

BRIEF REPORT

Change in Covid-19 infection and mortality rates in postmenopausal women

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Abstract

Objective: To evaluate whether the rates of COVID-19 infection and death in women versus men differ with age.

Methods: From data provided by the Italian National Institute of Statistics, we calculated the respective proportions of women among COVID-infected versus noninfected populations and male versus female infection and death rates, stratifying the results into 10-year age groups.

Results: The prevalence of COVID-19 infection was 3.6% higher in women than in the general population from 20 to 59 years of age, then decreased to –13.3% below that of the general population between 60 and 89 years of age. Death rates among infected women showed the opposite age-related trend. In infected women, the mortality rate was –77.4% lower than that of men aged 20 to 59 years. Between 60 and 89 years of age, the difference in women decreases to –34.5% below that of men.

Conclusions: Our results indicate opposing age-related trends among women in infection and death rates due to COVID-19. Further studies are needed to examine the contribution of the phases of the female reproductive cycle to the observed variations.

Key Words: Age – COVID-19 – Estrogens – Gender – Hormones – Infection – Menopause – Sex.

The number of deaths due to COVID-19 infection is lower in women than in men.^{1,2} However, epidemiology has not provided much support for a pathogenetic mechanism. When considering men and women of all ages, women seem to be infected at similar rates to men, but nevertheless die less frequently.² Several opinion pieces have been published to explain the possible mechanisms underlying this phenomenon.³⁻⁵ In particular, estrogens have been hypothesized to be crucial in modulating viral infection and the progression of the disease via an action on immune/inflammatory responses and ACE2 expression. As ACE2 is involved in both viral entry into the cell and in antagonizing the evolution of the disease,^{1,6,7} a complex modulation of ACE2 activity by estrogens has been theorized.³ However, thus far there has been no investigation distinguishing women in reproductive age from those in postmenopause to provide support for a role of reproductive factors, if any. A recent study performed in Chinese women reported a higher prevalence of infection and an overall lower mortality in women between 40 and 60 years of age,⁸ but those results were not

corrected for the natural age-related changes in the prevalence and mortality in the general female population, and failed to provide additional evidence on a possible role exerted by reproductive factors.

Here we present the results of a study of the Italian population designed to assess whether the rate of COVID-19 infection is sex-related, and if this relationship changes with age. The data are presented in conjunction with those of sex-related mortality by COVID-19 stratified by age, to provide a composite picture of the phenomenon.

METHODS

The Italian National Institute of Health has recently published data on COVID-19 infection and death rates in Italy for the period from the infection outbreak (February 22, 2020) to September 22, 2020.⁹ The data, stratified by sex and 10-year age groups, were based on COVID-19-positive swab tests analyzed by the Italian National Institute of Health-accredited laboratories and information reported on death certificates. The numbers of infections and deaths in individuals 20 to 89 years of age are reported, stratified by 10-year age categories.⁹

The proportion of women/100 individuals (women and men) was calculated in the cohort of infected individuals, and the same calculation was made for noninfected individuals, using the 2019 Italian National Institute of Statistics database pertaining to the Italian population.¹⁰ We calculated the percentage differences in the proportions of women in the infected versus noninfected populations by dividing the difference in proportions by the proportion of women in the

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noninfected population and multiplying by 100. Thus, the proportion of COVID-19 infections among women was expressed as a percentage variation with respect to the proportion of women among noninfected individuals. The death rates (deaths/100 individuals) among COVID-19-infected individuals were also calculated, as was the death rate for noninfected individuals, the latter using the 2018 Italian National Institute of Statistics database for the Italian population,¹¹ adapted for a period of 210 days. The excess death rate due to COVID-19 was considered as the difference in death rate between infected and noninfected individuals, and the excess death rate in women is expressed as a percentage variation from the excess death rate in men (female excess death rate/male excess death rate × 100). Contingency tables and the chi-squared test were used to compare frequencies.

RESULTS

The dataset contained 263,900 infected individuals. In individuals from 20 to 59 years of age, the proportion of women (women/100 individuals) among COVID-19-infected and noninfected individuals were 0.517 and 0.498 (+0.018), respectively (Table 1). In individuals of 60 to 89 years of age on the other hand, the proportion of women among infected and noninfected individuals were 0.480 and 0.557 (−0.077), respectively (Table 1). Accordingly, the prevalence of women in the COVID-19-positive cohort was 3.6% above that of the general population in the 20 to 59-year age group, and −13.3% below that of the general population in the 60 to 89-year age group (Fig. 1).

Among infected individuals, 29,190 died (11.1%). In a similar period of time, the death rate in noninfected individuals was 3.99%. Hence, the estimated excess death rate due to COVID-19 was 7.1%. In the 20 to 59-year age group, the COVID-19-related death rate in women was −74.4% that of men, and in the 60 to 89-year age group it was −34.5% (Fig. 1).

DISCUSSION

When corrected for data from the general population, infection by COVID-19 during the investigation period seemed to be

TABLE 1. Proportion and number (italics) of women among noninfected and COVID-19-infected individuals by age group and their difference

Age (y)	Noninfected (n/100)	Infected (n)	Infected–noninfected	P value
20-29	0.483 <i>62,012</i>	0.483 <i>27,284</i>	0.000	1.000
30-39	0.497 <i>70,742</i>	0.508 <i>28,366</i>	0.011	0.0002
40-49	0.503 <i>92,426</i>	0.544 <i>39,857</i>	0.041	0.0001
50-59	0.511 <i>93,522</i>	0.530 <i>51,318</i>	0.019	0.0001
60-69	0.522 <i>73,372</i>	0.412 <i>36,620</i>	−0.110	0.0001
70-79	0.543 <i>59,625</i>	0.434 <i>37,016</i>	−0.109	0.0001
80-89	0.607 <i>35,555</i>	0.595 <i>43,439</i>	−0.012	0.0001

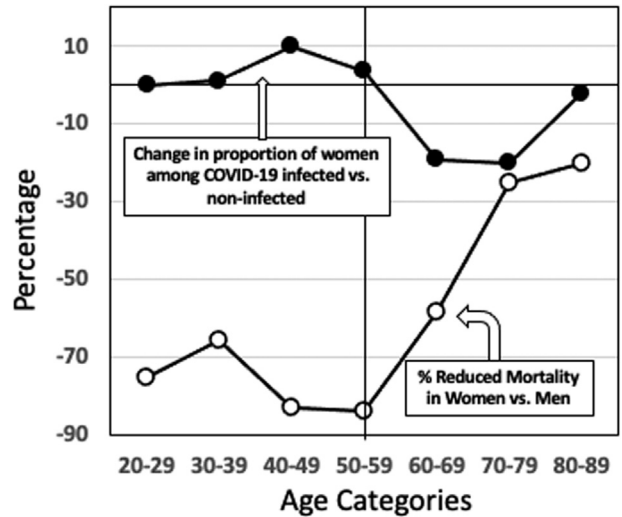


FIG. 1. Gender-related infection and death by COVID-19. Percentage variation in the prevalence of women among COVID-19-infected versus noninfected (line 0) individuals (closed circles). Percentage reduction in death rate in women versus death rate in men (line 1) (open circles). For each age group, sample size and proportion of woman (women/100 individuals) in infected/noninfected individuals was: 20 to 29 years, $n = 27,284$ (0.483/0.483); 30 to 39 years, $n = 28,366$ (0.508/0.497); 40 to 49 years, $n = 39,856$ (0.544/0.503); 50 to 59 years, $n = 51,318$ (0.529/0.511); 60 to 69 years, $n = 36,620$ (0.412/0.522); 70 to 79 years, $n = 37,016$ (0.434/0.543); 80 to 89 years, $n = 43,439$ (0.595/0.607).

slightly more frequent in women than in men of 20 to 59 years of age, but less frequent after the age of 60. Hence, the prevalence of infection of women versus men declined markedly in the postmenopausal age, reaching negative peaks of −25% between 60 and 79 years of age, then returning to values similar to those of men in the older age group (80–89 y). These data differ slightly from those published in a Chinese population, in which the infection rate in women seemed to increase between 40 and 60 years and decrease thereafter.⁸ As mentioned, however, those data were not corrected for age-related variations in the sex ratio in the Chinese population. Differences in genetics, lifestyle, and environmental conditions between China and Italy may also be involved.

Data on deaths of infected Italian women have previously been reported in a smaller sample of cases,¹² but present evaluation comprised 115,000 more infected individuals, and confirms that the COVID-19-related death rate markedly increases in women after 60 years of age, specifically from −74.4% to −34.5% ($P < 0.0001$) that of men. This highlights opposite trends in the COVID-19-infection and death rates in women, with the turning point for both phenomena occurring between 50 and 59 years of age. As the median age of menopause in Italy is 50 years of age (range 30–61 y), with residual ovarian activity being present in many women between 50 and 59 years of age, it is possible that the category 60 to 69 years of age is the one in which the absence of reproductive hormones becomes fully manifest.

Infection is the consequence of COVID-19 spike proteins binding to the ACE2 enzyme. ACE2 is expressed in several tissues, including pneumocytes, enterocytes, and vascular

endothelial cells of the heart, kidney, and brain.⁶ Few studies have thus far examined the modulation of ACE2 by estrogens, but one study has reported ACE2 stimulation on vascular endothelial cells of the heart,¹³ and another on ACE2 inhibition on bronchial epithelial cells in women.¹⁴ Our data indicate that the COVID-19 infection rate may be higher in women during the reproductive age, and lower in advanced postmenopause. This lends weight to the permissive role of estrogens on ACE2 expression. Further support for a permissive role of estrogens on ACE2 expression is provided by the lower mortality seen in our population of women in the reproductive age. Indeed, ACE2 has been hypothesized as exerting an important protective effect against disease progression. Similarly, the rapid reversal of infection and mortality trends after 50 to 59 years of age suggests that in the absence of gonadal steroids, ACE2 expression is reduced, the rate of infection by COVID-19 is decreased, but the mortality rate increased.

Alternatively, by acting on the immune system, estrogens may reduce disease progression and favor virus clearance,³⁻⁵ making COVID-19 infection less deadly in women in the reproductive age, whereas the opposite may occur in the estrogen-free environment characteristic of older, postmenopausal women. Further research is therefore needed to clarify whether hormones such as estrogens or estrogen receptor modulators may influence the rates of COVID-19 infection and mortality. Indeed, although our data seem to indicate that reproductive hormones play an important role in modulating women's susceptibility to infection, they fail to wholly explain the difference in COVID-19-related death rates between female and males, indicating that other, still unclear mechanisms are operative.

Moreover, our analysis has several limitations. The data analyzed were rather crude, and we were therefore unable to correct for many confounding variables, such as comorbidities or lifestyle.⁵ In particular, the age at menopause was not available, and we could not therefore perform a precise evaluation of the role played by menopause. Nonetheless, in comparison with other studies published to date, this is the only analysis in which data have been corrected for sex ratio and mortality among the general population.

CONCLUSION

Our results indicate opposing age-related trends among women in infection and death rates due to COVID-19. Further studies are needed to examine the contribution of the phases of the female reproductive cycle to the observed variations.

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