INTRODUCTION

The incidence of cancer under age 20 years is 187.9 per million [1]. Approximately 11,210 cases are diagnosed under age 15 years annually. Improvements in treatment strategies and supportive care have resulted in an increase in long-term survival (50% to 70%) in children with cancer since 1975 [1]; however, an increase in age adjusted incidence from 7.7 to 8.7 per million children has been observed during this time. From 2004 to 2008 the incidence increased by 0.5% per year. Prevention of cancer in children by identification and avoidance of exposure to environmental carcinogens is clearly of major importance [2].

Multiple lines of evidence suggest that prenatal exposure to alcohol may be carcinogenic. Alcohol and alcohol metabolites have been found to be teratogenic, mutagenic, and carcinogenic [3,4]. Worldwide alcohol abuse now accounts for 4% of total worldwide mortality and between 4% and 5% of all disability-adjusted life years [5]. Antenatal alcohol exposure is also a pandemic health problem and appears to be especially prevalent in much of the developing world [6]. In the United States, the prevalence of alcohol use by non-pregnant women during their childbearing years was 54.6% in 2001 [7–9].

The prevalence of alcohol exposure during pregnancy decreases from 50% prior to pregnancy to around 10% upon recognition of pregnancy [9–11]; however, approximately 3–5% of women continue to drink throughout pregnancy. Many drink heavily, more than five drinks per occasion and often several times per week [8]. Many of these women also smoke heavily [10,12]. As a result, of the four million pregnancies each year in the United States, at least 500,000 have experienced some and >60,000 have experienced high levels of alcohol exposure.

Based on the above, several million infants, children and adolescents from birth through 19 years of age in the United States have had antenatal alcohol exposure at levels increasing risk for a fetal alcohol spectrum disorder (FASD). FASD has four diagnostic categories: fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol related neurodevelopmental disorder, and alcohol related birth defects [10]. Current prevalence estimates of FASD from worldwide studies of school-age-children range from 20 to 50 per 1,000 live births [13]. Current prevalence estimates of FASD within the United States are 0.5–9.1 cases for every 1,000 live births [14].

Results of studies examining antenatal alcohol exposure as a risk factor for cancer have been inconsistent. A dose related increase in risk of developing acute myeloid leukemia following antenatal alcohol exposure has been reported [15–17]. Four studies found no increase in risk for neuroblastoma from maternal alcohol use [4,18–20] however, another study identified maternal alcohol use as risk factor [21]. This study also found a dose response for exposure; any drinking OR = 1.44 (0.94–2.21); >1 drink day OR = 9.0 (2.16–37.56); >3 drinks day “binge” OR = 6.0 (1.26–28.54); >1 drink day or 3 drinks (binge) OR = 12.0 (3.14–45.82).

A potential confounding factor in these studies is under reporting of alcohol exposure. Evaluating the relationship between FASD and cancer assures that alcohol exposure was sufficient to produce detectable adverse effects including potential co-vulnerability for the development of cancer. In this paper the published reports of FASD and cancer in children and adolescents are reviewed.

METHODS

Sources

A search strategy was developed and conducted by an expert reference librarian with guidance from the authors. The strategy was designed to locate potentially relevant articles regarding cancer and FASDs. The search was conducted through the following electronic databases and search engines: PubMed, Scopus, Cochrane Database of Systematic Reviews, Quertle, and Google Scholar. The following key words and subject headings were utilized in the search: cancer, tumor, ethanol, fetal, fetal alcohol syndrome, fetus, fetal, neonate, newborn, pregnancy, and prenatal...
exposure delayed effects. The search, which was completed to May 2013, placed no limits on language or publication date. All non-human data was restricted from this review. Hand-searching article reference lists and textbooks located additional relevant publications.

Study Selection

**Inclusion criteria:** Papers which reported any cancer in a subject with FASD were included if the child’s age was under 19 years of age. Exclusion criteria: Papers that did not report on co-occurrence of cancer and FASD and non-human studies. One report described a case of non-specific malignant disease that was not included in this review [22].

RESULTS

We located 10 papers that met our inclusion criteria. These papers reported on 13 subjects including an additional case from the authors’ institution. Findings are summarized in Table I. The age of the cases ranged from 4 months to 12 years 1 month with a mean age of 39.2 months ±38.7. The male to female ratio was 8 males 5 females (ratio of 1.6/1).

Neuroblastomas comprised 6 of the 13 (46%) case reports, yet neuroblastomas comprise only about 10% of childhood cancers (z = 4.1; P < 0.001). The mean age was 23.8 months (range from 110 days to 35 months). The male to female ratio was 5/1.

Rhabdomyosarcoma accounted for 15.3% (2/13) of cancer cases in these children with FAS, which was not significantly different from the proportion of rhabdomyosarcomas in the general population of childhood cancer cases of 5% (z = 1.7; P > 0.05). The mean age was 21 months and both were males.

All other childhood cancers accounted for 38.4% (5/13) of cases, and no other specific type of cancer was reported more than one in this group of children with FAS. The male to female ratio of the other group was 71.4 months ranging from 16 months to 155 months. The male to female ratio was 4 females to 1 male.

DISCUSSION

In this review of the published literature, only 13 cases of cancer developing in children with FASD were identified. The worldwide prevalence of FASD is estimated at 20–50/1,000 children and adolescents. If FASD does not have either a causal or protective effect on cancer development, 220–560 cases of cancer in children with FASD should be identified annually in the United States. Clearly, the co-occurrence of cancer and FASD is largely under reported which limits the validity of case-control and other epidemiological studies.

Under reporting may be due to a low rate of detection of FASD in children with cancer or limited attention to its co-occurrence. FASD may be under diagnosed because of lack of awareness of the disorder and/or lack of familiarity with diagnostic criteria (see Table I). The medical record may be limited, inaccurate or unavailable. This is particularly common in children with FASD as mothers are often not available due to death, ongoing substance abuse, and child placement in foster care or adoption [23,24]. Continuity of medical care is generally poor because of families relocating or becoming lost to follow-up. FASD may therefore have been previously diagnosed but the diagnosis may not be recorded in the current medical record.

In this review FASD was disproportionately associated with neuroblastoma. Of the 13 cases of children with FASD and cancer identified, neuroblastoma was present in 6 (46%) and rhabdomyosarcoma in 2 (15.3%). Other cancers were individually represented in 5 (38.4%). As discussed above, data on maternal alcohol use as a neuroblastoma risk factor have been conflicting with four studies reporting no significant association [4,18] and one study reporting a dose related increase in risk [21].

The association between FASD and neuroblastoma is of considerable interest as the ALK (anaplastic lymphoma kinase) gene may play a pivotal role in the genesis of both disorders. The risk of neuroblastoma is increased by the presence of ALK missense mutations [25] ALK has been reported to have multiple roles in fetal and neonatal neurodevelopment [26]—a primary target in FASD. ALK is involved in regulation of alcohol use in drosophila and mice [27]. In humans ALK is associated with multiple changes in behavioral responses to ethanol [27]. Four polymorphisms have been associated with response to ethanol and one phenotype has been identified that is associated with alcohol use disorders [27].

We are not aware of studies examining ALK as an effect modifier for the neurobehavioral features of the FASD phenotypes or as a biomarker for antenatal alcohol exposure. However, ALK

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gender</th>
<th>Age</th>
<th>FASD</th>
<th>Cancer</th>
</tr>
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<tbody>
<tr>
<td>[28]</td>
<td>M</td>
<td>28 months</td>
<td>Yes</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>[29]</td>
<td>M</td>
<td>21 months</td>
<td>Yes</td>
<td>Embryonalrhabdomyosarcoma</td>
</tr>
<tr>
<td>[30]</td>
<td>F</td>
<td>3 years 9 months</td>
<td>Yes, with hydantoin</td>
<td>Hodgkin disease</td>
</tr>
<tr>
<td>[31]</td>
<td>F</td>
<td>12 years 11 months</td>
<td>Yes</td>
<td>Adrenal carcinoma</td>
</tr>
<tr>
<td>[32]</td>
<td>M</td>
<td>27 months</td>
<td>Yes</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>[33]</td>
<td>M</td>
<td>25 months</td>
<td>Yes</td>
<td>Ganglioneuroblastoma</td>
</tr>
<tr>
<td>[34]</td>
<td>M</td>
<td>110 days</td>
<td>Yes</td>
<td>Neuroblastoma*; paravertebral found near kidney</td>
</tr>
<tr>
<td>[35]</td>
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<tr>
<td>[36]</td>
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<td>35 months</td>
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<td>Ganglioneuroblastoma</td>
</tr>
<tr>
<td>[37]</td>
<td>M</td>
<td>21 months</td>
<td>Yes</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>F</td>
<td>6 years</td>
<td>Yes</td>
<td>Nephroblastoma</td>
<td></td>
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<tr>
<td>F</td>
<td>16 months</td>
<td>Yes</td>
<td>Leukemia</td>
<td></td>
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<tr>
<td>New patient</td>
<td>F</td>
<td>16 months</td>
<td>Yes</td>
<td>Neuroblastoma</td>
</tr>
</tbody>
</table>

*Tumor found at autopsy.

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does seem to warrant additional study as an important gene in risk modification for at least some types of cancer (AML and neuroblastoma). Multicenter studies will also be required to determine if FASD is a risk modifier for cancer in children and if the effect is specific to any class of cancers.

REFERENCES