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Gender difference in the incidence of shingles

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SUMMARY

We investigated age- and gender-specific incidence of shingles reported in a large sentinel practice network monitoring a defined population over the years 1994–2001. In total, 5915 male and 8617 female incident cases were studied. For each age group, we calculated the relative risk of females to males presenting with shingles. Incidence rates of chickenpox and herpes simplex were examined similarly. Shingles incidence was greater in females in each age group (except for 15–24 years). Relative risks (female to male) were greatest in age groups 45–64 years (1·48) and 0–14 years (1·43). There were no gender differences in the incidence of chickenpox except in the 15–24 years age group (female excess): for herpes simplex there were female excesses in all age groups. Gender-specific age-standardized incidence rates of shingles were calculated for each year and showed a consistent female excess in each of the 8 years (average annual excess 28 %).

INTRODUCTION

Shingles is caused by the varicella-zoster virus. The precise pathogenesis is not fully understood but involves reactivation of latent varicella infection in individual dermatomes [1]. The clinical manifestation (vesicular rash in a dermatomal distribution accompanied by pain) is unlikely to be confused with other diagnoses but in the United Kingdom it is rare for diagnosis to be confirmed by virological investigation.

Published data on the incidence of shingles ranges between 1·3 and 4·8 per 1000 cases annually [2–5]. Few studies record age-standardized data and thus it is difficult to compare results. This study is concerned solely with possible gender differences. Liesegang, in a review of several epidemiological studies suggested there may be a slight excess incidence in females over males [6]. We investigated age- and gender-specific incidence of clinically diagnosed shingles as reported in the surveillance network of the Royal College of General Practitioners (RCGP). This practice network has been used to recruit practices to the national morbidity surveys in England and Wales [7]. A previous report from this database has shown remarkable constancy in the incidence of shingles [8]. The database now includes approximately 38 000 cases of shingles since 1967 and has been used extensively for epidemiological studies and for economic evaluation of the impact of shingles and of chickenpox [9–12].

MATERIALS AND METHODS

Incidence data on new episodes of illness reported in the Weekly Returns Service (WRS) of the RCGP for the years 1994–2001 were examined [13]. Participating general practitioners record morbidity data from every consultation distinguishing between new episodes of illness and ongoing consultations. From 1989 onwards the network increasingly used computerized information systems and in 1994, two-thirds

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Table 1. *Incidence of shingles, chickenpox, herpes simplex by age and gender per 100 000 person years; relative risk (F/M) and 95% confidence intervals (CIs)*

	Males		Females		Relative risk	
Age groups	Cases	Incidence	Cases	Incidence	F/M	(95% CI)
Shingles						
0–14	585	162	795	231	1·43	(1·29–1·59)
15–24	476	213	462	211	0·99	(0·87–1·13)
25–44	1119	199	1361	245	1·23	(1·14–1·34)
45–64	1776	399	2598	591	1·48	(1·39–1·57)
65–74	1090	775	1578	984	1·27	(1·18–1·37)
75+	869	958	1823	1104	1·15	(1·06–1·24)
Chickenpox						
0–14	7231	1996	6899	2004	1·00	(0·97–1·04)
15–24	367	163	575	263	1·61	(1·41–1·84)
25–44	908	162	987	178	1·10	(1·01–1·20)
45–64	123	28	123	28	1·00	(0·78–1·28)
65–74	19	14	23	14	1·00	(0·54–1·84)
75+	11	12	15	9	0·75	(0·34–1·63)
Herpes simplex						
0–14	1523	420	1900	552	1·31	(1·23–1·40)
15–24	629	280	2013	920	3·29	(3·01–3·60)
25–44	1273	227	3737	672	2·96	(2·78–3·15)
45–64	651	146	1475	335	2·29	(2·09–2·52)
65–74	245	174	544	339	1·95	(1·68–2·26)
75+	128	141	257	155	1·10	(0·89–1·36)

of the network practices were recording data from all consultations onto a computerized database within the practice. The population under surveillance is the number of patients registered within the practice according to the British National Health System. Data on the population and on new episodes of disease by diagnosis were summarized each week in age- and gender-specific groups and transmitted electronically to the Birmingham Research Unit for analysis.

Incidence was examined by gender in the following age groups: 0–14, 15–24, 25–44, 45–64, 65–74 and 75 years and over. Weekly incidence rates were aggregated to provide the annual incidence rate in each age and gender group in each year. Age-specific incidence rates for each sex for all years combined were derived, and for each age group the relative risk of females contracting shingles compared to males [and the 95% confidence interval (CI)] was computed.

The age- and gender-specific incidence rates for each year were applied to the European Union 15-country female population (1998) to generate standardized gender-specific incident rates [14]. The differences between the male and female rates, and the corresponding 95% CIs, were then obtained.

To assist in the interpretation of the findings, data for herpes simplex and chickenpox over the 8-year period were also examined.

RESULTS

Over the 8 years there were 14 532 cases of shingles: 40·7% were male, 9·5% were under 15 years of age, and 37·0% were 65 years or over. The numbers of cases and the annual incidence rates per 100 000 person years by age group and gender are given in Table 1. Female rates exceeded male rates except for the 15–24 years age group where they are almost equal. The relative risks (and 95% confidence limits) of females contracting shingles compared to males are also given; the risk was maximum in the 45–64 years age group, followed by that for children; the relative risk for females aged 75 years and over (1·15) was significant at the 95% level.

Mean annual age- and gender-specific incidence data for chickenpox and for herpes simplex are also given. For chickenpox there was a 61% increased risk of females aged 15–24 years consulting compared with males and a 10% increase in the 25–44 years age

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Table 2. *Age-standardized incidence of shingles per 100 000 by gender; gender difference and 95% confidence interval (CI)*

	Males	Females	Difference	95% CI	F/M % excess
1994	382	493	111	64–157	29
1995	416	487	71	24–118	17
1996	355	463	108	65–151	30
1997	376	496	120	79–161	32
1998	358	487	129	89–168	36
1999	375	443	68	32–104	18
2000	338	448	110	76–144	32
2001	336	444	108	74–142	32

group; in other age groups the risk was equal or close to unity. For herpes simplex the incidence in females considerably exceeded that in males in every age group except the oldest; the risk of females consulting was 2–3 times greater than that for males across the age range 15–74 years. Herpes simplex includes disease caused by virus types 1 and 2, both of which may cause genital herpes [15]. We examined incidence data for genital herpes reported over the last 4 years: 11% of the total herpes simplex reports were assigned to Read code diagnoses for genital herpes; 83% were aged between 15 and 44 years; the female to male case ratio was 2·7.

For each year age-standardized annual incidence rates of shingles are given by gender together with the difference between each pair with its 95% CI in Table 2. In every year, incidence was significantly greater in females at the 5% level (and excepting 1995, at the 1% level). The female excess varied between 17 and 36% around an average of 28%.

DISCUSSION

The study demonstrates, in a large database exceeding 14 000 cases of shingles, an average 28% age-standardized excess incidence in females over males. The surveillance population is representative of the national population and here analysis of unstandardized data showed a 40% female excess. Hitherto, gender differences in the incidence of shingles have been largely attributed to the greater longevity of females; but the analysis presented here indicates greater female incidence in all age groups except for 15–24 years.

The diagnosis of shingles (and of chickenpox and herpes simplex) is made clinically and patients are rarely investigated virologically. Kalman investigated 47 hospitalized patients referred with a clinical diagnosis of shingles and found 6 misdiagnosed cases of herpes simplex [16]. Rubben and colleagues reported the opposite; 65 cases of shingles correctly diagnosed and 9 out of 45 cases of herpes simplex were misdiagnosed zoster cases [17]. Helgason and colleagues reviewed general-practitioner records and rejected 38 out of 505 (7·5%) of zoster clinical diagnoses [18]. Liesegang in a comprehensive review of varicella zoster viral disease considered clinical diagnosis reliable in most clinical situations [6]. The possibility of gender bias in diagnostic error specifically attributable to the diagnosis of shingles and occurring systematically in every age group and year is remote. The exception in the 15–24 years age group contrasts with the converse exception in this age group for the incidence of chickenpox where there remains some doubt. Risks in pregnancy associated with chickenpox are widely known and a lowered threshold for consultation especially in doubtful cases among young pregnant women could occur. In the reproductive years, consulting rates (all conditions combined) are much higher in females than in males, but not in children or in the elderly.

The incidence of shingles as reported here is consistent with other European published data and with the age-specific incidence previously reported from the WRS covering the years 1967–1989 [2–5, 8]. Incidence rates of shingles in children reported here, based on large numbers of children (585 male and 795 female incident cases), are greater than the 1·6/1000 reported from Iceland [19] and substantially greater than those reported by Donahue [3]. Sixteen per cent of all cases were aged less than 25 years, which is similar to the 20% aged less than 30 years reported by Meister and colleagues [2].

We have not been able to identify any other substantial set of published data definitively indicating a true excess incidence of shingles in females. Incidence reported in the General Practice Research Database for 1997 (males 3·23/1000, females 4·38) was strikingly similar to that reported in the WRS for 1997 (males 3·14/1000, females 4·48); (V. Osborne, Office of National Statistics, personal communication). Clinical incidence rates reported in the Continuous Morbidity Registration Project in Scotland and reported in the Dutch Sentinel Network are higher in females [20, 21]. Among persons less than 65 years Donahue and colleagues reported 471 females compared to 428 males [3]. Helgason and colleagues reported a higher incidence in females over 60 years

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old [18]. More females were reported by Torrens and colleagues in Scotland and by Glynn and colleagues in Cheltenham, England [22, 23]. We have not found any study suggesting greater incidence in males, although some general practice-based studies have reported no gender difference [4, 5, 24]. A number of studies therefore suggest increased female incidence, but few are large enough or based on sufficiently secure denominators to explore gender differences in any detail. The patient registration system within the British National Health Service is particularly valuable for this type of epidemiological study because of the ability to define study populations by age and gender. The WRS takes a detailed population count from every practice each week using an automated routine.

Excepting the 15–24 and 25–44 years age groups there were no gender differences in the age-specific incident rates of chickenpox, the primary varicella zoster infection. The female excess in the incidence of herpes simplex (which is even greater than that for shingles), suggests that there is a true gender difference in response to reactivation of latent viral disease. In the last 4 years 11% of herpes simplex cases were diagnosed as genital herpes and the female to male ratio (2·7) was similar to that reported for all herpes simplex cases and consistent with other reports [15]. For herpes simplex, pregnancy has been recognized as a contributory factor [25] and this may also be relevant for chickenpox. It has been suggested that repeated exposure to varicella zoster virus infection reduces the likelihood of clinical shingles infection [26]. Since females have more frequent contact with children who are sick with chickenpox, greater incidence in females is a paradoxical finding. It remains possible that repeated exposure to chickenpox and/or shingles reduces the likelihood of acquiring clinical infection but the effect of gender on incidence outweighs the protective value of repeated exposure when comparing females to males. Gender difference in the incidence of herpes simplex adds strong support for the hypothesis that females have a differing response to latent viral infection. Opposing gender differences in the incidence of primary genital herpes (simplex type 2) infection (female excess) and recurrent infection (male excess) were reported by Benedetti and colleagues though the median follow-up period was limited to 391 days [27]. The possible impact of the menstrual cycle on resistance to infection, though relevant in females before the menopause cannot explain differences in children and older adults.

Gender difference in the incidence of shingles prompts questions on the pathogenesis of this condition and has importance for the determination of vaccination policy for the prevention of shingles. Given the size of this database, the relative security of clinical diagnosis and the precision of the denominator, we believe our finding of female excess incidence is robust and suggest further research is needed to explain the difference in immune response.

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