty

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From the Department of Obstetrics and Gynaecology, Cristo Re Hospital, and the [1]Laboratory of Epidemiology and Biostatistics, Istituto Superiore di Sanità, Rome, Italy

Correspondence to: Dr. Stefania Ricci, Department of Obstetrics and Gynaecology, Cristo Re Hospital, Via delle Calasanziane 25, 00167 Rome, Italy; e-mail: mc4699@mclink.it

and over, deaths due to all CVD accounted for 131,503 in Italy (47.8 % of all female deaths), whereas in the U.S.A., among women of the same age, mortality due to major CVD only, was 41.8 %.

Examining the two main causes of CVD mortality, it appears (Tab. 1) that in Italy among all female deaths, those due to IHD and to CeVD in women aged fifty and over were 12.6 % and 14.6 %, respectively, while in the U.S.A. 19.4 % were attributed to IHD and 8.1 % to CeVD.

Besides CVD, another significant cause of death are MN. In women aged fifty and over, MN accounted for 21.3 % of all female deaths in Italy, and for 20.3 % in the U.S.A. Deaths caused by BC were 3.6 % in Italy and 3.0 % in the U.S.A. (Tab. 1).

Considering different age decades (women aged 40 to > 80), the numbers of deaths registered for each decade were about twice as high as those registered for the previous decade both in Italy and in the U.S.A. (Tab. 2). In Italy, ISTAT data indicate that 1.8 % of all female deaths occurred in the 40–49 age decade, 4.2 % in the 50–59 age decade, 10.0 % in the 60–69 age decade, 22.5 % in the 70–79 age decade, and 59.1 % in women aged 80 and over. In the U.S.A., the respective percentages were 3.6 %, 5.9 %, 11.6 %, 23.7 % and 50.4 %.

In Italy, among women aged 40–49, IHD caused 0.07 % of 5,027 deaths (Tab. 3). This percentage increased to 0.23 % in the subsequent age group (50–59), to 0.94 % in women aged 60–69, to 2.99 % in women aged 70–79, and to 8.45 % in women aged 80 or more. In the U.S.A., IHD mortality amounted to 0.23 % of the total female mortality in the 40–49 age group, to 0.66 % in the 50–59 age group, to 1.78% in women aged 60–69, to 4.56 % in women aged 70–79, and to 12.39 % in women aged 80 or more.

In Italy, among the five age decade groups, CeVD mortality of the total female mortality was 0.10 %, 0.21 %, 0.74 %, 2.91 %, and 10.75 %, respectively. In the U.S.A., the corresponding figures were 0.17 %, 0.27 %, 0.59 %, 1.79 % and 5.44 % (Tab. 3).

Among women aged 40–49 deaths due to MN represented 1.00 % of all female deaths in Italy, the percentage increasing to 2.38 % in women aged 50–59, to 4.57 % in women aged 60–69, to 6.69 % in women aged 70–79 and to 7.62 % in the 80+ group. In the U.S.A., in the same age groups, MN mortality accounted for 1.32 %, 2.61%, 4.53%, 6.77% and 6.39%, respectively (Tab. 3). In Italy, BC caused 0.34 % of all female deaths in the 40–49 age group, 0.68 % in the 50–59 age group, 0.95 % in the 60–69 group, 1.00 % in the 70–79 group, and 0.99 % among women aged 80 and more. In the U.S.A., BC mortality was 0.42 %, 0.61 %, 0.71 %, 0.87 %, and 0.84 %, respectively (Tab. 3).

The different increases in IHD and CeVD mortality seem to follow different patterns in Italy and in the U.S.A., as shown in Figure 1. In Italy, IHD mortality and CeVD mortality show a similar increase up to the 70–79 age decade when the CeVD mortality starts to exhibit a steeper increase. In the U.S.A., IHD mortality shows a steeper increase from 50 years up, whereas CeVD shows a significantly lower incidence. Figure 1 also shows that BC mortality follows the same pattern in both countries throughout all age decades examined.

For each of the five age groups, the ratio between deaths attributed to IHD and to BC varied among Italy and the U.S.A.: in the first group of women, aged 40–49, the IHD/BC ratio was 0.2 in Italy vs 0.5 in the U.S.A.; the corresponding figures for the following age groups were 0.3 vs 1.0, 1.0 vs 2.5, 3.0 vs 5.2 and 8.5 vs 14.6 (Tab. 4).

Table 1. Number of deaths and mortality-% of total female deaths in Italy (n = 274,814) and in the U.S.A. (n = 1,160,206) due to ischaemic heart disease (IHD), cerebrovascular diseases (CeVD), all malignant neoplasms (MN) and breast cancer (BC), in women aged fifty and over (1997)

	ITALY		U.S.A.	
	Deaths	%	Deaths	%
IHD	34,701	12.6	225,257	19.4
CeVD	40,176	14.6	94,169	8.1
All MN	58,484	21.3	235,869	20.3
BC	10,042	3.6	35,399	3.0

Table 2. Number of deaths and mortality-% of total female deaths in Italy (n = 274,814) and in the U.S.A. (n = 1,160,206) by age decades in women aged forty and over (1997)

Age	40–49 deaths (%)	50–59 deaths (%)	60–69 deaths (%)	70–79 deaths (%)	80+ deaths (%)
ITALY	5,027 (1.8)	11,510 (4.2)	27,560 (10.0)	61,932 (22.5)	162,486 (59.1)
U.S.A.	41,816 (3.6)	69,598 (5,9)	135,157 (11.6)	275,402 (23.7)	585,057 (50.4)

Table 3. Number of deaths and mortality-% of total female deaths in Italy (n = 274,814) and in the U.S.A. (n = 1,160,206) due to ischaemic heart disease (IHD), cerebrovascular diseases (CeVD), all malignant neoplasms (NM) and breast cancer (BC), by age decades in women aged 40 and over (1997)

Age	40–49 deaths (%)	50–59 deaths (%)	60–69 deaths (%)	70–79 deaths (%)	80+ deaths (%)
ITALY					
IHD	193 (0.07)	643 (0.23)	2,604 (0.94)	8,217 (2.99)	23,237 (8.45)
CeVD	280 (0.10)	598 (0.21)	2,031 (0.74)	8,003 (2.91)	29,544 (10.75)
All MN	2,762 (1.00)	6,557 (2.38)	12,572 (4.57)	18,392 (6.69)	20,963 (7.62)
BC	953 (0.34)	1,891 (0.68)	2,633 (0.95)	2,774 (1.00)	2,744 (0.99)
Deaths for all causes	5,027	11,510	27,560	61,932	162,486
U.S.A.					
IHD	2,689 (0.23)	7,710 (0.66)	20,690 (1.78)	53,006 (4.56)	143,851 (12.39)
CeVD	1,979 (0.17)	3,196 (0.27)	6,921 (0.59)	20,877 (1.79)	63,175 (5.44)
All MN	15,426 (1.32)	30,355 (2.61)	52,655 (4.53)	78,619 (6.77)	74,240 (6.39)
BC	4,914 (0.42)	7,179 (0.61)	8,238 (0.71)	10,147 (0.87)	9,835 (0.84)
Deaths for all causes	41,816	69,598	135,157	275,402	585,057

Table 4. Ratio between numbers of deaths for ischaemic heart disease (IHD) and breast cancer (BC), in Italian women and in women from the U.S.A. aged 40 and over by age decades (1997)

Age	40–49	50–59	60–69	70–79	80+
Ratio IHD/BC (Italy)	0.2	0.3	1.0	3.0	8.5
Ratio IHD/BC (U.S.A.)	0.5	1.0	2.5	5.2	14.6

Discussion

1997 female mortality rates amounted to less than 1 % both in Italy and in the U.S.A., with a low incidence of death prior to the age of 50. In both countries, thus, mortality was quite similar, and well in agreement with what is to be expected in industrialized nations.

In both countries, CVD appears to be the leading cause of death in women aged fifty or over, thus being in focus as a main prevention issue. The proportion of deaths caused by CVD was higher in Italy (48 % of all deaths), than in the USA (approximately 42 %). This difference warrants further investigation since Italian data utilized in this study considers all CVD deaths, whereas American data includes only deaths attributed to major CVD. Malignant neoplasms, in both countries, accounted for approximately one out of five deaths in women aged fifty or over. BC, in particular, amounts to 3 % of total female mortality in this age-group in both countries.

Due to such great similarities between Italian and American statistical data, in terms of total female, CVD and MN mortality, interpretations, suggestions and risk/benefit balances originating from the U.S.A. frequently have been accepted as being equally valid for Italy. However, these equivalencies in mortality are too general to document definite similarities between the two populations. Thus, in this study, more detailed information has been incorporated to verify whether data and perspectives from one country can actually be safely applied to another population.

Cardiovascular diseases are a rather heterogeneous group, including myocardial infarction as well as peripheral thrombophlebitis. Among all these different pathologies, the two main causes of CVD deaths are IHD and CeVD. When focusing our attention on these two pathologies, several differences evolved between the two countries: in Italy, IHD mortality in women aged 50 or over is lower than in the USA. Also, while in Italy CeVD and IHD deaths show similar figures, in the USA CeVD mortality is lower than IHD mortality. Therefore, in contrast with the general impression of similarity in CVD mortality, apparently, IHD deaths are much more frequent in the U.S.A. than in Italy, whereas CeVD deaths are more common in Italy (Tab. 1).

These differences in CVD mortality are important in the light of HRT use: observational studies after long-term replacement therapy suggested a beneficial effect for IHD prevention but failed to register any substantial benefits for CeVD prevention [5–10]. In the light of these differences, long-term HRT should yield larger benefits in North American women – with a higher IHD mortality and a lower incidence of fatal CeVD – and probably less beneficial effects in Italian women, who exhibit a lower IHD mortality and a higher CeVD mortality.

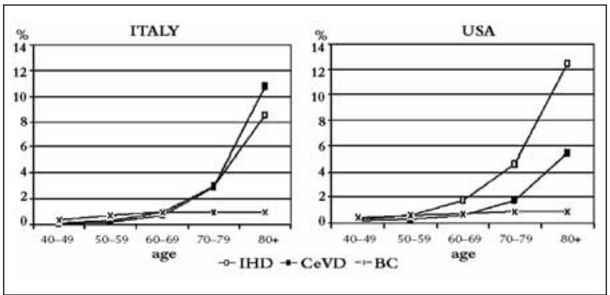

Figure 1. Mortality-% of total female deaths in Italy (n = 274,814) and in the U.S.A. (n = 1,160,206) due to ischaemic heart disease (IHD), cerebrovascular diseases (CeVD), and breast cancer (BC), by age decades in women aged 40 and over (1997)

If the HRT beneficial effect on CVD is less pronounced in Italy than in the U.S.A., but BC mortality remains very similar in both countries, specific evaluation is compulsory before transferring therapeutical strategies from one country to another [11–13].

Further consideration also has to be given to data on female deaths by age decades. While in Italy IHD and CeVD mortality increased in a similar pattern up to the 70–79 age decade, with a subsequent steeper incline of CeVD deaths, in the U.S.A. IHD mortality was constantly higher than CeVD mortality in all age groups, and always higher than the IHD mortality registered in Italy (Tab. 3 and Fig. 1). As already stated, MN and BC mortality were very similar among Italian and American women of all age decades.

HRT acceptance is quite heterogeneous, in Italy as well as in the U.S.A., exhibiting considerable North/South differences. In Italy, however, several observational studies indicate that only a small minority of women uses HRT, with a strong tendency to use HRT only for a short period of time, chiefly during the menopausal transition. This poor acceptance of estrogen therapy has been attributed to merely weak concerns about CVD incidence, but to an exaggerated fear of BC, both among women and general practitioners. Although several medical surveys confirm this attitude, our analysis of age group mortality indicates that in the 40–49 age group for each woman dying of IHD, 5 will die of BC in Italy but only 2 in the U.S.A. These differences between Italian and North American epidemiological data are confirmed by the calculated ratios between the number of deaths due to IHD and those due to BC in the 5 respective age groups (Tab. 4). While in the U.S.A. the IHD/BC mortality ratio reaches equilibrium in women aged 50–59, in Italy this equilibrium is reached a full decade later. In the light of these data it becomes quite comprehensible that Italian women in their fifties are much more concerned about BC than about IHD.

As IHD mortality in Italy is more common among older women whereas in the U.S.A. more younger women are affected, we may discuss whether HRT prevention should be postponed in our country. However, the risk/benefit balance in older women still remains to be ascertained. For the time being, although observational studies support HRT benefits for CVD prevention, no randomised studies have definitely confirmed HRT benefits for primary or secondary CVD prevention. The only randomised study of secondary prevention published so far [14] yielded some negative, often critisized results. Currently, randomised prevention studies are ongoing in the U.S.A. and in Europe, but results will not be available for the next years. Once these data have been presented, it will be mandatory to discern country-specific peculiarities regarding mortality and morbidity, before readily transferring any possible conclusions to other countries.

To conclude, we like to stress that in Italy, as well as maybe in other European countries with an equally low IHD-risk, women who are to receive long-term HRT, should be selected much more carefully than in countries where IHD mortality is altogether higher and more frequent in younger women.

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