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Diverging breast and stomach cancer incidence and survival in migrants in The Netherlands, 1996–2009

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Abstract

Background. Migrant populations usually experience a health transition with respect to their cancer risk as a result from environmental changes and acculturation processes. We investigated potentially contrasting experiences with breast and stomach cancer risk and survival in migrants to the Netherlands in a retrospective cohort study. *Methods*. Invasive breast (n = 96 126) and stomach cancer cases (n = 24 496) diagnosed 1996–2009 were selected from the population-based Netherlands Cancer Registry. Standardized Incidence Ratios (SIRs) were computed as the ratio of observed and expected cancers. Differences in survival were expressed as relative excess risk of mortality (RER). *Results*. Women from Morocco, Suriname and Turkey exhibited a significantly lower risk for breast cancer than native Dutch women (SIR range 0.5–0.9). Relative excess mortality was significantly increased in Surinamese (RER = 1.2, 95% CI 1.0–1.5) patients. The incidence of non-cardia stomach cancer was significantly elevated in all migrants, except in Indonesians, being highest in Turkish males (SIR = 2.2, 1.9–2.6). Cardia stomach cancer appeared to be less frequent in all migrants, being lowest in Surinamese males (SIR = 0.3, 0.2–0.5). Relative excess mortality was significantly lower in patients from the Antilles (RER = 0.7, 0.5–1.0), Suriname (0.8, 0.6–0.9) and Turkey (0.7, 0.6–0.9). *Conclusion*. The lower incidence rates of breast and cardia stomach cancer in migrants as well as their higher non-cardia stomach cancer rates reflect most likely early life exposures including pregnancy and/or dietary patterns during life-course. While higher relative excess mortality from breast cancer in migrant women might point toward inadequate access and treatment in this group, lower excess mortality from (especially non-cardia) stomach cancer remains to be explained.

Migration has substantially characterized the societies of Western European countries, which especially holds for The Netherlands with every fifth citizen having a foreign background of first or second degree [1]. Increasing ethnic diversity in populations demands new orientation of social services and healthcare. In particular the aging of relatively young migrant groups in The Netherlands entails new challenges regarding healthcare supply, appropriateness and equality. Social gradients in cancer burden need to be addressed and monitored carefully since especially the concomitance of low socioeconomic position and foreign ethnicity has been observed to increase health inequalities.

Cancer incidence varies greatly across and within countries and populations [2]. Although migrants from low-income countries usually experience lower all-cancer risks, substantial site-specific disparities develop in comparison with the populations of their home and their host countries: whereas cancers associated with a Western lifestyle (such as breast, colorectal and prostate cancer) occur significantly less in most migrant groups, contrasting cancers with viral or bacterial origins (like stomach, liver or oral cancers). This pattern has been confirmed by studies conducted in many industrialized countries, including The Netherlands [3]. Moreover, cancer risk differences between the native population and migrants were found to diminish over time and with upcoming migrant generations [4]. This process of converging cancer risks, likely to be induced by acculturation processes, is an interesting phenomenon and may

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help solving unclear etiology questions. Cancer survival not only reflects the incidence patterns but also accessibility and participation to early detection programs and possibly differences in treatment across population groups. Elucidating these differences is essential for providing adequate, culturally sensitive healthcare and for assuring high quality of preventive measures.

Breast cancer represents the most common malignancy among women worldwide and has become most frequent in developed regions of the world, especially since mass screening evolved. In particular reproductive patterns and to some extent lifestyle-related exposures are known to be key risk factors [5]. If detected at an early stage, survival rates for breast cancer are high [6]. Thus, population-based survival differences in breast cancer can partly be attributed to screening attendance, i.e. an early stage diagnosis, and to a lesser extent by treatment quality and the presence of co-morbidities [7]. Stomach cancer, however, is predominantly caused by chronic infection with the *Helicobacter pylori* bacterium, being endemic in many less-developed regions of the world [8]. Stomach cancer typically develops several decades after infection – exposure is most frequently experienced during childhood, in first generation migrants typically in the country of birth. As survival from stomach cancer is low [6], disparities are more likely due to differences in genetic predisposition or still unknown factors rather than treatment and detection.

We selected two very different and contrasting cancer sites – breast cancer occurring less and stomach cancer being more prominent in migrants compared to the local-born population of their host country – to demonstrate the effect of migration-related risk factors on cancer risk and survival in later life. The recently changed multicultural character in combination with the population-based cancer registry since 1989 make The Netherlands a unique place to conduct migrant studies on cancer. Following regional analyses, this is to our knowledge the first analysis of cancer incidence and cancer survival in the largest migrant groups in the Netherlands.

Material and methods

Cancer Cohort

Invasive stomach [International Classification of Diseases (ICD)9 (1510) and ICD10 (C16), excluding lymphomas] and female breast [ICD9 (1740) and ICD10 (C50)] cancer cases diagnosed between 1996 and 2009 were acquired from the population-based Netherlands Cancer Registry (NCR). We distinguished cardia from non-cardia stomach cancers, since they are known to be caused by different mechanisms and exhibit a different prognosis [5]. In breast cancer, pre- (below age 50) and postmenopausal (age 50 and older) patients were distinguished. Biannual organized mass screening for breast cancer was gradually introduced since 1991 at age 50–69, and was extended to 75 years from 1998.

The nationwide Dutch pathology laboratory network and registry for histo- and cytopathology (PALGA), regularly reports all diagnosed malignancies to the regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collect data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports, from the patient files using the registration and coding manual of the NCR. Stage at diagnosis was taken into account using the tumor node metastasis (TNM) classification at the year of diagnosis [9]. Hereby, pathological and clinical TNM were combined into one variable, primarily referring to the pathological stage unless missing.

We identified migrants based on their country of birth (COB) which is routinely collected in the NCR and supplemented with data from the nationwide database of all municipal population registries in case of death or emigration. Patients with unknown COB were excluded. The largest migrant groups, originating from Turkey, Morocco, Suriname, the Netherlands Antilles/Aruba as well as Indonesia, were analyzed separately. We applied an ecological proxy for Socio-economic Status (SES) by using four-digit postal code at the time of diagnosis, obtained from the Netherlands Institute for Social Research (a governmental organization). SES was based on mean income per household, the percentage of households with a low income and the percentage of households with a low education. SES was analyzed in deciles (1 = first-third decile, 2 = fourth-seventh decile, 3 = eighth-tenth decile), resulting in three SES levels: high, intermediate and low.

Incidence analyses

Incidence rates were calculated per age group (0–14, 15–29, 30–44, 45–64 and 65 years and older), sex and year of diagnosis with cancer incidence rates of the entire Dutch population as reference, acquired from Statistics Netherlands [1]. Population data of all legal residents of The Netherlands contained country of birth as a proxy for migration background and were available for the period 1996–2009. Expected numbers of cancer cases in each migrant group were derived from annual population data as well as age- and sex-specific cancer incidences and

were compared with the observed numbers of cases in our data. Standardized incidence ratios (SIRs) were computed as the ratio between observed and expected numbers of cases between 1996 and 2006 with their 95% confidence intervals (CIs), calculated after log transformation.

Survival analyses

Vital status was established either directly from the patient's medical record or through linkage of cancer registry data with the (automated) municipal population registries which record information on their deceased or emigrated inhabitants (follow-up until 31 December 2010). Not all of these regional cancer registries (which together constitute the NCR) had complete registration of COB. In case of cancers with low lethality, patients being alive at the end of follow-up may have missing COB. For breast cancer (low lethality), we therefore only included data of cancer registries with complete registration of COB for the survival analyses and stage distribution. These data were gathered from the former areas (both rural and urban) of the comprehensive cancer centers Amsterdam, West and Stedendriehoek Twente all together covering about 40% of the Dutch population.

Survival analyses were performed for patients diagnosed from 1996 onwards. Relative excess risk (RER) of mortality was calculated, incorporating country of birth-specific death rates to account for different competing risks and comorbidities among most migrants. This approach had been used earlier to correctly measure socioeconomic differences in cancer survival [10]. In order to correct for low numbers of deaths in some groups, we used log-linear regression with interaction terms for period, age and sex to smooth the mortality rates. For the calculation of RERs, a regression model with a Poisson error structure was fitted as suggested by Dickman and colleagues [11], including incidence year, age at diagnosis, sex (stomach only), stage, SES, country of birth and subsite (stomach: cardia/non-cardia) as main effects. RER is considered the hazard ratio of relative survival, with which we aimed to estimate cancer-specific survival. All analyses were generated using SAS 9.3 software.

Results

Table I summarizes the main characteristics of the study cohort. During the study period 96 126 invasive breast cancer cases and 25 496 stomach cancer cases were included. All migrants, except Indonesians, were on average much younger at cancer diagnosis compared to Dutch natives and came from lower socioeconomic backgrounds, especially migrants from Turkey and Morocco. The aging of originally relatively young migrant groups in the Netherlands was reflected in the increasing numbers of cancer cases over this 10-year period, especially among women from Turkey and Morocco. Substantial increases were also observed for stomach cancer in all migrant groups, except for Indonesians. Dutch natives showed an absolute decrease in breast cancer cases and a decrease in stomach cancer cases over time (data not shown).

Breast cancer

Migrants also had a slightly disadvantageous stage distribution in breast cancer when compared to Dutch natives (Table I). Migrant women from Turkey (SIR = 0.5), Morocco (SIR = 0.6) and Suriname (SIR = 0.7) exhibited significantly lower breast cancer risks than native Dutch women (Table II).

After adjusting for all important possibly confounding factors, five-year excess risk of dying was significantly higher in women from Suriname (RER = 1.2; 95% CI 1.0–1.5) in comparison with native Dutch women (Table III). After stratification for menopausal status, higher excess risks were more pronounced in premenopausal migrant women, however not statistically significant.

Stomach cancer

Stomach cancer risk was significantly lower in migrants from Indonesia (SIR = 0.5) and higher in (male and female) migrants from Turkey (1.7 and 1.8, respectively) and Suriname (1.2 and 1.3) as well as in males from the Antilles/Aruba (1.6) and Morocco (1.5). The risk for cancer of the cardia was lower in all migrant groups as compared to native Dutch patients, but only significantly in migrants from Indonesia and males from Morocco and Suriname. In contrast, non-cardia stomach cancer risk was significantly elevated in all groups except Indonesians and Moroccan females (Table II).

One-year relative excess mortality was significantly reduced in migrants from the Antilles/Aruba (RER = 0.7), Suriname (RER = 0.8) and Turkey (RER = 0.7) relative to Dutch natives (Table III). This pattern was especially pronounced in non-cardia stomach cancers cases.

Conclusion

Migrants carried significantly lower risks of breast and cardia stomach cancer, contrasting higher non-cardia stomach cancer risks relative to patients from the native Dutch population. High relative excess mortality was found among Surinamese breast

Table I. Description of cohort of newly diagnosed breast and stomach cancer cases in the Netherlands according to country of birth (1996–2009).

	Country of birth					
	Native Dutch	Antilles/ Aruba	Indonesia	Morocco	Suriname	Turkey
Breast cancer						
Total (n)	92 197	366	1964	325	888	386
Mean age (y)	63	53	67	46	54	49
SES high (%)	29	25	37	12	22	12
SES mid (%)	34	25	26	17	16	13
SES low (%)	37	49	37	71	62	75
SES unknown (%)	0.1	0.8	0.3	0.0	0.2	0.3
Stage (n included)*	45 927	221	1253	196	664	242
Stage 1 (%)	38	38	36	21	33	27
Stage 2 (%)	44	46	44	49	49	47
Stage 3 (%)	11	11	11	21	11	19
Stage 4 (%)	5.6	4.1	6.0	4.6	5.6	5.0
Stage unknown (%)	1.9	1.4	2.8	3.1	1.5	2.5
Median FU (y)	4.6	4.1	4.7	3.9	4.5	4.5
Stomach cancer						
Total (n)	24 443	83	279	154	263	274
Females (%)	36	46	37	32	41	30
Mean age (y)	71	57	70	57	61	56
Cardia (%)	16	38	13	28	11	14
Non-cardia (%)	84	62	87	72	89	86
SES high (%)	24	19	35	8	15	5
SES mid (%)	35	16	28	19	16	13
SES low (%)	41	65	37	72	68	81
SES unknown (%)	0	0	0	0	0.4	0.0
Stage cardia (n included)	6869	13	105	20	30	38
Stage 1 (%)	9.0	0	6.7	20	6.7	13
Stage 2 (%)	12	0	16	0	3.3	18
Stage 3 (%)	16	31	16	10	27	11
Stage 4 (%)	41	46	31	50	33	45
Stage unknown (%)	22	23	30	20	30	13
Stage non-cardia (n included)	17 574	70	174	134	233	236
Stage 1 (%)	13	7.1	10	16	17	17
Stage 2 (%)	11	5.7	7.5	14	9.4	13
Stage 3 (%)	15	14	11	19	16	19
Stage 4 (%)	38	57	38	41	39	37
Stage unknown (%)	23	16	33	10	18	13
Median FU (y)	0.5	0.9	0.6	0.7	0.9	1.0
Median FU (y), cardia	0.6	0.9	0.6	0.5	0.6	0.7
Median FU (y), non-cardia	0.5	0.9	0.5	0.9	1.0	1.1

FU, follow-up; SES, socioeconomic status. *data on stage distribution of breast cancer are based on the former regions of Comprehensive Centres Amsterdam, West and Stedendriehoek Twente.

cancer patients and was more pronounced in premenopausal migrant women. Excess mortality from stomach cancer was significantly reduced in migrants from the Antilles/Aruba, Suriname and Turkey relative to Dutch natives and especially pronounced in non-cardia stomach cancer cases.

The reasons for lower breast cancer risks in migrant women compared to native women of Western countries can partly be explained by differences in reproductive and lifestyle patterns. More specifically, reproductive indicators such as the early age at menarche and higher age at first birth as well as the number of children, breastfeeding behaviors and the use of hormonal therapies in postmenopausal women represent key risk factors in the carcinogenesis of breast cancer [5]. Migrant women from less developed countries often exhibit many protective risk factors that subsequently lower their breast cancer risk [12]. Low breast cancer incidences in migrant women of non-Western origin residing in The Netherlands have also been reported by several studies from The Netherlands [13,14] and other Western European countries [15,16]. Breast cancer is curable if detected at an early stage and treated adequately. Despite incorporating important prognostic factors such as stage at diagnosis, we found higher relative excess mortality in migrant women, especially in Surinamese, which is in

Table II. Standardized Incidence Ratios (SIRs) for breast and stomach cancer with 95% confidence intervals (CI) for males (M) and females (F) according to country of birth (1996–2009)*.

	Country of birth				
	Antilles/ Aruba	Indonesia	Morocco	Suriname	Turkey
	SIR 95%CI	SIR 95%CI	SIR 95%CI	SIR 95%CI	SIR 95%CI
Breast cancer					
F	1.0 (0.9–1.1)	**0.9** (0.9–1.0)	**0.6** (0.5–0.6)	**0.7** (0.7–0.8)	**0.5** (0.4–0.5)
Stomach cancer					
F	**1.6** (1.2–2.3)	**0.5** (0.4–0.5)	**1.5** (1.1–2.0)	**1.3** (1.1–1.6)	**1.8** (1.5–2.3)
M	1.2 (0.9–1.7)	**0.5** (0.4–0.5)	0.9 (0.8–1.1)	**1.2** (1.0–1.4)	**1.7** (1.4–1.9)
Cardia					
F	1.3 (0.6–2.9)	**0.6** (0.4–0.9)	0.5 (0.1–1.4)	0.9 (0.5–1.5)	0.8 (0.4–1.6)
M	0.5 (0.2–1.0)	**0.6** (0.5–0.8)	**0.4** (0.3–0.7)	**0.3** (0.2–0.5)	0.7 (0.5–1.0)
Non-cardia					
F	**1.7** (1.2–2.4)	**0.4** (0.3–0.5)	**1.7** (1.3–2.3)	**1.4** (1.2–1.7)	**2.1** (1.7–2.6)
M	**1.7** (1.2–2.4)	**0.4** (0.3–0.4)	1.2 (1.0–1.5)	**1.7** (1.5–2.0)	**2.2** (1.9–2.6)

*Native Dutch = Reference (SIR = 1.0); bold numbers are significant at $p \leq 0.05$ level.

accordance with the findings of studies from the US and New Zealand [17,18]. Disparities in breast cancer survival may reflect differences in screening attendance which has been observed to be significantly lower in migrant women in The Netherlands [19] but also in other countries [20,21]. Important barriers in migrant women residing in The Netherlands are lacking knowledge and awareness as well as socio-cultural aspects as important inhibiting factors influencing screening uptake.

High risks of non-cardia stomach cancer in migrant populations are likely to be associated with *Helicobacter pylori*, typically acquired during early childhood, i.e. before migration. *H. pylori* incidence is highest in developing countries, but also in southern and eastern Europe, and transmission is fostered by poverty associated factors such as unhygienic and crowded living conditions [5,8]. Thus, migrants from low-income countries experience a relatively high stomach cancer incidence when compared to the population of their host country, which is also evident in our data. Differences between cardia (proximal tumors, close to the gastro-esophageal junction) and non-cardia (distal tumors) stomach cancer incidence may be due to different underlying risk factor patterns. Whilst the association to *H. pylori* infection seems to be confined to non-cardia stomach cancers, risk factors for cardia stomach cancer are more similar to those of esophageal cancers, thus lifestyle-related factors such as diet, smoking and alcohol consumption [22]. In fact, adenocarcinomas of the distal esophagus and cardia stomach cancer were found to be one clinical entity [23]. This explains the high rates for non-cardia but low rates for cardia stomach cancer among migrants that we found in our study. Yet, possible modification

Table III. Relative excess mortality risk ratios (RERs) for breast and stomach cancer according to country of birth (1996–2009).

	Country of birth				
	Antilles / Aruba	Indonesia	Morocco	Suriname	Turkey
Breast cancer*					
5-year RER# (95% CI)	0.9 (0.6–1.3)	1.0 (0.8–1.2)	1.3 (0.9–1.8)	**1.2** (1.0–1.5)	1.0 (0.7–1.4)
Age < 50	1.3 (0.7–2.2)	1.1 (0.7–1.8)	1.4 (1.0–2.1)	1.2 (0.9–1.6)	1.1 (0.8–1.7)
Age ≥ 50	0.6 (0.3–1.3)	1.0 (0.8–1.2)	0.7 (0.3–1.7)	1.3 (1.0–1.7)	0.7 (0.4–1.4)
Stomach cancer					
1-year RER$ (95% CI)	**0.7** (0.5–1.0)	1.0 (0.8–1.1)	1.0 (0.8–1.2)	**0.8** (0.6–0.9)	**0.7** (0.6–0.9)
Cardia	0.9 (0.4–2.0)	1.0 (0.8–1.3)	1.2 (0.7–2.0)	0.9 (0.6–1.5)	0.9 (0.6–1.4)
Non-cardia	**0.7** (0.5–0.9)	0.9 (0.8–1.1)	0.9 (0.7–1.2)	**0.7** (0.6–0.9)	**0.7** (0.6–0.9)

CI, confidence interval; FU, follow-up; RER, relative excess mortality risk ratio.
Bold numbers are significant at $p \leq 0.05$ level; ref (RER = 1) = native Dutch.
*for the breast cancer survival analyses 48 503 patients were included.
#adjusted for age at diagnosis, incidence year, socioeconomic status, stage and country of birth.
$adjusted for age at diagnosis, sex, incidence year, socioeconomic status, stage, country of birth and stomach site (cardia/non-cardia).

of the carcinogenicity of *H. pylori* in concurrence with environmental factors cannot be excluded and still needs to be investigated.

Contrary to our expectations, the study revealed favorable stomach cancer survival rates in most migrant groups, irrespective of the exact tumor location and even though stage distribution at diagnosis was worse than among Dutch natives (Table I). Several other studies, however, found that stomach cancer survival was especially poor in migrants [3]. Due to the high fatality of stomach cancer in general, differences in survival are unlikely to be influenced by early detection measures or possible treatment inequalities. As a result, the observed differences are likely to be driven by other causes that are beyond the currently known risk factors. Differences in genetic predisposition might for instance play a causal role. Another explanation for the observed survival advantage might be the so-called salmon bias. The remigration of diseased persons back to their country of origin without de-registering with the Dutch authorities, renders them statistically immortal and results in low survival rates [24]. However, as most migrants and their families have settled permanently in The Netherlands and healthcare is better than in their country of origin, we think that this bias would only marginally affect our results.

Our results are limited with regard to the validity of the migrant definition we used in our study. Country of birth is currently the most accepted proxy for ethnicity, although it has limitations with regard to cultural and ethnic identity [25]. This limitation resulted in different results for migrants originating from Indonesia, formerly Dutch Indies being a colony, when compared to the other migrant groups. On the one hand, most people who were born in Indonesia and migrated to The Netherlands had Dutch ancestors and were ethnic Dutch, and on the other hand, their migration history to The Netherlands reaches back in the late 1940s and early 1950s, much longer than that of 'newer' migrants. Moreover, there was missing COB information for many individuals still alive at the end of follow-up. Due to generally low survival rates, this hardly affected stomach cancer survival in our study. However, for breast cancer with on average better survival, data from only three regional cancer registries with sufficient completeness could be included. Only by doing this, we were able to calculate reliable estimates of survival rates according to COB. We assumed that the completeness of registration of COB affects migrants and natives similarly, although registration clerks might have been more likely to register COB in case of a non-Dutch patient.

Due to lacking data availability in the reference population, we could not apply the SES proxy in the incidence analyses. This leaves uncertainty of how much of the effect may be attributable to socioeconomic circumstances. Yet, the survival analyses showed significant effects after adjusting for potentially confounding socioeconomic factors. As age at migration and duration of residence are not available in NCR data (as in few other cancer registries in the world), we were not able to assess the impact of these factors. However, we were able to accurately estimate relative survival using country of birth-specific background mortality provided by Statistics Netherlands.

Especially by the cancer experience of Indonesian migrants (most of whom reside in The Netherlands for more than 60 years), our results emphasize the importance of life course in the analysis of cancer risks in migrant populations. Exposures before, during and after migration underscore key hints for causal inferences in carcinogenesis. In particular, early life exposures (non-cardia stomach cancer) and acculturation processes (breast cancer) play important roles in the change of cancer risks over time and across generations.

Survival disparities require careful monitoring and counteraction with preventive means as well as improved access to healthcare. This is especially relevant for access to care for upper gastrointestinal section complaints and symptoms, but also for premenopausal women with breast cancer. Migrant-specific risk profiles should complement guidelines for the detection and management of both cancers.

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