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# Green tea consumption and gastric cancer in Japanese: a pooled analysis of six cohort studies

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## ABSTRACT

**Background:** Previous experimental studies have suggested many possible anti-cancer mechanisms for green tea, but epidemiological evidence for the effect of green tea consumption on gastric cancer risk is conflicting.

**Objective:** To examine the association between green tea consumption and gastric cancer.

**Methods:** We analysed original data from six cohort studies that measured green tea consumption using validated questionnaires at baseline. Hazard ratios (HRs) in the individual studies were calculated, with adjustment for a common set of variables, and combined using a random-effects model.

**Results:** During 2 285 968 person-years of follow-up for a total of 219 080 subjects, 3577 cases of gastric cancer were identified. Compared with those drinking <1 cup/day, no significant risk reduction for gastric cancer was observed with increased green tea consumption in men, even in stratified analyses by smoking status and subsite. In women, however, a significantly decreased risk was observed for those with consumption of ⩾5 cups/day (multivariate-adjusted pooled HR = 0.79, 95% confidence interval (CI) = 0.65 to 0.96). This decrease was also significant for the distal subsite (HR = 0.70, 95% CI = 0.50 to 0.96). In contrast, a lack of association for proximal gastric cancer was consistently seen in both men and women.

**Conclusions:** Green tea may decrease the risk of distal gastric cancer in women.

Green tea is one of the most popular beverages in the world and is widely consumed in Japan.[1] Green tea contains polyphenolic antioxidants, such as epigallocatechin gallate, which are thought to contribute to cancer prevention.[2] Early case–control studies found a reduced risk of gastric cancer in association with the consumption of green tea,[3–7] while previous in vitro and in vivo studies suggested many possible anti-cancer mechanisms for green tea. Together, these findings suggest that the consumption of green tea is associated with a decreased risk of gastric cancer.[2]

To date, however, epidemiological evidence for the effect of green tea consumption on cancer risk is conflicting. The recent review of the World Cancer Research Fund in 2007 did not support a possible protective effect of green tea against cancer,[8] and, presently, there is no convincing evidence to support a role for green tea in cancer prevention. In particular, several recent large-scale population-based cohort studies in Japan, established before the mid-1990s and with long-term follow-up, have actively examined the association between green tea consumption and the risk of gastric cancer.[9–14] As to results, however, these studies, which were prospective in design and thus free from recall and selection biases, provide no overall support for the idea that increased consumption of green tea protects against gastric cancer.[15]

Although Japanese tend to consume green tea in a similar manner and the studies estimated consumption dose using similar questions, the studies nevertheless varied in the factors used to adjust for potential confounders and in stratification. One finding was a difference in effect by sex. This may be noteworthy but is yet to be clarified, with some studies showing a decreasing risk tendency in women,[9 12 13] albeit that the strength of the effect appeared to be modest, if it exists at all. The null association in men may, in part, reflect insufficient adjustment for confounding factors such as cigarette smoking. Likewise, differences in the effect of green tea by subsite[12] may point to an inconsistent effect on gastric cancer overall. However, evidence for such specific issues is sparse, probably due to the relatively small number of gastric cancer cases occurring in the upper subsite among cohorts, particularly in women.

To better understand these issues, we conducted a pooled analysis of several large-scale population-based cohort studies in Japan on the association between green tea consumption and gastric cancer risk.

## METHODS

### Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan initiated a pooling project using original data from major cohort studies to evaluate the association between lifestyle and major forms of cancer in Japanese. Topics for the pooled analysis were determined on the basis of discussion among all authors from the viewpoint of both scientific and public health importance. To maintain the quality and comparability of data, we set inclusion criteria for the present purpose a priori, namely population-based cohort studies conducted in Japan; started in the mid-1980s to mid-1990s; included more than 30 000 participants; obtained information on diet, including green tea consumption, using a validated questionnaire at baseline; and collected incidence data for gastric cancer during the follow-up period. Six ongoing studies that met



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Gastric cancer

**Table 1** Characteristics of the six cohort studies included in a pooled analysis of green tea consumption and gastric cancer risk, 1988–2004

| Study | Population | Age (years) at baseline survey | Year(s) of baseline survey | Population size | Rate of response (%) to baseline questionnaire | For the present pooled analysis | | | | | | No of gastric cancer cases | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Method of follow-up | Age (years) | Last follow-up time | Mean duration of follow-up (years) | Size of cohort | | | |
| | | | | | | | | | | Men | Women | Men | Women |
| JPHC-I | Japanese residents of five public health centre areas in Japan | 40–59 | 1990 | 61595 | 82 | Cancer registry and death certificates | 40–59 | 2001 | 11.3 | 15111 | 16498 | 379 | 135 |
| JPHC-II | Japanese residents of 6 public health centre areas in Japan | 40–69 | 1993–1994 | 78825 | 80 | Cancer registry and death certificates | 40–69 | 2003–2004 | 10.6 | 19301 | 21108 | 565 | 206 |
| JACC | Residents from 45 areas throughout Japan | 40–79 | 1988–1990 | 110792 | 83 | Cancer registry (24 selected areas) and death certificates | 40–79 | 2001 | 10.2 | 21113 | 30017 | 639 | 346 |
| MIYAGI | Residents of 14 municipalities in Miyagi Prefecture, Japan | 40–64 | 1990 | 47605 | 92 | Cancer registry and death certificates | 40–64 | 2001 | 11.0 | 19007 | 20596 | 388 | 173 |
| 3-pref MIYAGI | Residents of three municipalities in Miyagi Prefecture, Japan | 40–98 | 1984 | 31345 | 94 | Cancer registry and death certificates | 40–98 | 1992 | 7.6 | 11902 | 14409 | 296 | 123 |
| 3-pref AICHI | Residents of two municipalities in Aichi Prefecture, Japan | 40–103 | 1985 | 33529 | 90 | Cancer registry and death certificates | 40–103 | 2000 | 11.5 | 14045 | 15973 | 228 | 99 |
| Total | | | | | | | | | | 100479 | 118601 | 2495 | 1082 |

JACC, The Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based prospective Study; MIYAGI, The Miyagi Cohort Study; 3-pref AICHI, The Three Prefecture Study – Aichi portion; 3-pref MIYAGI, The Three Prefecture Study – Miyagi portion.

these criteria were identified: (1) the Japan Public Health Center-based Prospective Study (JPHC)-I;[16] (2) JPHC-II;[16] (3) the Japan Collaborative Cohort Study (JACC);[17] (4) the Miyagi Cohort Study (MIYAGI);[10] (5) the Three Prefecture Study – Miyagi portion (3-pref MIYAGI);[19] and (6) the Three Prefecture Study – Aichi portion (3-pref AICHI).[19] JPHC was treated as two independent studies (JPHC-I and JPHC-II) because of the different questionnaire used at baseline. One area in JPHC-I and one in JPHC-II, both in Okinawa Prefecture, were excluded from the analysis since tea drinking habits in these areas differed from the rest of Japan and were not comparable with other areas. Further, with regard to JACC, since information on cancer incidence was collected in only 24 of 45 study areas, data from only those 24 areas were used.

We excluded data for subjects with missing information on green tea consumption or a history of cancer at baseline. Selected characteristics of these studies are presented in table 1. Each study was approved by the relevant institutional review board. Results on the association between green tea intake and gastric cancer risk in these cohorts have been reported.[9 10 12 18] For the present analysis, we used updated data sets with an extended follow-up period.

### Follow-up

Subjects were followed from the baseline survey (JPHC-I, 1990; JPHC-II, 1993–1994; JACC, 1988–1990; MIYAGI, 1990; 3-pref MIYAGI, 1984; 3-pref AICHI, 1985) to the last date of follow-up for incidence of gastric cancer in each study (JPHC-I, 2001; JPHC-II, 2003–2004; JACC, 2001; MIYAGI, 2001; 3-pref MIYAGI, 1992; 3-pref AICHI, 2000). Residence status in each study, including survival, was confirmed through the residential registry.

### Case ascertainment

In all cohorts included in the present study, cancer diagnoses were identified through population-based cancer registries and active patient notification from major local hospitals. Although the quality and completeness of the case ascertainment varied by cohort, the overall percentage of cases registered from a death certificate only was 8.7% and the estimated ascertainment of cancer diagnoses was nearly 90%. Cases were coded using the International Classification of Disease, Tenth Revision,[20] or the International Classification of Diseases for Oncology, Third Edition.[21] Study outcome was defined as incident gastric cancer (code: C16) diagnosed during the follow-up period of each study. In JPHC-I, JPHC-II, MIYAGI, and 3-pref MIYAGI, in which subsite information was routinely collected, gastric cancers were also classified into proximal (C16.0–C16.1) and distal subsite (C16.2–C16.6). In epidemiological studies using Japanese populations, it is not practical to restrict "cardia (C16.0)" in the analysis because clinical site in gastric cancer diagnosis in Japan is based on the Japanese Classification of Gastric Carcinoma,[22] in which tumour location is usually described anatomically in three parts, namely upper third, middle third, and lower third. In most cases this hampers the clear division of the upper third into "cardia" and "fundus," unless the medical record provided extra information. For this reason, we used the proximal subsite and distal subsite to perform subsite-specific analysis.

### Assessment of green tea consumption

In each study except JACC, the frequency and daily amounts of green tea consumption were asked about in the self-administered questionnaire in the same categories of almost none, 1–2 days/week, 3–4 days/week, and almost daily (1–2 cups/day, 3–4 cups/day, and ≥5 cups/day). In JACC, in contrast, daily consumption was asked about in terms of the actual number of cups of green tea consumed each day so these data were re-categorised into the same categories as the other studies. Spearman correlation coefficients for the correlation between green tea consumption (g/day) estimated from the questionnaire and that from the dietary record were JPHC-I, 0.57 in men and 0.63 in women;[23] JPHC-II, 0.39 in men and 0.48 in women;[12] JACC, 0.47;[24] and MIYAGI and 3-pref MIYAGI, 0.71 in men and 0.53 in women.[25] 3-Pref AICHI, for which information on the validation of green tea consumption was not available, utilised the same questionnaire as 3-pref MIYAGI.

### Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey in each study to the date of diagnosis of gastric cancer, migration from the study area, death, or the end of follow-up, whichever came first. In each individual study, sex- and area-(JPHC-I, JPHC-II, and JACC) adjusted hazard ratios (HRs) (model 1) and 95% confidence intervals (95% CIs) for gastric cancer were estimated for each green tea intake category using a Cox proportional hazards model. Green tea consumption of <1 cup/day was used as reference category in consideration of the fact that green tea is a common beverage in Japan and very few people are non-consumers. Further multivariate adjustments were made by including covariates in the regression model which were either known or suspected risk factors for cancer or had previously been found to be associated with the risk of gastric cancer.[6 26] The adjustments were made in two ways: first for smoking (for men: never smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of ≥20 cigarettes/day; for women: never smoker, past smoker, or current smoker), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (≥once/week): for men: <23 g/day, 23 to <46 g/day, ≥46 g/day; for women: <23 g/day, ≥23 g/day)), rice intake (<4 bowls/day, ≥4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ≥3 cups/day) in addition to adjustment in model 1 (model 2); second for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to adjustment in model 2 (model 3). In estimation of HR by model 3, each cohort used different food items for pickled vegetables and green–yellow vegetables due to the different food items asked about in each questionnaire. We further conducted stratified analysis by smoking status, namely among never smokers and among current smokers. Also, analyses confining the outcome to the proximal or distal subsite were conducted using JPHC-I, JPHC-II, MIYAGI and 3-pref MIYAGI, for which subsite information was available. An indicator term for missing data was created for each covariate. SAS (version 9.1) or Stata (version 10) statistical software was used for these estimations.

A random-effects model was used to obtain a single pooled estimate of the hazard ratios from the individual studies for each category. The study-specific hazard ratios were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. A study that had no cases for a category was not included in the pooled estimate for that category. The trend association was assessed in a similar manner: investigators from each study calculated the regression coefficient and its standard error of linear trend for green tea consumption category treated as an ordinal variable. These values from the individual studies were then combined using a random-effects model. We tested for and quantified the heterogeneity of the HRs for the highest category and the trend association of green tea consumption association among studies using the $Q$ and $I^2$ statistics. Stata 10 was used for meta-analysis.





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Gastric cancer

**Table 2** Study-specific multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) of gastric cancer incidence by green tea consumption

| | Green tea consumption | | | |
|---|---|---|---|---|
| | <1 cup/day | 1–2 cups/day | 3–4 cups/day | ≥5 cups/day |
| Total | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| *Men* | | | | |
| JPHC-I | | | | |
| Model 2 | 1.00 (Reference) | 0.85 (0.62 to 1.16) | 0.86 (0.64 to 1.15) | 0.95 (0.72 to 1.25) |
| Model 3 | 1.00 (Reference) | 0.85 (0.62 to 1.17) | 0.87 (0.65 to 1.16) | 0.97 (0.73 to 1.28) |
| JPHC-II | | | | |
| Model 2 | 1.00 (Reference) | 1.11 (0.81 to 1.51) | 1.08 (0.80 to 1.45) | 1.06 (0.79 to 1.43) |
| Model 3 | 1.00 (Reference) | 1.11 (0.82 to 1.52) | 1.08 (0.80 to 1.45) | 1.06 (0.78 to 1.43) |
| JACC | | | | |
| Model 2 | 1.00 (Reference) | 0.81 (0.60 to 1.09) | 0.76 (0.58 to 1.00) | 0.82 (0.64 to 1.05) |
| Model 3 | 1.00 (Reference) | 0.80 (0.59 to 1.08) | 0.75 (0.57 to 1.00) | 0.81 (0.63 to 1.05) |
| MIYAGI | | | | |
| Model 2 | 1.00 (Reference) | 0.92 (0.69 to 1.22) | 0.88 (0.66 to 1.18) | 0.89 (0.68 to 1.16) |
| Model 3 | 1.00 (Reference) | 0.90 (0.67 to 1.20) | 0.87 (0.65 to 1.17) | 0.88 (0.67 to 1.15) |
| 3-pref MIYAGI | | | | |
| Model 2 | 1.00 (Reference) | 1.24 (0.82 to 1.88) | 1.15 (0.76 to 1.73) | 1.50 (1.06 to 2.13) |
| Model 3 | 1.00 (Reference) | 1.28 (0.84 to 1.94) | 1.20 (0.79 to 1.80) | 1.55 (1.09 to 2.20) |
| 3-pref AICHI | | | | |
| Model 2 | 1.00 (Reference) | 1.31 (0.76 to 2.27) | 1.28 (0.77 to 2.13) | 1.69 (1.03 to 2.77) |
| Model 3 | 1.00 (Reference) | 1.27 (0.74 to 2.21) | 1.22 (0.73 to 2.03) | 1.60 (0.97 to 2.63) |
| *Women* | | | | |
| JPHC-I | | | | |
| Model 2 | 1.00 (Reference) | 0.74 (0.44 to 1.23) | 0.90 (0.57 to 1.41) | 0.58 (0.36 to 0.95) |
| Model 3 | 1.00 (Reference) | 0.75 (0.45 to 1.25) | 0.90 (0.58 to 1.42) | 0.58 (0.36 to 0.95) |
| JPHC-II | | | | |
| Model 2 | 1.00 (Reference) | 0.92 (0.55 to 1.54) | 1.14 (0.72 to 1.80) | 0.72 (0.45 to 1.17) |
| Model 3 | 1.00 (Reference) | 0.93 (0.56 to 1.56) | 1.18 (0.74 to 1.86) | 0.74 (0.45 to 1.20) |
| JACC | | | | |
| Model 2 | 1.00 (Reference) | 1.04 (0.71 to 1.54) | 0.85 (0.60 to 1.20) | 0.88 (0.64 to 1.21) |
| Model 3 | 1.00 (Reference) | 1.04 (0.71 to 1.53) | 0.85 (0.60 to 1.19) | 0.88 (0.64 to 1.21) |
| MIYAGI | | | | |
| Model 2 | 1.00 (Reference) | 0.83 (0.54 to 1.28) | 0.95 (0.63 to 1.43) | 0.73 (0.49 to 1.10) |
| Model 3 | 1.00 (Reference) | 0.81 (0.53 to 1.26) | 0.89 (0.59 to 1.35) | 0.67 (0.44 to 1.02) |
| 3-pref MIYAGI | | | | |
| Model 2 | 1.00 (Reference) | 0.81 (0.44 to 1.47) | 0.72 (0.41 to 1.26) | 0.82 (0.51 to 1.32) |
| Model 3 | 1.00 (Reference) | 0.82 (0.45 to 1.49) | 0.72 (0.41 to 1.27) | 0.83 (0.51 to 1.35) |
| 3-pref AICHI | | | | |
| Model 2 | 1.00 (Reference) | 1.19 (0.48 to 2.92) | 1.28 (0.59 to 2.78) | 1.52 (0.71 to 3.21) |
| Model 3 | 1.00 (Reference) | 1.20 (0.49 to 2.95) | 1.29 (0.59 to 2.80) | 1.54 (0.72 to 3.28) |

Model 2: Adjusted for age (continuous), area (JPHC-I, JPHC-II and JACC only), smoking (never smoker, past smoker, or current smoker), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (<23 g/day, ≥23 g/day)), rice intake (<4 bowls/day, ≥4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ≥3 cups/day).
Model 3: Adjusted for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to the variables included in Model 2.
JACC, The Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based prospective Study; MIYAGI, The Miyagi Cohort Study; 3-pref AICHI, The Three Prefecture Study – Aichi portion; 3-pref MIYAGI, The Three Prefecture Study – Miyagi portion.

## RESULTS

The present study included 219 080 subjects (100 479 men and 118 601 women) and 3577 cases of gastric cancer (2495 men and 1082 women) accumulated during 2 285 968 person-years of follow-up (table 1). Among both men and women, 80% of subjects consumed green tea every day, with 35% of men and 33% of women consuming ≥5 cups per day. Distribution of intake frequency was similar between men and women. In most cohorts, men and women with higher intake also tended to consume more rice, green–yellow vegetables, soy bean paste soup or pickled vegetables. The proportion of current smokers was also higher among men with higher green tea intake, but this characteristic was less clear among women.[9 10 12 18] The study-specific HRs and 95% CIs of total gastric cancer incidence by green tea consumption are presented in table 2.

In men (table 3), no notable association was found as a whole. No change in results was seen when subjects were stratified as never smokers and current smokers, and when outcome was confined to proximal or distal subsite. The results

**Table 3** Results from a pooled analysis (random-effects model) of gastric cancer incidence by green tea consumption in Japanese men, 1984–2004

| | | Green tea consumption | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <1 cup/day | 1–2 cups/day | 3–4 cups/day | ≥5 cups/day | | p For heterogeneity (for the highest category) | p For heterogeneity (for trend) |
| | Total | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | p For trend | | |
| *Total* | | | | | | | | |
| No of subjects | 100479 | 19877 | 21355 | 26369 | 32878 | | | |
| Person-years | 1035158 | 205165 | 219427 | 271469 | 339097 | | | |
| No of cases | 2495 | 420 | 452 | 610 | 1013 | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 241.12 | 236.20 | 236.06 | 222.44 | 257.18 | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 0.98 (0.85 to 1.14) | 0.95 (0.82 to 1.09) | 1.10 (0.90 to 1.34) | *0.394* | 0.026 | 0.110 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 0.97 (0.84 to 1.12) | 0.94 (0.81 to 1.08) | 1.06 (0.86 to 1.29) | *0.792* | 0.024 | 0.132 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 0.97 (0.83 to 1.12) | 0.93 (0.81 to 1.08) | 1.06 (0.86 to 1.30) | *0.739* | 0.025 | 0.104 |
| *Smoking status* | | | | | | | | |
| Never smokers | | | | | | | | |
| No of subjects | 19334 | 4257 | 4176 | 5229 | 5672 | | | |
| Person-years | 204380 | 45197 | 44025 | 54939 | 60219 | | | |
| No of cases | 312 | 56 | 60 | 73 | 123 | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 157.74 | 142.01 | 162.62 | 135.76 | 177.75 | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 1.12 (0.73 to 1.72) | 0.97 (0.67 to 1.41) | 1.28 (0.90 to 1.82) | *0.063* | 0.518 | 0.535 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 1.10 (0.74 to 1.64) | 0.96 (0.66 to 1.39) | 1.27 (0.89 to 1.81) | *0.337* | 0.581 | 0.730 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 1.15 (0.75 to 1.76) | 0.99 (0.68 to 1.45) | 1.34 (0.93 to 1.92) | *0.221* | 0.552 | 0.671 |
| Current smokers | | | | | | | | |
| No of subjects | 53438 | 10510 | 11540 | 13724 | 17664 | | | |
| Person-years | 555136 | 109862 | 119803 | 142719 | 182752 | | | |
| No of cases | 1366 | 227 | 254 | 342 | 543 | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 265.29 | 252.94 | 272.87 | 256.63 | 272.79 | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 0.99 (0.83 to 1.19) | 1.00 (0.82 to 1.22) | 1.05 (0.82 to 1.35) | *0.564* | 0.064 | 0.050 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 0.99 (0.82 to 1.19) | 0.99 (0.81 to 1.20) | 1.03 (0.81 to 1.31) | *0.817* | 0.090 | 0.107 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 0.98 (0.81 to 1.18) | 0.97 (0.80 to 1.19) | 1.01 (0.79 to 1.29) | *0.727* | 0.086 | 0.053 |
| *Subsite* | | | | | | | | |
| Proximal (upper third) | | | | | | | | |
| No of subjects | 65321 | 15019 | 14943 | 16517 | 18842 | | | |
| Person-years | 662495 | 155665 | 152476 | 168202 | 186152 | | | |
| No of cases | 217 | 38 | 41 | 42 | 96 | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 36.82 | 30.61 | 31.60 | 26.53 | 49.10 | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 1.11 (0.71 to 1.74) | 0.76 (0.46 to 1.26) | 1.43 (0.97 to 2.12) | *0.069* | 0.973 | 0.847 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 1.09 (0.70 to 1.72) | 0.77 (0.46 to 1.29) | 1.42 (0.96 to 2.11) | *0.080* | 0.994 | 0.785 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 1.10 (0.70 to 1.73) | 0.79 (0.46 to 1.35) | 1.43 (0.96 to 2.14) | *0.081* | 0.919 | 0.737 |

Continued







**Table 3** Continued

| | | Green tea consumption | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <1 cup/day | 1–2 cups/day | 3–4 cups/day | ≥5 cups/day | | p For heterogeneity (for the highest category) | p For heterogeneity (for trend) |
| | Total | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | p For trend | | |
| Distal (lower two thirds) | | | | | | | | |
| No of subjects | 65321 | 15019 | 14943 | 16517 | 18842 | | | |
| Person-years | 662495 | 155665 | 152476 | 168202 | 186152 | | | |
| No of cases | 947 | 185 | 185 | 249 | 328 | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 151.35 | 136.73 | 144.95 | 154.07 | 160.99 | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 0.92 (0.74 to 1.13) | 0.97 (0.80 to 1.18) | 1.02 (0.84 to 1.24) | *0.690* | 0.370 | 0.270 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 0.89 (0.72 to 1.11) | 0.93 (0.77 to 1.14) | 0.95 (0.78 to 1.15) | *0.746* | 0.469 | 0.299 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 0.91 (0.73 to 1.12) | 0.95 (0.77 to 1.16) | 0.96 (0.79 to 1.17) | *0.856* | 0.481 | 0.316 |

Model 2: Adjusted for age (continuous), area (JPHC-I, JPHC-II and JACC only), smoking (never smoker, past smoker, current smoker of 1–19 cigarettes/day, or current smoker of ≥20 cigarettes/day), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (≥once/week: <23 g/day, 23-<46 g/day, ≥46 g/day), rice intake (<4 bowls/day, ≥4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ≥3 cups/day).
Model 3: Adjusted for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to the variables included in Model 2.



between studies for the highest category of green tea consumption for male total gastric cancer risk showed significant heterogeneity ($p = 0.025$), and the $I^2$ statistic suggested that 61% of between-study heterogeneity among the highest category was attributable to variability in the true effect of green tea.

In women (table 4), in contrast, subjects who consumed ≥5 cups of green tea every day had a significantly decreased risk of gastric cancer (HR = 0.79, 95% CI = 0.65 to 0.96). We also observed a significant trend of decreased risk with increasing consumption ($p$ for trend = 0.043). Results did not change for never smokers (HR = 0.79, 95% CI = 0.64 to 0.97 for ≥5 cups of green tea). When outcome was confined to gastric cancer at a distal site, similar decreased risk was observed (HR = 0.70, 95% CI = 0.50 to 0.96 for ≥5 cups of green tea; $p$ for trend = 0.042). Results between studies for female never smokers showed significant heterogeneity ($p$ for heterogeneity <0.001), and the $I^2$ statistic suggested 85% of between-study heterogeneity for trend association was attributable to variability in the true effect of green tea.

## DISCUSSION

Although many experimental studies have indicated a role for green tea in cancer prevention,[7] epidemiological evidence for the effect of green tea consumption on cancer risk is conflicting. To address this discrepancy, we carried out a pooled analysis of major population-based cohort studies in Japan. Results showed a significant decrease in risk only among women in the highest category of green tea consumption. This decrease in risk was similarly observed among never smokers and for distal gastric cancer. We observed no association between green tea consumption and gastric cancer in men.

For the heterogeneity of results among the highest category of total men, two studies which were started in the mid 1980s, in other words earlier than other studies, tended to show an increased risk while the other later studies showed a decreased risk tendency. This heterogeneity may have resulted from a slight difference in the birth cohort due to the earlier starting point. In women, in contrast, heterogeneity was observed only for the trend association among never-smokers, in which one of the two studies started in the mid 1980s showed different results from the other studies. Therefore, these heterogeneities observed in men and women may not be solely attributable to such differences in birth cohort.

Our results raise several noteworthy issues on the association between green tea consumption and gastric cancer risk. First, we observed a clear sex difference in the association between green tea consumption and gastric cancer risk. Although most previous cohort studies in Japan have reported a null association, those which conducted separate analyses by sex[9 12 13] in fact observed a decreased risk tendency in women, whereas those which only reported combined results tended to observe an overall null association.[10 11]

Several possibilities may explain the null association for men. The first is that the highest category in women may have included more subjects with a higher consumption of green tea than the highest category in men, hampering the detection of an effect in men, if any. One of the cohorts, JACC, in which information was obtained on the number of cups consumed per day, showed no such trend.[9] Further, the null association in men may have been partly due to residual confounding effects, especially cigarette smoking. In our previous systematic review, we concluded that there is convincing evidence that cigarette smoking moderately increases the risk of gastric cancer among

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**Table 4** Results from a pooled analysis (random-effects model) of gastric cancer incidence by green tea consumption in Japanese women, 1984–2004

| | | Green tea consumption | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <1 cup/day | 1–2 cups/day | 3–4 cups/day | ≥5 cups/day | | p For heterogeneity (for the highest category) | p For heterogeneity (for trend) |
| | Total | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | p For trend | | |
| *Total* | | | | | | | | |
| No of subjects | 118601 | 23316 | 21460 | 32459 | 41366 | | | |
| Person-years | 1250810 | 244097 | 226618 | 342038 | 438057 | | | |
| No of cases | 1082 | 215 | 174 | 303 | 390 | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 86.50 | 99.89 | 87.01 | 87.88 | 78.96 | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 0.98 (0.84 to 1.15) | 0.92 (0.77 to 1.11) | 0.81 (0.67 to 0.97) | 0.031 | 0.416 | 0.415 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 0.90 (0.73 to 1.10) | 0.93 (0.77 to 1.11) | 0.80 (0.66 to 0.96) | 0.063 | 0.402 | 0.265 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 0.90 (0.73 to 1.10) | 0.92 (0.76 to 1.11) | 0.79 (0.65 to 0.96) | 0.043 | 0.351 | 0.283 |
| *Smoking status* | | | | | | | | |
| Never smokers | | | | | | | | |
| No of subjects | 95558 | 18422 | 17360 | 26897 | 32879 | | | |
| Person-years | 1023763 | 196333 | 185652 | 287616 | 354163 | | | |
| No of cases | 871 | 171 | 144 | 246 | 310 | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 86.36 | 100.79 | 89.07 | 85.78 | 78.61 | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 0.90 (0.72 to 1.14) | 0.90 (0.73 to 1.11) | 0.80 (0.66 to 0.98) | 0.692 | 0.574 | <0.001 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 0.91 (0.72 to 1.15) | 0.91 (0.74 to 1.12) | 0.80 (0.65 to 0.98) | 0.770 | 0.548 | <0.001 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 0.91 (0.73 to 1.15) | 0.90 (0.73 to 1.11) | 0.79 (0.64 to 0.97) | 0.780 | 0.531 | <0.001 |
| Current smokers | | | (≥1 cups/day) | | | | | |
| No of subjects | 7694 | 1636 | 6058 | | | | | |
| Person-years | 78141 | 16561 | 61580 | | | | | |
| No of cases | 66 | 12 | 54 | | | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 88.54 | 74.54 | 89.21 | | | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 0.94 (0.48 to 1.82) | | | 0.744 | 0.715 | 0.882 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 0.86 (0.44 to 1.68) | | | 0.690 | 0.488 | 0.459 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 0.90 (0.41 to 1.97) | | | 0.799 | 0.299 | 0.383 |
| *Subsite* | | | | | | | | |
| Proximal (upper third) | | | (≥1 cups/day) | | | | | |
| No of subjects | 72611 | 16271 | 56340 | | | | | |
| Person-years | 758865 | 173390 | 585474 | | | | | |
| No of cases | 53 | 8 | 45 | | | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 7.60 | 7.05 | 7.80 | | | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 1.23 (0.56 to 2.71) | | | 0.869 | 0.993 | 0.828 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 1.17 (0.53 to 2.59) | | | 0.844 | 0.974 | 0.834 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 1.17 (0.52 to 2.60) | | | 0.874 | 0.979 | 0.850 |

Continued







**Table 4** Continued

| | | Green tea consumption | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <1 cup/day | 1–2 cups/day | 3–4 cups/day | ≥5 cups/day | | p For heterogeneity (for the highest category) | p For heterogeneity (for trend) |
| | Total | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | p For trend | | |
| Distal (lower two thirds) | | | | | | | | |
| No of subjects | 72611 | 16271 | 14878 | 18983 | 22479 | | | |
| Person-years | 758865 | 173390 | 157522 | 199008 | 228944 | | | |
| No of cases | 370 | 83 | 64 | 117 | 106 | | | |
| Age-standardised rate (per 100 000) (Random effect model) | 52.10 | 58.86 | 45.95 | 61.30 | 44.24 | | | |
| Age- and area-adjusted (model 1) | | 1.00 (Reference) | 0.80 (0.57 to 1.12) | 0.97 (0.72 to 1.31) | 0.74 (0.53 to 1.03) | 0.100 | 0.221 | 0.314 |
| Multivariate-adjusted (model 2) | | 1.00 (Reference) | 0.80 (0.57 to 1.12) | 0.96 (0.71 to 1.30) | 0.70 (0.50 to 0.995) | 0.051 | 0.274 | 0.889 |
| Multivariate-adjusted (model 3) | | 1.00 (Reference) | 0.80 (0.57 to 1.13) | 0.96 (0.71 to 1.30) | 0.70 (0.50 to 0.96) | 0.042 | 0.358 | 0.361 |

Model 2: Adjusted for age (continuous), area (JPHC-I, JPHC-II and JACC only), smoking (never smoker, past smoker, or current smoker), ethanol intake (never/former drinker, occasional drinker (<once/week), regular drinker (<23 g/day, ≥23 g/day)), rice intake (<4 bowls/day, ≥4 bowls/day), soy bean paste soup (<daily, daily), and coffee intake (<1 cup/day, 1–2 cups/day, ≥3 cups/day).
Model 3: Adjusted for pickled vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) and green–yellow vegetable intake (<weekly, 1–2 times/week, 3–4 times/week, daily) in addition to the variables included in Model 2.

the Japanese population.[27] In the present study, however, adjustment for smoking status did not change the results. Likewise, in stratified analysis by smoking status, we observed no substantial difference in the effect of green tea consumption between never smokers and current smokers. An anti-*Helicobacter pylori* effect by green tea is another possible explanation. A previous nested case–control study in two of the six cohorts[28] reported that *H pylori* did not distribute differentially in relation to tea polyphenol level in men, while positivity of *H pylori* infection was higher among women with lower tea polyphenol levels. This suggests some possibility in the sex difference in relation to the effect of green tea on *H pylori*, although this does not explain directly why green tea is associated with a decreased risk in women only. Further research on this issue is needed.

A difference in the effect of green tea by sex has also been observed for cardiovascular disease,[14 29] for which an oestrogen-related mechanism has been proposed. In support of this, tea flavonoids such as kaempferol have been shown to exhibit oestrogenic activity in vitro.[30] In addition, tea contains lignan polyphenols, such as secoisolariciol, which are considered phytoestrogenic.[31] The phytoestrogens in tea might also partly account for the stronger protective effect of green tea against cancer in women than in men,[32 33] although an oestrogen-related protective mechanism against gastric cancer, if any, warrants further investigation. The pro-oxidant properties of tea polyphenols[34 35] or other factors related to men may explain the null findings observed in men.[28]

Second, a decreased risk in women was only seen for the distal subsite, and not for the proximal subsite. Only three studies have investigated the association by anatomical subsite,[5 7 12] of which two showed a decreased risk for the distal but not proximal subsite.[7 12] Consumption of tea at scalding temperatures increases the risk of proximal gastric cancer,[7] if present, this practice may have attenuated the risk reduction by green tea itself, confounding the results for the proximal subsite. Although the association with proximal gastric cancer was not clear in women, the risk appeared to be increased in the highest green tea consumption category in men. This may have been partly due to the effect of scalding hot tea. Due to the small number of proximal cancer cases in women, we bundled several frequent consumption categories together, and this may also partly explain the unclear risk trend for proximal cancer in women. Additional factors may include the proposed difference in aetiology between proximal and distal subsites, as well as the influence of *H pylori*. Specifically, *H pylori* may be associated with an increased risk of distal gastric cancer but not of cardia or oesophageal adenocarcinoma, in which eradication of the bacteria rather increases the risk of gastro-oesophageal reflux.[36] Experimental studies support the notion that green tea catechins have an inhibitory effect on *H pylori* infection and suppress *H pylori*-induced gastritis.[37–39] These findings suggest that the protective effect of green tea on gastric cancer may operate by decreasing the effect of this bacterium.

The present study had several strengths. First, we analysed data from cohort studies that used validated questionnaires to collect data on green tea consumption. In particular, the question used to assess green tea consumption was almost identical across the studies. Second, each study controlled for a common set of variables that are known or suggested to cause or prevent gastric cancer. Third, with a large number of habitual consumers of green tea, we were able to examine the effect of green tea with reasonable statistical power, albeit that power appeared insufficient in the sub-analyses in each cohort.



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Our study also had several limitations. First, we used only baseline information on green tea consumption, and thus could not assess the effects of lifetime consumption on risk or changes in consumption during follow-up. Non-consumers of green tea are rare in Japan and it is possible that these subjects are a selection of the population that is at increased risk of gastric cancer. Some subjects with gastric cancer might have decreased their consumption before the diagnosis because of their symptoms. Likewise, it is possible that the observed protective effect of green tea among heavy drinkers only might be that the gastrointestinal symptoms associated with *H pylori* infection might force a person to avoid drinking green tea. Such change in practice might have biased their recall of past intake in such a way that they underestimated their true consumption, resulting in spurious inverse association. However, analyses of each cohort which excluded the early cases did not substantially change the results.[9 10 13 14] Second, the proportion of missing values for green tea consumption among the study subjects was 4.2% and excluded from the study. The exclusion of these subjects may have distorted the results, although the proportion was low and any influence may not have been substantial. Third, random variation related to exposure measurement might have attenuated the associations. In addition, we used the indicator terms for missing covariates, and this may have introduced bias. The proportion of missing data was 8.6% for smoking, 8.1% for alcohol intake, 2.7% for rice intake, 2.2% for soy bean paste soup intake, 15.7% for coffee intake, 4.1% for pickled vegetable intake and 4.5% green–yellow vegetable intake, showing variation by covariate, some cases of which were not negligible. We conducted analyses which were restricted to subjects with complete information and obtained closely similar values. Fourth, we are unable to exclude the possibility that our estimates were distorted because of residual confounding. Finally, we did not obtain information on *H pylori* infection status for the whole population, a strong risk factor for gastric cancer. Green tea is suggested to have antibacterial effects,[37–39] and green tea may be associated with gastric cancer risk through the effect of green tea on this infection. It is therefore likely that the failure to adjust for this infection may have resulted in the apparent protective effect of green tea on gastric cancer risk.

Allowing for these methodological issues, this pooled analysis of data from large prospective studies in Japan confirmed a significant decrease in risk of gastric cancer among women with high green tea consumption, especially for the distal subsite. Further investigation of our findings of differences in effect by sex and subsite will help elucidate the mechanism underlying the etiology of gastric cancer.

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# Editor's quiz: GI snapshot

Robin Spiller, *editor*

## Epigastric pain in a man with previous subtotal gastrectomy

### CLINICAL PRESENTATION

A 68-year-old man presented to our hospital with a 2-day history of upper abdominal pain and non-bilious vomiting. Twenty years previously he had undergone a subtotal gastrectomy with Billroth II reconstruction because of a gastric ulcer. He denied alcohol consumption or trauma. Physical examination revealed that his upper abdomen was tender with muscle guarding and rebound tenderness. Laboratory tests showed the following: haemoglobin 11 g/dl (normal, 14–16 g/dl), white blood count $12.9\times10^9$/l (normal, 4.0–$10.0\times10^9$/l), amylase 1744 IU/l (normal, 27–131 IU/l) and lipase 4587 IU/l (normal, 8–58 IU/l). Abdominal CT scan demonstrated a markedly distended, fluid-filled afferent loop crossing the midline (fig 1). Additionally, a 5×3 cm lesion was identified on CT images showing the target sign in the proximal segment of the afferent loop (fig 2). A diagnosis of afferent loop syndrome (ALS) complicated by acute pancreatitis was made based on symptoms, laboratory studies and CT images. The patient underwent an emergency laparotomy.

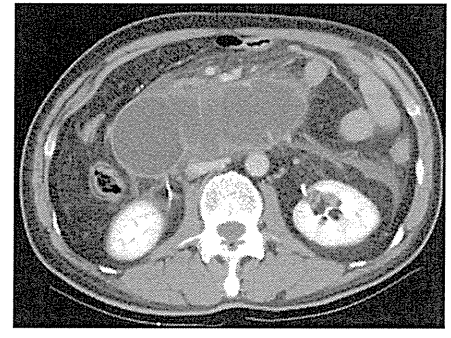

**Figure 1** Abdominal CT scan demonstrated a markedly distended, fluid-filled afferent loop crossing the midline.

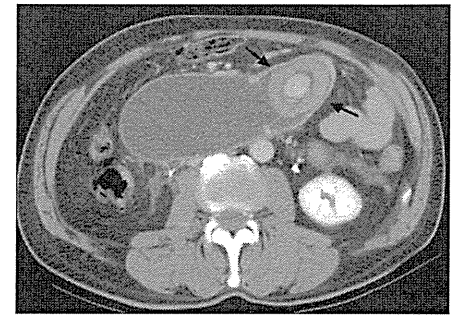

**Figure 2** A 5×3 cm lesion with target sign in the proximal segment of afferent loop was identified on CT images (arrows).

### QUESTION

What is the cause of afferent loop syndrome?
*See page 1436 for the answer.*

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REVIEW

# Cancer Epidemiology and Control in the Arab World - Past, Present and Future

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## Abstract

**The Arab world, stretching from Lebanon and Syria in the north, through to Morocco in the west, Yemen in the south and Iraq in the east, is the home of more than 300 million people. Cancer is already a major problem and the lifestyle changes underlying the markedly increasing rates for diabetes suggest that the burden of neoplasia will only become heavier over time, especially with increasing obesity and aging of what are now still youthful populations. The age-distributions of the affected patients in fact might also indicate cohort effects in many cases. There are a number of active registries in the region and population-based data are now available for a considerable number of countries. A body of Arab scientists are also contributing to epidemiological research into the causes of cancer and how to develop effective control programs. The present review covers the relevant PubMed literature and cancer incidence data from various sources, highlighting similarities and variation in the different cancer types, with attempts to explain disparities with reference to possible environmental factors. In males, the predominant cancers vary, with lung, urinary bladder or liver in first place, while for females throughout the region breast cancer is the greatest problem. In both sexes, non-Hodgkins lymphomas and leukemias are relatively frequent, along with thyroid cancer in certain female populations. Adenocarcinomas of the breast, prostate and colorectum appear to be increasing. Coordination of activities within the Arab world could bring major benefits to cancer control in the eastern Mediterranean region.**

*Asian Pacific J Cancer Prev,* **10**, 3-16

## Introduction

The countries of the Arab Middle-east share a great deal in terms of culture while markedly differing in their levels of economic development. The variation between and within populations is reflected in different disease profiles, although in all cases the burden of cancer is already appreciable. The available data indicate that incidence rates are rising and with aging as well as continued population growth this means that the problem will loom larger in the future.

Since the literature regarding cancer registration data and associated epidemiological findings are scattered, the present research was undertaken to provide an overview. The countries/populations included are the Lebanon, Syria, Palestine (the West Bank and Gaza and Israeli - Palestinians), Jordan, Egypt, Sudan, Djibouti and Eritrea and the Maghreb countries of North Africa (Libya, Tunisia, Algeria, Morocco and Maruitania) as well as Saudi Arabia, Yemen, the Sultanate of Oman, the United Arab Emirates, Qatar, Bahrain, Kuwait and Iraq. Although population-based cancer incidence rates in Jordan, with and without Egypt, have been published (Freedman et al., 2003; Freedman et al., 2007), a more general coverage has not been hitherto been available. All sources available to the authors were therefore accessed to give as comprehensive a picture as possible regarding the cancer burden, risk factors and preventive approaches. Representative relevant papers in PubMed were cited with the focus on individual organ sites, in an attempt to explain variation in incidence rates in terms of accepted risk and beneficial factors.

## Cancer Registration in the Arab World

The established cancer registries within the Arab world are shown in Figure 1. The oldest population-based

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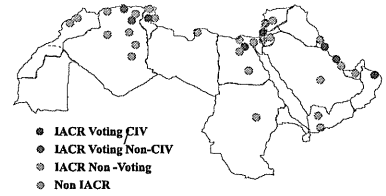


**Figure 1. Cancer Registries in the Arab Countries of Asia and the North African Region**

**Table 1. Numbers of Middle Eastern Countries and Registries in the Series of Nine Volumes of CIV**

| Volume | I | II | III | IV | V | VI | VII | VIII | IX |
|---|---|---|---|---|---|---|---|---|---|
| Kuwait* | | | | | 1 | 1 | 1 | 1 | 1 |
| Oman* | | | | | | | | 1 | 1 |
| Algeria: Setif | | | | | | | | | 1 |
| Bahrain* | | | | | | | | | 1 |
| Egypt: Gharbia | | | | | | | | | 1 |
| Tunisia: Sousse | | | | | | | | | 1 |

*: National Cancer Registry

registry is that of Kuwait, which has been reporting to Cancer Incidence in Five Continents since 1987 (see Table 1), with Algeria, Bahrain, Egypt and Tunisia being included in the last issue, in 2007. The population-based age-standardized cancer incidence data for the major body sites in Volume IX were examined for the present paper (see Tables 2 and 3 for females and males respectively). In addition, findings for Jordan and the Palestinian Authority were obtained from http://mecc.cancer.gov (Freedman et al., 2007) and for Lebanon, Saudi Arabia and Qatar, from Shamseddine et al (2004), Bazarbashi et al (2001) and Bener et al (2008), respectively.

Percentages of all neoplasms for the five most frequent cancers for these and other countries illustrated graphically in Figure 2 were from Globocan 2002 or from hospital-based registries in Libya (El Mistiri et al., 2007), Yemen (Al-Thobhani et al., 2001), Bahrain (Alsayyad and Hamadeh, 2007) and Iraq (Habib et al., 2006; 2007).

In males, while lung cancer featured in the most frequent neoplasms in the latest data in all but the Yemen case, urinary bladder tumours were more prevalent in three countries and liver and oral cavity lesions occupied the first position in Saudi Arabia and the Yemen, respectively. Mauritania was also exceptional in having prostate cancer as number one. For countries not included in Figure 2, Syrian males in Aleppo demonstrated age-adjusted incidence rates highest for bladder, leukaemia and lung cancers, in that order (Mzayek et al., 2002), while in Libya the most frequently diagnosed malignancies were lung cancer (19%) and colorectal cancer (10%), followed by cancers of the head and neck (9%) and bladder (9%) (El Mistiri et al., 2007). In the Moroccan National Oncology Institute, for 1986 and 1987 in males, nasopharyngeal cancer accounted for 12.3%, lymphoma 10.1%, laryngeal cancer 8.2% and lung cancer 6.5% of the total (Chaouki and el Gueddari, 1991). In the Al Jouf region of Saudi Arabia, lymphomas and leukemias combined, colorectal and skin cancers have been reported to be the most common (El Hag et al., 2002). In Gaza, lung cancer, and again leukaemia and lymphoma appear to be the most frequent (Kahan et al., 1997).

Breast cancer, almost without exception, is the most

**Table 2. Population-based Cancer Registry Data for Arab Countries - Females**

| | Jordan# | Palestine* | Egypt* | Saudi** | Algeria* | Tunisia* | Oman* | Qatar## | Bahrain* | Kuwait* |
|---|---|---|---|---|---|---|---|---|---|---|
| Buccal | 2.3 | 0.7 | 0.1 | 1.3 | 0.2 | 0.7 | 1.0 | 0.7 | 1.6 | 1.5 |
| Pharynx | 0.2 | 0.4 | 1.8 | 0.3 | 0.6 | 0.3 | 0.5 | - | 1.5 | 0.2 |
| Nasopharynx | 0.5 | 0.4 | 1.8 | 0.7 | 1.7 | 1.9 | 0.3 | - | 0.3 | 0.8 |
| Oesophagus | 0.7 | 0.4 | 0.9 | 0.9 | 0.2 | 0.2 | 2.7 | 1.1 | 1.8 | 1.6 |
| Stomach | 3.5 | 3.5 | 2.0 | 1.7 | 3.1 | 2.5 | 6.2 | 2.5 | 5.4 | 2.6 |
| Colon | 7.2 | 10.8 | 2.7 | 3.1 | 2.8 | 6.1 | 2.2 | 2.2 | 5.1 | 7.6 |
| Rectum | 3.0 | 3.7 | 1.7 | 1.8 | 3.8 | 2.9 | 1.4 | 6.1 | 2.2 | 4.2 |
| Liver | 1.3 | 0.7 | 4.5 | 2.2 | 0.8 | 0.7 | 3.2 | 1.8 | 3.1 | 3.6 |
| Gallbladder | 0.3 | 2.8 | 1.0 | 1.1 | 10.0 | 3.1 | 1.1 | 0.7 | 0.9 | 1.7 |
| Pancreas | 1.0 | 2.4 | 2.3 | 0.6 | 0.3 | 1,9 | 1.6 | 1.1 | 2.8 | 3.0 |
| Larynx | 0.4 | 0.6 | 0.3 | 0.1 | 0.1 | 0.2 | 0.3 | - | 0.7 | 0.5 |
| Trachea, lung | 3.1 | 5.1 | 3.6 | 1.4 | 1.7 | 1.7 | 2.3 | 2.5 | 11.8 | 4.6 |
| Breast | 38.0 | 38.5 | 42.5 | 11.8 | 18.8 | 29.8 | 14.6 | 30.1 | 46.8 | 41.3 |
| Ovary | 4.6 | 3.7 | 5.1 | 2.3 | 2.1 | 3.3 | 6.2 | - | 7.4 | 5.4 |
| Corpus uteri | 5.8 | 9.0 | 2.6 | 2.0 | 1.1 | 3.4 | 0.9 | - | 5.2 | 3.6 |
| Cervix uteri | 2.6 | 2.4 | 2.1 | 2.2 | 11.6 | 7.1 | 6.5 | - | 6.0 | 4.5 |
| Kidney | 1.9 | 1.6 | 1.5 | 1.2 | 1.2 | 1.6 | 1.6 | 1.8 | 3.5 | 2.0 |
| Bladder | 1.8 | 1.7 | 3.1 | 1.2 | 0.5 | 2.2 | 2.2 | 0.7 | 3.8 | 2.9 |
| Brain | 3.6 | 3.3 | 6.2 | 1.3 | 1.6 | 1.8 | 2.6 | 1.4 | 0.9 | 3.1 |
| Thyroid | 4.5 | 7.0 | 2.6 | 4.4 | 3.6 | 3.1 | 5.9 | 5.7 | 7.7 | 7.3 |
| Non-Hodgkin | 5.4 | 9.1 | 9.9 | 4.1 | 3.8 | 3.7 | 4.4 | 6.8 | 5.6 | 6.5 |
| Leukemia | 4.9 | 3.9 | 4.1 | 2.7 | 2.4 | 3.6 | 3.3 | - | 3.3 | 3.8 |
| Total | 112 | 134 | 122 | 58 | 85 | 106 | 91 | 87 | 143 | 129 |

From: *Curado et al., 2007; **Bazarbashi et al., 2001; #Freedman et al., 2007; ##Bener et al., 2008

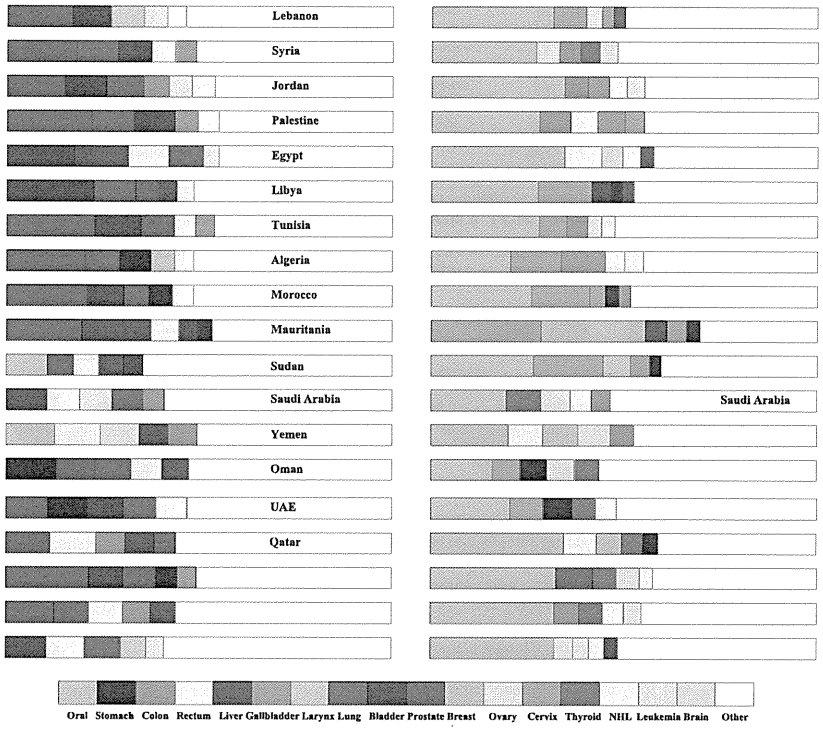


**Figure 2. Percentage Data for the Five Most Prevalent Cancers in Countries of the Middle East**

**Table 3. Age-standardized Cancer Incidence Data for Arab Countries - Males**

| | Jordan# | Palestine* | Egypt* | Saudi** | Algeria* | Tunisia* | Oman* | Qatar## | Bahrain* | Kuwait* |
|---|---|---|---|---|---|---|---|---|---|---|
| Buccal | 2.6 | 2.7 | 0.5 | 1.0 | 1.4 | 2.6 | 2.3 | - | 3.3 | 1.8 |
| Pharynx | 2.3 | 0.5 | 1.8 | 0.3 | 4.5 | 0.7 | 0.4 | - | 0.8 | 0.3 |
| Nasopharynx | 2.3 | 1.1 | 1.8 | 2.5 | 5.4 | 4.6 | 1.0 | 0.7 | 2.9 | 1.7 |
| Oesophagus | 1.5 | 1.1 | 1.7 | 1.3 | 0.2 | 0.5 | 2.6 | 0.4 | 4.2 | 2.2 |
| Stomach | 6.0 | 6.7 | 3.3 | 2.4 | 7.1 | 5.1 | 13.4 | 2.0 | 8.5 | 3.4 |
| Colon | 7.6 | 10.6 | 4.2 | 2.4 | 3.0 | 6.5 | 2.5 | 3.4 | 7.9 | 8.4 |
| Rectum | 3.9 | 8.3 | 2.1 | 2.4 | 3.6 | 5.1 | 2.1 | 3.0 | 4.4 | 5.2 |
| Liver | 1.9 | 2.6 | 21.9 | 5.9 | 1.1 | 2.2 | 7.4 | 3.4 | 5.3 | 8.1 |
| Gallbladder | 0.8 | 2.0 | 1.2 | 0.8 | 2.1 | 1.8 | 0.7 | - | 0.8 | 1.8 |
| Pancreas | 1.8 | 5.0 | 4.0 | 1.1 | 0.5 | 2.5 | 2.1 | 0.7 | 4.9 | 3.7 |
| Larynx | 4.8 | 6.1 | 4.2 | 1.4 | 2.8 | 5.7 | 1.4 | 0.9 | 4.7 | 2.7 |
| Trachea, lung | 16.4 | 40.4 | 14.0 | 4.1 | 19.9 | 37.1 | 9.8 | 5.9 | 34.2 | 15.6 |
| Prostate | 11.2 | 20.0 | 8.5 | 3.4 | 7.5 | 14.1 | 10.5 | 3.0 | 14.3 | 10.5 |
| Kidney | 3.4 | 4.4 | 2.5 | 1.7 | 0.7 | 2.6 | 1.7 | 1.6 | 4.7 | 5.8 |
| Bladder | 13.2 | 18.1 | 27.9 | 2.9 | 4.5 | 19.0 | 5.1 | 1.8 | 14.7 | 6.3 |
| Brain | 4.4 | 4.9 | 4.0 | 1.9 | 0.7 | 3.7 | 3.5 | 2.0 | 3.0 | 5.1 |
| Thyroid | 1.7 | 2.0 | 1.1 | 1.5 | 1.4 | 1.3 | 1.7 | - | 1.1 | 3.5 |
| Non-Hodgkin | 7.3 | 10.0 | 16.9 | 4.4 | 5.3 | 6.7 | 8.2 | 5.9 | 7.1 | 10.4 |
| Leukemia | 7.3 | 7.3 | 5.4 | 3.9 | 3.1 | 5.1 | 4.8 | - | 7.7 | 4.9 |
| Total | 115 | 183 | 162 | 59 | 94 | 160 | 105 | 51 | 160 | 121 |

From: *Curado et al., 2007; **Bazarbashi et al., 2005; #Freedman et al., 2007; ##Bener et al., 2008





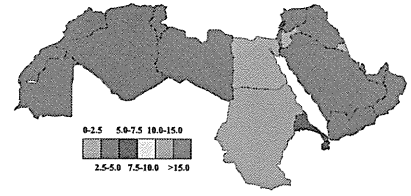


**Figure 3. Male Melanoma Incidences/100,000** ((Globocan, 2002: Ferlay et al., 2004)

frequent tumour type in females, followed by colon in five populations and cervix in three. In Syrian females age-adjusted incidence rates were highest for breast, uterus (+ cervix) and leukaemia (Mzayek et al., 2002). In Gaza, leukaemia and lymphoma occupy second and third place (Kahan et al., 1997). Cervical cancer was earlier found to be number one in Morroco (Chaouki and el Gueddari, 1991), but it is conceivable that the situation has now changed.

## Organ Specific Epidemiology

*Skin Cancer*

Skin cancer, including melanoma, is rare in the region, with the exception of Sudan (see Figure 3). The most common skin cancers seen, at least in Saudi Arabia, are the basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), with site distributions similar to studies in Caucasians pointing to sun as the risk factor, followed by Kaposi's sarcoma (Al-Maghrabi et al., 2004). In Qatar, BCC is the commonest skin cancer but expatriates account for a large proportion, especially Europeans (Mahmoud and Azadeh, 1996).

*Oral Cancer*

Cancer of the buccal cavity is relatively rare across the Arab countries, with the exception of parts of the Yemen where it may be number one (see Figure 4), thought to be related to the habits of chewing tobacco and qat (Sawair et al., 2007). Qat chewing can provoke the development of oral keratotic white lesions which become more severe with duration (Ali et al., 2004; Scheifele et al., 2007).

Furthermore, in Saudi Arabia there are very wide regional disparities in incidence, with an almost thirty-fold difference between the lowest and highest rates (Brown et al., 2006). The lower lip may be the most

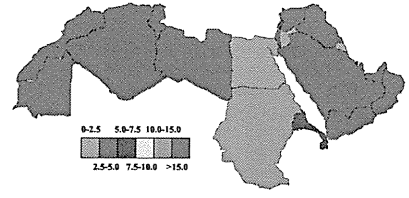


**Figure 4. Male Oral Cancer Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)

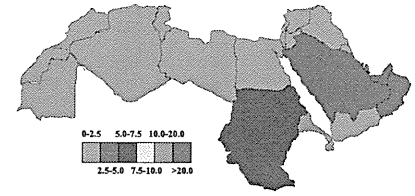


**Figure 5. Male Oesophageal Cancer Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)

commonly affected site followed by the tongue in Iraq (Al-Rawi and Talabani, 2008). In Jordan, the floor of the mouth is the most common site, then again the tongue (Ma'aita, 2000). Of the cases of cancer recorded in the Kuwait Cancer Registry in the 10 years 1979-1988, 7.4% involved the lip, oral cavity or pharynx (Morris et al., 2000).

*Oesophageal Cancer*

In clear contrast to Iran, the Arabic world has generally very low incidences of oesophageal cancer (see Figure 5). CIV data for relative incidence of the squamous cell carcinoma and adenocarcinoma types are listed in Table 4.

The reason for the variation between countries and sexes remains unclear. In Bahrain, in direct opposition to the CIV data, SCC (males) and adenocarcinomas (females) were reported to be the main histological types, with the lower and upper third of the oesophagus as the most and least frequently involved sites, respectively (Al-Hilli and Malik, 2003). The reason why the CIV data are not in agreement is unclear. In the Yemen, a preponderance of women with carcinoma of the mid-oesophagus was noted, previously only recorded in areas of high prevalence, with a high frequency of Qat chewing and water-pipe smoking found for both men and women (Gunaid et al., 1995). A slight preponderance of female cases was also earlier found for Qataris, in this case with nutrition and social status reported to be probable etiologic factors (Ejeckam et al., 1993).

*Stomach Cancer*

With the exception of males in Oman, gastric cancer incidences are low (Figure 6). The fact that Omani females also have a relatively high value suggests a specific factor in this country. The marked difference from Iran is not

**Table 4. Oesophageal Cancer Histopathology: SCC-AC Percentages (Curado et al., 2007)**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | SCC | AC | Ratio | SCC | AC | Ratio |
| Egypt | 60 | 25 | 2.4:1 | 80 | 14 | 5.7:1 |
| Palestine | 28 | 27 | 1.0:1 | 18 | 37 | 0.5:1 |
| Algeria | 33 | 0 | --- | 33 | 33 | 1.0:1 |
| Tunisia | 100 | 0 | --- | 50 | 50 | 1.0:1 |
| Bahrain | 52 | 52 | 1.0:1 | 80 | 0 | --- |
| Kuwait | 38 | 38 | 1.0:1 | 67 | 33 | 2.0:1 |
| Oman | 28 | 26 | 1.0:1 | 25 | 31 | 0.8:1 |

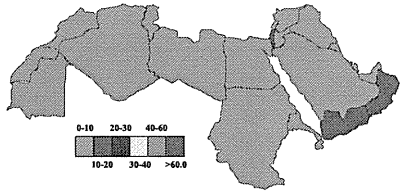


**Figure 6. Male Gastric Cancer Incidences/100,000**
(Globocan, 2002: Ferlay et al., 2004)

due to a lower frequency of the more virulent *H. pylori* strains, at least from data for Iraq (Hussein et al., 2008). Furthermore, in the Gulf, there was no difference found between farmers with a lower standard of living and non-farmers in respect of their *H. pylori* profiles (Bener et al., 2006). The prevalence of infection with the bacteria in dyspeptic patients in Yemen appears high (Gunaid et al., 2003).

*Colorectal Cancer*

The incidences of colon and rectum cancer in the Arab world are relatively low, although in some of the more affluent countries it is number two after breast (see Figure 7). There is only limited variation in incidence rates between sexes and the colon-rectum ratio varies from approximately 1:1 to 3:1 (see Table 5), with the one exception of Algeria where rectal cancers are in the majority.

In Yemen there is a relatively high proportion of early-onset tumors (19.3% of cases were <40 years), with a left sided subsite distribution (49.4% of cases in the rectum and rectosigmoid junction) (Basaleem and Al-Sakkaf, 2004). Similarly, in Egypt 38% of patients are younger than 40 and 75% of lesions are on the left side (Abou-Zeid et al., 2002), and in Qatar the descending and sigmoid colon is the most common anatomical site affected (Rasul et al., 2001). Cases in Saudi Arabia also tend to be relatively young (Mansoor et al., 2002). The profound rightward shift of colorectal carcinoma described in Saudi Arabia, compounded with a rising incidence of advanced lesions in younger age group, is also of interest (Guraya and Eltinay, 2006). Arab patients appear to be relatively young in Palestine with a high percentage of poorly-differentiated and mucinous, advanced stage cancers (Shpitz et al., 2006). A high proportion of familial MSI cases and a lowincidence of TP53 mutations were recently reported to be hallmarks of Saudi colorectal carcinomas (Bavi et al., 2008).

The low incidence of colorectal cancer in the Arab countries could be due to the dietary factors, with high intake of fruit and vegetables (Al-Shamsi et al., 2003). One environmental factor might be pesticides. Thus farming in Egypt is associated positively with high serum organochlorines and serum levels in colorectal cancer patients may be higher than in appropriate controls (Soliman et al., 1997).

*Liver Cancer*

Liver cancer, while much less frequent than in high-incidence countries, is nevertheless a major problem in males in Egypt and Saudi Arabia and to a lesser extent in the other countries of the Gulf (see Figure 8). The hepatocellular carcinoma accounts for the majority of tumours although there some variation between the sexes in the relative incidence of cholangiocellular carcinomas (CCC) (see Table 6). The hepatitis B virus (HBV) is the leading cause of HCC in Lebanon (Yaghi et al., 2006) and in Egypt (Anwar et al., 2008), but in the latter HCV has now become the predominant factor associated with the more recent epidemic. It has been well documented

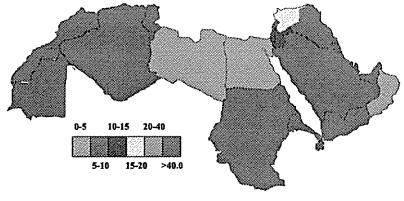


**Figure 7. Male Colorectal Cancer Incidences/100,000**
(Globocan, 2002: Ferlay et al., 2004)

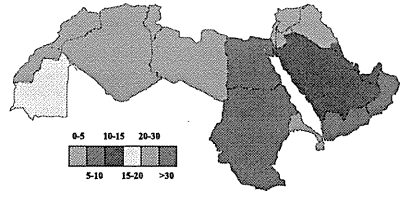


**Figure 8. Male Liver Cancer Incidences/100,000**
(Globocan, 2002: Ferlay et al., 2004)

**Table 5. Colorectal Cancers: Colon and Rectal Carcinoma Incidences and Ratios(Curado et al., 2007)**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Colon | Rectum | Ratio | Colon | Rectum | Ratio |
| Egypt | 4.2 | 1.2 | 3.5:1 | 2.7 | 1.7 | 1.6:1 |
| Palestine | 10.6 | 8.3 | 1.3:1 | 10.8 | 3.7 | 2.9:1 |
| Algeria | 3.0 | 3.6 | 0.8:1 | 2.8 | 3.8 | 0.7:1 |
| Tunisia | 6.5 | 5.1 | 1.3:1 | 6.1 | 2.9 | 2.1:1 |
| Bahrain | 7.9 | 4.4 | 1.8:1 | 5.1 | 2.2 | 2.3:1 |
| Kuwait | 8.4 | 5.2 | 1.5:1 | 7.6 | 4.2 | 1.8:1 |
| Oman | 2.5 | 2.1 | 1.2:1 | 2.2 | 1.4 | 1.6:1 |

**Table 6. Liver Cancer Histopathology: HCC-CCC Percentages (Curado et al., 2007)**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | HCC | CC | Ratio | HCC | CC | Ratio |
| Egypt | 88 | 4 | 22.0:1 | 80 | 6 | 13.3:1 |
| Palestine | 69 | 3 | 23.0:1 | 42 | 14 | 3.0:1 |
| Algeria | 39 | 31 | 1.3:1 | 0 | 60 | --- |
| Tunisia | 65 | 18 | 3.6:1 | 60 | 20 | 3.0:1 |
| Bahrain | 75 | 15 | 5.0:1 | 54 | 27 | 2.0:1 |
| Kuwait | 77 | 8 | 9.6:1 | 89 | 11 | 8.1:1 |
| Oman | 77 | 16 | 7.7:1 | 67 | 27 | 2.5:1 |





that Egypt has one of the highest prevalence rates of HCV infection in the world with different strains involved (Abdel-Hamid et al., 2007), but there may also be an etiological role for aflatoxin B1 (Hifnawy et al., 2004). There is significant geographic variation in incidence among districts (Lehman et al., 2008). Prevalence of HCC is high in the Nile Delta area, and is more common in males, rural residents and farmers so that pollution due to insecticides might be a risk factor (Abdel-Wahab et al., 2007).

*Gallbladder Cancer*

Algerian females appear to be exceptional in having a relatively high proportion of gallbladder cancer cases (see Figure 2), the tumour elsewhere in the region being generally rare.

*Pancreatic Cancer*

Except in the Lebanon and Syria, rates for pancreatic cancer are generally low (see Figure 9), the reported clustering of cases in the northeast Nile delta region possibly being related to water pollution (Soliman et al., 2006), very probably linked to cadmium and farming (Kriegel et al., 2006). In general, multiple tobacco consumption methods, passive smoking, pesticide exposures, and diabetes are associated with an increased risk for pancreatic cancer, with prolonged lactation and increased parity associated with a reduced risk (Lo et al., 2007).

*Nasopharyngeal Cancer*

Nasopharyngeal cancer is relatively common in Western North African males but otherwise rare. Characteristics of NPC patients in Lebanon and their parameters of outcome are comparable to those reported in Western series (Geara et al., 2005). Early onset suggests a possible underlying genetic susceptibility in Saudi Arabians (Andejani et al., 2004).

*Laryngeal Cancer*

Iraq, the Lebanon and to a lesser extent the Yemen, Egypt and relatively developed North Africa, have high incidences of laryngeal cancer, it elsewhere appearing of relatively minor importance (see Figure 10).

*Lung Cancer*

Although incidences are lower than in the West (see Figure 11) , of the countries included in Figure 2, seven of

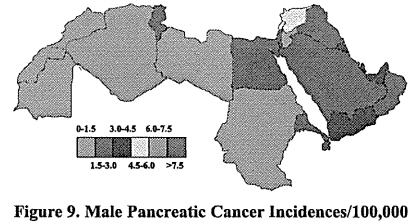


**Figure 9. Male Pancreatic Cancer Incidences/100,000**
(Globocan, 2002: Ferlay et al., 2004)

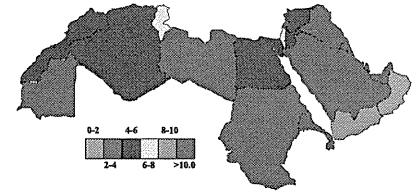


**Figure 10. Male Laryngeal Cancer Incidences/100,000**
(Globocan, 2002: Ferlay et al., 2004)

thirteen have lung cancer as number one, and all but one include the site in the most frequent five. In a recent survey, the highest ASR was in Bahrain (34.3 for males, 12.1 for females) followed by Qatar (18.5 and 5.5 ) and Kuwait (13.8 and 4.0); the lowest rates were in Saudi Arabia (4.8 and 1.3 for females) (Al-Hamdan et al., 2006). From CIV data, squamous cell carcinomas and adenocarcinomas account for approximately the same proportions in males, while adenocarcinomas (AC) tend to predominate in females (see Table 7). In Tunisia, the AC incidence was relatively low in 1990 when compared to western countries, but this has been shown to increase to become more common than the SCC type (B'chir et al., 2007). This was not evident in the CIV data, however.

The marked increase in the incidence of lung cancer among Palestinain Arab men during the last decade, without any evidence of increased smoking prevalence, might reflect a gradual loss of some apparent protection in this subpopulation (Tarabeia et al., 2008). In Egypt there has been a report that pleural mesothelioma is increasing, survival being linked to genetic alteration (Gaafar and Eldin, 2005).

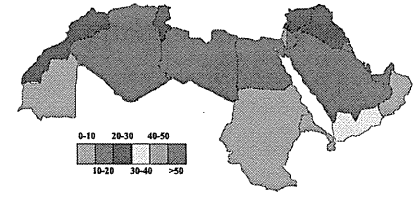


**Figure 11. Male Lung Cancer Incidences/100,000**
(Globocan, 2002: Ferlay et al., 2004)

**Table 7. Lung Cancer Histopathology: SCC-Adenocarcinoma Ratios (Curado et al., 2007)**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | SCC | AC | Ratio | SCC | AC | Ratio |
| Egypt | 22.4 | 24.2 | 0.9:1 | 9.1 | 50.0 | 0.2:1 |
| Palestine | 28.0 | 26.6 | 1.1:1 | 7.4 | 50.0 | 0.1:1 |
| Algeria | 63.0 | 6.4 | 9.8:1 | 43.8 | 28.1 | 1.6:1 |
| Tunisia | 46.6 | 18.5 | 2.5:1 | 23.5 | 29.4 | 0.8:1 |
| Bahrain | 34.5 | 21.6 | 1.6:1 | 26.9 | 30.8 | 0.9:1 |
| Kuwait | 17.1 | 18.9 | 0.9:1 | 18.8 | 37.5 | 0.5:1 |
| Oman | 28.5 | 26.0 | 1.1:1 | 25.0 | 31.3 | 0.8:1 |

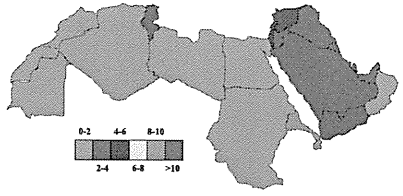


**Figure 12. Male Kidney Cancer Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)

*Kidney Cancer*

With the exception of males in Syria, Lebanon and Palestine, renal cancer incidences are low in the Arab world (see Figure 12).

*Urinary Bladder Cancer*

While urinary bladder cancers are well known to be the predominant neoplasm in Egyptian males (see Table 2), high rates are also present in Iraq, Jordan Tunisia and Bahrain, but not in Qatar and elsewhere in the Gulf, pointing to considerable variation in risk factors across the Arab world (see Figure 13). Data for the histopathological distribution are summarized in Table 8.

Traditionally, *Schistosoma haematobium* has been considered the most important etiological agent (Bedwani et al., 1998), but transitional cell carcinoma has recently become the most frequent type in Egypt, replacing lesions with squamous features generally associated with parasites, corroborating findings from small-scale hospital-based studies indicating that the etiology of bladder cancer has changed significantly over the past 26 years (Felix et al., 2008). A remarkably strong association with various measures of cigarette smoking has been found that could explain 75% of bladder cancer cases among males from

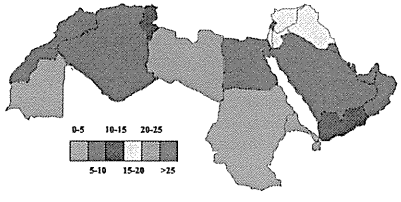


**Figure 13. Male Urinary Bladder Cancer Incidences/ 100,000** (Globocan, 2002: Ferlay et al., 2004)

**Table 8. Urinary Bladder Cancer Histopathology: TCC-SCC Ratios (Curado et al., 2007)**

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | SCC | TCC | Ratio | SCC | AC | Ratio |
| Egypt | 19.9 | 69.0 | 0.29:1 | 40.1 | 47.4 | 0.85:1 |
| Palestine | 0.0 | 96.4 | INF:1 | 0.0 | 96.2 | INF:1 |
| Algeria | 11.4 | 58.6 | 0.19:1 | 0.0 | 60.0 | INF:1 |
| Tunisia | 1.1 | 94.3 | 0.01:1 | 4.5 | 90.9 | 0.05:1 |
| Bahrain | 2.7 | 79.5 | 0.04:1 | 10.0 | 75.0 | 0.13:1 |
| Kuwait | 4.3 | 91.3 | 0.04:1 | 4.8 | 81.0 | 0.06:1 |
| Oman | 12.0 | 80.7 | 0.15:1 | 8.6 | 68.6 | 0.13:1 |

Alexandria (Bedwani et al., 1997). This is in line with the fact that polymorphisms in glutathione S-transferase genes are associated with increased risk of bladder cancer (Saad et al., 2005). Interestingly, odds ratios were 15.8 for male ever-smokers with a history of urinary schistosomiasis, compared with never-smokers without such a history, and 3.2 for men ever-infected with urinary *Schistosoma haematobium* and ever-employed in high-risk occupations, compared with those never-infected and with no high-risk occupational history (Bedwani et al., 1998).

Despite the high prevalence, there are no population-based bladder screening programs in place. Combining NMP22 with malignant or suspicious cytological result improved sensitivity for the detection of bladder cancer but with a major decrease in specificity, suggesting a potential role in screening rather than diagnosis (Kapila et al., 2008).

*Prostate Cancer*

In many of the countries of the Middle-east, prostate cancer is already a problem (see Figure 14) and in Mauritanian males it is the most frequent neoplasm (see Figure 2). A Egyptian case-control study pointed to sausages, butter and natural ghee as risk factors, while vegetables were protective (Kamel et al., 2006).

Screening is opportunistic. However, data should be interpreted with caution because public awareness campaigns have led to large numbers of individuals being found positive. Arab Kuwaiti and Omani men were reported to have lower serum PSA levels and prostate volumes than those reported for Caucasians, but similar to those reported for Asians (Japanese and Chinese) (Kehinde et al., 2005). Mean PSA values for Saudi men are also low (Kamal et al., 2003). Although raised serum PSA is commonly associated with prostate cancer, subclinical prostatitis is a significant source of high serum PSA in over 40% of men in Kuwait, suggesting the need for a locally applicable paradigm to identify prostate cancer (Anim et al., 2007).

*Breast Cancer*

Breast cancer now occupies the number one position in all countries of the Arab world, even if absolute rates are relatively low (see Figure 15). Cases tend to be young and almost half of patients are below 50, with a median age of 49-52 years as compared to 63 in industrialized nations (El Saghir et al., 2007). A preponderance in

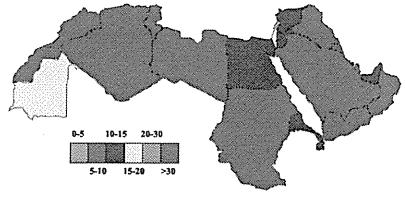


**Figure 14. Prostate Cancer Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)





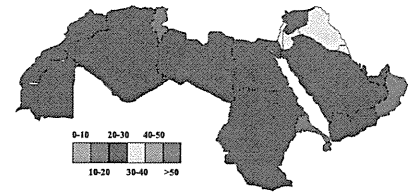


**Figure 15. Female Breast Cancer Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)

relatively young individuals has been reported for the Lebanon (El Saghir et al., 2002), Alexandria in Egypt (Hosny and Elkaffas, 2002a), and Aden in the Yemen (Abdul Hamid et al., 2001).

Epidemiological findings point to the same risk factors as in the Western world. A positive family history of breast cancer, young age at menarche, late age at last full-term pregnancy and wide inter-birth interval were significant predictors for occurrence in Egypt (Kishk, 1999). Postmenopausal obesity is a significant risk factor in Jordan, along with number of pregnancies (more than 4) (Atoum and Al-Hourani, 2004a). On the other hand, longer period of breast feeding (more than 24 months) decreases the risk (Atoum and Al-Hourani, 2004b). Risk factors in Kuwait include high BMI, lack of regular exercise, early age at menarche, late age at first pregnancy, hormonal therapy, and frequent consumption of carbohydrate, sweets, animal fat, and vegetable oil (margarine) with low intake of fresh vegetables and olive oil (Saleh et al., 2008). In Iraq, family history and oral contraceptives use were found to be associated (Fakri et al., 2006). Parental consanguinity in Arabs, even when a marriage is between first cousins or double first cousins, was not associated with an altered risk of breast cancer (Denic et al., 2005). Infertility and usage of infertility drugs in general are not associated with increased risk for breast cancer (Lerner-Geva et al., 2004). One analysis yielded an estimated 73% higher breast cancer incidence in the highest compared to the light at night exposed communities (Kloog et al., 2008). High-risk HPV infections are associated with human breast cancer progression in Syrian women (Akil et al., 2008).

Locally advanced disease is very common in Egypt, Tunisia, the Yemen, Saudi Arabia, Kuwait, Syria, Palestine and others, and total mastectomy is the most commonly performed surgery (Abdul Hamid et al., 2001; Chiedozi et al., 2003; El Saghir et al., 2007; Saleh et al., 2007; Tarabeia et al., 2007). Metastases were reproted to be relatively low in one study (Abuzallouf et al., 2007), but this appears exceptional. Overall 5 year survival rates available from the literature are 59.6% in Saudi Arabia (Ravichandran et al., 2005) and 68.8% in Bahrain (Fakhro et al., 1999) while in Oman 5-year relapse-free and overall survival rates were reported to be 62% and 64%, respectively (Al-Moundhri et al., 2004). Prevalence of HER2/neu overexpression in a small sample of Qatari female cases was found to be 26%, linked to an elevated relapse rate and mortality (Rasul et al., 2003).

Results from recent studies like the Cairo Breast Cancer Screening Trial show a positive impact of clinical breast examination leading to more early diagnosis and breast-conserving surgery, so that population-based screening in those countries with affluent resources and accessible care should be implemented (El Saghir et al., 2007).

Knowledge of breast cancer risk-factors and screening awareness are high among women nurses and teachers in Amman, Jordan (Madanat and Merrill, 2002) but health workers infrequently offered screening examinations and women were found to lack adequate knowledge about breast cancer screeningin Qatar (Bener et al., 2001). Health planners and healthcare providers must capitalize on encouraging factors and minimize deterring factors to optimize breast cancer screening practices (Bener et al., 2002). Screening campaigns should aslo target husbands to encourage their wives to enrol (El Saghir, 2007).

Positive correlations were found between nursing students BSE practice and their academic experience in nursing college in Saudi Arabia (Alsaif, 2004). Female secondary-school students in Jeddah demonstrated only low knowledge of risk factors and presentation in those not having familial experience (Milaat, 2000), although the vast majority demonstrated a positive attitude towards learning breast self-examination (Altaf et al., 2004). There is a significant association between failure to practise breast self-examination and diagnostic delay in Egypt (Abdel-Fattah et al., 2000). Guidelines are clearly needed (Altaf, 2004). Husbands whose wives have breast cancer may also need a network of support to address their specific issues and concerns (Woloski-Wruble and Kadmon, 2002)

*Ovarian Cancer*

Ovarian cancer is moderately frequent in the Middle-east (see Figure 16). The majority of lesions are seroud, followed by mucinour and adeocarcinoma types (Curado et al., 2007). It has been suggested that substitution of non-animal for animal fat during adult life might reduce the risk of ovarian cancer (Lubin et al., 2006).

*Endometrial Cancer*

Endometrial cancer of the corpus uterus is relatively infrequent, with a picture similar to that for the ovary (see Figure 17). Research has indicated elevated risk with increased number of abortions, ovarian cycles and live births, and decreased risk with increased parity as compared to the nulliparous case (El-Khwsky et al., 2006). In another study, endometrial thickness >5mm, diabetes, hypertension and obesity were not found to be among the risk factors, in contrast to age and occurrence of post

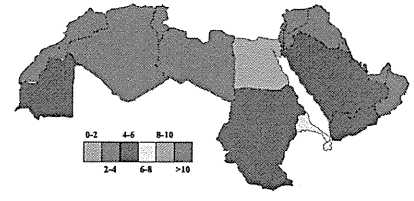


**Figure 16. Ovarian Cancer Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)

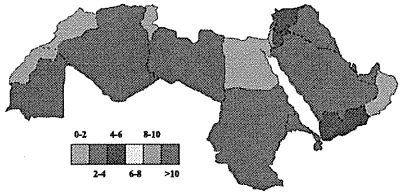


**Figure 17. Endometrial Cancer Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)

menopausal bleeding (Al-Kadri et al., 2004).

*Cervical Cancer*

While cervical cancer is generally low in the Arab world (see Figure 18) and does not appear to be increasing, it still occupies second place for frequency in Algeria, Tunisia and Oman. Furthermore, there may be some under-reporting and in a prospective study in Saudi Arabia the percentage of abnormal pap smears was 4.7%, much higher than the 1.6% reported in the compounded literature (Altaf, 2006). Adeocarcinomas account for approximately 10% of the lesins (Curado et al., 2007).

Clearly the human papilloma virus is the prime risk factor and the Muslim religious background is naturally of great significance in this regard. It should be mentioned in this context that penile cancer is also extremely rare, as for example documented in Saudi Arabia (Abomelha, 2004). Regarding risk factors, early marriage, frequent coitus started early in life and increasing number of pregnancies are predisposing factors, while abortions and age at menarche are without influence (Ejeckam et al., 1994). Polygamy, smoking and hormonal contraception were not identified as risk factors in one study, whereas positive women again showed higher parity (Hajjaj et al., 2006). In Egypt, HPV 16/18 is the major risk factor, frequently with mixed infections and bilharzial infestation (el-All et al., 2007).

Screening programs are not in place and one problem is with attitudes. Of 98 physicians who participated in a study in the UAE. only 40% reported ever having performed a Pap smear, so that a training programme on cervical screening was considered necessary (Badrinath et al., 2004). In Jordan, about a third of women were found to be unaware of the significance of a positive cervical smear and three-quarters did not know the causes of

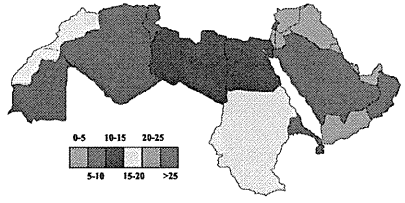


**Figure 18. Cervical Cancer Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)

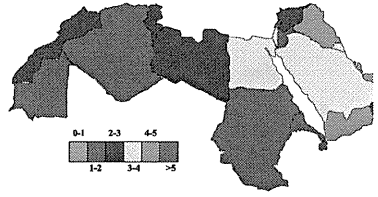


**Figure 19. Male Brain and Nervous Cancer Incidences/ 100,000**(Globocan, 2002: Ferlay et al., 2004)

neoplastic devekopment (Maaita and Barakat, 2002).

*Brian and Nervous Tissue Cancer*

Relative to world levels, incidence rates for brain and nervous cancer in the region are relatively high (see Figure 19). The incidence of acoustic neuroma in Qatar is slightly higher than that in other countries, with a possible link to frequent cellular phone use (Salahaldin and Bener, 2006).

*Thyroid Cancer*

Thyroid cancer is of medium importance (see Figure 21), but occupies the number two position in females in Saudi Arabia and is prevalent in other coutries of the Gulf as well as Jordan. The dramatic decline in the incidence of follicular thyroid carcinoma combined with the increase in the advanced forms in Central Jordan may suggest a possible environmental factor (Shomaf et al., 2006). In contrast, papillary carcinomas form the bulk of cases in the Yemen, where the salt iodization program might have an effect on the incidence (Abdulmughni et al., 2004).

*Leukemias and Lymphomas*

In both sexes, Non-Hodgkins lymphomas and to a lesser extent leukemias, are relatively important neoplasms across the region (see Figures 21 and 22). However, research findings are limited, especially as to risk factors. There is some support for the hypothesis that NHL is a malignant outcome of chronic HCV infection (Cowgill et al., 2004). It is possible that the tumour type is increasing, from data for Alexandria, particularly in the elderly population (Abdel-Fattah and Yassine, 2007).

*Childhood cancers*

There are only limited research data for cancers of childhood in the Middle-East. However, it is likely that

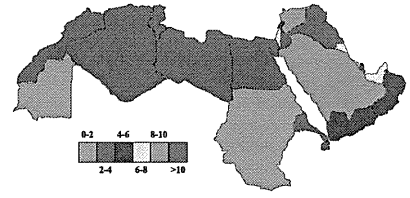


**Figure 21. Male Thyroid Cancer Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)





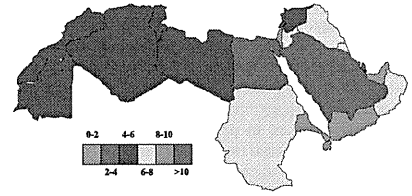


**Figure 22. Male Non-Hodgkins Lymphoma Incidences/ 100,000** (Globocan, 2002: Ferlay et al., 2004)

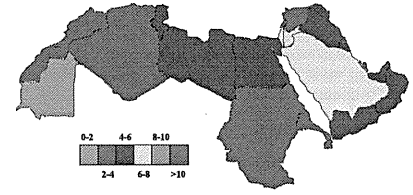


**Figure 23. Male Leukemia Incidences/100,000** (Globocan, 2002: Ferlay et al., 2004)

lymphatic and haemopoietic cancer incidences are increasing (Hosny and Elkaffas , 2002b).

## Future Perspectives

It should be stressed that cancer registry data in the regionare scanty, especially for those countries with large populations, so that emphasis should be palced on better development of regional and national registries. There may be too much reliance on pathology reports and luekemias, for example are likely to be under-reported. Optimally, governments would make registration mandatory, with roles for WHO/UICC/OARC in assuring quality and reliability. To create an environment conducive to more allocation of resources and personnel, Arab scientists need to report their data in peer-reviewed journals (El-Saghir et al., 2007).

Although most of the registries in the Middle east have not been operating for a sufficient length of time to give information on time trends, data are available over 30 years for Palestinians and for 25 years for Kuwaitis (see Table 9). Common to both are relatively consistent increases in cancers of the colon, prostate, endometrium and breast, as well as Non-Hodgkins lymphomas and perhaps ovarian and thyroid cancers. All of the adenocarcinomas are considered linked to a Westernized lifestyle. A nutrition transition, as well documented for Egypt (Galal, 2002) has occurred in the context of abundant dietary energy availability, urbanisation and moderate fat intakes. The prevalence of obesity in adults in the region is very high, particularly among women. The prevalences of diabetes mellitus and of hypertension parallel that of obesity. Smoking, physical inactivity, and obesity contribute substantially to the burden of chronic disease (Centers for Disease Control and Prevention, 2002; Kulwicki and

**Table 9. ASR Cancer Incidence Over Time - CIV**

| Volume | IV* | V** | VI$^{s}$ | VII$^{\#\#}$ | VIII$^{\#\#}$ | IX$^{+}$ |
|---|---|---|---|---|---|---|
| **Kuwait** | | | | | | |
| Oesophagus | --- | 1.7 | 3.7 | 1.7 | 1.7 | 2.2 |
| Stomach | --- | 5.6 | 4.1 | 4.1 | 5.6 | 3.4 |
| Colon | --- | 6.3 | 1.9 | 3.5 | 6.3 | 8.4 |
| Rectum | --- | 4.0 | 2.4 | 3.9 | 4.0 | 5.2 |
| Liver | --- | 4.4 | 7.2 | 7.3 | 8.4 | 8.1 |
| Prostate | --- | 11.4 | 4.4 | 6.5 | 11.4 | 10.5 |
| Breast | --- | 15.9 | 17.2 | 32.8 | 32.8 | 41.3 |
| Ovary | --- | 3.3 | 3.7 | 4.7 | 5.7 | 5.4 |
| Endometrium | --- | 1.8 | 2.4 | 2.4 | 3.8 | 3.6 |
| Cervix | --- | 3.9 | 4.1 | 7.6 | 4.2 | 4.5 |
| Thyroid | --- | 6.3 | 1.4 | 6.1 | 7.6 | 7.3 |
| Larynx | --- | 3.5 | 2.4 | 2.5 | 3.5 | 0.5 |
| Lung | --- | 21.5 | 14.5 | 20.3 | 21.5 | 15.6 |
| Kidney | --- | 3.8 | 2.4 | 2.1 | 3.8 | 5.8 |
| Bladder | --- | 4.6 | 5.7 | 7.0 | 4.6 | 6.3 |
| NHL | --- | 8.6 | 7.3 | 5.5 | 8.6 | 10.4 |
| Leukemia | --- | 5.5 | 7.4 | 5.1 | 5.5 | 4.9 |
| **Palestine** | | | | | | |
| Oesophagus | 1.0 | 1.0 | 1.1 | 0.5 | 0.7 | 1.1 |
| Stomach | 7.2 | 7.9 | 6.9 | 6.8 | 6.7 | 6.7 |
| Colon | 3.3 | 4.7 | 4.6 | 6.2 | 9.6 | 10.6 |
| Rectum | 3.1 | 3.0 | 3.6 | 3.1 | 3.8 | 8.3 |
| Liver | 2.4 | 2.9 | 3.0 | 2.6 | 3.2 | 2.6 |
| Prostate | 4.9 | 6.5 | 7.7 | 10.4 | 14.8 | 20.0 |
| Breast | 11.0 | 14.0 | 17.0 | 21.3 | 27.7 | 41.3 |
| Ovary | 3.8 | 3.4 | 2.4 | 3.0 | 4.0 | 5.4 |
| Endometrium | 1.2 | 3.1 | 2.8 | 4.9 | 5.7 | 3.6 |
| Cervix | 2.1 | 3.0 | 2.6 | 3.0 | 2.5 | 4.5 |
| Thyroid | 1.8 | 2.5 | 2.6 | 4.1 | 4.8 | 7.3 |
| Larynx | 6.4 | 4.9 | 4.1 | 3.7 | 5.4 | 6.1 |
| Lung | 28.8 | 23.4 | 26.2 | 29.1 | 35.1 | 40.4 |
| Kidney | 8.6 | 2.5 | 3.3 | 3.3 | 3.3 | 4.4 |
| Bladder | 1.8 | 12.5 | 9.1 | 13.1 | 15.5 | 18.1 |
| NHL | 7.5 | 6.7 | 5.4 | 8.3 | 9.7 | 10.0 |
| Leukemia | 5.9 | 5.1 | 6.2 | 6.0 | 7.8 | 7.3 |

*Waterhouse et al., 1982; **Muir et al., 1987; #,##,###Parkin et al., 1992;1997;2002; +Curado et al., 2007

Kepler, 2001).

It is well known from migrant studies that Arab populations were earlier characterized by generally low rates for cancers of colon and rectum, lung, ovary and prostate (McCredie et al., 1994). Cancers which tended to be more common in migrants were stomach, liver, and bladder. These still are important but the future will see the main burden in diabetes-associated tumours, as in the developed world. To what extent these are affluence-related needs to now be determined by epidemiological research into psychosocial factors. The Arab countires are particulary interesting in this regard, given the wide variation in Gross National Product. Hopefully, such enigmas as the decreasing lung rates in Kuwait and very low incidences in some of the Arab countries, despite clear increase in Palestinians, will thereby also be explained.

Given the recent increase in 'hubble bubble' (Arkila, Narkila) smoking by youth across the region, more stress needs to be placed on anti-smoking efforts. Advertising is rampant and uncontrolled in many countries and more protection is clearly required for adolescents. Other areas which need particular attention aresmoking nutrition

including the role played by local vegetables and herbs (Abu-Rabia, 2005). The importance of environmental exposure to pesticides and other contaminants has also be highlighted (Safi, 2002). Given the clear variation in cancer burden within the Arab world, despite a shared culture, collaboration across individual registries across the region should lead to a far better understanding of the status and the evidence base which is essential for effective cancer control programs.

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# Epidemiology of Breast Cancer in Japan and the US

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## Abstract

A comparison of breast cancer occurring in American and Japanese women reveals that both the incidence and mortality rates are markedly higher in the US. However, both the age-adjusted incidence and mortality rates have been increasing in Japan. On the other hand, in the US, where the age-adjusted incidence rate tended to increase before the 1990s, the rate has tended to decline after reaching a peak in the late 1990s. The age-adjusted mortality rate has also tended to decline since the 1980s in the US.

Risk factors for breast cancer include early menarche, late menopause, and late first delivery. The higher frequencies of these risk factors in American women than in Japanese women may explain the higher incidence and mortality rates of breast cancer in the US. The recent increase in the incidence and mortality rates of breast cancer in Japan seems to be a reflection of a trend toward late marriage and declining birthrates in this country. The recent decrease in the mortality rate from breast cancer in the US may be attributable to the spread of screening by mammography and improved therapeutic modalities. Major risk factors for breast cancer are difficult to control at the individual level, and effective prevention of the disease is unlikely. Improvement in the screening rate will be necessary for achieving a decrease in the mortality from breast cancer.


Key words Mortality, Incidence, Risk factors

## Introduction

Although the incidence and mortality rates of breast cancer among women in Japan are lower than those in western countries, they have been increasing recently. In Japan in 1994, the age-adjusted breast cancer incidence rate ranked first among cancer incidence rates by site of cancer. Understanding the trends in the incidence and mortality rates and established risk factors for breast cancer, and considering Japan's differences from the US, where the incidence and mortality rates have been decreasing, has important implications for the future prevention of breast cancer in Japan.

## Descriptive Epidemiology

### Number of new cases and incidence rate of breast cancer

Information on cancer morbidity in Japan is available from the Research Group for the Population-Based Cancer Registry in Japan, whereas that in the US is available from the Surveillance Epidemiology and End Results (SEER) and the National Program of Cancer Registries (NPCR). However, it should be noted that Japanese data include cases of carcinoma in situ.

In 2001, there were 40,675 women with breast cancer in Japan (ranking second among cancer cases by site of cancer), accounting for 16.7% of all cases of cancer. In 2002, the number of American women with breast cancer was 168,632

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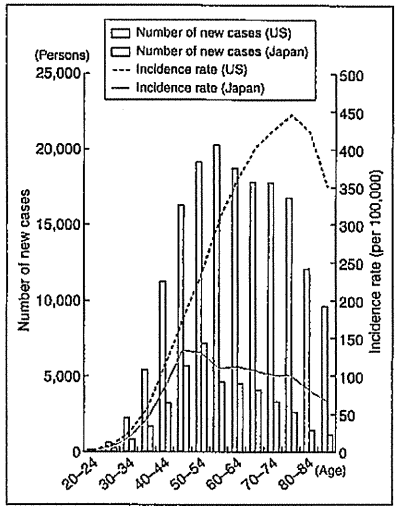
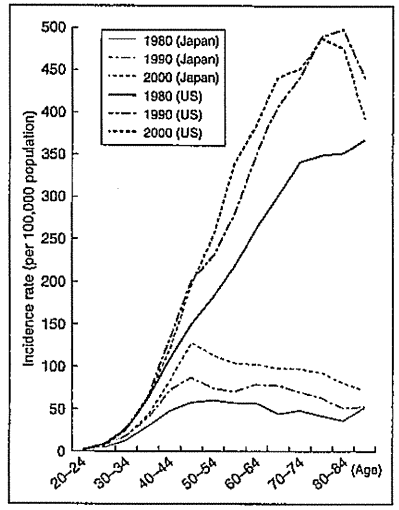


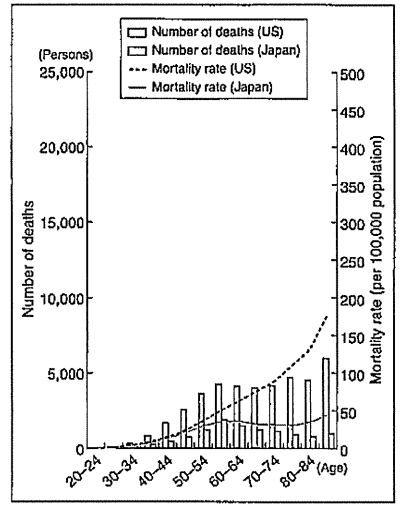

(Japan: Research Group for the Population-Based Cancer Registry in Japan,* US: US Cancer Statistics**)
* Including carcinoma in situ.
** Excluding Connecticut, Hawaii, Iowa, Kansas, Maryland, Mississippi, New Mexico, South Dakota, Tennessee, Utah, Virginia, and Wyoming.

**Fig. 1 The number of breast cancer new cases and incidence rates by age group in Japan (2001) and the US (2002)**



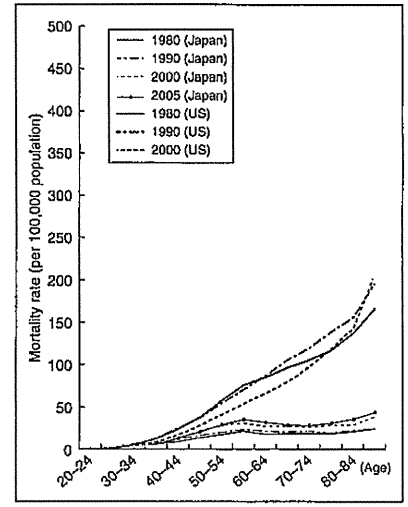

(Japan: Research Group for the Population-Based Cancer Registry in Japan, US: SEER database)

**Fig. 2 Breast cancer incidence rates by age group**




(Japan: Vital statistics of Japan, Ministry of Health, Labor and Welfare; US: WHO database)

**Fig. 3 The number of breast cancer deaths and mortality rates by age group in Japan (2006) and the US (2004)**




(Japan: Vital statistics of Japan, Ministry of Health, Labor and Welfare; US: WHO database)

**Fig. 4 Breast cancer mortality rates by age group**

(ranking first among cancer cases by site of cancer), accounting for 30.4% of all cases of cancer.

The age-adjusted incidence rate has been increasing in Japan since 1975, with the 1985 model population being used as the reference population. The incidence rate of breast cancer was third highest (21.7 per 100,000 population) among various cancers in 1975, following stomach cancer and uterine cancer. After reaching a peak (101.4 per 100,000 population) in 1999, the incidence rate has been declining, showing a figure of 89.8 per 100,000 population in 2004.

Figure 1 shows the number of new cases and incidence rates by age group in Japan (2001) and the US (2002). In both countries, the number of new cases began to increase after the age of 20 years, reaching a peak at the age of 50–59 and declining thereafter. Breast cancer was most frequent in women 50–54 years of age in Japan, whereas the corresponding age was 55–59 years in the US. The incidence rate began to increase after 20 years of age in both Japan and the US, continuing to increase similarly until 45–49 years. However, the incidence rate reached a peak (133.7 per 100,000 population) at the age of 45–49 years in Japan, whereas there was a continuous increase (446.8 per 100,000 population) until 75–79 years in the US.

Figure 2 shows the trend in the incidence rates of breast cancer by age group at 10-year intervals. In Japan, the peak incidence rate was found in women aged 50–54 (59.8 per 100,000) in 1980, and in those aged 45–49 (86.4 and 126.4 per 100,000 in 1990 and 2000, respectively). The peak has been even more dramatic in recent years. In addition, regardless of age group, the incidence rate has been higher in recent years. In the US, the incidence rate was higher in women of more advanced age in 1980. The peak incidence rate was found in women aged 80–84 (497.7 per 100,000) in 1990, and in those aged 75–79 (487.4 per 100,000) in 2000. Although there was a marked increase in the incidence rate of breast cancer from 1980 to 1990, no substantial changes were noted from 1990 to 2000.

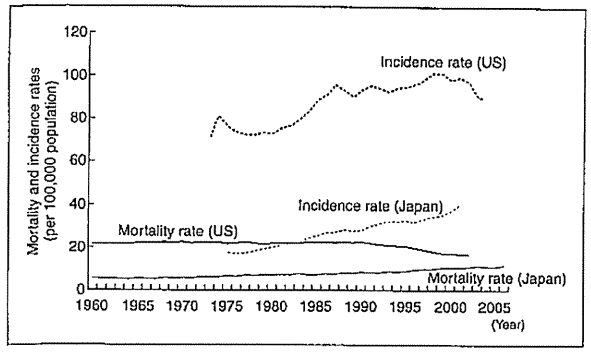
### Trends in the number of deaths and the mortality

Data on cancer mortality in Japan were obtained from the Vital Statistics by the Ministry of Health, Labor and Welfare, and data on cancer mortality in the US were obtained from the Vital Statistics of the United States.

In 2006, the number of breast cancer deaths in Japan was 11,174 (ranking fourth by site of cancer), accounting for 8.5% of all cancer deaths. The number of cancer deaths in the US in 2004 was 40,954 (ranking second by site of cancer), accounting for 15.3% of all cancer deaths, about two-fold higher than in Japan. The age-adjusted breast cancer mortality rate in Japan has tended to increase since 1960; although the mortality rate ranked fifth (5.1 per 100,000) in 1960, following stomach cancer, uterine cancer, liver cancer, and colorectal cancer. In 2006, it ranked third (11.7 per 100,000) together with lung cancer, following colorectal cancer and stomach cancer. In the US, the breast cancer mortality rate was ranked first (21–22 per 100,000) from 1960 to 1986, but it has dropped to second place since 1987, having been replaced by lung cancer, which had increased rapidly.

Figure 3 shows the number of deaths and mortality rates of breast cancer in Japan (in 2006) and the US (in 2004) by age group. The number of deaths began to increase in individuals after 30 years of age both in Japan and the US. Deaths were most frequent in women aged 55–59 (1,897 individuals) in Japan. In contrast, in the US, a peak was found in those aged 55–59 (4,282 individuals), but breast cancer deaths were most frequent (5,986 individuals) in those aged 85 years old or older. The mortality rate tended to be higher with advancing age in both Japan and the US, although there was a peak at age 60–64 in Japan. Differences in the mortality rate between Japan and the US were noteworthy in women after 50 years of age.

Figure 4 presents breast cancer mortality rate




[Incidence rates (Japan: Research Group for the Population-Based Cancer Registry in Japan*; US: SEER database), Mortality rates (Japan: Vital statistics of Japan, Ministry of Health, Labor and Welfare; US: WHO database)]
*Including carcinoma in situ.

**Fig. 5 Trends in the age-adjusted breast cancer mortality and incidence rates (age adjusted for world population)**

by age group at 10-year intervals. In Japan, the mortality rates have been higher in more recent years in all age groups. On the other hand, in the US, although there were no marked changes in the mortality rates in women aged 75 years or older, the mortality rates tended to be lower in 2000 than in 1990 in all of the age groups from 20–74 years.

The proportions of particular age groups to overall breast cancer deaths were influenced by the increased population of elderly individuals both in Japan and the US. Women in their 50s and those aged 75 years or older accounted for higher proportions among all patients who died of breast cancer in Japan, whereas the group 75 years or older accounted for a higher proportion in the US. The percentage of Japanese women in the 50s remained at 25–30% during the period from 1960 to 2006. Those aged 75 years or more accounted for 12% in 1960, but increased to 24% in 2006. In the US, the proportion of women aged 75 years or older was 18.8% in 1960, and increased to 37.2% in 2004.

### Comparison of incidence and mortality rates

Figure 5 shows the trends in the age-adjusted breast cancer incidence and mortality rates in Japan and the US (the reference population is world population). Although both breast cancer incidence and mortality rates among Japanese women have been tending to increase, the incidence/mortality ratio increased from 3.4 in 1975 to 4.2 in 2001. In the US, although the mortality rate declined after 1990, and the incidence rate has decreased since 2000, the incidence/mortality ratio increased from 2.9 in 1973 to 4.8 in 2004.

### Survival rate

According to data on survival from population-based cancer registries in Japan, the 5-year relative survival rate for women with breast cancer diagnosed from 1993 to 1996 was 83.1%.[1] On the other hand, according to the SEER database in the US, the 5-year relative survival rate for patients diagnosed from 1993 to 1995 was 86.6%.

## Risk Factors

### Reproductive factors

Estrogen plays an important role in the development of breast cancer. Many of the established risk factors for breast cancer are known to influence endogenous estrogen levels. It is apparent that prolonged exposure to estrogen increases the risk of breast cancer, as in cases of early menarche, late menopause, late first delivery, low parity, and absence of breast-feeding.[2,3]





### Exogenous hormones

Although it is apparent that postmenopausal hormone replacement therapy increases the risk of breast cancer, most previous studies have focused on estrogen-progestin combined therapy. No consistent results have been obtained from reports on estrogen-only therapy. High postmenopausal blood estrogen levels and high premenopausal blood IGF-I levels are also established risk factors.[2]

In regard to oral contraceptives, it has been reported that the rate of oral contraceptive use and the risk of developing breast cancer are higher among Japanese and other Asian immigrants in the US than among women in their home countries.[4] However, a relation between the use of oral contraceptives and the increased risk of breast cancer has not been established.

### Nutritional factors and physical activity

While attention has been given to fat, fiber, fruits and vegetables, and soy isoflavones as possible prophylactic factors for breast cancer, only alcohol is a clearly established risk factor for premenopausal breast cancer. For postmenopausal breast cancer, fat as well as alcohol are regarded as established risk factors.[4]

Physical activity may be associated with a reduction in the risk of postmenopausal breast cancer.[4]

### Anthropometric factors

Being tall and postmenopausal obesity are established risk factors. However, it has been reported that obesity is associated with a reduced risk in premenopausal women.[4]

### Genetic and familial susceptibility

A family history of breast cancer in a first-degree relative is an established risk factor, and BRCA1 and BRCA2 are known to be the responsible genes. However, BRCA abnormality may not be the only cause of familial breast cancer; it is possible that environmental factors in the family are involved.

## Prevention

It is difficult to modify such risk factors as reproductive factors, genetic and familial susceptibility of breast cancer, for the purpose of preventing breast cancer. However, it is possible to cut down on alcohol consumption or to exercise regularly. Early detection of breast cancer by mammographic screening also helps reduce deaths from breast cancer.

## Differences between Japan and the US as Related to Risk Factors

Both the incidence and mortality rates of breast cancer are considerably lower in Japan than in the US. This may be explained by the higher proportion of obese people in the US than in Japan and differences between people in the two countries in eating habits, physical features, age at menarche, and reproductive history.

The age-adjusted incidence rates in the US had been increasing until 2000, partly because mammographic screening became widespread in the 1980s. It is reported that the percentage of women aged 40 years of age or over who received screening within the previous 2 years was 29.1% in 1987, but increased to 70.1% in 2000.[5] Improved therapeutic efficacy may be involved in the decrease in the mortality rate in the US after 1990, because there was improvement in survival rates in addition to the benefit of early detection by screening and early treatment after screening. In recent years, tamoxifen has been widely used since its efficacy as an agent for postoperative chemotherapy was demonstrated. The decrease in the age-adjusted incidence rates after 2000 in the US may be partially attributable to a decrease in women who were receiving postoperative hormone replacement therapy, a risk factor for breast cancer.[6]

In contrast to the decrease in the incidence and mortality rates in the US, both the incidence and mortality rates have been increasing in Japan. This may be explained by an increased population of women at risk of breast cancer due to an overall tendency to late marriage and declining birthrates as well as changes in the lifestyle and physical features of the Japanese people. A clinical breast physical examination had been carried out in women aged 30 years or more as a part of the cancer screening based on the Health and Medical Services Laws for the aged since 1987. Mammography began to be used for women aged 50 years or more in 2000, and for those aged 40 or more in 2005. The screening rate, however, was 12.4% for breast cancer screenings conducted

by municipal governments in 2002, with the mammographic screening rate as low as 2.1%,[7] showing hardly any influence on the incidence rate or mortality rate. The breast cancer screening rate increased to 17.6% in 2005,[8] and it is expected that, if the screening rate continues to increase, it may lead to a reduction in the breast cancer mortality rate.

## Breast Cancer in Men

The crude mortality rate of breast cancer in men was 0.2 (per 100,000 population) in Japan in 2006, and 0.3 (per 100,000 population) in the US in 2004. The mortality rates were 85- to 90-fold higher in women than in men in both Japan and the US. Risk factors of breast cancer in men are also unclear.

## Conclusion

The increase in the breast cancer incidence and mortality rates in Japan may be attributable to changes in eating habits and physical features, the tendency to marry late, and decreased birthrates. On the other hand, the recent decrease in the breast cancer mortality rate in the US may be due to early detection of the disease by mammographic screening, implementation of early treatment, and the efficacy of tamoxifen therapy. To decrease the breast cancer incidence rate, it is important to modify lifestyle, e.g., to decrease alcohol consumption and to practice adequate exercise. To increase the screening rate is important in decreasing the mortality rate.

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# A Joinpoint regression analysis of long-term trends in cancer mortality in Japan (1958–2004)

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**Cancer is one of the major targets of disease control programs in Japan. A Joinpoint regression model was used to analyze the long-term trends of mortality related to overall cancer and the 15 most common cancers based on published data from the National Vital Statistics of Japan between 1958 and 2004. Since 1996, a decline has been seen in overall cancer for both sexes in Japan. Most of the common sites, including cancers of the stomach, colon, liver, gallbladder and lung and leukemia in both sexes, cancer of esophagus in men and rectal and ovarian cancers in women showed a decreasing trend, and cancers of the rectum, pancreas, prostate and urinary bladder and malignant lymphoma in men and cancers of the esophagus and uterus in women leveled off during the most recent period. However, an increasing trend was confirmed for cancers of the pancreas, breast and urinary bladder and malignant lymphoma in women. An effective cancer control program including prevention, early detection and treatment should be implemented to further reduce the cancer mortality, particularly for cancer sites that show higher mortality rates or increasing trends.**


**Key words:** cancer; mortality; trend; Joinpoint analysis; Japan

In Japan, cancer has been the leading cause of death since 1981. The total number of cancer deaths is actually increasing annually. The number of deaths due to cancer in 2004 was 320,358, exceeding the 288,680 deaths due to cardiovascular disease, and comprised approximately 31% of total deaths.[1] Age-standardized mortality rate (ASR) (using the World Standard Population) was 99.4 per 100,000 (138.0 for men, 69.9 for women). Recently, the trend for ASR of overall cancer deaths has tended to decline for both men and women, but has shown diversification for different anatomical sites. Because cancer is one of the major targets of disease control programs in Japan, an accurate understanding of current trends in overall cancer and common cancers using statistical methods is important.

Recently, Joinpoint analysis has been commonly used to describe the changing trends over distinct periods of time and significant increases or decreases in cancer mortality for foreign countries.[2–5] However, similar analyses of trends for cancer have yet to be performed in Japan. We therefore analyzed the long-term trends in overall cancer and major cancers mortalities in Japan between 1958 and 2004 using Joinpoint analysis.

## Material and methods

Data regarding the number of deaths due to cancer were obtained according to sex, anatomical sites and age (grouped by 5-year age groups: 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85+) for the years 1958–2004 from the National Vital Statistics in Japan. Corresponding Japanese population data were derived from the Statistics Bureau, Ministry of Internal Affairs and Communications: the Japanese Population Census Report from 1960 to 2000 (conducted every 5 years) and population estimates for the remaining years. During the specific calendar period, cancer deaths in Japan were coded according to the International Classification of Diseases, 7th Revision (ICD-7) for 1958–1967, 8th Revision (ICD-8) for 1968–1978, 9th Revision (ICD-9) for 1979–1994 and 10th Revision (ICD-10) for 1995–2004. Sites for analysis included overall cancer and the 15 most common cancers: esophagus (C15), stomach (C16), colon (C18), rectum (C19-C21), liver and intrahepatic bile duct (liver) (C22), gallbladder and extrahepatic bile duct (gallbladder) (C23-C24), pancreas (C25), lung and bronchus (lung) (C33-C34), breast (C50, D05), uterus (C53-C55), ovary (C56), prostate (C61), urinary bladder (C67), malignant lymphoma (C81-C85, C96) and leukemia (C91-C95). Annual ASRs for the 47-year time span were calculated by the direct method using the World Standard Population.

Long-term trends in ASRs of cancer in Japan were analyzed using Joinpoint regression model.[6] Joinpoint regression program is a trend analysis software developed by the US National Cancer Institute for the analysis of data from the Surveillance Epidemiology and End Results Program. This method describes changes in data trends by connecting several different line segments on a log scale at "joinpoints." Analysis starts with the minimum number of joinpoints (*i.e.*, 0 joinpoint, representing a straight line) and tests for model fit with a maximum of 4 joinpoints. Tests of significance use a Monte Carlo permutation method. In addition, an annual percent change (APC) in ASRs for each line segment and the corresponding 95% confidence interval were estimated. The APC is tested to determine whether a difference exists from the null hypothesis of no change (0%). In the final model, each joinpoint informs a statistically significant change in trends (increase or decrease) and each of those trends is described by an APC.[5–7]

## Results

Tables I and II show the crude death rate and ASR by cancer site at the beginning (1958) and end (2004) of the study period, together with results of Joinpoint analysis for ASRs in men and women for all ages, respectively. The results of Joinpoint analysis on ASRs from overall cancer, stomach, colon, rectum, liver, pancreas, lung, prostate, breast and uterus are presented in Figure 1. Changing trends in ASRs in Joinpoint analysis will be described in 3 patterns as follows in this study. Pattern 1, ASRs reached a plateau or started decreasing in the 1990s after constant increases from 1958. Pattern 2, ASRs decreased continuously from 1958. Pattern 3, ASRs increased continuously from 1958.

In men, ASRs for overall cancer showed Pattern 1, increasing by 0.32% per year from 1958 to 1989, stabilizing from 1989 to 1993 and 1993 to 1996, and declining by 1.71% per year from 1996 to 2004. ASRs for cancers of the esophagus, colon, rectum, liver, gallbladder, pancreas, lung, prostate and urinary bladder, malignant lymphoma and leukemia also showed Pattern 1. ASRs for cancers of the colon, liver, gallbladder and lung decreased from the 1990s, was similar to the results for overall cancer, whereas ASRs for cancers of the rectum and prostate leveled off from the 1990s. ASRs of malignant lymphoma and pancreatic cancer leveled off from 2001 and 1987, respectively, leukemia

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TABLE I – CRUDE MORTALITY RATES, ASR[1] AND JOINPOINT ANALYSES FOR 1958 THROUGH 2004 IN JAPAN: MEN OF ALL AGES

| Site | Year 1958 | | Year 2004 | | Joinpoint analyses (1958–2004) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Trend 1 | | Trend 2 | | Trend 3 | | Trend 4 | | Trend 5 | |
| | Crude death rate | ASR[1] | Crude death rate | ASR[1] | Period | APC[2] | Period | APC[2] | Period | APC[2] | Period | APC[2] | Period | APC[2] |
| All sites | 104.4 | 133.3 | 313.4 | 138.0 | 1958–1989 | 0.32[3] | 1989–1993 | −0.42 | 1993–1996 | 1.84 | 1996–2004 | −1.71[3] | | |
| Esophagus | 5.1 | 6.8 | 15.3 | 7.1 | 1958–1970 | 1.44[3] | 1970–1978 | −1.70[3] | 1978–1994 | 0.08 | 1994–1997 | 2.53 | 1997–2004 | −0.70[3] |
| Stomach | 55.6 | 71.3 | 53.3 | 23.4 | 1958–1969 | −0.72[3] | 1969–1980 | −2.82[3] | 1980–1993 | −3.31[3] | 1993–1996 | −0.53 | 1996–2004 | −3.55[3] |
| Colon | 1.8 | 2.3 | 21.6 | 9.5 | 1958–1987 | 4.52[3] | 1987–1996 | 2.70[3] | 1996–2004 | −1.23[3] | | | | |
| Rectum | 3.3 | 4.4 | 14.1 | 6.6 | 1958–1974 | 2.13[3] | 1974–1998 | 0.60[3] | 1998–2004 | −0.74 | | | | |
| Liver and intrahepatic bile duct | 10.6 | 13.6 | 38.0 | 17.4 | 1958–1974 | −0.67[3] | 1974–1985 | 4.54[3] | 1985–1996 | 1.28[3] | 1996–2004 | −3.21[3] | | |
| Gallbladder and extrahepatic bile duct | 0.9 | 1.2 | 12.1 | 4.9 | 1958–1965 | 10.01[3] | 1965–1986 | 4.11[3] | 1986–1992 | 1.34[3] | 1992–1999 | −0.98[3] | 1999–2004 | −2.41[3] |
| Pancreas | 2.0 | 2.5 | 19.4 | 8.7 | 1958–1968 | 7.23[3] | 1968–1987 | 2.74[3] | 1987–2004 | 0.09 | | | | |
| Lung and bronchus | 6.5 | 8.3 | 71.3 | 29.8 | 1958–1963 | 7.43[3] | 1963–1981 | 4.22[3] | 1981–1989 | 2.08[3] | 1989–1996 | 0.91[3] | 1996–2004 | −1.05[3] |
| Prostate | 1.0 | 1.4 | 14.4 | 5.4 | 1958–1993 | 3.13[3] | 1993–1996 | 7.98[3] | 1996–2004 | 0.37 | | | | |
| Urinary bladder | 1.4 | 1.9 | 6.2 | 2.4 | 1958–1979 | 1.03[3] | 1979–1992 | −1.05[3] | 1992–1995 | 4.14 | 1995–2004 | −0.07 | | |
| Malignant lymphoma | 1.7 | 2.0 | 7.8 | 3.6 | 1958–1967 | 3.71[3] | 1967–1980 | 2.03[3] | 1980–2001 | 0.35[3] | 2001–2004 | −2.20 | | |
| Leukemia | 3.0 | 3.1 | 6.7 | 3.5 | 1958–1976 | 1.69[3] | 1976–1987 | 0.25 | 1987–2004 | −1.23[3] | | | | |

[1]ASR, age-standardized mortality rates adjusted to the World Standard Population (per 100,000).–[2]APC, annual percent change.–[3]The annual percent change is significantly different from 0 (two-side $p < 0.05$).

TABLE II – CRUDE MORTALITY RATES, ASR[1] AND JOINPOINT ANALYSES FOR 1958 THROUGH 2004 IN JAPAN: WOMEN OF ALL AGES

| Site | Year 1958 | | Year 2004 | | Joinpoint analyses (1958–2004) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Trend 1 | | Trend 2 | | Trend 3 | | Trend 4 | | Trend 5 | |
| | Crude death rate | ASR[1] | Crude death rate | ASR[1] | Period | APC[2] | Period | APC[2] | Period | APC[2] | Period | APC[2] | Period | APC[2] |
| All sites | 86.9 | 97.0 | 197.1 | 69.9 | 1958–1967 | −0.22 | 1967–1993 | −0.98[3] | 1993–1996 | 0.98 | 1996–2004 | −1.22[3] | | |
| Esophagus | 2.1 | 2.3 | 2.7 | 1.0 | 1958–1969 | −0.42 | 1969–1989 | −4.01[3] | 1989–2004 | −0.29 | | | | |
| Stomach | 33.3 | 37.2 | 27.4 | 9.2 | 1958–1970 | −0.90[3] | 1970–1980 | −3.43[3] | 1980–1990 | −4.51[3] | 1990–2004 | −3.52[3] | | |
| Colon | 2.3 | 2.6 | 20.4 | 6.5 | 1958–1982 | 3.29[3] | 1982–1993 | 2.32[3] | 1993–2004 | −0.52[3] | | | | |
| Rectum | 3.0 | 3.4 | 8.1 | 2.9 | 1958–1974 | 1.15[3] | 1974–1994 | −1.37[3] | 1994–2004 | −0.61[3] | | | | |
| Liver and intrahepatic bile duct | 7.4 | 8.4 | 17.2 | 5.4 | 1958–1975 | −2.56[3] | 1975–1993 | 0.27[3] | 1993–1996 | 3.73 | 1996–2001 | −1.34[3] | 2001–2004 | −3.86[3] |
| Gallbladder and extrahepatic bile duct | 1.1 | 1.2 | 13.8 | 3.8 | 1958–1963 | 11.55[3] | 1963–1972 | 5.83[3] | 1972–1985 | 3.73[3] | 1985–1992 | −0.31 | 1992–2004 | −2.98[3] |
| Pancreas | 1.5 | 1.7 | 16.0 | 5.1 | 1958–1966 | 6.86[3] | 1966–1988 | 2.43[3] | 1988–1993 | −0.61 | 1993–2004 | 0.63[3] | | |
| Lung and bronchus | 2.9 | 3.3 | 24.8 | 7.9 | 1958–1966 | 5.27[3] | 1966–1974 | 1.90[3] | 1974–1982 | 3.48[3] | 1982–1998 | 0.91[3] | 1998–2004 | −1.88[3] |
| Breast | 3.6 | 4.0 | 16.3 | 8.7 | 1958–1963 | −1.20 | 1963–1975 | 2.50[3] | 1975–1992 | 1.68[3] | 1992–1997 | 3.63[3] | 1997–2004 | 1.18[3] |
| Uterus | 15.2 | 17.0 | 8.6 | 3.9 | 1958–1968 | −3.22[3] | 1968–1975 | −4.35[3] | 1975–1987 | −5.39[3] | 1987–1993 | −3.00[3] | 1993–2004 | −0.15 |
| Ovary | 1.2 | 1.3 | 6.8 | 3.3 | 1958–1981 | 3.58[3] | 1981–1994 | 1.20[3] | 1994–2004 | −1.07[3] | | | | |
| Urinary bladder | 0.7 | 0.8 | 2.7 | 0.7 | 1958–1969 | 1.09[3] | 1969–1993 | −1.92[3] | 1993–2004 | 1.22[3] | | | | |
| Malignant lymphoma | 1.0 | 1.1 | 5.6 | 1.9 | 1958–1981 | 2.24[3] | 1981–2004 | 0.31[3] | | | | | | |
| Leukemia | 2.3 | 2.4 | 4.5 | 2.1 | 1958–1964 | 3.68[3] | 1964–1975 | 0.56[3] | 1975–1989 | −0.69[3] | 1989–2004 | −1.88[3] | | |

[1]ASR, age-standardized mortality rates adjusted to the World Standard Population (per 100,000).–[2]APC, annual percent change.–[3]The annual percent change is significantly different from 0 (two-side $p < 0.05$).