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Declining cancer incidence at the oldest ages: hallmark of aging or lower diagnostic activity?

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Abstract

Background: The incidence of most cancers increases with age from early adulthood into old age, but tends to level off or decrease at the highest ages. This decline may be caused by age-related mechanisms or due to lower diagnostic activity, leaving some cancers undiagnosed at the oldest ages.

Methods: For breast, colon, lung, and all sites except non-melanoma skin cancer, age-specific incidence rates of verified as well as suspected cancer were estimated up to ages 95+ years for a random sample of the Danish population, 1994-2011, based on nationwide health registers (40,008 verified and 9,110 suspected cancers). Moreover, for cancers diagnosed in Denmark, 1978-2012 (613,384 cancers), age-specific percentages of tumors with microscopic verification (histological/cytological/hematological examination) were calculated.

Results: The age-specific cancer incidence rates reached a peak at ages 65-89 years followed by a decline. The corresponding incidence pattern of suspected but not verified cancer was similar, with a trend of a slight absolute and relative decrease with age compared to verified cancer incidence. The proportion of cancers with microscopic verification decreased linearly from approximately 95% at ages 0-69 years all years to 70% (1978-1982) and to 80% (2010-2012) at ages 90+ years.

Conclusions:

The lower diagnostic verification of cancer at the highest ages suggests a lower diagnostic activity among the oldest-old. However, the proportion of suspected but not verified cancers did not increase with age, possibly partially due to lack of registration. The declining cancer incidence at oldest ages is probably partly due to lower diagnostic activity.

Keywords: Epidemiology – Neoplasms – Incidence – Aged – Aged, 80 and over – Bias
Introduction

With few exceptions, cancer incidence and mortality rates increase with age from early adulthood and into old age, but tend to level off or even decrease at the highest ages [1-7]. Two not mutually exclusive explanations are suggested: 1) the decline is a hallmark of aging. The decline may due to a lower susceptibility to cancer, or even insusceptibility, at the oldest ages [4, 8]: if part of the population is particularly susceptible to cancer, i.e. if there is a heterogeneous susceptibility to cancer, then the increasing risk of cancer development with age due to the continuous exposure to carcinogenic agents may deplete the population of susceptible individuals leading to an old-age population strongly selected for protective factors against cancer [9, 10]. Additionally, the decline may also be caused by a general condition of old age related to age-dependent biological processes that impede tumor growth at old age [11-13] or of decreased proliferative potential of cells at the oldest ages [14-16].

2) The decline in cancer incidence at advanced age is due to lower diagnostic activity [17]. Older adults may be less interested in being diagnosed despite a suspicion of cancer, and less willing to go through intensive diagnostic procedures. The risk of comorbidity, i.e. diseases other than cancer, also increases with age [18-23]. Among patients with breast cancer in Denmark, 1990-2008, comorbidity prevalence at diagnosis was 31% at ages 70-79 years and 40% at ages 80+ years [21].

Such comorbidity, especially if severe like stroke or Alzheimer’s disease, could mask the symptoms of cancer and even if the symptoms were present, reduce the likelihood of pursuing a diagnosis involving invasive procedures. Omission of microscopic verification of cancers could lead to an underestimation of incidence among the oldest individuals. Finally, it has been suggested that cohort effects may influence the rates of cancer incidence, when the age-specific rates are measured cross-sectionally [24].

Here we aim to study whether the diagnostic activity of cancer is lower at the oldest ages, reflected by a relatively larger proportion of suspected but neither verified nor rejected cancers at these ages,
and whether the combined incidence of both verified and suspected cancers has a peak in age or continues to increase even at the oldest ages. We also aim to assess whether diagnostic procedures tend to be less comprehensive among the oldest patients with cancer.

**Methods**

A more detailed method description is provided as supplement. Individual level data were derived from three nationwide population registers: Danish Civil Registration System (DCRS) (sex, date of birth, vital status, migration status) from April 2, 1968 [25], Danish Cancer Registry with information on all cancers since 1943 [26, 27], and Danish National Patient Register, containing dates and diagnoses for in-patients since 1977 and out-patients since 1995 for all somatic conditions in Danish wards [28].

**Study population**

The study of verified and suspected cancer was based on a 5% randomly chosen sample of every Danish birth cohort in DCRS supplemented with the entire birth cohorts of 1895-96, 1905, 1910-12 and 1915 in order to increase the statistical power for the oldest age groups. As data in the Danish National Patient Register on suspected cancer were scarce before 1994, and because in 1994 the coding of diagnoses formerly performed using ICD-8 codes was replaced by coding using the ICD-10 classification of diseases, the study population was restricted to individuals from the cohorts alive and residing in Denmark from January 1, 1994 to December 31, 2011. For the study of the comprehensiveness of diagnostic verification, the study population consisted of all incident cancers in Denmark in the periods 1978-1982, 1988-1992, 1998-2002, 2003-2007 and 2010-2012, excluding non-melanoma skin cancer.

*Incidence of verified and suspected cancer*
The age-specific pattern of verified cancer incidence was compared with the corresponding pattern of suspected cancer neither verified nor rejected. Incidence rates for the study population were calculated for the period 1994-2011. For cancers of the breast, colon, and lung, only the first diagnosis of the specific site was counted as an incident cancer, whereas for all sites except non-melanoma skin cancer, incident cancers comprised the first diagnosis of each of the 40 cancer entities constituting this composite category: 39 of these entities are shown in Table 2 of [29]; the remaining entity represents cancer with poorly specified, secondary and unspecified localizations. For each cancer category, a suspected (Table 1) but not verified (Table 1) cancer comprised the first appearance of a suspicion that was not rejected according to hospital records (supplemental ICD-10 rejection code ZDW71) and where the individual had not been diagnosed with any cancer within one year after date of hospitalization.

**Diagnostic verification of cancers**

We calculated the proportions of cancers in categories of diagnostic verification: microscopic verification (histology of tumor or metastasis, cytological or hematological examination), clinical suspicion (clinical examination, x-ray, biochemical or immunological examination), death certificate only, or unknown. The distribution across these categories was calculated for the age intervals of 0-69, 70-74, 75-79, 80-84, 85-89 and 90+ years and for the entire Danish population in the periods 1978-1982, 1988-1992, 1998-2002, 2003-2007 and 2010-2012.

**Statistical analysis**

In the estimation of incidence rates in different age categories and periods, censoring occurred at death, emigration or incidence of the diagnosis of interest (assuming independent censoring). Tests for age trend and departures from these in proportions of diagnosed cancers with the different degrees of verification used the method proposed in [30].
The study has been approved by The Research & Innovation Organization of the University of Southern Denmark (SDU-RIO; J. no. 18/26166; The Danish Data Protection Agency, # J.nr. 2015-57-0008).

**Results**

Over the 18-year study period, 221,422 men contributed with 2.9 million person-years and 247,487 women contributed with 3.1 million person-years of observation time (Table 2). There were 5,052 verified female breast cancers, and a total of 3,918 colon cancers, 4,776 lung cancers, and in total 40,008 cancers of all sites except non-melanoma skin cancer. The suspected but not verified cancers included registrations of 562 female breast cancers, 81 colon cancers, 1,177 lung cancers, and 9,110 cancers of all sites except non-melanoma skin cancer. Each of the 5-year age groups contributed 5-6% of the risk time except at ages 65-79 and 90-94 with 3% in each 5-year interval and 0.6% of the risk time above age 95 (Table 3).

For female breast cancer, the incidence peaked at age 65-69 years and then decreased to a constant level after age 70 (Figure 1). For all sites except non-melanoma skin cancer, the peak age of incidence occurred within the age interval 70-89 years followed by a steep decrease at the highest age categories. For the group of all sites but non-melanoma skin cancer the ratio of verified and suspected cancer to the verified peaked at adolescence/young adulthood and then declined with age.

From age 60 years and onwards, the ratio was slightly decreasing and almost constant, so that the shape of the curve of age-specific incidence rates of verified and suspected cancers combined closely resembled a scaled-up version of the incidence curve of verified cancers. In absolute terms, the incidence rates of suspected but not verified cancer (the difference between curves) was nearly constant from age 60 years.

After an early peak at ages 10-14 age-specific incidence rate ratios (IRRs) of suspected cancers decreased with age, reaching a plateau from age 65 years onwards at 10-20% of the cancer incidence, perhaps with a slight increase from age 85 onwards (Table 3).
For each of the two sub-periods presented in Figure A1, the comparisons of suspected to verified cancer incidence had all the same characteristics as the comparison for the entire study period of an early relative peak followed by a decline with increasing age and almost constant from age 60 onwards with a small relative increase for lung cancer but not for breast cancer. Comparing 2003-2011 to 1994-2002, there was a small to moderate increase in the incidence of verified cancer and a large increase in the reporting of suspected but not verified cancers.

Though the frequency of reported suspected but not verified cancers was low for the period 1977-1993 (results not shown), the ratio of suspected to verified cancer rates was constant over all ages, and, similarly to 1994-2011, did not suggest lower diagnostic activity at the oldest ages.

When assessing any cohort influence on the age-period cancer incidence rates the cohort-specific peak ages were similar to the period-specific peak ages both occurring at ages 80-94 and both with a small tendency to peak earlier in more recent periods/cohorts (Figure A2).

Whereas 95% of tumors had microscopic verification at ages 0-69 years, this proportion decreased approximately linearly with increasing age category reaching a percentage at ages 90+ years in the upper 60s in the early study period and in the upper 70s in the later periods (Figure 2). The other three verification categories (clinical verification, death certificate only, and unknown) reciprocated this pattern in all five periods, except for the last period 2010-2012, where the percentage of cancers with unknown verification was constant over different age categories (Table 4).

**Discussion**

In our study, we found no evidence for an increase in suspected but not verified nor rejected cancers at the oldest ages. However, our findings of a decreasing proportion with increasing age of verified cancers that were based on a thorough verification does suggest an age-differential diagnostic investigation, with a lower tendency to pursue a validated cancer diagnosis at the oldest ages. That no signs of this were found in the comparison of suspected with verified cancer incidence may partly reflect the source of suspected cancers in our study. Suspected cancers were only identified in
hospital contacts. If there truly is less diagnostic activity at the oldest ages, it is likely that it is an intentional act to spare an old patient with e.g. serious comorbidities or a lack of interest in being diagnosed via an invasive diagnostic procedure. If so, then there may also be less readiness to report suspicions in the discharge records, as otherwise the suspicions would lead to subsequent, unwanted (by patients) investigations in the health care system.

Manifestations of an age-differentiated diagnostic activity that may suggest an abated impetus to pursue diagnostic confirmations for the oldest patients have previously been reported: In a survey study among care physicians in the Netherlands [31], more than 33% of nursing home patients with suspected breast cancer were not referred for further testing, and reasons for nonreferral were listed as dementia, patient/family preference, and limited life expectancy. Moreover, in a population-based study of cancer among older Dutch adults, the percentage of cancers with histological or cytological examination decreased from 98% at ages 55-64 years to 85% at ages above 95 [3], and in a Californian study, relatively fewer cancers were staged among patients above 90 compared to below 90 years, whereas for those staged, relatively more were found at distant stages among the older patients [6].

Also, autopsy studies support a lower diagnostic activity contributing to, but not fully explaining the decline in cancer rates at the oldest ages. An Italian study reported a decline in prevalence of malignancies from 36% at ages 75-90 years to 16% at ages 100-106 years, but also found that 67% of the malignancies were correctly diagnosed at ages 75-90 years while only 29% at ages 100-106 years [32]. Moreover, a systematic review of cancer prevalence and mortality in centenarians based on studies with either registry data or autopsy data [33] reported that latent or incidental cancers were more frequent in very old people.

For breast cancer in women, a decreasing surveillance at the oldest ages has been suggested as explanation for the observed decrease, as strong similarity between age-specific breast cancer incidence rates and mammography rates has been observed [5].
Several biological mechanisms compatible with an old age decline in cancer incidence have been proposed. One is that the population is heterogeneous with respect to susceptibility to cancer [4, 8]. When the population ages and susceptible individuals die, the remaining population consists of more insusceptible individuals. However, a heterogeneous susceptibility as the sole reason for a decline at the highest ages was found to be inconsistent with the pattern of incidence curve curvature in 11 populations with different levels of cancer incidence [8].

Another mechanism could be the presence of age-related biological processes that impede tumor growth. Several specific processes have been proposed. One is the suggestion that the remodeling that the immune system undergoes with age could create a hostile environment for cancer cells [11]. Another process is the change with age in the inductive properties of the connective tissue due to the aging of the cells that make up the tissue and the continued restructuring of the tissue [13]. Here, the initiation of neoplastic growth could be inhibited by arteriosclerosis through subsequently limiting the development of angiogenesis. Thirdly, higher levels of estrogen are associated with an increased risk of breast cancer [34]. The post-menopausal decrease in ovarian production of estrogen and progesterone may result in an environment which is less friendly to the proliferation of cells and therefore inhibit the growth of malignant cells [12].

Our study used age-period cancer incidence rates and is thus confounded by cohort effect, but the observed age of peak cancer incidence in the present study was not suggested to be linked to specific cohorts (figure A2). The suggested low influence of cohort effects on the “peak age” of incidence is in concordance with findings from the Utah population where age-period-cohort modeling showed very limited cohort effects [24].

The major strengths of our study is the sample size and the high quality of the population-based, continuously updated registers, and that data on suspicion of cancer have provided a unique opportunity to study the relationship between age and the rate of suspected cancers. The period stratified analysis indicated a large increase from the early to the recent period in the registration of
suspicion of cancer. However, the comparisons in each of the two 9-year sub-periods confirm the overall comparison over the entire study period in the conclusion that no increase in suspected cancers is found at the oldest ages, so the comparison is not likely to be biased by the increase in recording of suspected cancers. A limitation of our study is that, although validation studies of the DNPR have found high degree of completeness and validity of colorectal cancer and any tumor [35], we are not aware of any validation of suspected cancers. Another limitation is the inclusion of suspicion from hospital contacts only (in 1994, inpatient contacts): if the cognitively intact older adults together with their GPs agree not to pursue further investigation of cancer suspicions, or for the cognitively impaired older adults, if similar considerations lead the GPs to refrain from further referral, then these suspicions are not included. The same considerations may apply to the hospital setting, either in the out-patient clinic or the in the bed-ward, resulting in no registration being done. If there is some degree of underdiagnosing cancer among the oldest, the reason for choosing not to pursue a diagnosis for a cancer suspect may vary between different countries. Ageism in the strict sense of withholding health care services from individuals over a specific age is no longer allowed in Denmark, but e.g. screening for breast and cervical cancer is restricted to women between ages 50-69 years and 23-64 years, respectively.

Conclusion

The age patterns of incidence rates of suspected but neither verified nor rejected cancers did not show an increase at the oldest ages. However, a marked lower tendency to pursue microscopic verification of diagnosed cancers in the highest age categories does suggest a lower diagnostic activity. The reason that this did not manifest itself in higher rates of suspected cancers at these ages is probably partially due to lack of registration. Consequently, the declining cancer incidence at the oldest ages is likely to be partly due to lower diagnostic activity.

Acknowledgments
This work is supported by the Odense University Hospital AgeCare program (Academy of Geriatric Cancer Research). The Danish Aging Research Center is supported by a grant from the VELUX Foundation (grant number: Velux 31205).

Conflicts of interest

None declared

References:


Table 1. Diagnostic codes for verified and suspected† primary cancer

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Verified cancer</th>
<th>Suspected cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICD-7</td>
<td>ICD-10</td>
</tr>
<tr>
<td>Breast</td>
<td>170</td>
<td>C50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Z031 (+) C50.9 (but not C50.9X)</td>
</tr>
<tr>
<td>Colon</td>
<td>153</td>
<td>C18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>162.0, 1, 8</td>
<td>C33-34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sites except</td>
<td>140-204 \ 191</td>
<td>CXX.X \ (C44 +</td>
</tr>
<tr>
<td>non-melanoma</td>
<td></td>
<td>C46.0) + D09.0 + D41.4 + D32-33 + D42-43</td>
</tr>
<tr>
<td>skin cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Suspected cancer of a hospitalized patient comprise the first reported suspicion of cancer that was neither rejected nor verified according to hospital records and where the patient had not been diagnosed with any cancer within one year after date of hospitalization.

††Codes for suspected cancer comprise the codes in the table supplemented with a diagnosis modification indicating that the ICD-8 code represents a suspicion and not an actual diagnosis.
Table 2. Characteristics of the study population of a 5% random sample of the Danish population supplemented with the entire birth cohorts of 1895-96, 1905 and 1910-12, for the period 1994-2011.

<table>
<thead>
<tr>
<th></th>
<th>Individuals (number of)</th>
<th>Risk time (person-years)</th>
<th>Verified cancers (number of)</th>
<th>Suspected cancers† (number of)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>243,523</td>
<td>3,073,237</td>
<td>5,052</td>
<td>562</td>
</tr>
<tr>
<td><strong>Colon</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>220,658</td>
<td>2,873,079</td>
<td>1,685</td>
<td>23</td>
</tr>
<tr>
<td>Females</td>
<td>246,188</td>
<td>3,114,628</td>
<td>2,233</td>
<td>58</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>221,098</td>
<td>2,878,628</td>
<td>2,717</td>
<td>657</td>
</tr>
<tr>
<td>females</td>
<td>247,348</td>
<td>3,127,704</td>
<td>2,059</td>
<td>520</td>
</tr>
<tr>
<td><strong>All sites except non-melanoma skin cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>221,422</td>
<td>2,882,114</td>
<td>19,187</td>
<td>4,211</td>
</tr>
<tr>
<td>Females</td>
<td>247,487</td>
<td>3,130,516</td>
<td>20,821</td>
<td>4,899</td>
</tr>
</tbody>
</table>

† But neither verified nor rejected as cancer
Table 3. Age distribution of risk time, age-specific incidence rates of verified and suspected cancers and the incidence rate ratios (IRR) of suspected† to verified cancers with 95% confidence intervals (CI) based on all sites but non-melanoma skin cancer in Denmark for a 5% random sample of the population and the entire birth cohorts of 1895-96, 1905 and 1910-12 in the period 1994-2011.

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk time (person-years)/100,000</th>
<th>Verified cancer rates (per 100,000 py)</th>
<th>Suspected cancer rates (per 100,000 py)</th>
<th>IRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 4</td>
<td>3.17572</td>
<td>22.4</td>
<td>13.5</td>
<td>0.61</td>
<td>0.41 - 0.88</td>
</tr>
<tr>
<td>5 - 9</td>
<td>3.35794</td>
<td>13.4</td>
<td>13.1</td>
<td>0.98</td>
<td>0.65 - 1.48</td>
</tr>
<tr>
<td>10 - 14</td>
<td>3.57070</td>
<td>10.4</td>
<td>19.6</td>
<td>1.89</td>
<td>1.27 - 2.82</td>
</tr>
<tr>
<td>15 - 19</td>
<td>3.76835</td>
<td>18.6</td>
<td>31.0</td>
<td>1.67</td>
<td>1.24 - 2.25</td>
</tr>
<tr>
<td>20 - 24</td>
<td>3.77862</td>
<td>28.1</td>
<td>34.7</td>
<td>1.24</td>
<td>0.96 - 1.60</td>
</tr>
<tr>
<td>25 - 29</td>
<td>3.73034</td>
<td>51.7</td>
<td>61.7</td>
<td>1.19</td>
<td>0.98 - 1.44</td>
</tr>
<tr>
<td>30 - 34</td>
<td>3.83093</td>
<td>80.9</td>
<td>78.3</td>
<td>0.97</td>
<td>0.83 - 1.13</td>
</tr>
<tr>
<td>35 - 39</td>
<td>3.79598</td>
<td>125.4</td>
<td>100.6</td>
<td>0.80</td>
<td>0.70 - 0.92</td>
</tr>
<tr>
<td>40 - 44</td>
<td>3.66816</td>
<td>203.1</td>
<td>131.7</td>
<td>0.65</td>
<td>0.58 - 0.73</td>
</tr>
<tr>
<td>45 - 49</td>
<td>3.53483</td>
<td>308.1</td>
<td>166.6</td>
<td>0.54</td>
<td>0.49 - 0.60</td>
</tr>
<tr>
<td>50 - 54</td>
<td>3.41528</td>
<td>505.4</td>
<td>225.2</td>
<td>0.45</td>
<td>0.41 - 0.49</td>
</tr>
<tr>
<td>55 - 59</td>
<td>3.13011</td>
<td>797.1</td>
<td>263.2</td>
<td>0.33</td>
<td>0.31 - 0.36</td>
</tr>
<tr>
<td>60 - 64</td>
<td>2.74663</td>
<td>1,169.4</td>
<td>337.1</td>
<td>0.29</td>
<td>0.27 - 0.31</td>
</tr>
<tr>
<td>65 - 69</td>
<td>2.22282</td>
<td>1,634.0</td>
<td>373.4</td>
<td>0.23</td>
<td>0.21 - 0.25</td>
</tr>
<tr>
<td>70 - 74</td>
<td>1.81456</td>
<td>2,045.7</td>
<td>374.7</td>
<td>0.18</td>
<td>0.17 - 0.20</td>
</tr>
<tr>
<td>75 - 79</td>
<td>1.85150</td>
<td>2,253.3</td>
<td>350.5</td>
<td>0.16</td>
<td>0.14 - 0.17</td>
</tr>
<tr>
<td>80 - 84</td>
<td>3.60897</td>
<td>2,182.6</td>
<td>187.6</td>
<td>0.09</td>
<td>0.08 - 0.09</td>
</tr>
<tr>
<td>85 - 89</td>
<td>3.24467</td>
<td>2,122.6</td>
<td>241.9</td>
<td>0.11</td>
<td>0.11 - 0.12</td>
</tr>
<tr>
<td>90 - 94</td>
<td>1.49753</td>
<td>1,756.9</td>
<td>309.2</td>
<td>0.18</td>
<td>0.16 - 0.19</td>
</tr>
<tr>
<td>95 +</td>
<td>0.38265</td>
<td>1,364.2</td>
<td>308.4</td>
<td>0.23</td>
<td>0.19 - 0.28</td>
</tr>
</tbody>
</table>

All ages | 60.12630 | 100.0% |
†Suspected cancer of a hospitalized patient comprise the first reported suspicion of cancer that was neither rejected nor verified according to hospital records and where the patient had not been diagnosed with any cancer within one year after date of hospitalization.
Table 4. The distribution of all tumors except non-melanoma skin cancers diagnosed in Denmark according to whether the diagnosis was based on microscopic verification, clinical verification, death certificate only, or unknown - stratified on age and period†.

<table>
<thead>
<tr>
<th>Period</th>
<th>Microscopic verification</th>
<th>Clinical Suspicion</th>
<th>Death certificate only</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (years)</td>
<td>N</td>
<td>percent</td>
<td>n</td>
<td>percent</td>
</tr>
<tr>
<td></td>
<td>0 - 69</td>
<td>54,503</td>
<td>95.2%</td>
<td>1,811</td>
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<td>12,572</td>
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<td>1,178</td>
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<td>67.5%</td>
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<td>1,198</td>
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<td>14,737</td>
<td>88.6%</td>
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<td>80 - 84</td>
<td>9,955</td>
<td>84.1%</td>
<td>1,498</td>
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<td>4,630</td>
<td>78.2%</td>
<td>982</td>
<td>16.6%</td>
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<td>68.8%</td>
<td>404</td>
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<td>3,835</td>
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<td>816</td>
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<tr>
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<td>96.1%</td>
<td>1,799</td>
<td>3.0%</td>
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<tr>
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<td>70 - 74</td>
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<td>95.4%</td>
<td>535</td>
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<td>680</td>
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<td>80 - 84</td>
<td>8,787</td>
<td>90.6%</td>
<td>744</td>
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<td>4,780</td>
<td>85.4%</td>
<td>683</td>
<td>12.2%</td>
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<tr>
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<td>90+</td>
<td>1,627</td>
<td>77.5%</td>
<td>359</td>
<td>17.1%</td>
</tr>
</tbody>
</table>

†For every period and each category of verification, test for trend in proportions with age was statistically significant, as was test for departures from trend except for unknown verification in 2010-2012. With Bonferroni correction for multiple testing (40 tests), there was no significant age

Figure captions

Figure 1. Cancer incidence in Denmark, 1994-2011: age pattern of diagnosed and suspected cancer
Figure 2. Proportion of diagnosed cancers in Denmark with microscopic verification of cancer – stratified on five calendar periods

*Supplement figures*


Figure A2. Age-specific cancer incidence rates in Denmark, 1968-2011, stratified on 5-year periods for ages 60-64, ..., 95+ years with indications of age of peak incidence for each of the corresponding birth cohorts with mid-year 1988, 1893, …, 1928 – males in upper and females in lower panel.
Denmark, 1994-2011

- Suspected and diagnosed
- Diagnosed
- Difference between curves
- Ratio between curves

Breast cancer

Females

Colon cancer

Males

Lung cancer

Males

All sites except nonmalignant melanoma of the skin

Males

Females

221,422 individuals
19,187 diagnosed cancers
4,211 suspected cancers
2,882,114 riskyears

247,487 individuals
20,821 diagnosed cancers
4,899 suspected cancers
3,130,516 riskyears
All sites except nonmelanoma skin cancer

Proportion with microscopic verification of cancer (in percent)

- Denmark - All diagnosed cancers
  - 2010-2012: 106,014 cancers
  - 1998-2002: 132,630 cancers
Supplemental methods

Data sources

The included study population was based on individuals identified in register data from the Danish Civil Registration System (DCRS), which was established in 1968 and in which each person alive and living in Denmark after April 2, 1968, is assigned a unique personal identification number linkable to other Danish population-based registers [1]. The DCRS contains information on sex, place and date of birth, citizenship and continuously updated information on vital status, migration status, place of residence and spouses. The completeness and validity of information recorded in the DCRS is generally accepted to be of high quality. Information on incidence of cancer was obtained by linkage to data from the Danish Cancer Register (DCR) [2]. The DCR was established in 1943 and contains information on all incident cancers in the Danish population since 1943. Up to 1977 the diagnosis has been recorded using a modified ICD-7 code [3], while the ICD-10 coding is available from 1978 and onwards. Variables recorded in the DCR include tumor characteristics such as date of diagnosis, stage, laterality, and basis of diagnosis. Initially, the registration was based on voluntary reporting from all hospitals involved in the diagnosis, treatment and follow-up of patients with cancer, with a small fee paid for each notification, but since 1987 notification has been compulsory. The cross link to death certificates and, since 1987, the Danish National Patient Register (DNPR) has resulted in a high validity and completeness of the DCR, and with the modernization of DCR in 2004, the proportion of morphologically verified tumors was 89% [2], although the proportion is lower at higher ages [4].

Information on suspicion of cancer was obtained by linkage to the DNPR, which was established in 1977 and originally contained information on all somatic inpatients in Danish wards gradually to be expanded to include all somatic outpatients from 1995 onwards, and since 2007 comprising all patient contacts to Danish hospitals (i.e. including psychiatric in- and outpatients) [5]. Linked to
individuals by the unique personal identification number, the register contains information on hospital department, dates of hospitalization and discharge from hospital department, outpatient contact, treatments and operations (including dates of) as well as referral diagnosis, action diagnosis and other diagnoses. Since 2000, the payment to public hospitals has been based on the reporting of services in the DNPR and thereby securing a high priority of the reporting of hospitalizations, which is considered to happen in close to 100% of the cases. Since 2000, private hospitals in Denmark have been allowed, and the reporting to the DNPR of hospitalizations at these hospitals is mandatory.

Study population
The study was based on a 5% random sample of every Danish birth cohort in the DCRS together with the Danish entire birth cohorts of 1895-96, 1905, 1910-12 and 1915 also from the DCRS. The particular choice of including the latter birth cohorts was based on their accessibility for this study and the fact that they increased power especially among the oldest ages. As the observed reporting to the DNPR of suspicion of cancer was very limited before 1994, the study population consisted of individuals from the above Danish birth cohorts alive and living in Denmark on or after January 1, 1994, and before December 31, 2011, the end of study.

Incidence of diagnosed and suspected cancer
For each of the three cancer sites: breast, colon and lung, only an individual’s first diagnosis in that site in the DCR (i.e. first diagnosis after 1943) was here considered to be an incident case in this study. For all sites except non-melanoma skin cancer, the same approach was used for each of 40 cancer entities comprising this cancer category and used in the NORDCAN collaboration of cancer registries in the Nordic countries: 39 of these entities are presented in table 2 of [6] while the last
category consists of the remaining cancers with poorly specified, secondary or unspecified localizations.

This approach deviates slightly from the IARC/IACR rules for multiple cancers used in NORCAN, where cancers in the same site but with different morphologies should count as primary cancers [7]. However, as for all the cancer sites in this study the proportion of patients with cancer with more than one primary cancer diagnosis in the same cancer site was below 2%, this deviation is unlikely to affect the results (see supplemental Table A1). For each of the cancer entities we considered, the category of suspected but not verified cancers thus comprised all first appearances (on or after 1977) of suspicion of the cancer in question. Prior to this, we excluded all records of suspicion of cancer that were either rejected according to the hospital records (supplemental ICD-10 code ZDW71) or where the individual in question had received any cancer diagnosis within one year after the date of discharge of the hospital record for the suspected cancer. The exact ICD-7, ICD-8 and ICD-10 codes defining the diagnosed and suspected site specific cancers are given in Table 1.

Comparisons

Based on the available study population and the study period of 1994-2011, incidence rates for diagnosed as well as diagnosed and suspected site specific cancer were calculated for 5 year age groups starting from age 0 and with the last group comprising ages 95+ years. While the calculated incidence rates allowed for a comparison of the age pattern of the incidence of diagnosed cancer to that of diagnosed or suspected cancer over the entire life span, the focus was the age pattern after the peak age of cancer incidence.

Diagnostic verification of cancers

To further assess whether there might be signs of an old age association with the diagnostic investigation we calculated the proportions of diagnosed cancers based on different degrees of
verification and how these proportions varied with age. The degree of verification of cancer was
categorized as microscopic verification (histology of tumor or metastasis, cytological or
hematological examination), clinical verification (clinical examination, clinical x-ray, biochemical
or immunological examination), verified by death certificate only, or unknown verification.
Microscopically verified entailed diagnosis based on histology, cytology, peripheral blood, cipher
count, M-component at S-electrophorese or marrow puncture. Remaining diagnoses (no histology/
cytology/marrow/cipher count, or pathology alone) were categorized in the three other categories
as: Clinical verification comprising clinical examination only, examination by x-ray, endoscopy,
operation, or other specified examination (ultrasound, scintigraphy, etc.); Death certificate only; and
Unknown.
The distribution of diagnosed cancers in these categories was calculated for each of the age
intervals of 0-69, 70-74, 75-79, 80-84, 85-89 and 90+ years and were calculated for the entire
2012.

Statistical analysis

In the estimation of incidence rates at specific sites (breast, colon, lung) in different age categories
and periods, censoring occurred at death, emigration or incidence of the event of interest (while
assuming independent censoring). For all sites except non-melanoma skin cancer, an incident
cancer did not entail censoring after the event, as the individual was still considered under risk of
cancer at other sites. Tests for age trend and departures from these in the proportions of diagnosed
cancers with different degrees of verification was based on the methods described in [8, 9] using
equidistant trend scores for the six age categories.
**Supplemental references**


Table A1. Distribution of number of primary cancers per individual for each cancer site (in % of individuals with at least one cancer with the specific site diagnosed in Danish Cancer Register)

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Once</th>
<th>Twice</th>
<th>Thrice††</th>
<th>Total number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>n</td>
<td>percent</td>
<td>n</td>
<td>percent</td>
</tr>
<tr>
<td>Breast</td>
<td>18,570</td>
<td>98.9%</td>
<td>215</td>
<td>1.1%</td>
</tr>
<tr>
<td>Colon</td>
<td>14,632</td>
<td>98.4%</td>
<td>231</td>
<td>1.6%</td>
</tr>
<tr>
<td>Lung</td>
<td>20,898</td>
<td>99.7%</td>
<td>57</td>
<td>0.3%</td>
</tr>
<tr>
<td>All sites except non-melanoma skin cancer</td>
<td>145,862</td>
<td>99.4%</td>
<td>928</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

†For the 'all sites cancer' category the sites considered were the cancer entities corresponding to each of the NORDCAN entities 1-29 and 31-41, where the category 30 of non-melanoma skin cancer has been excluded from the considered cancer diagnoses.

††For the 'all sites cancer' category an individual in this cell represents either an individual with three primary diagnoses of the same cancer site or an individual with two different cancer sites each diagnosed as primary twice.
Titles and captions to supplemental figures:


Figure A2. Age-specific cancer incidence rates in Denmark, 1968-2011, stratified on 5-year periods for ages 60-64,…, 95+ years with indications of age of peak incidence for each of the corresponding birth cohorts with mid-year 1988, 1893, …, 1928 – males in upper and females in lower panel.