Gynecologic Oncology 127 (2012) 75–82

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Stage at diagnosis and ovarian cancer survival: Evidence from the International Cancer Benchmarking Partnership

Camille Maringe [a,*], Sarah Walters [a], John Butler [b], Michel P. Coleman [a], Neville Hacker [c], Louise Hanna [d], Berit J. Mosgaard [e], Andy Nordin [f], Barry Rosen [g], Gerda Engholm [h], Marianne L. Gjerstorff [i], Juanita Hatcher [j], Tom B. Johannesen [k], Colleen E. McGahan [l], David Meechan [m], Richard Middleton [n], Elizabeth Tracey [o], Donna Turner [p], Michael A. Richards [q], Bernard Rachet [a]
and ICBP Module 1 Working Group

[a] Cancer Research UK Cancer Survival Group, London School of Hygiene and Tropical Medicine, London, UK
[b] Gynaecological Oncology Fellow, St. Bartholomew's and Royal Marsden Hospitals, London, UK
[c] School of Women's and Children's Health, University of New South Wales, and Gynaecological Cancer Centre, Royal Hospital for Women, Sydney, New South Wales, Australia
[d] Velindre NHS Trust, Cardiff, UK
[e] Herlev University Hospital, Copenhagen, Denmark
[f] East Kent Hospitals University NHS Foundation Trust, Canterbury, Kent, UK
[g] University of Toronto, Toronto, Ontario, Canada
[h] Department of Cancer Prevention and Documentation, Danish Cancer Society, Copenhagen, Denmark
[i] Danish Cancer Registry, Statens Serum Institut, National Institute for Health Data and Disease Control, Copenhagen, Denmark
[j] Alberta Health Services, Edmonton, Alberta, Canada
[k] Norwegian Cancer Registry, Oslo, Norway
[l] Cancer Surveillance & Outcomes, British Columbia Cancer Agency, Vancouver, British Columbia, Canada
[m] Trent Cancer Registry, Sheffield, UK
[n] Northern Ireland Cancer Registry, Belfast, UK
[o] Cancer Institute New South Wales, Sydney, New South Wales, Australia
[p] CancerCare Manitoba, Winnipeg, Manitoba, Canada
[q] National Cancer Action Team, Department of Health, London, UK

ARTICLE INFO

Article history:
Received 10 May 2012
Accepted 20 June 2012
Available online 27 June 2012

Keywords:
International
Ovary
Cancer survival
Stage

ABSTRACT

Objective. We investigate what role stage at diagnosis bears in international differences in ovarian cancer survival.

Methods. Data from population-based cancer registries in Australia, Canada, Denmark, Norway, and the UK were analysed for 20,073 women diagnosed with ovarian cancer during 2004–07. We compare the stage distribution between countries and estimate stage-specific one-year net survival and the excess hazard up to 18 months after diagnosis, using flexible parametric models on the log cumulative excess hazard scale.

Results. One-year survival was 69% in the UK, 72% in Denmark and 74–75% elsewhere. In Denmark, 74% of patients were diagnosed with FIGO stages III–IV disease, compared to 60–70% elsewhere. International differences in survival were evident at each stage of disease; women in the UK had lower survival than in the other four countries for patients with FIGO stages III–IV disease (61.4% *vs.* 65.8–74.4%). International differences were widest for older women and for those with advanced stage or with no stage data.

Conclusion. Differences in stage at diagnosis partly explain international variation in ovarian cancer survival, and a more adverse stage distribution contributes to comparatively low survival in Denmark. This could arise because of differences in tumour biology, staging procedures or diagnostic delay. Differences in survival also exist within each stage, as illustrated by lower survival for advanced disease in the UK, suggesting unequal access to optimal treatment. Population-based data on cancer survival by stage are vital for cancer surveillance, and global consensus is needed to make stage data in cancer registries more consistent.

* Corresponding author at: Cancer Research UK Cancer Survival Group, Department of Non Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. Fax: +44 20 7580 6897.
E-mail address: Camille.Maringe@lshtm.ac.uk (C. Maringe).

0090-8258/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2012.06.033

Introduction

International differences in ovarian cancer survival are wide, persistent and largely unexplained, even between high-income countries with similar health systems [1]. We investigate whether these differences in overall survival may be explained by variation in stage at diagnosis or in stage-specific survival.

The International Cancer Benchmarking Partnership (ICBP) is a consortium of cancer registries, clinicians and epidemiologists using population-based data to examine international survival differences. We aim to provide benchmarks against which progress in outcomes can be evaluated, and which will help to refine policy for cancer control. Five countries (Australia, Canada, Denmark, Norway and the UK) contributed to this study of ovarian cancer.

Material and methods

Data

The ICBP collected population-based cancer registration data from Australia (New South Wales, Victoria), Canada (Alberta, British Columbia, Manitoba, Ontario), Denmark, Norway and the UK (eight regional registries covering all of England; Northern Ireland, Wales) for 137,199 women diagnosed with a cancer of the ovary (including Fallopian tubes and adnexa: ICD-10 C56; C57.0-C57.9) during 1995–2007. Women diagnosed with a benign, uncertain or borderline malignancy, in situ or metastatic tumour were ineligible (webappendix para 1). Extensive quality control has been documented [1].

To conduct survival analyses by stage at diagnosis, we used data from the most recent 4 years of the period 1995–2007, for which stage data were more complete, and from the 11 (of 18) cancer registries in which at least half of all women diagnosed in 2004–07 had a valid stage. The excluded registries (Victoria, Australia; Ontario, Canada; four English regional registries and Wales, UK) represented 54% of the original population base. Finally, 20,073 women were included in the analyses, of whom 14,948 (74.5%) had complete stage information on their registry record.

The classification and coding of stage at diagnosis varies, both clinically and between cancer registries. We developed guidelines for harmonising data on stage from disparate classification systems into a final, comparable variable for survival analysis [2]. We requested data coded to the TNM classification of stage, including separate information on the extent of the tumour (T), nodal involvement (N) and metastases (M) [3]. We prioritised pathological stage data (pT, pN) except for metastases, where we preferred clinical stage (cM). For some patients, only the grouped TNM stage was available. For many patients, registries submitted data coded to the International Federation of Gynaecology and Obstetrics (FIGO) staging system, which maps to the grouped TNM stages. For patients with TNM and/or FIGO data, we defined a final FIGO stage.

In New South Wales (and for some Norwegian patients with no TNM or FIGO stage) stage was categorised as 'localised', 'regional', or 'distant'. We also mapped TNM and FIGO to a 'localised, regional, distant' structure, based on the US Surveillance, Epidemiology and End Results Summary Stage 2000 (SEER SS2000) [2]. SEER SS2000 is closely equivalent to the Australian and Norwegian systems, but better documented and more widely known [4]. We present results using both SEER SS2000 (all countries) and FIGO (without Australia). There is general equivalence between FIGO stages I–II and SEER SS2000 'localised' and 'regional', and between FIGO stages III–IV and SEER SS2000 'distant'. For simplicity here, stages I–IV will refer to FIGO, and 'localised', 'regional' or 'distant' to SEER SS2000.

Statistical analyses

We used flexible parametric models with the *stpm2* command [5] implemented in Stata version 12 (StataCorp LP, College Station, TX; webappendix para 2) to model net survival [6]. We censored patients at 3 years and estimated net survival and excess mortality up to 18 months after diagnosis, to ensure greater stability in the modelled estimates. Background mortality was derived from life tables of all-cause mortality rates for women in each jurisdiction by single year of age and calendar year at death [1]. Excess mortality is the excess (cancer-related) hazard of death at specific time points since diagnosis, and can be thought of as the mortality rate from the cancer alone.

Models were stratified by stage at diagnosis, including patients with missing data on stage as a distinct category. We allowed for variation with time since diagnosis in the effect of age at diagnosis and country; interactions were included to model non-proportionality between countries (webappendix para 3). All-ages estimates were age-standardised using stage-specific weights (webappendix Table 1) derived from the age distribution of patients in all jurisdictions combined, in the age categories 15–44, 45–54, 55–64, 65–74, 75–84 and 85–99 years.

We conducted multiple imputation by chained equations to ascertain the probable stage distribution for tumours with missing stage, using the *ice* command in Stata [7–9] (webappendix para 4). We ran the imputation model 15 times, obtaining 15 imputed datasets. We report the overall stage distribution combined under Rubin's rules [9]. The same modelling strategy for stage-specific survival was then repeated on each of the 15 imputed datasets, and the range of estimates compared to the estimate based on the observed stage data.

Findings

Distributions by stage and age

Mean age at diagnosis varied from 63.8 to 65.2 years. Women with more advanced stage were older in all jurisdictions (Table 1, Fig. 1), but the age distribution of unstaged women varied: compared to women with metastatic disease (stage IV; 'distant'), unstaged women were on average 4–12 years older in Norway and Canada, 1–2 years older in Denmark and the UK, and slightly younger in Australia.

The proportion of unstaged tumours ranged from 4% (Norway) to 32% (UK). The proportion increased with age, reaching 40% of 70–99 year-old women in Canada and the UK (Fig. 1).

Among women with a recorded stage, Canada and Norway had similar stage distributions, with nearly half of all women diagnosed in stage III. The UK and Australia also had similar distributions, with a higher proportion of 'localised' tumours (23% *vs.* less than 15% elsewhere).

Denmark had a very high proportion of women with stage IV tumours (43% *vs.* 23% or less elsewhere) and the lowest proportion in stage III (31% *vs.* 38% or more). The proportion with stage I tumours was similar in Canada, Denmark and Norway (20–23%) and higher in the UK (33%) (Table 1).

Imputing stage where it was missing did not substantially alter the distribution of stage in any country. The range of proportions of women diagnosed in stages III–IV changed from 61–74% to 64–75% (Table 1).

Net survival

Age-standardised one-year net survival was lowest for women in the UK (68.8%), intermediate in Denmark (72.5%) and highest in Canada (74.2%), Norway (74.3%) and Australia (74.9%). In each age group, overall net survival (all stages combined) was lowest in the UK (Table 2).

In all countries, one-year net survival was about 40% lower for women aged 70–99 years than for women aged 15–49 years, and for women diagnosed at stage IV than at stage I. The international differences in survival by age were larger for women with more advanced disease or missing stage (Table 2).

Among women with early disease (stage I; 'localised'), women in Denmark and Australia had lower age-standardised survival (94–95%)