Ovarian Cancer Incidence (1989–1991) and Mortality (1954–1993) in the Netherlands

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Objective: To examine ovarian cancer incidence and mortality in the Netherlands, and to relate trends in mortality to changes in parity and use of oral contraceptives.

Methods: Age-standardized and age-specific incidence and mortality rates are presented using incidence data from the Netherlands Cancer Registry, 1989–1991, and mortality data from the Netherlands Central Bureau of Statistics, 1954–1993.

Results: In the period 1989–1991, age-standardized incidence of ovarian cancer was 14.9 per 10^5 woman-years. The majority (89%) of these tumors had an epithelial origin. Two-thirds of all newly diagnosed ovarian cancers already showed extension to the pelvis or beyond at diagnosis. From the period 1954–1958 to 1969–1973, age-standardized mortality rates increased from 10.6 to 13.1 per 10^5 woman-years. Thereafter, a decline was noted to 11.4 per 10^5 woman-years in the period 1989–1993. Age-specific mortality rates showed a pattern of rising mortality in the elderly, whereas mortality in the younger age categories was declining. The number of live births has declined gradually, and oral contraceptive use has increased.

Conclusion: Incidence of ovarian cancer is high in the Netherlands, but comparable to other countries in northwestern Europe and North America. Mortality rates are rising in the elderly and declining in the young. Further research is needed concerning the effects of oral contraceptives, fertility drugs, and hormone replacement therapy on the incidence and mortality of ovarian cancer. *(Obstet Gynecol 1996;88:387–93)*

Ovarian cancer is one of the most frequent malignancies in women and shows a wide geographic variation in incidence. Highest risks are observed among the more affluent populations in northwestern Europe and North America, with a 1–2% cumulative risk of being diagnosed with ovarian cancer before the age of 75.[1,2] The majority of the ovarian cancers remain unnoticed until disease has spread beyond the ovary. Survival rates have increased since the introduction of more aggressive treatment modalities in the late 1970s (extensive surgery followed by platinum-based chemotherapy regimens), but are still extremely poor. Reported stage-specific 5-year survival rates range from approximately 80% for localized disease to less than 10% in case of distant metastases.[2–7] At present, ovarian cancer remains the most lethal gynecologic malignancy in the western world.[7]

Extensive research has been done in the etiology of ovarian cancer, but so far the pathogenesis is only partially understood.[8] The key findings in this field are the identification of genetic factors related to ovarian cancer and the important role of the hormonal system in the etiologic pathway.[5,8–13] Fathalla (Incessant ovulation: A factor in ovarian neoplasia [letter]. Lancet 1971; ii:163) suggested that the disruption of the ovarian epithelium at ovulation may represent the key step leading to malignant transformation. Consequently, fewer ovulations during a woman's lifetime might lead to a lower risk of ovarian malignancy. The protective effect of increased parity, breast feeding, and use of oral contraceptives (OC) found in several studies is consistent with this hypothesis of "incessant ovulation."[8–13] Oral contraceptives were introduced in the 1960s and gained widespread use thereafter. Consequently, the potential protective effect of OCs could result in a decline in the occurrence of ovarian cancer. Evidence of such a decreasing trend in incidence and/or mortality is already found in several countries around the world.[1,2,14–23] However, large geographic variations exist, and the major decrease is still to come because most women who used OCs are only now reaching high-risk

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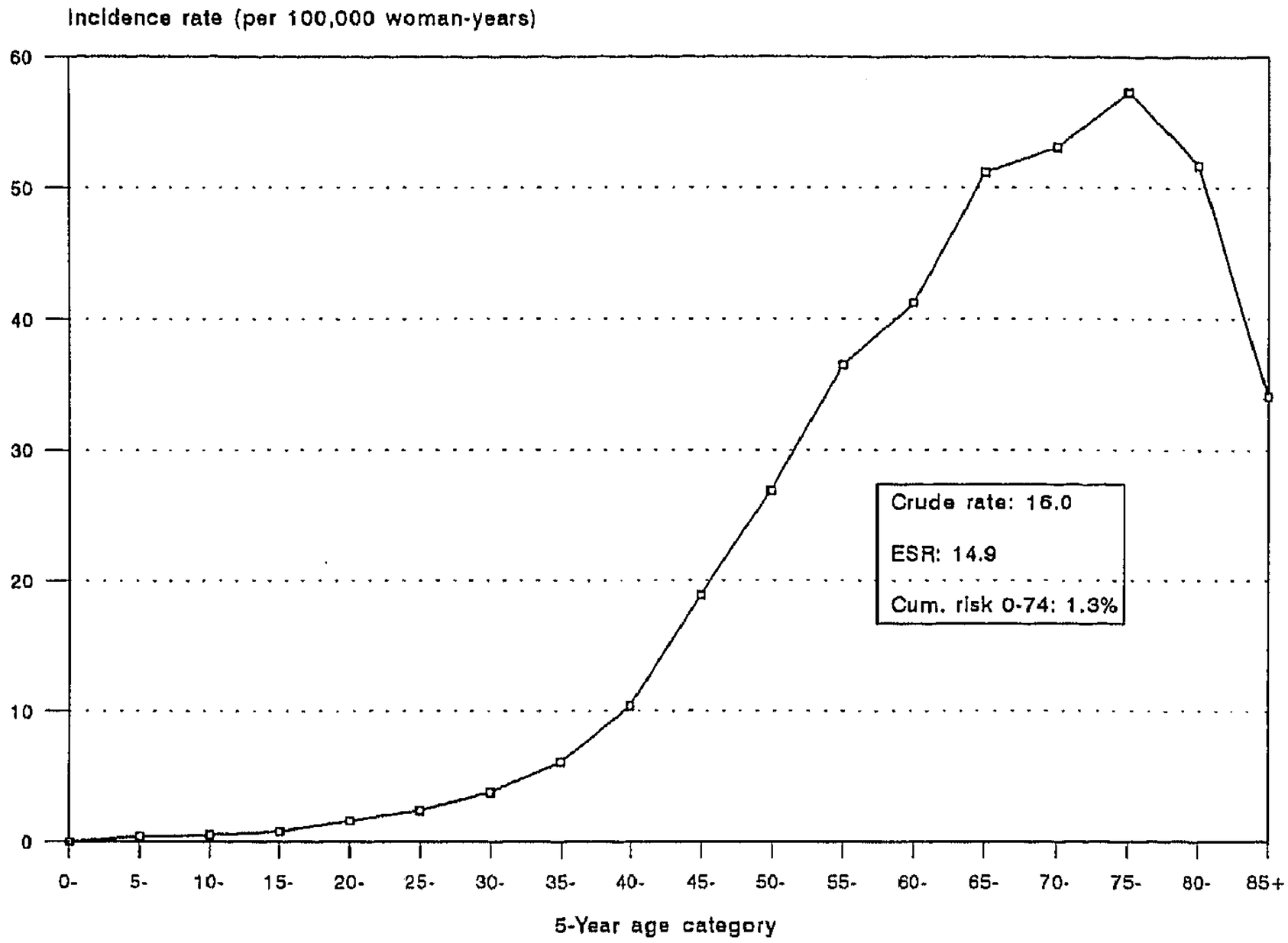

Figure 1. Age-specific ovarian cancer incidence in the Netherlands, 1989–1991. Cum. = cumulative.

ages for developing ovarian cancer.[24] The aim of this study was to investigate the incidence and mortality of ovarian cancer in the Netherlands. Because national incidence data were available only recently, the emphasis will be on the analysis of mortality data.

Materials and Methods

Numbers of newly diagnosed ovarian cancers for the period 1989–1991 were derived from the Netherlands Cancer Registry.[25] For ovarian cancer, we used International Classification of Diseases (ICD) for Oncology code 183.0.[26] Data regarding morphology and lateralization were derived directly from the registry records. The Netherlands Cancer Registry records International Federation of Gynecology and Obstetrics (FIGO) stage from 1992 onward. Therefore, the FIGO stage of all diagnosed cases had to be assigned retrospectively by using the clinical and pathologic tumor node metastasis classification.[27]

Data regarding the number of women with ovarian cancer as the underlying cause of death as well as the age- and calendar year-specific numbers of Dutch females were abstracted from publications of the Netherlands Central Bureau of Statistics for the years 1954–.1993.[28,29] During this period, death from ovarian cancer was coded as 175.3–175.5 according to the ICD-6 (1954–1957), 175.0 according to ICD-7 (1958–1968), and thereafter as 183.0 according to ICD-8 and ICD-9.

Age-specific incidence rates are presented for the years 1989–1991 combined. All rates are expressed in 10^5 woman-years. In addition to the crude incidence rate, the age-standardized incidence rate using the European Standard Population[30] and the cumulative risk of ovarian cancer before the age of 75 are presented. Age-specific mortality rates are presented by 5-year calendar periods (1954–1958 to 1989–1993). Age-standardized rates (all ages) are presented for the same periods.

Results

Since the start of the Netherlands Cancer Registry in 1989, 3622 new cases of ovarian cancer have been registered in the Netherlands in the period 1989–1991. Age-specific incidence rates gradually increased to 57.3 per 10^5 woman-years for the 75–79 age category (Figure 1). The age-standardized incidence rate is 14.9 per 10^5 woman-years. Of all ovarian cancers diagnosed in the period 1989–1991, 89% had an epithelial origin (adeno, endometrioid, and clear cell carcinomas), with the majority being serous and mucinous cystic adenocarcinomas (Table 1). Germ cell tumors were especially frequent at younger ages; 66% (43 of 65) occurred at ages under 40. Moreover, 30% (30 of 99) of all ovarian cancers of known morphology that occurred before the age of 30 were of germ cell origin. In two of every three cases of ovarian cancer diagnosed in this period, the tumor showed extension to the pelvis (FIGO stage II) or beyond (FIGO stage III or IV). In 239 cases (6.6%), the

Table 1. Distribution of Morphology, Stage, and Lateralization of Ovarian Cancer in the Netherlands, 1989–1991

	Cases (*n*)	(%)
Morphology		
Serous cystic adenocarcinoma	1090	(30.1%)
Mucinous cystic adenocarcinoma	498	(13.7%)
Other adenocarcinoma	1193	(32.9%)
Endometrioid carcinoma	305	(8.4%)
Clear cell carcinoma	139	(3.8%)
Sex cord stromal tumor	50	(1.4%)
Germ cell tumor	65	(1.8%)
Other specified morphology	136	(3.8%)
Unspecified morphology	71	(2.0%)
Tumors not microscopically verified	75	(2.1%)
FIGO stage		
Tumor limited to one or both ovaries		
I*	86	(2.4%)
Ia	75	(13.1%)
Ib	55	(1.5%)
Ic	328	(9.1%)
Pelvic extension		
II*	9	(0.3%)
IIa	51	(1.4%)
IIb	150	(4.1%)
IIc	124	(3.4%)
Microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis		
III*	334	(9.2%)
IIIa	174	(4.8%)
IIIb	362	(10.0%)
IIIc	630	(17.4%)
Distant metastasis†		
IV	605	(16.7%)
Unknown*	239	(6.6%)
Lateralization		
Bilateral	1177	(32.5%)
Left	893	(24.6%)
Right	999	(27.6%)
Unknown*	553	(15.3%)
Total	3622	(100.0%)

FIGO = International Federation of Gynecology and Obstetrics.
* Not enough information available to allot cases to subcategories.
† Liver metastasis must be of parenchymal tissue to allot a case to FIGO stage IV. Pleural effusion must have positive cytology for FIGO stage IV.

necessary requirements for FIGO staging were not met. Almost one-third of all patients (1177 cases) had bilateral disease. The right-to-left ratio was 1.12, indicating that right-sided tumors occurred slightly more often. In 15.3% of all cases, no lateralization was specified.

In 1954, ovarian cancer was the underlying cause of death of 443 Dutch women. This number has steadily increased, reaching 1029 in 1993. However, after adjustment for population growth and aging of the Dutch female population, age-standardized mortality rates are fairly stable. Age-standardized ovarian cancer mortality increased gradually until 1969–1973, but we found a decline to 11.4 per 10^5 woman-years in 1989–1993 thereafter (Table 2). When age-specific mortality rates are considered, a more diverse pattern in mortality rates can be observed (Table 2, Figure 2). Whereas the younger age groups showed relatively stable or even slightly declining mortality rates after the period 1969–1973, the older age groups showed an increasing trend in mortality. This is illustrated in Figure 2 (for clarity, age-specific mortality rates are presented by 10-year age groups).

Discussion

The age-standardized incidence of ovarian cancer in the Netherlands is in the same order of magnitude as described for Sweden, Denmark, Germany, and Canada.[14,16,18,19] The distribution of morphology, FIGO stage, and lateralization of all ovarian cancer cases in the Netherlands is also comparable to those reported in other studies.[21,31] The slightly higher occurrence of ovarian cancer in the right ovary is probably due to chance because it was not found in a much larger study of unilateral ovarian cancers in the United States.[31] Age-specific rates are climbing with age. Several studies have described a pattern of declining incidence rates over time in younger ages, whereas an increase in incidence is described in older ages.[18–21,23] Because the Netherlands Cancer Registry has been operational only since 1989, it was not possible to investigate the trend in incidence rates in our data. Instead, we investigated whether such a trend could be observed in mortality data available for the Netherlands over a much longer period. Ovarian cancer mortality in the Netherlands was relatively stable. However, age-specific mortality rates are rising in the older age-groups and are declining in the young. Several other studies, dealing with data from other countries, described a similar pattern in age-specific mortality over time,[1,2,15–17,19–23] and many factors have been put forward to explain the observed changes.

Ewertz and Kjaer[16] suggested that changes in parity between different birth cohorts of women could explain some of the observed variation in Danish ovarian cancer mortality rates. Recently, Dos Santos Silva and Swerdlow[23] confirmed this hypothesis in their study of trends in incidence and mortality from breast, ovarian, and endometrial cancers in England and Wales. In their study, the marked decrease in family size was paralleled by an increase in the risk of ovarian cancer for successive birth cohorts born before 1920. In the Netherlands a similar pattern has been observed.[32–34] The number of live births in the Netherlands has gradually

Table 2. Age-Specific and Age-Standardized (European Population) Ovarian Cancer Mortality Rates (per 10^5 Woman-Years) in the Netherlands, 1954–1993

	Period of mortality							
	1954–1958	1959–1963	1964–1968	1969–1973	1974–1978	1979–1983	1984–1988	1989–1993
Age (y)								
40–44	8.6	7.6	8.0	8.8	7.4	5.6	5.1	4.1
45–49	14.3	13.9	14.5	16.7	15.9	10.8	9.4	8.9
50–54	19.4	20.5	21.2	25.0	22.3	19.2	17.1	15.7
55–59	27.6	26.4	26.1	30.0	31.6	26.9	23.1	24.9
60–64	29.9	33.8	34.5	35.1	36.7	34.9	34.9	33.7
65–69	31.4	36.8	40.1	44.1	40.4	39.0	44.7	44.8
70–74	38.1	41.3	43.7	51.3	51.0	46.9	50.5	55.0
75–79	40.0	37.5	50.5	57.4	61.7	62.1	63.2	60.7
80–84	38.2	41.2	51.4	54.4	56.9	56.0	67.9	65.6
≥85	38.9	35.2	52.9	47.6	55.9	55.6	66.2	68.4
Age-standardized rate								
0–85	10.6	11.0	11.8	13.1	12.8	11.5	11.5	11.4

decreased since the beginning of this century (Figure 3). There was a temporary increase just after World War II, but the number of live births has decreased further and stabilized in recent years. Therefore, the increase in ovarian cancer mortality in the oldest age groups (born around the turn of the century) may in part be attributed to their declining parity. This decrease in the number of live births is accompanied by an increase in the number of nulliparous women in the period 1945–1970.[35] It is not clear how this lower parity and higher number of nulliparous women in the Dutch population will affect the ovarian cancer risk of younger birth cohorts. Moreover, one should be aware of the so-called "ecologic fallacy," which implies that caution should be exercised when inferences are made from observed trends in population statistics because the apparent relationship may not hold on an individual level.

Dos Santos Silva and Swerdlow[23] also found an inverse relationship between the number of women using OCs and the risk of ovarian cancer. This relationship had already been observed earlier by Villard-Mackintosh et al.[20] In the Netherlands, OCs were marketed at the end of 1961 and gained widespread use (Figure 4). Apart from a slight decline in the number of women using OCs in the period 1977–1980 due to negative reports on the increased risk of cardiovascular

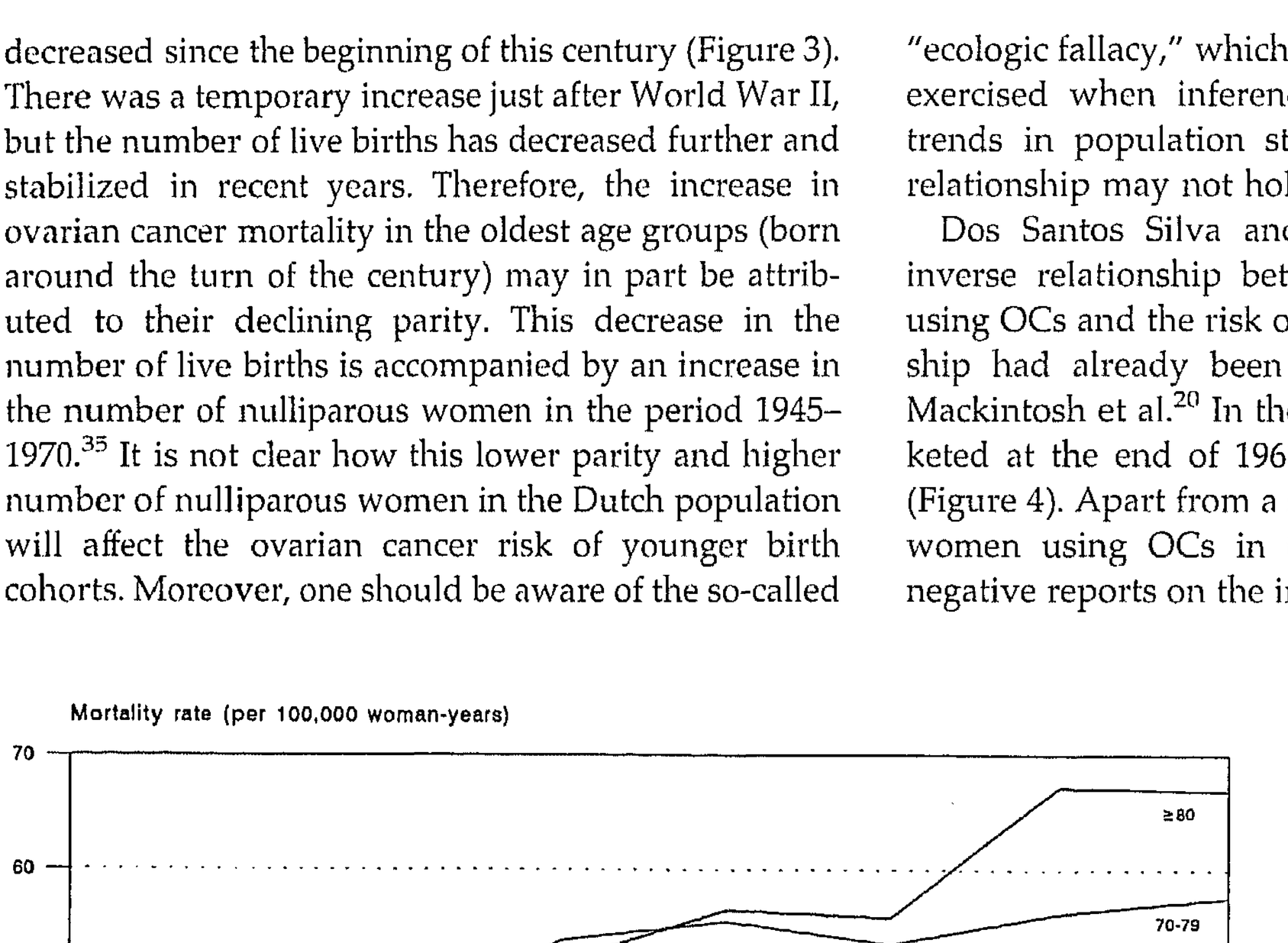

Figure 2. Age-specific ovarian cancer mortality in the Netherlands, 1954–1993.

Figure 3. Number of live births per 1000 women aged 15–44 years in the Netherlands, 1900–1993.

disease among women using OCs in that period, the percentage of women age 10–54 using OCs increased to 32% in 1993. The dip in 1991 was caused by a lack of information on the quantity of parallel imported OCs in that year and thus can be considered a registration anomaly due to underreporting. There appears to have been a trend to younger starting ages and prolonged use at older ages.[34,36] These developments may have contributed to the stabilization and the onset of the decrease in ovarian cancer mortality in the younger age groups in the Netherlands. If this is true, then the decreasing trend might continue when more birth co-

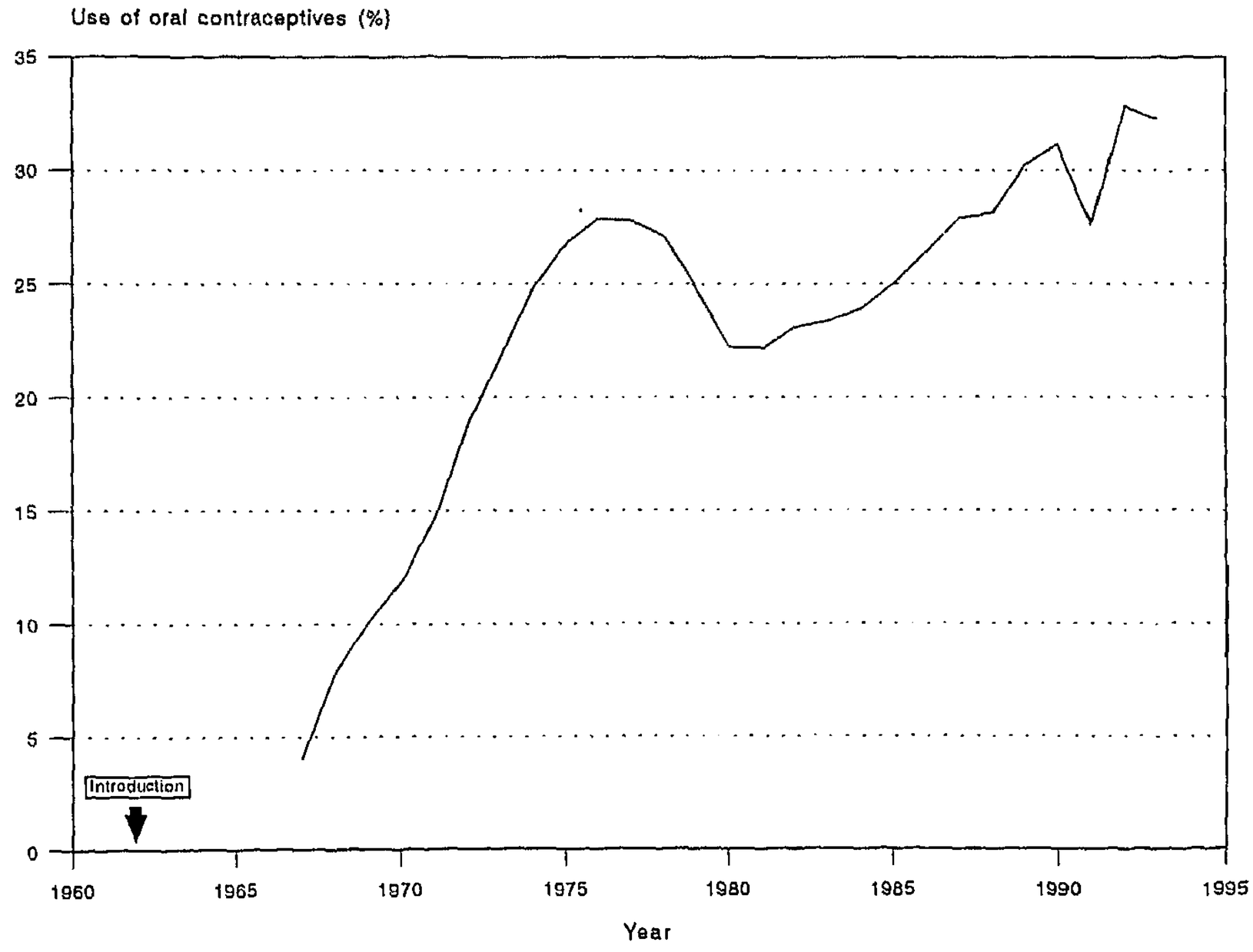

Figure 4. Percentage of women aged 10–54 years using oral contraceptives in the Netherlands, 1967–1993. (Source: Institute for Medical Statistics, the Netherlands.)

horts with a history of OC use reach high-risk ages for developing ovarian cancer. However, the use of third-generation OCs may decrease the protective effects of OCs because ovarian activity remains possible with these pills.

Apart from the more widespread use of OCs as a potential explanation of the decline in ovarian cancer mortality rates in the younger age groups, Ayiomamitis et al[19] suggested that earlier diagnoses and earlier and better treatment in the young could explain the observed change. Furthermore, they suggested that older women are treated less aggressively and/or respond less effectively to therapy compared with younger women, as suggested earlier by Yancik et al.[37] This difference in treatment over age was affirmed by Ries,[38] who investigated treatment information of more than 20,000 women diagnosed during 1973–1987 in the United States. This could apply to the situation in the Netherlands, because we have no indication that systematic differences exist with other countries in therapeutic decisions or patient response to treatment. Also, a more accurate death certification and registration is suggested as an explanation for the increase in mortality in older age groups.[19] Indeed, since 1954, techniques in pathology have emerged, but it is uncertain whether this explanation holds for the increase visible in recent years as well.

The influence of changes in oophorectomy rates in the Netherlands should also be considered in this regard. Data obtained from the annual reports of the National Medical Register in the Netherlands show that oophorectomy rates increased steadily to 130 per 10^5 woman-years in the early 1980s but declined to less then 85 per 10^5 woman-years in 1990. The influence of these changes in oophorectomy rates on age-specific ovarian cancer mortality is difficult to estimate in more detail because we have no information about the age distribution of these patients. Nevertheless, these changes seem difficult to reconcile with the onset of the decrease in ovarian cancer mortality in the younger age groups. The increase in the older age groups might have contributed in part to the changes in oophorectomy rates. But similar analysis regarding the influence of changing hysterectomy rates on cervical cancer mortality in the Netherlands have shown that this contribution is estimated to be about 6% of the observed change.[39]

Another suggested reason for the increase in ovarian cancer mortality in the elderly is the increased use of estrogen replacement therapy in peri- and postmenopausal women.[40] Indeed the use of estrogens by elderly women to prevent osteoporosis and other climacteric and menopausal complaints is increasing. And although the normal dose of estrogen has decreased since the 1970s and the composition of the medication used changed with the inclusion of progesterone, this may have influenced ovarian cancer mortality. On the other hand, estrogen replacement during menopause lowers the blood gonadotropin levels, which might decrease the risk of ovarian cancer, according to the gonadotropin hypothesis put forward by Stadel.[41] Therefore, definitive conclusions about the effect on ovarian cancer risk of hormone replacement therapy cannot be drawn.

Whittemore et al[9–11] suggested ovarian stimulation for in vitro fertilization could increase the risk of ovarian cancer. Recently, Venn et al[42] reported an increase in ovarian cancer risk after ovarian stimulation for in vitro fertilization in a cohort of 10,358 Australian women. Although the number of cases in this large study was very small ($n = 6$), which limits the conclusions that can be drawn, this finding supports the hypothesis of Whittemore et al. However, it is doubtful whether IVF has a large impact on population incidence and mortality even if the hypothesis is true. Further research into this matter is indicated.

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